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REVIEW - SYSTEMATIC REVIEW - META-ANALYSIS

Clinicians' perceived barriers and enablers to the dietary management of adults with type 2 diabetes in primary care: A systematic review

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Abstract

Background: Dietary management of type 2 diabetes is considered as a key remission and management strategy. This review explored clinicians' perceived barriers and enablers to the dietary management of adults with type 2 diabetes in primary care.

Methods: MEDLINE, EMBASE, CINAHL, PsycINFO and ASSIA were searched from 1980 to 26 June 2020.

Results: Of 2021 records, 14 studies met the inclusion criteria, describing the 14 domains of the refined Theoretical Domains Framework. The data synthesised to the domains of *environmental context and resources, intentions* and *beliefs about capabilities* were considered most trustworthy, closely followed by *knowledge, behavioural regulation* and *beliefs about consequences*. Two-thirds of studies cited time for staff training or patient education as major constraints to type 2 diabetes management. Clinicians also identified lack of patient engagement and poor dietary adherence as issues. Despite this, clinician confidence about giving dietary advice to patients was high. With further exploration, knowledge gaps were apparent and feelings of despondency as a result of poor outcomes were visible.

Conclusions: This review revealed four clinician behaviours: (2) the perception of the dietitian; (2) the definition of a clinician qualified to give dietary advice; (3) clinician belief in dietary management as a treatment; and (4) clinician belief in a patient's capability to change dietary behaviour. These behaviours, if challenged and changed, have the potential to improve dietary management and outcomes for people with type 2 diabetes in primary care.

KEYWORDS
dietary management, type 2 diabetes, clinician, perceptions

INTRODUCTION

The number of people living with diabetes continues to rise with recent UK prevalence data reported as 3.9 million for 2018–2019, with an estimated 90% of these having type 2 diabetes.[1] In the UK, diagnosis and management predominantly sits in primary care with general practitioners and nurses. Self-management education for people with type 2 diabetes by trained educators including dietitians is recommended.[2] Diabetes care closer to home offers potential advantages such

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as improved uptake of care, good patient–primary care clinician relationships and short frequent appointments.[3]

Dietary management is the cornerstone of type 2 diabetes remission and treatment strategies, with excessive weight carrying the greatest risk for development and progression of the condition.[4] Although diabetes standards and guidelines pertinent to practice exist, recent reviews offer no clear conclusions on optimal diet choice.[5–7] Indeed, professional dietetic debate is coloured by personal opinion and the cherry picking of evidence to support a particular viewpoint.[8] This may invoke apathy in other clinicians and underutilisation of both education and dietetic services.[9,10]

A systematic review of the effects of specialist tier 3 tailored weight management interventions for adults in the UK, reported weight reduction in the range of 2–6 kg.[4] Such weight loss offers health benefits, including improved glycaemic control reducing the risk of disease progression and related complications for people with type 2 diabetes, although it is unlikely to bring about remission.[11] For type 2 diabetes remission, weight reduction of 10–15 kg is needed.[12,13] Here, the low calorie diet with its associated rapid weight loss appears to offer the best chance of reversing this condition; a short-term diet of 800–1200 calories daily, generally made up of formula food products.[4]

Despite the apparent advantages of weight reduction for people with type 2 diabetes, patient outcomes on lifestyle advice, including diet, in primary care have historically been poor.[14] Even now, weight loss remains elusive to many and outcomes have not been fully explained by patient characteristics such as lack of knowledge, comorbidities, financial resources and non-adherence to therapy.[15]

A recent systematic review identified the need to address clinician pessimism around a patient's ability to alter health behaviours.[16] Additionally, negative clinician attitudes toward people living with obesity may act as a barrier to optimal diabetes dietary management.[17] Almost 20 years ago, studies reported the absence of lifestyle behaviour counselling of patients by physicians.[18,19] Barriers cited related to lack of time, necessary skills and reimbursement for this activity.[20] Other studies have acknowledged the difficulty and considerable clinician frustration of empowering patients to adopt healthy behaviours.[21–23] Such negativity may correlate with reported clinician lack of dietary knowledge and behaviour change skills and heighten feelings of inadequacy.[24] Training has the potential to alter clinician behaviour.[25] Similarly physicians who are willing to change their own diet appear more receptive to use of nutritional counselling.[26] Alternatively, clinicians (nurses and physicians) may still favour the traditional medical model, where they feel a duty to prescribe care rather than permit patients to share decision making despite changes to the pre-registration curriculum.[27] Furthermore, ignoring patient-related factors may hamper efforts.[28]

Expanding on specific barriers and enablers for clinicians to the dietary management of diabetes may enable clinicians in primary care to reimagine dietary treatment and remission strategies. Behaviour change interventions are fundamental to implementation of evidence-based practice and effective patient care. The Behaviour Change Wheel (BCW) was developed following review of 19 frameworks of behaviour change interventions. This new framework emphasises the value of analysing the behaviour that a patient wants to change and taking into account all of the relevant aspects of the behaviour being targeted.[29] Shared challenges likely cross international and health system borders. This systematic review identifies healthcare professionals' perceived barriers and enablers to the dietary management of adults with type 2 diabetes in primary care.

Key Points

- Dietary management of type 2 diabetes in primary care is key but outcomes remain poor.
- This review describes clinician's perceptions of the dietitian, who should give dietary advice, whether it works and whether people with diabetes can follow it.
- Changing such attitudes may help people achieve type 2 diabetes remission or enable them to self-manage with less medical treatment.

METHODS

Protocol and registration

This review is registered with PROSPERO (International Prospective Register of Systematic Reviews). The registration number is CRD42020190471. The protocol is available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020190471.

Eligibility criteria

Qualitative study designs were included. Studies that only used quantitative data were excluded. The condition of interest was adults with type 2 diabetes managed in primary care. The specific management aspect under consideration was diet. The acronym PEO (Population, Exposure, Outcome) was used to formulate the question.

The years under consideration were from 1980 to 2020. The search was limited to reflect when the World Health Organisation called for diabetes care to be incorporated into community-based healthcare systems.[30] English and non-English studies were identified and data extracted.

Information sources

Databases searched included MEDLINE (exported 23/04/2020), EMBASE (exported 12/06/2020), CINAHL

(exported 26/06/2020), PsycINFO (exported 24/06/2020) and ASSIA (exported 18/06/2020). Reference lists of included studies, Conference proceedings, National Research Register and grey literature were also searched.

Search

The full electronic search strategy for MEDLINE via EBSCO is available from: https://www.crd.york.ac.uk/PROSPEROFILES/190471_STRATEGY_20200604.pdf.

Lifestyle counselling or modification was added to the terms in this search strategy to identify relevant papers that did not include diet in the MeSH headings. Two qualitative filters identified by Wagner *et al.*[31] were tested: the Health Information Research Unit[32] filter retained 691 references, whereas the University of Texas Health Science Center at Houston[33] filter retained 135 references. For each database, the filter retaining the larger number of references was used. This strategy was adapted from Rushforth *et al.*[16] and translated to the relevant interfaces for the other databases listed above.

Study selection

All of the references identified by the search strategy were initially screened (stage 1) by title and abstract by the researcher (RB). Researcher 2 (HM or AH) independently looked for inconsistencies in the screening decisions. Inconsistencies not readily resolved by joint review (RB, HM and AH) were referred to team member (AL). Where agreement was not possible, the paper was included in next review stage.

In stage 2, full papers were assessed for inclusion by reviewers (RB and one other from HM and AH). Any uncertainty was resolved by discussion between the team (RB, HM and AH), with additional input from team member (AL) as required. Discussion took an iterative approach, allowing for future alignment of decision making based on inclusion and exclusion criteria.

Data collection process

During stage 3, data were extracted (study details, perceptions and quality/risk of bias in individual studies assessment) by the researcher (RB). Perceptions were mapped to the 14 domains (nodes) of the refined Theoretical Domains Framework (TDF)[34,35] using NVIVO, version 12 (QSR International) (see Supporting information, Appendix S1). This refined TDF offered a method for theoretically assessing implementation problems, as well as professional and other health-related behaviours. Domains were further grouped into three categories (i.e., capability, motivation and opportunity), which sit at the centre of the BCW framework for understanding behaviour.[29] Findings were organised into a grid using an Excel spreadsheet. Researcher 2 (HM) independently undertook data extraction of the included studies. Where inconsistencies were identified, joint review (RB, HM and AH) and, where needed, further discussion with team member (AL) resolved disputes.

Data items

ENDNOTE X9 (Clarivate Analytics) was used to remove duplicates from subsequent databases following an initial Medline search. As a result of the character limit per search line in ASSIA, the full range of terms for health professionals and attitudes was retained; however, the diet and diabetes sections were simplified. Broad search terms for diet and diabetes were considered reasonable for a non-health database.

Risk of bias in individual studies

Risk of bias of individual studies at study level was assessed using the NICE Methodology checklist for qualitative studies[36] by two researchers (RB and HM) (see Supporting information, Appendix S2). Inconsistencies between the researchers was resolved through full team review and discussion. Results are incorporated through narrative synthesis.

Summary measures

The principle outcomes of interest were influences on primary care-based dietary management of type 2 diabetes that might be amenable to change via any subsequent implementation strategy. Factors relating to the clinician, patient and organisation were reported. No formal effect measures were undertaken.

Synthesis of results

Thematic synthesis, involving the systematic search for patterns to generate full descriptions (themes) capable of shedding light on the phenomenon was undertaken. A combined deductive/inductive approach permitted exploration of domains within the existing refined TDF at the same time as accommodating other unexpected aspects of participants' experiences or way of assigning meaning to phenomena.

The Framework Method,[37] commonly used for semi-structured interview transcripts, facilitated rigorous and transparent data management. The stages of analysis included: (1) Transcription; (2) Familiarisation with interview; (3) Coding; (4) Developing analytical framework; (5) Applying analytical framework; (6) Charting data into framework matrix; and (7) Interpreting data. In this systematic review, transcription was undertaken by authors of the published studies and transcripts limited to excerpts used to illustrate their findings. Becoming familiar with the study context and research questions by carefully reading each paper was essential to interpretation of the qualitative data within these studies.

Risk of bias across studies

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines were used to assess risk of bias in the review during synthesis.[38] Studies at high risk of bias were acknowledged in the discussion. Conflicts of interest of study investigators or funders were examined.

RESULTS

Study selection

From 2021 records, 64 full-text articles were assessed with 14 studies included in the qualitative synthesis (Figure 1). Five of the retained studies were from the UK, four were from the USA, two were from Europe, two were from the Middle East and one was from New Zealand.

Study characteristics

The studies retained were published between 1993 and 2020 with two-thirds being within the past 10 years. The majority of the conducted questionnaires often relied on closed questions,[11] with the remaining three using semi-structured interviews. Study size varied from 9 to 743 participants, comprising a total of 382 nurses, 2652 general practitioners and 12 other clinicians. The research aims for the included studies considered healthcare professional attitudes to diet counselling, nutritional knowledge and skills, issues faced, services provided, resources available, referral efforts and

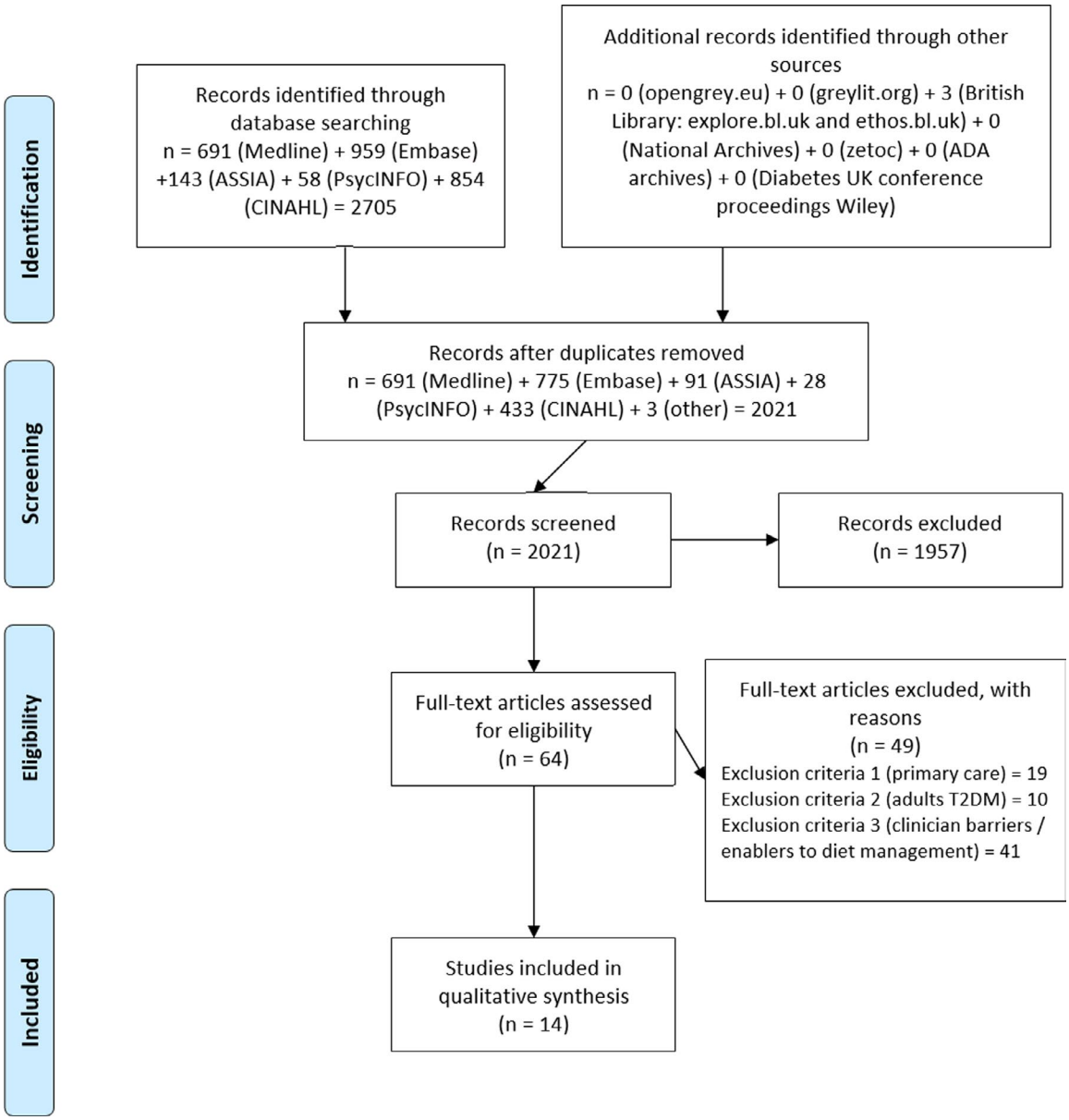

FIGURE 1 PRISMA flow chart

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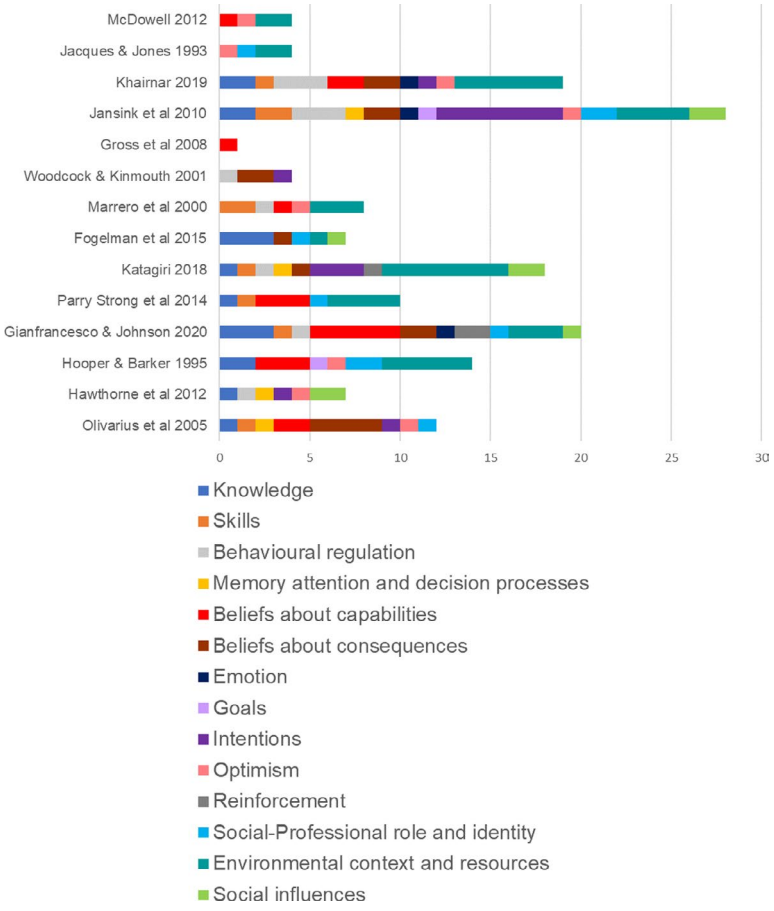

FIGURE 2 Coding of records to theoretical domains framework

perceived patient concerns or barriers to self-efficacy. Study characteristics are summarised in the Supporting information (Appendix S3).

Risk of bias within studies

Four studies were given the highest quality rating, three of which were published between 2018 and 2020 (see Supporting information, Appendix S2). Although all studies included a qualitative approach, four studies chose to analyse their questionnaires quantitatively.[39–42] Olivarius *et al.*[43] comprised a mixed methods study and Hooper and Barker[44] focused on nutrition education rather than solely diabetes dietary advice. The studies were considered trustworthy, although half did not offer detail concerning the role of the researcher. Five of the studies presented 'rich' data by adopting a thematic approach to qualitative analysis and including quotes verbatim.

Results of individual studies

Study findings were coded to one or more of the 14 domains in the refined TDF (Figure 2). A detailed summary of evidence is provided in the Supporting information (Appendix S1). The records[3,14,45,46] offering the richest data extraction were also rated highly for quality (Appendix S2).

Gianfrancesco and Johnson[3] commented most frequently on *beliefs about capabilities*. Here, nurses who received confirmatory messages from general practitioners were more confident in their practice role as 'nutrition expert'. Some acknowledged the importance of onward referral to dietitians, recognising the impact dietary change can make on the physical wellbeing of people with diabetes.

Katagiri[45] offered insight into the *environmental context and resources*. Two key clinician-related points were cited as significant or very significant: limited time for education and lack of access to education services, partly as a result of to poor financial reimbursement to the provider and an absence of staff education. Similarly, Khairnar *et al.*[46] found lack of time for patient follow-up to be extremely or very important to primary care physicians. In that study, patient-related factors were identified as reasons: patient nonadherence or indifference to dietary advice. Meanwhile Jansink *et al.*[14] found that the data in their study shed light on healthcare professionals' *intentions*. Again two viewpoints emerged. First, a hesitancy to offer dietary advice which would put the relationship with the patient at stake. Second, a belief that patients are unable or unwilling to alter dietary or lifestyle behaviours.

Synthesis of results

Figure 3 displays the frequency of coding per TDF domains. Here, the results are presented in order of most frequent report.

Environmental context and resources

Two-thirds of studies cited time for staff training and lack of patient dietary education as major constraints to diabetes management in primary care. Lack of clarity around minimum staffing levels for primary care-based dietary education, the definition of a suitably qualified health professional and infrequent training opportunities often pitched at the incorrect level for generalist healthcare professionals presented further obstacles within the UK.[44] Staff education in the UK was briefly given priority in 2013 recalled one nurse when 'dietary advice' was a Quality and Outcomes Framework (QOF) indicator (DM013).[3] For this year, this indicator measured the percentage of people with diabetes, on the register, who had a record of a dietary review by a suitably competent professional in the preceding 12 months.

More recently, despite attempts to free up nursing time for patient education by utilising healthcare assistants, a meagre 5–10 min annually was reported by one UK study[3] compared to 4–15 min mentioned by the New Zealand based study.[47] Katagiri[45] pointed out that repetition is necessary for patients to understand educational content which can be difficult to achieve under such time constraints. Furthermore in the Netherlands, a lack of high-quality patient education materials was found to be a barrier.[14] Dietitians, particularly in the USA, were not always tasked with providing dietary education to people with diabetes due to their availability, reimbursement and patient and clinician beliefs.[48] In 2019, nurses in the Netherlands[14] corroborated such patient beliefs with reports of 'Some patients refuse to see a dietician because they think that they already know everything there is to know about diet'. Furthermore, these nurses felt 'There is not enough consultation with the dietician. I often do not know what kind of diet arrangement has been made with the patient'.

FIGURE 3 Frequency of coding per theoretical domains framework domains

Beliefs about capabilities

Across the years and in different countries, physicians and nurses have reported feeling confident about giving dietary advice to patients.[40,44,46,47] For some, positive feedback from staff and patients, alongside sufficient training bolstered that belief. The most recent UK study[3] recorded nurses recalling 'I can think of quite a few people who have lost weight and their diabetes has practically disappeared'. An alternative viewpoint was expressed by an advanced nurse practitioner who stated 'I talk to people about healthy eating but I also see who else could get involved because I think it's important because they only see me fairly rarely …'. The task of changing a patient's dietary habits was generally considered to be more challenging than medical management, although the studies were older or considered of lesser quality to this review.[39,42,43,48]

Knowledge

With further exploration of that confidence in a clinician's ability to give diabetes dietary advice, gaps in nutritional knowledge have been documented. Hooper and Barker[44] reported that half of nurses correctly answered a series of diet-related questions compared with a fifth of general practitioners. Furthermore, the more specific the 'diet' question, the more likely clinicians felt out of their depth. Gianfrancesco and Johnson[3] described one nurse's immediate thought to a question about how many slices of bread a patient should have daily was 'Do you know, I've got absolutely no idea'. In another study, a nurse recognised the need to give dietary advice even if limited:[14]

> Some patients have had bad experiences with dieticians and refuse to go to them … I can tell the patients what is good or bad for them but for specific diet advice they still have to go to the dietician

Beliefs about consequences

An overwhelming feeling of despondency was visible across the studies reviewed. This was summed up by a nurse in the most recent UK based study:[3]

> You know what I have to do in 10 minutes is not enough because that is the whole basis of diabetes when you think about it. It is diet. And if they can't get that right … you're on a losing battle …

A study in the Netherlands,[14] corroborated the findings above, when nurses spoke of having little hope that a patient will change their behaviour despite repeating 'diet' messages, believing patients to have limited insight into their own behaviour. Meanwhile, US physicians[46] admitted cherry picking patients for dietary advice who they perceived to be receptive, whereas others[43] relied on medications rather than diet. Finally, patient-related factors identified by clinicians included powerlessness, fear, denial and hesitancy resulting in poor engagement.[45]

Intentions

Patient-related factors identified above appear to impact the patient-clinician relationship. On the one hand, Jansink *et al.*[14] discovered that nurses did not wish to be judgemental, whereas others failed to understand why patients were unable to change their dietary behaviours. According to these nurses, a patient's unwillingness to change was in part due to previous experiences with a dietitian. Moreover, the nurses believed that patients actively searched for reasons not to alter their dietary habits. That said, there was recognition of a mismatch of dietary advice 'Sometimes I supply information too fast. The patients are in an earlier stage of change'.

Behavioural regulation

Self-care in diabetes management is undisputed by the majority of clinicians; however, that same majority believed less than half of patients are adherent with a recommended diet.[46] The view of clinicians that patients simply do not wish to comply with nutrition counselling may instead reflect a behaviour change *skills* gap.[40] Nurses in the Netherlands[14] expressed their frustrations around 'diet' care planning as follows 'I do not know what the best way is to counsel patients … It is difficult to make things (action plan) concrete and do this in a structured manner'. The quality of this clinician-patient dialogue has been shown to predict patient self-efficacy.[49]

Other domains

Historically, twice as many nurses as general practitioners have assumed the *social / professional role identity* of dietary advice giver in primary care.[44] Interestingly, within the UK, nurses still perceive this to be their responsibility to the exclusion of others.[3,49] Elsewhere, this role falls to the dietitian.[14,47] Nurses picking up a range of duties including dietary advice have expressed *emotions* such as isolation, uncertainty and despair.[3] Likewise, a sizeable proportion of US physicians took responsibility for their patient's failure to self-manage diabetes.[46] Lastly, *social influences* included today's obesogenic environment[45] and peer pressure within local communities.[14] The remaining coded domains offered no new information. New codes were not created because data fitted into existing refined TDF domains.

Risk of bias across studies

Outcome specific bias was classified using GRADE as high, moderate, low and very low quality for transparency and simplicity where high was defined as 'further research is very unlikely to change our confidence …'.[38] For the domains above, *environmental context and resources, intentions* and *beliefs about capabilities* were rated to be of high quality; *Knowledge, Behavioural regulation* and *beliefs about consequences* were rated as moderate quality; and *Skills* and *Social influences* rated as low quality. The remaining domains were rated as very low quality based on the internal validity of data within included studies. No conflicts of interest were declared. Gross *et al.*[42] and Jansink *et al.*[14] benefited from national research monies. Olivarius *et al.*[43] part funded their study through the Health Insurance Foundation.

DISCUSSION

Exploration of domains within the existing refined TDF enabled clinicians' behaviours to be identified and potentially targeted. Four behaviours or themes emerged and are further considered below.

Perception of dietitian

Registered dietitians are qualified healthcare professionals who are able to advise on all aspects of diet. The negative views expressed by a number of clinicians in this narrative synthesis is sadly not surprising to the profession. In the Netherlands, Spikmans *et al.*[50] recorded that almost three-quarters of patients with diabetes were hesitant or reluctant to visit the dietitian. Here, the behaviours of *intention* (feeling obligated) and *beliefs in capabilities* (self-efficacy) predicted whether a patient attended. This raises the question of the impact on patient attendance of those clinicians who do not believe that dietary management works. To dispel myths of patients and clinicians that persist to this day, the process of professionalisation into dietetics through supporting students as they become part of the dietetics and specialty-specific communities of practice may merit further exploration. Maclellan *et al.*[51] raised questions concerning 'the gap between theory and practice actualities, the disconnect between perceived and actual professional roles and the implications of the highly

feminised nature of the profession'. McDowell *et al*.[52] suggested that dietitians may struggle to work collaboratively with primary care clinicians where their offices are located elsewhere.

Definition of a clinician qualified to give dietary advice

On the surface, clinicians perceived themselves to be capable of giving dietary advice to people with type 2 diabetes (*beliefs in capabilities*). However, further exploration of this narrative suggested significant gaps in both *knowledge* and *skills*. Arguably similar barriers identified in the literature almost 20 years ago remain today.[18,19] Dietetic mentorship of primary care staff was limited,[53] investment in behaviour change skills training lacking, dietary education *ad hoc* and arguably not always fit for purpose, and supporting educational material sparse. Dietary management is not the easy option, one size does not fit all and the best choice comprises the diet that works for that particular patient.[8]

Belief in dietary management

Beliefs about consequences of an intervention may cause clinicians to second guess what might work for a patient, rather than invest in shared decision making. This is perhaps understandable given the lack of protected time for diabetes dietary advice. The short appointment times for people with type 2 diabetes in primary care are not fit for purpose. It is hardly surprising that the success rates for remission through dietary management of recently diagnosed type 2 diabetes remain relatively low, leading to clinician feelings of frustration and failure.[46] Emerging evidence suggests that diet holds the key to the management of type 2 diabetes, whether that be through remission or delayed progression of the condition.[4,12] Clinicians would do well to embrace these positive clinical outcomes and strive to attain meaningful change for their primary care-based patients by addressing the barriers identified in the *environmental context and resources* domain. Relying on a toolkit of diabetes medications may at best compliment dietary and lifestyle behaviour changes in people with type 2 diabetes.

Belief in patient capability

Although patient-related factors likely impact the dietary behaviour change process, clinician behaviours may influence or overcome such barriers.[54] Negative attitudes of healthcare professionals towards people with type 2 diabetes living with obesity can act as a barrier to self-efficacy.[17] Similar to a number of healthcare professionals in this synthesis, patients too will invariably feel more confident in response to positive feedback regarding knowledge, behaviour and skills acquired.[3]

Limitations

A qualitative systematic review by its nature is a subjective process with significant differences in the approaches employed. Limitations were minimised through extensive database searches using database-specific search strategies, assessing for both sensitivity and specificity. Inclusion and exclusion criteria were used to screen studies and validated tools to reduce researcher subjectivity in the assessment of quality and bias.

CONCLUSIONS

Dietary management of type 2 diabetes predominantly sits in primary care with nurses and physicians. Successful dietary behaviour change interventions leading to type 2 diabetes remission or delayed progression with streamlining, or reduction, of diabetes medications is unlikely to be fully realised without significant investment and change to current practice. Dietitians appear to be an underutilised resource. The dietetic profession could fulfil a greater role in type 2 diabetes patient education and also in the training and mentorship of the primary care clinicians, as well as in the provision of robust educational resources. However, negative clinician attitudes about the dietetic profession or the role of dietary advice in type 2 diabetes management may inadvertently hamper outcomes for people with type 2 diabetes.

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CONFLICT OF INTERESTS
The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS
RB was responsible for the study conception and design. RB, AL, AH and HM were responsible for the literature search. RB, AH and HM were responsible for data collection. RB, AH and HM were responsible for analysis and interpretation. HM was responsible for the integrity of data analysis. RB was resposible for the writing the article. RB, AL, AH and HM were responsible for critical revision of the article. RB, AL, AH and HM approved the final version of the article submitted for publication.

ETHICAL APPROVAL
This review used only published sources of data. Ethical review by a Research Ethics Committee was not required.

TRANSPARENCY DECLARATION
The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with PRISMA guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned (PROSPERO registration number CRD42020190471) have been explained.

PEER REVIEW

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Helen J. Moore is a Research Fellow, leading the day to day work of the Evaluation and Impact Team. Helen studied at Durham University, where she obtained a BSc (Hons) in Cell Biology. This was followed with an MSc in Information Technology, and a PhD in Nutrition and Obesity both from Teesside University. Her PhD consisted of two Cochrane systematic reviews and an analysis of data from a large cohort of patients living with Type 2 Diabetes. Helen has worked on many different trials and evaluation projects examining subjects including Education, Nutrition, Obesity, Physical Activity, as a Lecturer in Research Methods, a Knowledge Transfer Partnerships Manager at Teesside University and, most recently, as the EPSRC Knowledge Exchange Manager at Durham University.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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