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- Public health nutrition and nutritional epidemiology
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- Food choice and the psychology of eating behaviour
- Food intake and nutritional status
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EDITORIAL

Editorial: How to Write

Introduction

As a discipline, dietetics has not traditionally been research-focused. As I wrote in an earlier editorial [1], the dependence of the dietetic profession upon a robust evidence base to shape clinical practice is drawing increasing numbers of dietitians into the research process. Many researchers submitting to the *Journal of Human Nutrition and Dietetics* are very early in their writing careers and, understandably, can find the process of writing a paper for publication difficult. The aim of this editorial is to give some insight into how to effectively communicate research findings in research publications.

Planning your paper

I think that before plunging into the maelstrom of producing actual text, it is important to think about what comes first. Many of the common errors that lead a paper to rejection (sometimes without going for peer review), rather than successful publication, lie in a lack of attention to detail and a failure to clearly map out a simple narrative. Careful planning can avoid some of the perils and pitfalls of the publication process. Writing a research paper really requires you to apply the simple rules of story writing that you learned in primary school. Your work needs a clear beginning, middle and end. You need to identify what all of those elements are going to be, before you start and then plan the flow of the story up front. I say 'story' because that is a great model for most scientific papers. We are all essentially following the pattern of:

We are interested in this subject because previous work has shown it to be important. To advance the field we set out to assess _____, which we did using these methods_____. Our findings were _____ and _____ and _____. These were largely expected given previous work, but the novel finding from our research was _____. In conclusion, we have confirmed the importance of this area.

The trick is to expand this up to 4000 words and put in some data as evidence!

In developing the plan, I always start by thinking about what the bit in the middle is. For all intents and purposes, this is about looking at your data and deciding what is going to be in the results section. Generally, there is a need to be reasonably selective. We don't throw in every bit of material that was collected just because it is available. Your readers don't want to wade through dozens of dense tables of numbers that don't contribute to the 'story'. Don't try and hide material that you don't like, but appreciate that you only need to provide enough data to make your story cohesive and evidence-based. The nature of the data that you do put in to the paper shapes the ending. Your discussion is going to reflect the outcomes of your work and how it fits with the literature. The beginning should be easy to frame. You are writing a paper because you have done some research. Your introductory text just has to spell out why you did it and why the research was necessary.

The best papers have the same flow as a work of fiction. Think about how you will link threads together, which order the data should be presented in and how best to portray something complex in a clear and concise manner. Look at some papers by other authors [2–5]. We all have papers that we really like and value. How were they structured? Why do you think they were effective? What can you borrow for your own writing?

It helps a lot to decide on the target journal before you start to write. Each journal has a guide to formatting of papers, length of papers, referencing style, etc. Being aware of these from the start makes the writing process simpler and avoids irritating last minute edits. There will be lots of factors that influence your choice of journal including impact factor, speed of editorial decision-making, standing within your discipline, time to actual publication, availability of early online publication or cost of page charges and open access. These are all legitimate factors to shape your target, but it is also important to avoid wasting your time, so do some research on the target journals you have in mind. Does the journal actually publish papers that are in your area? Do they have local rules about specific aspects of the work that you cannot meet (e.g. systematic reviews must meet PRISMA standard, weight-loss studies need more than 12-month follow-up)? Does it meet the requirements of your university or funder for open access? Will it be the most suitable vehicle to showcase your work? Is there going to be a charge for publication? Check the guidance to authors very carefully before jumping in to writing.

Writing the Abstract

The abstract is obviously the first section of the paper, although it will certainly not be the first part that you write. The typical research paper is written in chunks, in

no particular order, which are then stitched together to form what is hopefully a coherent whole. The abstract is the last thing to tackle and is one of the hardest components to get right. The importance of this little blurb at the head of the paper cannot be overstated because it has to serve many functions.

Primarily, it is a short summary of your research that acts as advertising. Journal editors will use it to assess (i) whether your research fits the scope of their journal; (ii) whether the quality of your writing is up to scratch; and (iii) whether your research design is appropriate. If you write a bad abstract, you will almost certainly not get published. Potential readers will use the abstract to decide whether they want to go on to read the rest of your paper. And, of course, we should never forget that the vast majority of readers may read only your abstract and perhaps nothing else in your paper. The modern way of reading means that we like to find information instantly and with a minimum of critical effort.

There are several basic components that should be incorporated into this important part of your paper:

- Problem statement: Why did you carry out your research? Was there a specific question that needed to be answered? What previous research were you building on?
- Methodological approach: What did you actually do to get your results?
- Results: As a result of completing the above procedure, what did you learn?
- Conclusion/implications: What are the larger implications of your findings, especially for the problem/question that was your initial motivation for the research?

The length of your abstract isn't going to vary much. Journal abstracts are more or less unfailingly 250 words, which fits well with PubMed and Web of Science type search engines and what they display. There will be variation in structure as some journals, including *Journal of Human Nutrition and Dietetics,* such as a formal structured abstract with discrete sections (Background, Methods, Results, Conclusion), although most do not. Writing as if you have those formal subheadings is a good idea because it will help you pull the whole piece together. If the journal does not use them, simply take them out as a final step. The balance ought to be somewhere along the lines of Background = 10%; Method = 30%; Results = 50% and Conclusions = 10%, although these obviously can vary according to your needs.

Bearing in mind you only have 250 words in total, your background and conclusions are going to have to be very focused. Essentially, these are a couple of sentences each, so simple clear statements are key. The methods section of the abstract needs to be packed with information to grab the attention of editors more than anyone else. What/who was sampled? How many samples? How was data collected? What sort of research was it (qualitative, animal study, cell culture, epidemiological, case–control, cohort, randomised controlled trial, cross-sectional?) Were there different treatment groups? Are there drug/supplement doses to report? It is all about facts, facts, facts.

The results will make up the bulk of the abstract. The emphasis is different to the conference abstract where you might insert tables or graphs and essentially try to put in detail of as many of your findings as you can cram into the space allowed. For the paper, stick to headline findings and don't feel obliged to give too much detail; just *P* values will do, for example, as you weave together 3–4 sentences that show the main points of your data. Table 1 shows three simple methods that can be used to compile a first draft of an abstract, which can then be edited into a more polished version.

Writing the Introduction

Almost everyone who works in science struggles with writing. The natural skills that earn us careers in science or clinical practice, such as observation or technical abilities, tend to leave us disadvantaged relative to those with a flair for the arts or languages. There are also many aspects of the way we are trained that do not equip us for something that (at least in academia) we end up doing on a daily basis. Most young scientists will not perfect the art of writing until they have written a PhD thesis, although that particular writing exercise leaves them ill-equipped for writing papers. The thesis rewards excessive length and detail, whereas the scientific paper requires brevity. Many PhD students first papers are poorly compiled because they try to take a big pair of scissors to a successful PhD chapter, cutting down, rather than starting from the beginning and writing in the shorter format. At the early stages of our writing careers, we are not trained to deal with the paper format. Thesis writing, or producing undergraduate essays, instils the instinct to write a comprehensive review of the literature when we write the introduction to a paper. We forget that this element of the research article isn't about showing how clever and knowledgeable we are to gain a qualification. Editors and reviewers don't like long introductions and providing one with your paper may prompt rejection or extensive revisions.

Hopefully, the paragraph above spells out what the introduction section isn't for. It isn't a literature review. The introduction to a paper has one simple function, which is to present the rationale for the work described in the paper. It should be short and provide a brief account of the landmark studies that got the field to where it is, what is currently known and what are the

Table 1 Approaches to writing the abstract for a paper

Approach	What to do	What to include
'Make a list' method	Use a predetermined checklist against to insert one sentence at a time into the abstract, to create a first draft	What is the problem under study?; What was the hypothesis?; What was the study design?; What was sampled?; How many subjects?; What sub-groups were studied?; What was measured?; When was it measured?; What was compared?; Headline finding number 1; Headline finding number 2; Headline finding number 3; What do you think it means?; Why is this important?
'Key phrases' method	Use the coloured highlighters in your word processor to pick out phrases and points that could be important for the abstract. Take two from the Introduction, four or five from the Methods, four from the Results and the final statement from the Discussion. Pull those highlighted points out and stitch them together to create a first draft	The first will be clumsy and will need a lot of polishing. You should generate an outline which simply follows the Background/Methods/Results/Conclusion structure
'Write it for your mum' method	Describe the research in very simple language that a well-educated lay person would understand. Imagine it as a conversation	Follow Background/Methods/Results/Conclusion structure and build up the abstract as these small sections

unanswered questions. The introduction gives an indication of what are you going to be presenting in the main body of the text. Above all, this section of the paper should spell out why this work was important, why it is timely and why your readers should be interested in reading any further.

Writing a good introduction involves doing something rather counter-intuitive and starting with the last few lines of the section. These will generally be the statement or statements of intent for the paper. You set out clearly what you were trying to achieve when you did your research. Not all research is hypothesis driven but, if yours is, then your hypothesis should be stated at the end of your introduction. Where there is no hypothesis, you will still have had aims or objectives when you began your project, so end the introduction with those. At the end of your introduction, the reader should be in no doubt about what you were trying to achieve.

With this in place, work backwards from that closing statement. Where did the hypothesis or aims come from? Is there some doubt or controversy that the study aimed to clarify? Is this work just the next logical step in a chain of research? Where did that controversy or chain of research come from? These are all questions that you should be able to answer as you prepare your introduction. You won't have done your research on a whim or conjured a hypothesis from nowhere. Your introduction should succinctly pull together the strands of other research that led to your particular piece of work. Moving still further back from your final statements, you will need to open the introduction with something fairly general but topical and up-to-date about your subject area. This will be the hook on which you hang the whole paper. Think in terms of an opening that says X is an emerging problem; X has been of concern for some time and is increasing; X may represent a novel strategy for dealing with Y. All of these statements are just ways of saying that the general field in which you are adding just one small piece of new knowledge is really, really interesting or topical. Hopefully, you believe that is the case because you have invested your precious time in researching it. Working in this way should give you a framework for your paper that essentially follows the outline shown in Table 2.

Writing the Methods

The importance of the methods section cannot be overstated. The validity and quality of any piece of research is generally assessed solely through consideration of how the study was done. A paper that has interesting results but invalid methods is relatively worthless, whereas a well-designed and executed piece with null findings is potentially valuable to the field of study. Nobody should ever take the findings of a paper at face value, and it is the methods section that acts as the focal point for questioning and quality assessment.

The methods section needs to convey a variety of information to your reader, in order to meet their needs. People will be reading your methods for a number of reasons:

- They want to do the same measurements themselves and want to follow your technique
- They are assessing the quality of your study
- They want to understand how you generated your results

Table 2 A simple introduction toolkit

This area of research is of importance/interest because _____. This is a new/old/well-established/emerging area.
The current state of knowledge in this area is _____. Researchers in this field disagree on several key areas/agree that it is now essential to explore. We know a certain amount, such as _____, but _____ and _____ are still unanswered questions/unknowns/areas of controversy.
As a result of an inconsistent literature/ following on from previous work in this field, we set out to address the hypothesis that/aim of _____. We did this by conducting an experiment/systematic review/qualitative study/survey/randomised controlled trial/etc.

Follow this basic structure to develop a simple introduction to a research paper. A maximum of 500 words will suffice.

This means that your methods section needs to provide a description of your study protocol and what you did to answer your research questions, along with the reasoning behind the choice of methods used to measure endpoints. You should also provide a clear description of how you made your measurements and obtained your data and an account of how your data were analysed.

The way that your methods section opens will depend upon what sort of study you have done. If it is a laboratory-based study, working with animals or *in vitro* systems, then your first paragraph will need to state what species you used, what type of cells and give details of where you purchased materials such as chemicals and reagents. If you are describing an epidemiological or clinical study, then these elements are not required and you can move on to describing the protocol.

This is the most important part of your methods section and is where all of the detail and uniqueness of your study is concentrated. In the simplest terms, this is the part where you explain what you did to generate your data. Start off by doing just that to build a framework for the detailed version. For example, you might write this.

> Men and women were recruited from a clinic and were randomised to receive either a placebo or a supplement of calcium 1200 mg day^{-1}. Bone mineral density was determined by dual X-ray absorptiometry (DXA) at the start of the study. Supplementation was maintained for 24 months at the end of which bone mineral density was again determined by DXA.

This is a good start and it delivers the bare bones of the protocol, although there is a lot more detail that must be added to make this suitable for publication:

> Men and women (why men and women? – justify this) (how old were they?) (how many?) (was a power calculation done to determine the required number?) were recruited from a clinic (where was the clinic?) (were they attending because they had particular health conditions?) (how were they recruited?) and were randomised (how were they randomised?) (is this a double-blind study?) to receive either a placebo or a supplement of calcium 1200 mg day^{-1} (in what form?) (is this an oral supplement?). Bone mineral density was determined by dual X-ray absorptiometry (DXA) at the start of the study. Supplementation was maintained for 24 months (why 24 months) at the end of which bone mineral density was again determined by DXA. (was there any measurement of compliance?) (did anyone drop out?) (were reasons for drop out recorded?)

So, the full version of the protocol would become this,

> Recruitment was from a general practice clinic (East Midlands, UK) and included participants aged between 45 and 65 years. The main objective of the study was to examine the effect of calcium supplementation on bone health, but a secondary objective was to consider the sex-specificity of the effect on both men (n = 150, age range 46–63 years) and women (n = 150 age, range 45–65 years) who were included in the study. All participants completed a pretrial screening questionnaire and were excluded if they were undergoing treatment for osteoporosis or other bone conditions (Paget's disease, osteomalacia) or had suffered a fracture in the preceding 12 months. The trial was performed double-blind, with randomisation being performed by allocation of a code set by a third party.
>
> Controls (administered placebo) were matched by sex and age (±2 years) to participants receiving supplement (calcium carbonate, 1200 mg day^{-1}, administered as one daily oral tablet). Participants were provided with their doses once per month (28-day supply) and unused tablets were collected to determine compliance with the protocol. The duration of the study was 24 months to allow for sufficiently long follow-up between baseline and final outcome measure for an effect of supplementation to develop based on the results of Brown *et al.* (2001) and Smith *et al.* (2005). Bone mineral density was determined by dual X-ray absorptiometry (DXA) at the start of the study and at 24 months. Prior to study, the sample size required to detect a 4% increase in

> BMD at the femoral next was determined based on the work of Smith *et al.* (2005). The required sample size was 132 per group and, based upon the experience of Jones *et al.* (2010) and Cooper *et al.* (2011), we allowed for 12% loss to follow-up in establishing the initial group sizes. Among the placebo group, six men and five women were lost to follow-up (7.3%), whereas 10% of the supplement group failed to complete the 24-month protocol with a compliance of more than 95% of doses taken (eight men and seven women).

Obviously, the nature of your protocol will depend upon the type of research that you have done. The key message to take on board is that you need to capture as much detail as you possibly can. Pack the section with detail but remember that you are not writing a novel. There are no prizes for florid language and lengthy description. Short, sharp and focused is the requirement.

Next, you will need to describe the methods used for measuring the endpoints in the study. By contrast to the protocol, be brief and cross-reference to methods in other papers unless you really need to describe something that you have developed from scratch or modified very heavily. Most of us are simply repeating standard methods from our own papers, or from other researchers papers. It is sufficient to state that 'total circulating insulin concentration was measured using ELISA following the method of Jones et al. (2007)'. If you have used an off the shelf kit, then it can be even simpler. 'total circulating insulin concentration was measured using an CrystalChem ELISA kit, in accordance with the manufacturer's instructions'. Where a method has been adapted from a published method, then cite the published method and describe what your adaptations were. If your method is completely new, then write it up in full and give all the detail that readers would need to replicate it.

Break the methods up into subsections to make it easier to follow. Your reader may be interested only in a small element of your methods section and so headings will direct them to what they want. Use a logical sequence when listing the methods that you used. Try to do this following a chronological sequence, as shown in recently published examples [6,7].

With very few exceptions (e.g. *in vitro* studies working with cell lines), your work will have required some level of ethical approval. This needs to be stated briefly and clearly. For example, 'Ethical approval was obtained from the local medical ethical committee'. Many journals, including *Journal of Human Nutrition and Dietetics*, will also require you to give details of clinical trial registration, or compliance with codes of practice (e.g. CONSORT) as a condition of publication, and you might consider recording these in the methods section.

Unless your data have been collected using qualitative methodology (which is beyond my expertise and not covered within this article), you will have performed at the very least some basic statistical analysis. Your methods section must describe what you have done and ideally how your data were presented. For example,

'Data are presented as the mean (SEM) throughout the paper. All data were analysed using one-way ANOVA with Tukey's test for post-hoc testing. $P < 0.05$ was considered statistically significant.', would be an absolute minimum, which may be sufficient for many papers. Obviously, the more complicated your analysis was, the more you will need to say. You might also, within this section want to write a statement about the statistical power of your study, or what power calculation was used to define the sample size before you started work.

Writing the Results

Most journals, though not all (some will combine the results and discussion sections) require the results to be an objective presentation of the findings of your research without any interpretation of the outcomes. Interpretation is reserved for the discussion. The results section should comprise tables and figures that enable summaries of your findings to be presented for the reader to consider and interpret for themselves, and an accompanying text commentary that describes the content of those tables and figures.

By contrast to writing a thesis or dissertation, word limits and the need for brevity and clarity are key drivers in a paper. The text in your results section is there to signpost the tables and figures and to deliver key highlight messages and help your reader navigate to what you want them to look at. A lengthy description of null findings or the inclusion of material that is really just there as background context is not necessary. The major function of the text in the results section is to provide additional information that clarifies aspects of the data. Make sure that you refer to each table and/or figure individually and in sequence and explain to the reader the most important results that each is showing.

Usually, the decision to write a paper has followed the completion of some statistical or other data analysis. This is the point where you will have found something in your study that you consider to be interesting or that has either led you to reject or support your initial hypotheses. With this being the case, the perfect place to start putting your results section (and in fact your paper) together is to plan and draw your tables and figures. Tables are best for presenting large volumes of data. If you have

measured say four or more variables that are closely related, it makes far more sense to put them all in a table together rather than having four or more figures. They are also ideal for presenting data that is very general and scene-setting. Readers often won't pore over the detail of your tables but will need to refer to them for specific pieces of information. By contrast, figures are the best way of showing simple data. They should be reserved for showing your highlights because graphs or pictures are visually striking and so are the most effective way of presenting the really important pieces of data.

With tables and figures planned, you now need to arrange them into a logical sequence that enables you to use them to evaluate your hypothesis. This order will usually be obvious to you but, as a basic rule of thumb, you would put the paper 'fodder' in first. By fodder, I mean the very general background material that isn't that interesting but has to be there. This might include a table providing basic demographic information about your cohort. Moving on from there, the data will become more specifically related to the hypotheses. Each additional item would add a further layer of complexity to the data set.

It is unusual for authors to struggle to decide on the order in which tables and figures are presented; more usually, the issues lie with deciding which mode of presentation to use, as described above, or with presenting too much. Once the tables and figures are drawn, you will need to write legends for each of them. Here, there is a rule of thumb that applies to papers and theses alike. Your legends should enable your reader to understand exactly what you are presenting in your figure/table without having to look at any other part of the paper. The legend should at the very least contain a title for the table/figure and basic statistical information. Have a look at some published examples to see how this is done well [8–10].

Once the tables, figures and their legends are in place, you can write the text of the results section. That is relatively easy because you just describe what you see, crafting the text to follow the sequence of data, as well as highlighting the evidence that addresses the hypotheses and research questions that you aimed to test. There is no great art to this, although vthere are many things that you can do badly (Table 3).

Authors who are new to academic writing often struggle because of an obsession with the outcome of statistical tests when describing data. I call this the 'stats-goggles' effect. What I mean by this is that the focus switches entirely to statistical significance and the author loses sight of the need for thinking about what significance might mean biologically. For example, we might write this sentence,

Table 3 Mistakes to avoid in the presentation of data

Too many tables and figures: As rule of thumb, a combined total of six to eight tables and figures should be the maximum that you are considering for presentation in the paper
Presentation of raw data: Always use appropriate summaries; mean (or median) with a measure of variance such as SD, SEM or range
Repetition of data: Avoid showing the same data in different formats, e.g. a table and a figure
Omission of units of measure: Make sure that you are using the correct units for the journal that you are writing for

> 'Weight in the intervention group was significantly different to the control group ($P < 0.01$) and there was an interaction between the effect of intervention and sex ($P < 0.05$) (Table 2)'.

This is meaningless gobbledygook and does not tell the reader what the outcomes of the measurement were. The task in the results section is to say what you observed. The statistical analysis is just a tool to decide which bits of the observations have come about for reasons other than random chance. In describing the data you need to give more information. Think about embellishing the statements you make with the following points:

- Directionality: You have a significant difference between groups, but what is the nature of that difference. Is the value measured in the test group bigger or smaller than in the control group? Is there a way of expressing this that makes the sentence more interesting than just a report of the outcome of statistical tests.
- Magnitude: How great a difference have you detected? It may be useful to your reader to report the difference between mean values between two groups, or maybe you could report it as a percentage or fold-difference if that is appropriate. Mix up the way in which you report the magnitude of differences as you move through the Results section so that it doesn't become repetitive.
- Relevance: Sometimes, we might see an effect that is statistically significant but, when we look at the actual mean values that were determined, the difference isn't of genuine importance from a biological or clinical perspective. For example, if a treatment has lowered total cholesterol concentrations by around 0.1 mmol L^{-1} (2% of the range of normal values), is that really noteworthy? When that is the case then certainly mark as significant in your data presentation, but don't highlight it in the text.

So if we take the example above,

> 'Weight in the intervention group was significantly different to the control group ($P < 0.01$) and there was an interaction between the effect of intervention and sex ($P < 0.05$) (Table 2)'.

We can remove the stats-goggles and translate it into human:

> 'As shown in Table 2, at the end of the study, the participants in the intervention weighed on average 5 kg less than the control group ($P < 0.01$). This effect appeared to be greater in men than in women (interaction of intervention and sex $P < 0.05$) and, although men in the intervention were on average 5.8 kg lighter than control men, the difference was marginal among women (0.5 kg difference)'.

Wearing sophisticated and discerning stats-goggles is vital at the stage of research where the statistical analysis takes place, but, with respect to writing, all of the *P* values need to be put to one side, allowing the writer to look at the summary data with a fresh eye. The paper should describe what the data really show and the *P* values are used in the same way that we use references in the introduction and discussion. They are the evidence base on which an argument is constructed.

Writing the Discussion

The discussion section is a core part of the write up for any piece of research, whether it is to be published as a paper, or presented as a dissertation. It is the element of the paper where you have greatest freedom to show critical awareness of your data and how it fits in with the wider body of research in the field. The discussion has a very clear purpose, which is to explain the meaning of your observations. The focus should be to help your readers to understand your study and how your data have extended understanding of your field.

Most people who have to write papers, reports or dissertations will find that writing the discussion is the hardest part of the work. More thought will go into writing this than any other part of the paper and yet, ironically, it is one of the sections that most readers will never look at in any detail. Most experienced readers of papers prefer to just look at the methods and the results and draw their own conclusions. You will also find it is the section that peer reviewers will make most comment about. It is commonplace for reviewers to add in statements that suit their own prejudices, or which tone down the power of your conclusions. You will probably end up having to do this if you want the paper published and it will be very frustrating.

As should be clear from earlier sections of this article, brevity is important in academic publishing, and so keeping the discussion under control is a major challenge. For a research paper where the overall length is going to be maybe 4000 words, then your discussion is going to be no more than 750–1000 words. Just as the introduction isn't the place to show off your encyclopaedic knowledge of the literature in your field, the discussion isn't a place to expound on lengthy theories. Keep things simple and keep things very clearly focused upon the data and upon the evidence that is available. The most common criticism that reviewers level at discussions is that they are too long and contain too much speculation that isn't backed up by the data.

All discussions are different and obviously need to be tailored to the individual needs of the paper and the data that you have generated. Despite this diversity, I have found that, as a basic framework for planning a first draft of any discussion, the seven points shown in Table 4 are a good starting point. Once these are in place, you will have a framework that you can rearrange as necessary, add in relevant linking pieces and expand or cut specific areas.

Think about what will sell your paper

The purpose of publishing our research is to get it noticed by the people who may use it to change clinical practice, develop new techniques or pursue further research in the area. This means that, as an author, you

Table 4 A seven-step plan for writing a discussion

Step 1: Briefly summarise the findings of the project. Only give highlights and avoid repeating what was in the results section. One paragraph should suffice
Step 2: 'Has anyone done work like this before?'
a NO – then trumpet the fact that your work is novel. Why is what you've done important?
b YES – Who did it? What have you done that is different? How are you taking the area forward?
Step 3: Do your findings agree with the literature?'
a NO – You need to try and explain why you disagree. Is it a methodological issue? Have you studied different populations/samples? Was your experimental design better, making your findings more reliable than others?
b YES – Comment on this as it strengthens your results. You can now use similar explanations to those given by others in the field in Step 4
Step 4: What do your results mean. How do you explain what you have observed? This is the heart of your discussion and should be approximately one third of this section of the paper
Step 5: What are the limitations of your study? Critique your own approach and methodologies
Step 6: What future work should arise from your project? What is the broader impact of your findings? Do you have any specific recommendations to make for practice and policy?
Step 7: Conclusion. One concise paragraph to sum it up with a definite statement. If you were following a hypothesis-driven approach, then your data either supported or disproved your hypothesis and you should state the outcome in these terms

need to think about what will attract the attention of potential readers, as well as what will encourage a busy journal editor to give you careful consideration.

First of all, appreciate how important the title of a paper is. A good title should tell the reader everything he or she needs to know about the contents of the paper in as few words as possible. First and foremost, consider whether you need to state what kind of paper you have written. Is it a review? Is it a systematic review? Often, these are sought out by readers who want to capture the overview of a topic and so, by stating that it is a review in your title, you draw your work to their attention. *Food and functional dyspepsia: a systematic review* [11], for example, leaves no doubt about the content of the paper.

It is also useful to get the true subject of your paper early in the title. For example, '*Improved use of on-admission screening tools is required to identify nutrition impact symptoms among cancer patients in hospice care*' is a less effective title than '*Nutritional status and interventions in hospice: physician assessment of cancer patients*' [12]. The reader scanning through lists of search results on PubMed or similar engines will pick up the paper more quickly if 'Nutrition' and 'Hospice' are near the start of the title. Although incorporating detail into a title is important for conveying the subject matter to potential readers and attracting their attention, too much detail can be a turn off for both readers and editors. Short and focused should be the rule of thumb.

The other key element of selling the paper is the abstract. The abstract, as described above, may be the only part of your paper that most users actually read, and so making it clear and readable is essential. Get the title and abstract right and the editor is more likely to send a manuscript for review and if published more people will read and cite the paper.

Conclusion

The *Journal of Human Nutrition and Dietetics* particularly welcomes submissions from authors who are clinically active. We appreciate that for such authors the world of publishing research articles may be unfamiliar. I hope that this editorial helps with the process and sets you on the way to disseminating exciting research findings to a large audience.

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CANCER

Longitudinal alterations in nutrient intake and food pattern in patients with non-small cell lung cancer during anti-neoplastic treatment: a cohort study

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Keywords
cancer, dietary pattern, food, nutrients, nutrition, weight loss.

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Abstract

Background: Unintentional weight loss is frequently observed in cancer patients. Nutritional therapy is essential, and dietary counselling is the first step. The present study aimed to explore the nutrient intake and food patterns in weight-stable and weight-losing patients with non-small cell lung cancer (NSCLC) during anti-neoplastic treatment.
Methods: Patients with NSCLC (n = 62) were observed during first-line systemic anti-neoplastic treatment. Body weight and dietary intake were assessed on the first and second cycle, and after completing three cycles of treatment. Longitudinal changes were analysed in three groups: *weight stable*, *weight losers* and *mixed weight*.
Results: Nutrient intake did not change during treatment in *weight stable*, although *weight losers* significantly increased the relative protein intake. *Weight stable* maintained the food pattern during treatment apart from a decreased consumption of oral nutritional support (ONS). At baseline, *weight losers* were characterised by pretreatment weight loss, high consumption of ONS, as well as low consumption of grains and animal products. During treatment, *weight losers* increased the consumption of protein, fatty foods and ONS but decreased the consumption of sweets and alcohol.
Conclusions: Large heterogeneity in nutrient and food intake was observed in NSCLC patients during anti-neoplastic treatment. *Weight losers* and *weight stable* had a similar nutrient intake although protein intake increased in *weight losers*. Grains and animal products were lower and ONS higher in *weight losers* compared to *weight stable* during treatment. *Weight losers* further increased the consumption of ONS and fatty foods, while the consumption of sweets and alcohol decreased during treatment.

Introduction

Unintentional weight loss is commonly observed in cancer patients [(1)]. Weight loss can precede the time of diagnosis and occur at any stage in the disease trajectory, although it is often more frequent and severe during the later stages of cancer [(1,2)]. Weight loss is associated with a decreased quality of life, reduced physical performance, crippled immune function and negative clinical outcomes [(3–13)]. Food intake amongst cancer patients is complicated by symptoms induced by physical responses to tumour growth (i.e. systemic inflammation) and side effects of anti-neoplastic regimes (i.e. nausea, early satiety and taste alterations). Recent advances in the treatment of non-small cell lung cancer (NSCLC) have prolonged the survival of patients, and optimal supportive care is imperative in modern treatment.

Nutritional interventions in cancer patients aim to ensure sufficient protein-energy intake [(14)]. Although this

task may appear to be easy, nutritional interventions in cancer patients often fail to reach desired compliance and thus exert blunted effects on the nutritional status of patients [15–17]. Current guidelines consider nutritional counselling to be the first step of nutritional therapy before advancing to medical nutrition (oral nutritional support, enteral nutrition and parenteral nutrition) and encourage counselling to help manage symptoms and also encourage the intake of energy-enriched foods and fluids that are better tolerated [14,18]. To tailor nutritional interventions, an understanding of patients' food selection and spontaneous nutrient intake is important.

Few studies have described nutrient intake and food patterns in NSCLC patients. Only two previous studies have described food patterns amongst patients with lung cancer, although both studies used a cross-sectional study design. Thus, little is known about dietary changes during anti-neoplastic treatment in patients with lung cancer and whether changes in food selection are similar or different amongst *weight losers* and weight maintainers. Hence, the present study aimed to explore the longitudinal nutrient intake and food pattern in patients with NSCLC, focusing on longitudinal changes in nutrients and foods amongst weight-losing and weight-stable patients.

Materials and methods

Design

The present study is part of a larger longitudinal observational study (LUCANU-1) investigating changes in body composition, health-related quality of life, dietary habits and functional status in patients with inoperable NSCLC undergoing first-line systemic anti-neoplastic treatment in an outpatient unit at the Department of Oncology, Aalborg University Hospital, Denmark. Patients were consecutively screened for inclusion and exclusion criteria upon referral to the oncology department and invited to participate in the study if eligible.

The inclusion criteria were inoperable NSCLC, naïve to systemic anti-neoplastic treatment for lung cancer or at least 3 years subsequent to the previous systemic anti-neoplastic treatment for other cancer diagnoses; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; age ≥ 18 years; and an ability to understand oral information and provide written consent. Patients were excluded if surgery with curative intent was indicated. Furthermore, patients with excessive alcohol abuse were excluded because of possible cognitive impairment. Patients were recruited from January to December 2017.

Patients were assessed at the outpatient unit on three occasions: the day of the first cycle (T_1, week 0) and the day of the second cycle of anti-neoplastic treatment (T_2, week 3) and the day of clinical examination after three cycles of anti-neoplastic treatment (T_3). The time of T_3 was 3 weeks after the third cycle of anti-neoplastic treatment for patients receiving palliative platinum-based chemotherapy or immunotherapy (T_{3a}, week 9) and 9 weeks after the third cycle of anti-neoplastic treatment in patients in curative intended chemoradiation (T_{3b}, week 18) (Table 1). Patients did not receive dietetic counselling as part of the standard of care in the outpatient unit. However, if patients were hospitalised and dietary intake was severely compromised, a nutritional intervention with enteral or parenteral nutrition could be initiated.

Assessments

Nutritional status

Nutritional risk screening was performed using Nutritional Risk Screening 2002 (NRS2002) [19]. Body weight was measured in kilograms (kg) on the same calibrated digital scale under standardised procedures [20].

Weight loss was defined as weight loss ≥2% relative to the preceding month (pretreatment weight loss) or ≥2% from one cycle to the next cycle of anti-neoplastic treatment. Pretreatment body weight was calculated from self-reported body weight the preceding 1 month. To minimise error in weight measure or biological variation, a cut-off of 2% weight loss was chosen to identify patients early in the weight loss trajectory [21,22].

Height was measured in a standing position using a wall-mounted stadiometer to the nearest 0.1 cm under standardised procedures [20].

Table 1 Schedule of study visits, anti-neoplastic treatment and data collection

	T_1	T_2		T_{3a}			T_{3b}
Week	0	3	6	9	12	15	18
Palliative chemotherapy or immunotherapy (n = 49)							
Chemotherapy or immunotherapy	x	x	x	(x)			
Data collection	x	x		x			
Curative treated radiochemotherapy (n = 13)							
Chemotherapy	x	x	x	x			
Radiation		x	x	x	x		
Data collection	x	x					x

T_1, T_2, T_{3a}, and T_{3b} represent the scheduled study visits. T_1 (baseline) is the first cycle of commencing treatment; T_2 is the second cycle of treatment; and T_{3a} and T_{3b} represent the clinical examination after the third cycle of treatment. Patients receiving palliative anti-neoplastic treatment received a fourth cycle of treatment at T_{3a}, if indicated.

Body mass index was calculated as body weight/height^2 (kg m^{-2}).

Dietary intake

Patients' dietary intake was assessed by a single 24-h recall at T_1, T_2 and T_3. The 24-h recall interview was performed manually by clinical dietitians or healthcare professionals intensively trained for the study using a structured multiple-pass procedure, as inspired by Conway *et al.* [23]. First, patients were asked to report their exact intake of foods and beverages consumed the previous day. Second, the interviewer used standardised neutral probing questions to increase the accuracy of dietary information, including a full description of the foods and beverages, foods likely to be eaten in combination, recipes for home-made food and beverages, and amounts consumed. Third, the interviewer asked the patients about any additional foods or beverages not mentioned. Portion size of foods and drinks was estimated using household measures (g/dL/serving/cup) [24] or by visual aid (portion-size images developed and pilot tested for this project). The nutritional value was analysed using an online food database (Vitakost, 2006–2018, Denmark; https://www.vitakost.dk).

To describe dietary patterns, food items were coded and classified into 15 categories based on similarities and differences in nutrient composition and functional use in accordance with typical Danish dietary habits (Table 2). A quality control of the nutritional data that were manually imputed from Vitakost to a research database (REDcap, version 7.4.14; Vanderbilt University, Nashville, TN, USA) was performed by ensuring that the sum of the calories from each of the foods was equal to the total caloric intake in all individual dietary records. Sufficiency of energy and protein intake was defined as 105–125 kJ kg^{-1} day^{-1} and ≥1.0 g protein kg^{-1} day^{-1} in accordance with current recommendations [14].

Nutritional data and food patterns were analysed in three groups according to patients' weight development during the study. Patients who maintained (±1.9%) or increased their body weight were defined as *weight stable*. Patients who lost at least 2.0% of body weight and continuously lost weight at every scheduled visit were defined as *weight losers*. Finally, patients who lost ≥2% of their body weight but had episodes of weight gain during the study were defined as *mixed weight*.

Demographic and clinical data

Demographic data were obtained from patient charts. The presence of nutritional impact symptoms was self-reported systematically at each scheduled visit using the Patient Generated-Global Subjective Assessment short form [21]. All data were handled in accordance with Good Clinical Practice and treated in accordance with Danish legislation.

Table 2 Definition of food categories used to analyse the food patterns of 24-h recall food items

Food category	Food items
Liquids	
Dairy	Milk or fermented milk, yoghurt, any beverages with milk products and cream
Beverages	Juice, soft drinks, coffee and other non-alcoholic, nonfortified beverages
Medical nutrition	Food supplements such as protein powder and protein-enriched ice cream, as well as medical nutrition (oral nutritional support, enteral and parenteral nutrition)
Alcohol	Alcoholic beverages
Soup	Soups
Plant food	
Grains	Bread and rolls (high and low fibre), cereals, rice and pasta
Vegetables	All vegetables, including ketchup, olives, beans and legumes; fresh, frozen or canned
Fruits	All fruits, including jam, nuts, avocado and berries; fresh, dried or canned.Not juice
Potatoes	All potatoes; boiled, baked, mashed, fried potatoes. Not potato chips
Animal products	
Meat	Beef, pork, and chicken in warm and cold dishes and as cold cuts or pâté; fresh, frozen or canned
Fish	All fish, seafood and roe in warm and cold dishes; fresh, frozen or canned
Egg	Boiled, fried, or baked in warm and cold dishes
Cheese	Cheese; hard, soft and spread (of any fat percentage)
Sweets and fatty foods	
Sweets	Sweet snacks such as hard candy, chocolate, crackers, pastry, honey, sugar, cookies, cakes, pancakes, ice cream and desserts. Salty snacks such as potato chips and popcorn
Fatty foods	Butter, margarine, oils, crème fraiche, sour cream, mayonnaise, rémoulade, pesto and sauce

Statistical analysis

Statistical analyses were performed in SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). Most of the demographic data were calculated as the mean (SD). Baseline characteristics between groups were assessed using chi-square of homogeneity, one-way analysis of variance (ANOVA) or by the Kruskal–Wallis *H*-test if the underlying assumption of outliers was violated. Longitudinal changes in nutrients were assessed using one-way repeated measures ANOVA or Friedman's test if the underlying

assumption of normality was violated. The underlying assumptions for outliers were assessed by inspection of box plots; normality by Shapiro–Wilk's test; homogeneity of variance by Levene's test of equality of variances; and sphericity by Mauchly's test of sphericity. Post-hoc tests were performed for pairwise comparisons using Dunn's procedure with a Bonferroni correction for multiple comparisons. Differences in nutrition impact symptoms between groups were assessed by Fishers' exact test because the underlying assumption of meeting the sample size requirement was violated. $P < 0.05$ (two-sided) was considered statistically significant. The characteristics of food patterns were calculated as the mean energy intake from each food category.

Ethical statement

Patients provided their written informed consent prior to inclusion. The study protocol was approved by the North Jutland Ethics Board (N-20160018) and conducted in accordance with the Declaration of Helsinki.

Results

One hundred and eighty-six consecutive patients were referred to the oncological department during the inclusion period and 64 agreed to participate in the study (Fig. 1). Two of the patients withdrew their written consent prior to starting the study, leaving 62 patients for the data analyses. Fifteen patients dropped out of the study because of death ($n = 10$), premature cessation of anti-neoplastic treatment ($n = 2$), withdrawal of consent as a result of a large symptom burden ($n = 2$) and prolonged hospitalisation ($n = 1$). Hence, 47 patients completed all three scheduled visits.

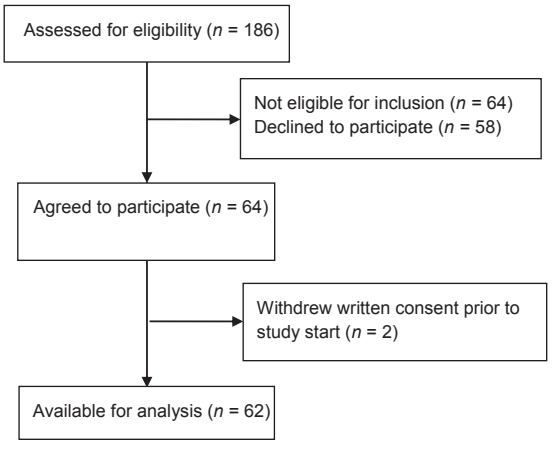

Figure 1 Flow chart of the inclusion and exclusion of patients.

The patients' baseline characteristics are shown in Table 3. Apart from pretreatment weight loss, all groups were similar with regard to baseline characteristics.

Weight loss occurred at every scheduled visit and the individual weight development is visualised in Fig. 2.

Longitudinal development in nutrient intake and macronutrient profiling

Significant heterogeneity in individual nutrient intake was observed in all three groups at every scheduled visit. The nutrient intake and macronutrient profile in *weight stable* and *weight losers* is shown in Table 4, whereas nutritional details in the *mixed weight* group is shown in the Supporting information (Appendix S1). Statistically, the relative protein intake was significantly altered in *weight losers* ($P = 0.045$) and *mixed weight* ($P = 0.011$) and the energy intake ($P = 0.047$) in *mixed weight*.

Amongst patients who dropped out during the study, an insufficient energy intake was observed in three of the six patients who dropped out after one cycle of treatment and in one of the two patients who dropped out after two cycles of treatment.

Longitudinal development in food patterns

The longitudinal development in food patterns in all three groups can be seen in Fig. 3 and details of the food patterns amongst *weight stable* and *weight losers* are described further. In general, a wide variation in the energy intake from the various food groups was seen, although *weight stable* and *weight losers* displayed different tendencies during treatment (Fig. 3).

Liquids contributed 16–32% of the total energy intake during the study. Liquid consumption was lower in *weight stable* compared to *weight losers* at all time points. During the study, *weight stable* decreased their consumption of liquids by 9 E% (percentage energy) during the study, primarily driven by a lower intake of medical nutrition (−4.5 E%) and dairy (−4.0 E%). *Weight losers* had a stable consumption of liquids during the study but experienced a small decrease in alcohol (−2 E%) and an increase in medical nutrition (+3 E%). Initially, *weight losers* had a two-fold higher consumption of medical nutrition compared to *weight stable*, which increased to a 12-fold higher consumption after three cycles of anti-neoplastic treatment.

Plant foods contributed 23–35 E% of the total energy intake during the study. Grains were the most important source of energy in both groups at all time points although 6–8 E% lower in *weight losers* than in *weight stable* during the study. Both groups displayed a similar pattern in plant foods during the treatment trajectory with an increase of 4 E% in *weight stable* and 6 E% in *weight losers*.

Table 3 Patients' baseline characteristics

Characteristics	All patients (n = 62)	*Weight stable* (n = 21)	*Weight losers* (n = 18)	*Mixed weight* (n = 23)	*P*-value
Sex					
Male	36	12	9	15	0.554*
Female	26	9	9	8	
Age, mean (SD)	67.2 (7.4)	65.9 (8.9)	66.4 (6.7)	68.9 (6.4)	0.462†
Disease stage (TNM)					
Ia	2	0	1	1	0.427*
IIa	1	1	0	0	
IIb	2	2	0	0	
IIIa	7	3	0	4	
IIIb	8	3	2	3	
IV	40	11	15	14	
Unknown	2	1	0	1	
Anti-neoplastic treatment					
Palliative chemotherapy	35	12	13	10	0.426*
Palliative immunotherapy	13	4	3	6	
Curative treated chemoradiation	14	5	2	7	
Nutritional status					
NRS2002, score ≥3 points	17	3	7	7	0.216*
Weight (kg), mean (SD) (range)	68.8 (13.9) (44.5–107.7)	71.9 (17.4) (47.9–107.7)	65.7 (9.7) (49.7–81.9)	68.4 (12.9) (44.5–89.7)	0.372‡
Body mass index (kg m^{-2}), mean (SD) (range)	24.0 (3.7) (16.1–34.0)	24.6 (4.6) (16.3–34.0)	23.2 (2.8) (18.1–27.8)	24.1 (3.5) (16.1–29.9)	0.486§
<18.5	2	1	1	1	
18.5–24.9	34	11	10	12	
25–29.9	24	7	7	10	
30–34.5	2	2	0	0	
Pretreatment weight loss (%)					
Mean (SD)	−3.0 (4.2)	0.1 (1.2)	−6.6 (4.7)	−3.0 (3.3)	<0.001†
2.0–4.9%	13	0	5	8	
≥5%	16	0	10	6	

Pretreatment weight loss (%) was significantly different between the three groups, $\chi^2 = 28.9$, $P < 0.001$. Post-hoc Bonferroni analysis revealed statistically significant differences in pretreatment weight loss (%) between *weight stable* and *weight losers* (30.8, $P < 0.001$) and between *weight stable* and *mixed weight* (18.0, $P = 0.003$) but no difference between *weight losers* and *mixed weight*.

*Chi-squared test.

†Kruskal–Wallis *H*-test.

‡Welch's analysis of variance (ANOVA).

§ANOVA.

Animal products contributed 20–27 E% of the total energy intake during the study and were consistently higher (4–8 E%) in *weight stable* compared to *weight losers*. Meat products were the second most important source of energy in both groups during treatment, but exceeded by fatty foods at T_2 in *weight losers*. Although the energy percentage from meats declined by 7 E% in *weight stable* during the study, a concurrent increase in alternative animal products was observed, resulting in a relatively stable intake of animal products, from 26 E% at baseline, 24 E% at T_2 to 27 E% at T_3.

Sweets and fatty foods contributed 20–24 E% of the total energy intake during the study. Like liquids, the two groups displayed different patterns of these foods during the treatment. At baseline, *weight stable* had the lowest intake of these foods: 4 E% lower than that of *weight losers*. *Weight stable* had a small increase in sweet consumption (+3 E%) and a stable intake of fatty foods during treatment, whereas *weight losers* rapidly decreased the consumption of sweets (−7 E%) and had a small increase in fatty foods (+3 E%).

Amongst users of medical nutrition in all three groups (n = 14 at T_1, n = 12 at T_2 and n = 10 at T_3), the average energy contribution was 26 E% at T_1 and T_3, and 21 E% at T_2, thus providing substantial amounts of energy in these patients. One patient in the *mixed weight*

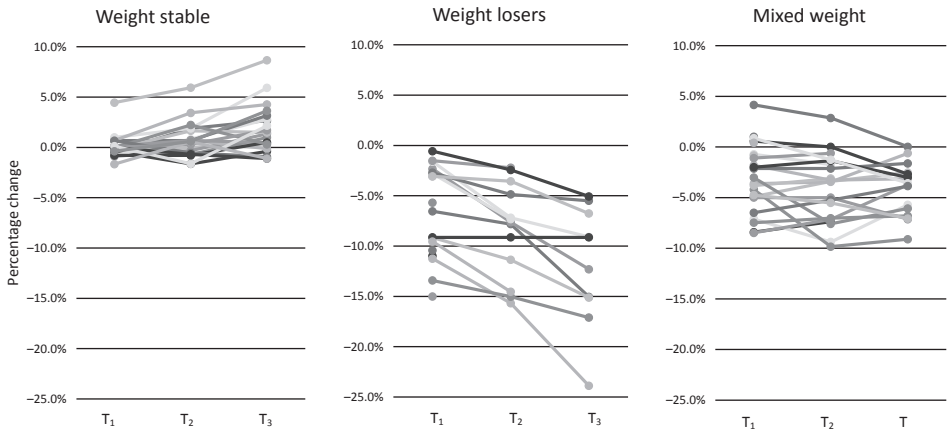

Figure 2 Accumulated weight change (%) in the three groups during the first three cycles of anti-neoplastic treatment.

group received parenteral nutrition at T_3, whereas the remaining medical nutrition users consumed ONS. Compared with non-users, users of medical nutrition were characterised by a higher relative energy intake and a lower consumption of animal products throughout treatment. Despite using medical nutrition, most users failed to maintain their body weight.

Nutrient intake and food patterns amongst patients who dropped out

The 15 patients who dropped out during the study had a median energy intake of 125 kJ kg^{-1} day^{-1} and 1 g protein kg^{-1} day^{-1} at T_1. Compared to the study completers, slightly more of the patients who dropped out had insufficient energy intake (38% versus 35%) and insufficient protein intake (44% versus 37%). The macronutrient distribution was similar to that of the other patients, although the proportion of patients who consumed alcohol was higher amongst patients who dropped than amongst study completers (five of 15 versus 20 of 47). For patients who dropped out, the contributions of most food categories were similar to those of the study completers, except for meat intake, which was lower (12 versus 18 E%), and medical nutrition, which was higher (12 versus 4 E%). The average energy contribution from medical nutrition was similar between patients who dropped out and users of medical nutrition who completed the study.

Discussion

This is the first study to provide a longitudinal description of food patterns in patients with advanced NSCLC during anti-neoplastic treatment. The results obtained describe the dietary intake during the first three cycles of systemic anti-neoplastic treatment at the same time as characterising differences between weight-stable and weight-losing patients newly diagnosed with NSCLC. As expected, a large inter-individual variation within the nutrients and foods was observed. The energy intake did not change in *weight stable* or *weight losers* during the study. Surprisingly, the relative protein intake increased during the study in *weight losers* but not in *weight stable*. The groups displayed different food patterns during treatment, especially in regard to medical nutrition, sweets and fatty foods.

Energy intake and macronutrients during systemic anti-neoplastic treatment

Large heterogeneity in energy and nutrient intake was observed in all groups. Surprisingly, neither *weight stable*, nor *weight losers* changed the energy or absolute protein intake, although the proportion of *weight losers* who failed to achieve their estimated energy and protein requirements was higher than the proportion of *weight stable*. W*eight losers* increased their relative protein intake during treatment amongst those who completed the study. These findings can be explained by the increased use of medical nutrition.

The macronutrient distribution in all groups complied quite well with the recommendations for hospitalised patients, which are higher in fat (35–45 versus 25–40 E%) and protein (15–20 versus 10–20 E%) and lower in carbohydrates (40–45 versus 45–60 E%) than the recommendations for the healthy population. Although a high fat intake is generally promoted amongst patients with weight loss, doing so may complicate sufficient energy intake by delaying gastric emptying, which is a well-known dilemma [25].

Similar to the findings of the present study, previous longitudinal studies observed an unchanged energy

Table 4 Nutrient intake and nutrition impact symptoms in patients with non-small cell lung cancer during anti-neoplastic treatment

	Weight stable				*Weight losers*			
	T_1 (n = 21)	T_2 (n = 21)	T_3 (n = 21)	*P*-value	T_1 (n = 18)	T_2 (n = 12)	T_3 (n = 10)	*P*-value
Total energy intake								
Absolute (MJ)	9.13 (5.06–16.16)	8.09 (5.33–18.22)	9.58 (5.21–17.48)	0.867*	7.51 (4.34–13.78)	7.88 (3.17–11.00)	7.57 (2.86–14.79)	0.717*
Relative (kJ kg^{-1})	121.8 (79–252)	134.4 (67–310)	138.6 (71–214)	0.897*	119.7 (71–277)	128.1 (50–176)	142.8 (46–340)	0.459*
≥125 kJ kg^{-1}	9	11	11		7	6	5	
≥105 kJ kg^{-1}	15	13	15		9	9	7	
<105 kJ kg^{-1}	6	8	6		9	3	3	
Total protein intake								
Absolute (g)	94.2 (51–214)	82.1 (53–171)	84.7 (45–169)	0.538*	68.3 (32–145)	61.1 (17–91)	70.0 (27–118)	0.057†
Relative (g kg^{-1})	1.2 (0.6–2.4)	1.1 (0.6–1.9)	1.1 (0.6–1.9)	0.443†	1.0 (0.4–2.1)	1.0 (0.3–1.7)	1.1 (0.4–2.6)	0.045†
≥1.0 g protein kg^{-1}	18	16	16		9	6	8	
<1.0 g protein kg^{-1}	3	5	5		9	6	2	
Energy by macronutrient (E%) (range)								
Protein	18.0 (11–25)	16.0 (10–24)	16.0 (11–28)	0.446*	15.5 (9–22)	12.5 (8–18)	16.0 (12–24)	0.253†
Fat	40.0 (26–62)	38.0 (23–63)	40.0 (25–64)	0.170*	41.5 (23–57)	46.5 (38–63)	42.0 (34–63)	0.279†
Carbohydrate	39.0 (23–56)	40.0 (26–61)	40.9 (19–52)	0.334*	40.0 (27–53)	36.5 (26–47)	33.0 (19–49)	0.414†
Dietary fibre	16.8 (9–38)	17.7 (11–38)	19.7 (11–38)	0.464*	13.0 (0–29)	12.5 (1–29)	12.8 (6–31)	0.088*
Alcohol	0 (0–21)	0 (0–16)	0 (0–15)	0.690*	0 (0–17)	0 (0–11)	0 (0–16)	0.195*
Nutrition impact symptoms	5	9	6	>0.05‡	10	10	4	>0.05‡

Nutritional values are presented as the median (range). Sufficient energy is presented as the number of patients. Nutrition impact symptoms are presented as the number of patients experiencing one or more symptoms. For differences in nutrients over time, one-way repeated measures analysis of variance (ANOVA) or Friedman's test was used. Differences in nutritional impact symptoms between groups were assessed by Fishers' exact test.

*Friedman's test.

†One-way repeated measures ANOVA.

‡Difference in nutritional impact symptoms between *weight stable*, *weight losers* and *mixed weight* (T_1, P = 0.062; T_2, P = 0174; T_3, P = 0.891).

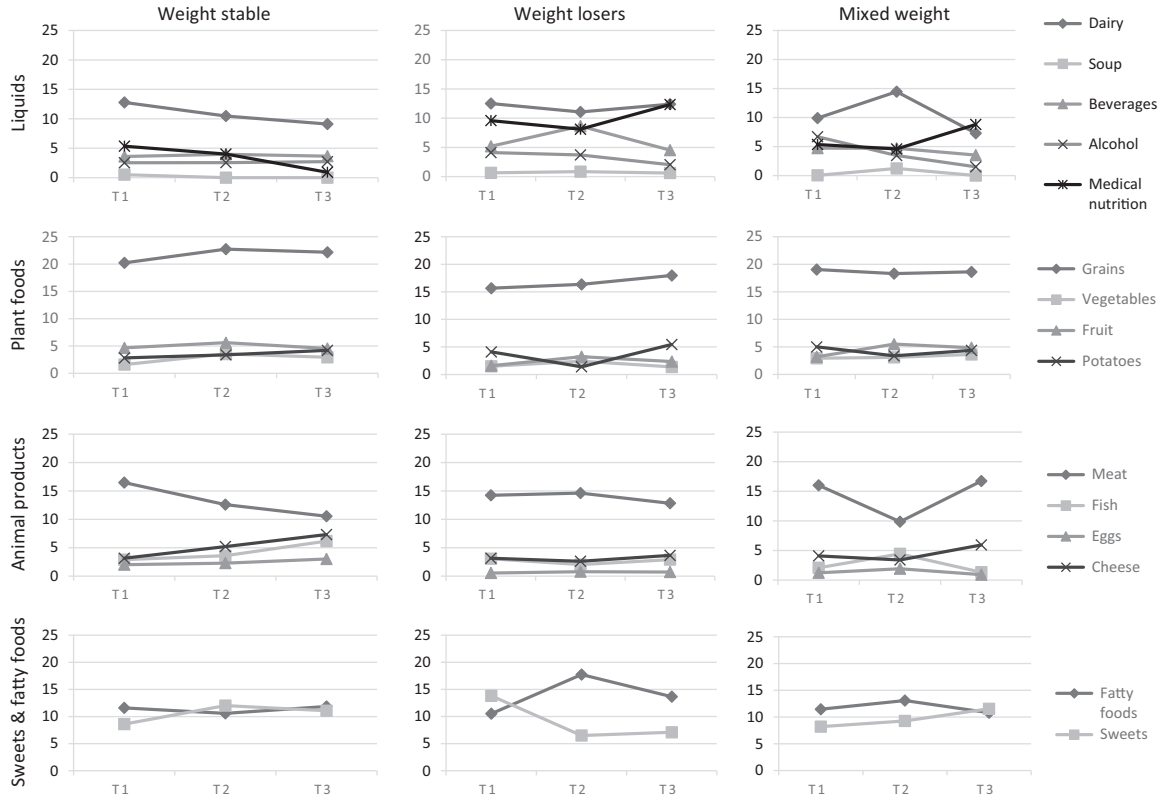

Figure 3 Longitudinal energy percentage from the different food groups, expressed as the mean energy percentage, in *weight stable*, *weight losers* and *mixed weight*, respectively.

intake in lung cancer patients during anti-neoplastic treatment [26,27]. By contrast to the findings of the present study, cross-sectional studies reported a lower energy intake amongst weight-losing patients than weight-stable patients [7,28]. The lack of difference in energy intake amongst our patient population can be explained by an overestimation of the patients' true energy intake between cycles as a result of the dietary method or an elevated energy requirement, which was not assessed in the present study.

Food patterns during systemic anti-neoplastic treatment

Similar patterns were observed in consumption of plant foods and animal products, which increased slightly during the treatment in both groups. However, *weight stable* had a consistently higher consumption of these foods. Beverages and soup intake were stable throughout treatment in both groups.

The most profound differences in food patterns between the two groups were observed in the consumption of ONS, sweets and fatty foods. Consumption of ONS was initially higher in *weight losers*. During treatment, the consumption of ONS became more polarised as *weight losers* increased and *weight stable* decreased ONS consumption. Sweets, on the other hand, rapidly decreased in *weight losers*, although they slightly increased in *weight stable*. The opposite pattern was observed in fatty foods as *weight losers* increased and *weight stable* maintained the consumption of fatty foods. Small differences were also observed in dairy and alcohol consumption. *Weight stable* slightly decreased the consumption of dairy and maintained the consumption of alcohol, whereas *weight losers* maintained dairy consumption and decreased alcohol consumption.

Nutritional impact symptoms were more commonly observed in *weight losers* than in *weight stable.* This higher prevalence of nutrition impact symptoms may have challenged the intake of solid foods and affected their pleasure to eat as indicated by a lower intake of plant foods and animal products, an increased consumption of ONS and a decreased intake of sweets and alcohol.

Longitudinal changes in food patterns in this patient population have not previously been reported, although two studies have assessed food patterns in a cross-sectional study design [28,29]. One of these studies identified three clusters of food patterns in which the highest incidence of weight loss was found in patients with a low variation in

foods, primarily consisting of milk, cereals and medical nutrition [28]. Similarly, the E% of medical nutrition and dairy was higher in *weight losers* than in *weight stable* in the present study, and this difference became markedly increased during the course of treatment.

Relevance to practice

As previously identified in the literature, approximately half of the patients in the present study lost weight before commencing and when receiving anti-neoplastic treatment, emphasising the need for awareness of patients' weight history, nutritional status and nutritional therapy before and during the whole treatment trajectory. The clinical and patient-related implications associated with weight loss are extensive, and regaining lost body weight and muscle mass is difficult and perhaps unachievable for cancer patients. Hence, early identification and regular monitoring of patients' nutritional status is recommended [14].

The large inter-individual variation in nutrient intake and food patterns within all three groups across all time points makes the interpretation and generalisation of these results challenging. However, baseline factors associated with weight-losing patients were pretreatment weight loss, higher prevalence of nutrition impact symptoms, high consumption of ONS and low intake of grains and animal products. Clinicians should thus be aware of these key characteristics and refer these patients to a clinical dietitian or a nutritional support team. When weight loss is observed during treatment, the simple approach of sporadic encouragement to use medical nutrition does not prevent patients from losing weight, as observed by the many weight-losing patients in the present study. It is therefore important to perform a thorough nutrition assessment and identify nutritional and symptom diagnoses to plan and initiate an appropriate nutritional intervention.

Study limitations and future research

Conducting studies in a patient population with advanced cancer is challenging, as indicated by the accrual rate (approximately 50%) and attrition rate (approximately 25%). Most of the patients who declined to participate did so as a result of feeling overwhelmed by the diagnosis and the load of information regarding planned anti-neoplastic treatment, whereas death was the primary reason for drop-out during the study. Because of the current privacy act, we were unable to collect sensitive data on patients who declined participation; hence, selection bias could not be ruled out. A high incidence of pretreatment weight loss was observed amongst patients who dropped out during the study. Despite the small sample size, differences between the three groups were evident and provide clinicians with important insights into the longitudinal alterations during anti-neoplastic treatment and characterise differences between *weight stable* and *weight losers*.

Although a 24-h dietary method has been shown to underestimate the intake of energy and protein compared to the estimates of the weighted food method, the 24-h method was found to be sensitive with respect to estimating energy and protein intake in hospitalised patients [30]. However, a single 24-h recall method provides valid estimates of energy and protein intake at the group level only and should not be generalised to an individual patient; hence, future studies need to acquire dietary information at an individual level. In addition, the single 24-h recall obtained at each scheduled visit did not enable the detection of all alterations during the 3 weeks between cycles of anti-neoplastic treatment because the nutrient intake was recorded for 1 out of 21 days. It is therefore likely that the patients' true intake from one cycle to the next is insufficiently represented. A French observational study found that nutrition impact symptoms affected the patients' nutrient intake for an average of 11 days during anti-neoplastic treatment [31]. It is therefore reasonable to suggest that patients' dietary intake was challenged the first 1½ weeks after treatment but not necessarily the last days prior to the next cycle. Perhaps the observed increase in relative energy intake amongst *weight losers* during the study was a compensatory effect that resulted in overfeeding just before the next treatment. Therefore, future studies should obtain dietary information at least once a week.

Conclusions

At baseline, *weight losers* were characterised by a high intake of ONS and a low consumption of grains and animal products. During treatment, *weight losers* increased the intake of relative protein, consumption of ONS and fatty foods but decreased the consumption of sweets and alcohol. The nutrient and food pattern during treatment remained unchanged in *weight stable*, except for a decreased consumption of ONS. These findings can guide clinical dietitians when providing dietary counselling in weight-losing cancer patients. Considering the high prevalence of weight loss, despite increased consumption of ONS, these patients should receive special individual attention regarding nutritional challenges and requirements by a multi-professional nutrition support team.

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 STROBE2 guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

HHR has received a research grant from Fresenius Kabi. RT, NAJ, AC, MH and UF declare that they have no conflicts of interest.

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All authors contributed to the conception of the paper. RT and NAJ conducted and supervised the data collection. RT, UF, HHR, MH and AC interpreted the results. RT wrote the initial draft of the manuscript. All authors critically revised and approved the final manuscript submitted for publication. All authors agreed to be accountable for the integrity and accuracy of the work.

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Supporting information

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

Appendix S1. Nutrient intake and nutrition impact symptoms in patients with non-small cell lung cancer during anti-neoplastic treatment for the *mixed weight* group.

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Lifestyle in patients at increased risk of colorectal cancer

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Abstract

Background: The present study aimed to assess modifiable risk factors in patients at high risk for colorectal cancer (CRC) and their experience of lifestyle advice.
Methods: A questionnaire study was conducted in high-risk CRC patients attending for surveillance colonoscopy. Current lifestyle behaviours [smoking, alcohol, diet (fruit and vegetables, wholegrains, red meat, processed meat), physical activity and bodyweight] related to CRC were ascertained, and experience on receiving, seeking and desire for advice was queried.
Results: In total, 385 study invitations were sent and 208 (54%) questionnaires were returned. The majority of participants (72%) were estimated to have a body mass index beyond the healthy range, 89% achieved a fibre score indicative of a low plant-based diet and 91% reported eating processed meat. Overall, 36% were achieving at least four recommendations and 2% were adhering to all recommendations examined. The main area in which participants reported receiving advice on was body weight (33%) and 31% reported that they had personally sought information on this topic, although the data suggest that 72% of people may benefit from such guidance. Fewer participants reported receiving (18–26%) and seeking (15–17%) dietary advice on fruits, vegetables and wholegrains. Many participants said they would find lifestyle information useful, notably in relation to body fatness (43%) and physical activity (38%).
Conclusions: The development of a process for supporting lifestyle change in this patient group, comprising individuals who are already engaging in positive health practices (regular colonoscopy surveillance), could usefully be identified and tested.

Introduction

Colorectal cancer is the third most common cancer worldwide. Risk for the disease includes non-modifiable factors (principally age, presence of inflammatory bowel disease and a strong family history) [(1)]. The influence of these factors on disease development may be modified by lifestyle factors [(1,2)]. Current estimates for the role of lifestyle factors in the development of colorectal cancer (CRC) in the general population suggest that approximately half of the incidence of disease can be accounted for by high intakes of red and processed meat and alcohol, raised body weight, and low levels of dietary fibre intake and physical activity [(3)].

People considered at increased risk of CRC (a previous diagnosis of adenomatous polyps, previous CRC, a strong family history of CRC and long-standing inflammatory bowel disease) are probably equally (or more) susceptible to lifestyle-related risk than the general population. In a pooled analysis, Cho *et al.* [(4)] reported that the relative risks of CRC with alcohol intakes of ≥30 g day^{-1} were 1.23 [95% confidence interval (CI) = 0.96–1.57] among those with no family history and 2.02 (95% CI = 1.30–3.13) among those with a family history of the disease.

There is some evidence of an increased risk by family history and body mass index (BMI) as most recently highlighted by Movahedi *et al.* [1], who reported that, in patients with Lynch syndrome in the CAPP 2 study [5], obesity was associated with a 2.41 (95% CI = 1.22–4.85) relative risk of developing CRC compared to participants with a BMI <25 kg m^{-2} (reference group) and that CRC risk increased by 7% for each 1 kg m^{-2} increase in BMI. The relative risk of all lifestyle-related cancers in obese people was 1.77 (95% CI = 1.06–2.96; $P = 0.03$). In addition, it is important to acknowledge that, for people who are diagnosed with CRC, obesity is associated with a poorer prognosis, increases in disease recurrence and overall mortality [6]. Red and processed meat also appear to be associated with a greater risk in people with a family history, although the results vary by type of meat, cooking methods and processing [7]. There is less evidence of protective effects of physical activity and dietary fibre in high-risk groups, although, in part, this may be a result of the small number of studies reported [8]

There is little evidence that current information about the relationship between lifestyle and CRC has been widely disseminated to the general population or to those at increased risk of colorectal cancer. Participants in the BeWEL study [9] ($n = 329$) who had a colorectal adenoma and BMI >25 kg m^{-2} reported having a very low knowledge about lifestyle risk [10]. Formative work for the study reported that patients with colorectal adenomas need to be aware of the relevant risk factors and need to be able to relate these to current personal behaviours before the 'teachable moment' opportunity for promoting change can be perceived as relevant [11]. It was noted that, although there is a shared and accepted understanding of the relationship between smoking and lung cancer, there is much less awareness of the relationship between colorectal cancer and lifestyle and considerable confusion exists over definitions of desirable levels of relevant behaviours (e.g. meat consumption, activity levels). These findings have been echoed by Dowswell *et al.* [12] who found that patients with high-risk colorectal adenomas considered their current behaviour to be appropriate or that they perceived no risk between health behaviour and disease outcome. Thus, even where knowledge of current recommendations for disease reduction is high, translation to appropriate action is often hindered by pre-existing beliefs about the perceived healthiness of current diet and lifestyle.

However, in the BeWEL intervention trial, it was demonstrated that approximately half (49%) of all patients with colorectal adenomas (and therefore at increased risk of CRC) were interested in participating in lifestyle interventions. When offered a comprehensive intervention programme, participants responded well and achieved significant lifestyle changes (in diet, alcohol, and physical activity and body weight), maintained over a 12-month period with a high degree of study retention (91%) [13].

It is clearly important to communicate relevant lifestyle messages to this high-risk group, although little is known about current diet and lifestyle (notably in those with BMI <25 kg m^{-2} who may perceive themselves to be healthy due to weight status). Data related to lifestyle behaviours in people at increased risk of colorectal cancer are sparse. Caswell *et al.* [14] reported a study conducted in a group of 37 patients with adenomas where 37% failed to meet the minimum recommended levels of physical activity, 8% of total energy was supplied by alcohol (12% in men), mean fibre was low, and red and processed meat was higher than recommended.

In Scotland, only one study [15] has examined diet and lifestyle factors in people diagnosed with CRC, although this was a case–control study of CRC patients, and it is unclear whether behaviours may have changed as a result of disease status (notably physical activity and sugary drink consumption).

The present study assessed current modifiable risk factors in patients at high risk for colorectal adenomas and their experience of lifestyle advice aiming to explore the need for evidence-based communications for disease risk reduction.

Materials and methods

The lifestyle assessment study was undertaken as part of an investigation on the utility of a Faecal Immunochemical Test (FIT) for haemoglobin in patients with a greater risk of CRC (compared to general population) who were enrolled in a colonoscopy surveillance programme [16]. This cohort included patients with a past history of adenomatous polyps, previous bowel cancer and a strong family history of bowel cancer. All patients were invited to complete a FIT test before attending their routine surveillance colonoscopy. On receipt of stool samples at the laboratory, a patient information sheet (as required by ethics procedures), a questionnaire about current lifestyle and a stamped address envelope was then sent to the participant by the research centre. None of the research staff had access to any National Health Service (NHS) patient data (including contact details). The completed questionnaires were anonymous, which meant that participants/nonparticipants could not be re-contacted.

Sample size

Study size was pragmatically based on the FIT study recruitment plan that estimated 840 patients would

participate. Based on response rates for previous questionnaire studies, we aimed to achieve a 50% response rate (i.e. 420 participants).

Lifestyle questionnaire measures

Because this questionnaire study was an additional request to an existing study, the researchers wanted to reduce participant burden to a minimum and aimed to keep the data collection tool short and in a form that could be administered as a self-completion tool. The questionnaire aimed to gather key lifestyle data from previously validated questionnaires but recognised that the use of a full food frequency questionnaire for the purpose of estimating nutrient intake was unpractical.

The self-completion questionnaire elicited data on:

1 Demographics: gender, age, ethnicity, marital status and education.

Socio-economic position was based on the variable Scottish Index of Multiple Deprivation (SIMD) [17] determined by postal code. This measure is a categorical system for identifying social position based on the area of residence, which takes account of housing, crime, access to services, education, health, income and employment.

2 Self-reported height and body weight (which enabled BMI to be estimated).

3 Lifestyle behaviours pertinent to cancer prevention were assessed as markers of adherence to cancer prevention guidelines:

- Smoking: Participants were asked to report smoking status (and number of cigarettes smoked if current smokers).
- Alcohol: Intake was estimated using a 7-day recall to indicate how many drinks containing alcohol had been consumed over the previous 7 days. This total was then recoded to provide an approximate number of units of alcohol as described by Emslie *et al.* [18].
- Physical Activity: This was estimated using the short form International Physical Activity Questionnaire (IPAQ) [19]. The IPAQ assesses walking, activities of moderate and vigorous intensity as estimates of frequency (days per week), and duration (time per day). These are combined to provide a summation of duration (in minutes) and frequency (days). Participants were then categorised as active if they achieved either 3 days of 20 min vigorous activity $week^{-1}$, 5 days of 30 min moderate activity $week^{-1}$ (walking), or 5 or more days of any combination of walking, moderate or vigorous activity, achieving a minimum of at least 600 metabolic equivalent of task (MET) minutes $week^{-1}$ (i.e. the equivalent of 150 min of moderate activity per week as recommended by World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) expert report] [20]. If none of the above were achieved, they were categorised as inactive.
- Red and Processed Meat: Consumption was estimated by frequency of consumption scales using the relevant questions in the validated EPIC food frequency questionnaire [21] and average portion measures for Scots adults obtained from work undertaken by Wrieden and Barton [22]. Processed meat was defined as beef burgers, sausage, liver products, savoury pies, corned beef, ham, luncheon meat and bacon.
- Plant Foods: In the WCRF/AICR 2007 [2] report definition of plant foods, three food categories are highlighted: nonstarchy vegetables and fruit, unprocessed cereals and/or pulses and limited refined starchy foods. No short questionnaire was available that captured all of this information. However, the validated DINE questionnaire [23], which encompassed vegetables, fruit, cereals and legumes, was considered to be the most efficient measure for estimating a dietary fibre score that could then be used as a proxy for plant foods. It also allows a greater emphasis on total plant foods rather than the commonly used proxy of fruits and vegetables, which can provide misleading results on total plant foods consumption. The DINE questionnaire estimates dietary fibre based on the fibre content of standard portion sizes of fibre rich foods, weighted by frequency of consumption (e.g. less than once per week, one or two times per week). Full details of analytical procedures are reported by Roe *et al.* [23]. A fibre score of <30 ('low') is equivalent to a fibre intake of 20 g day^{-1} or less, a score of >30 to <40 is moderate, whereas a score >40 ('high') is equivalent to an intake of more than 30 g day^{-1}. The upper value of 40 was selected as greatest likelihood of complying with recommendations because this is consistent with UK guidance on dietary fibre.

4 Lifestyle advice

Experience on receiving advice on the following topics was sought: smoking, alcohol, diet (fruit and vegetables, wholegrains, red meat, processed meat), physical activity (and inactivity) and bodyweight. The items queried if they

- Had ever personally been advised on any of these topics?
- Had ever searched for or sought information on these topics?
- Would find it useful to have information on any of these topics?

Finally, for the same list of topics, participants were asked to rate each of these lifestyle variables in influencing their risk of colorectal cancer. Responses were rated from 1 (Not at all important) through to 5 (Very important), with a 'Don't know' option added.

A health behaviour score was then calculated where +1 was scored for each health measure which was in accordance with behavioural recommendations (or a proxy in the case of plant foods) for cancer prevention by the 2007 WCRF [20] and consistent with those of the 2018 WCRF report [2]. The domains scored were smoking, body fatness, alcohol intake, physical activity, red and processed meat consumption, and plant food proxy (dietary fibre). No weighting was applied to domains. The possible score ranged from 0 to 7 points (a higher score = engaging in a greater number of healthy behaviours).

Questionnaire data underwent double entry and checking procedures (double entry checking with 1 : 5 questionnaires).

Questionnaire responses were analysed for descriptive summaries using SPSS, version 22 (IBM Corp., Armonk, NY, USA).

Ethical approval was granted by the East of Scotland Research Ethics Committee (REF no 14/ES/1091).

Results

Over 15 consecutive months (during 2014 and 2015), 1103 patients were appointed for surveillance colonoscopy and, of these, 643 returned a FIT sample and were therefore eligible to be sent a questionnaire. However, permission for the current questionnaire study was not attained until later in the main study period, which resulted in 385 study invitations being sent out over a 20-month recruitment period (2015–2016) and 208 (54%) questionnaires were returned. Similar numbers of men and women responded (51% male) with a mean (SD) age of 63 (11.3) years (range 33–88 years). Most respondents were Caucasian (99%), married or cohabiting (70%), had post school educational qualifications (62%), and were retired from employment (52%). One-fifth were resident in areas of high social deprivation (Table 1).

With respect to reported behaviours, most (91%) participants reported being nonsmokers (with 51% having never smoked). Eighty percent were consuming meat within the red meat limits and 74% reported meeting minimum physical activity recommendations. The majority (62%) also reported drinking alcohol within the limits set by national guidelines. Sixty-seven (32%) reported no alcohol consumption, in line with current WCRF recommendations. The majority of participants (72%) were estimated to have a BMI beyond the healthy range, 89% achieved a fibre score indicative of a low plant diet and 91% reported eating processed meat (Table 2). Overall, the mean (SD) composite score for lifestyle risk was 3.5 (1.1), with 36% achieving at least four recommendations and 2% adhering to all recommendations examined.

Table 1 Socio-demographic characteristics of respondents (n = 208)

Variable	Category	n (%)
Age (years)	Range	33–88
	Mean (SD)	63.0 (11.3)
Gender	Male	107 (51)
	Female	95 (46)
	Missing	6 (3)
SIMD quintiles	1 (highest deprivation)	18 (9)
	2	22 (11)
	3	53 (25)
	4	60 (20)
	5 (lowest deprivation)	41 (20)
	Missing	14 (6)
Marital status	Single	16 (18)
	Married/co-habiting	152 (73)
	Divorced/widowed/separated	35 (17)
	Missing	5 (2)
Ethnicity	White	205 (99)
	Asian/Asian British	1
	Missing	2
Qualifications	Secondary school	79 (38)
	Other professional/technical qualification after school	91 (44)
	University degree	28 (14)
	Postgraduate degree (e.g. Masters or PhD)	7 (3)
Employment	Retired	102 (52)
	Unemployed	7 (3)
	Employed full-time	53 (26)
	Employed part-time	25 (12)
	Student full-time	2 (1)
	Other	10 (5)
	Missing	2 (1)

SIMD, Social Index of Multiple Deprivation [16].

The scores for the perceived importance of the lifestyle topics as a risk factor for CRC were high (>4.3 out of a possible 5) and suggest a population familiar with current recommendations. However, the proportion of respondents receiving and seeking advice on these topics was low (less than one-third). Overall, many participants said they would find guidance useful, notably in relation to body fatness (43%) and physical activity (38%) (Table 3).

Some participants reported behaviours parallel to the experience of reported advice. For example, 26% reported low physical activity levels and 30% had been advised on this topic. For red meat, 20% were consuming high intakes and 15% had received advice. For smoking, 9% of participants reported smoking and 17% had received advice on this topic (which includes ex-smokers). These are, however, in contrast to alcohol, where 38% reported alcohol intakes higher than desirable and only 14% having received advice.

Turning to the areas where lifestyle guideline adherence was low (BMI and diet), the area in which most

Table 2 World Cancer Research Fund (WCRF) cancer prevention recommendations and participant achievement of these recommendations

Recommendation	Criteria for meeting recommendation	Meeting recommendations, *n* (%)
Alcohol*	<14 units week^{-1}	127/205 (62%)
Body fatness: Be as lean as possible within the normal range of body weight	BMI 18.5–24.9 kg m^{-2}	55/197 (28%)
Fibre: Eat mostly foods of plant-based origin	High fibre diet (DINE score >40)	22/208 (11%)
Physical activity: Be physical active	IPAQ ≥30 min moderate 5 days per week	153/208 (74%)
Processed meat: Avoid	Avoid all processed meats	18/205 (9%)
Red meat: Limit intake	≤500 g of red meat per week	166/208 (80%)
Smoking: Avoid	Non/ex smoker	189/208 (91%)

*The WCRF guide for drinking recommendation was within 14 units week^{-1} as recommended by Chief Medical Officers.
BMI, body mass index; IPAQ, International Physical Activity Questionnaire.

participants reported receiving advice on was body weight (33%) and 31% reported that they had personally sought information on this topic, although the data suggest that 72% of people may have benefited from guidance. Fewer participants reported receiving (18–26%) and seeking (15–17%) dietary advice on fruits, vegetables and wholegrains. In addition, approximately one-third of participants said they would find advice on this topic useful. A low proportion of participants reported receiving (14%) and seeking (12%) advice on processed meat, although 90% reported consuming such foods and one-quarter of participants said they would find this information useful.

Discussion

Despite evidence concerning the importance of lifestyle in the aetiology of colorectal cancer, current behaviours in high-risk patients are sub-optimal with respect to body weight and dietary factors, which are often less well known for increasing the risk of cancer [10]. In part, these findings are similar to the general Scottish adult population where 66% of individuals are overweight or obese [24] and they emphasise the need for public health approaches to support healthy lifestyles. Although it is clear that patients under colonoscopy surveillance have greater opportunities to engage with NHS staff (and the health promoting health service) [25], the findings suggest that this 'teachable moment' opportunity is often missed. The results suggest that there is considerable interest in receiving advice about lifestyle topics related to CRC and, indeed, many have searched by themselves for such information. Generally, the findings indicate that patients regard all of the lifestyle topics as influential, which may make any lifestyle counselling more acceptable. In addition, there is a growing body of evidence [26,27] that people respond positively to health professional advice on weight management.

The main strength of the present study is that, to the best of our knowledge, our work is the first to report on current lifestyles and the experience of lifestyle advice in this group of high-risk patients. In addition, many men participated (reflecting the higher incidence of the disease in men), which is less common for lifestyle questionnaire studies. The main weakness of the study is the socio-demographic profile of the participants recruited, who were predominantly Caucasian, with small numbers from the two lowest deprivation quintiles (e.g. higher socio-economic status). Although this distribution reflects the general demographic for high-risk attendees in this region (where there is little ethnic diversity), it highlights the difficulties in offering both surveillance and lifestyle interventions to affected people from more deprived areas. It

Table 3 Experience of lifestyle advice

	Smoking (*n* = 208)	Alcohol (*n* = 205)	Physical activity (*n* = 208)	Body fatness (*n* = 197)	Red meat (*n* = 208)	Processed meat (*n* = 205)	Fruit and vegetables (*n* = 195)	Wholegrains (*n* = 208)
Personally advised, *n* (%)	36 (17.3)	28 (13.5)	62 (29.8)	69 (33.2)	31 (14.9)	29 (13.9)	55 (26.4)	37 (17.8)
Searched for information, *n* (%)	26 (12.5)	29 (13.9)	52 (25.0)	65 (31.3)	25 (12.0)	24 (11.5)	36 (17.3)	31 (14.9)
Would find it useful, *n* (%)	28 (13.5)	44 (21.2)	79 (38.0)	90 (43.3)	57 (27.4)	59 (28.4)	68 (32.7)	63 (30.3)
Rating for influence on CRC (1–5), mean (SD)	4.5 (1.5)	4.5 (1.5)	4.4 (1.3)	4.5 (1.1)	4.3 (1.3)	4.5 (1.3)	4.4 (1.2)	4.4 (1.3)

The numbers for each response vary because some people omitted to respond to some items.

is important to note that these findings are illustrative rather than representative. We are unable to report a comparison between socio-demographic characteristics of responders and nonresponders because we were not granted access to NHS data for this purpose. The sample size was less than planned as a result of the numbers of people participating in the FIT study being less than expected, although the response rate was adequate and better than anticipated. The current data collection method did not allow detailed nutrient data to be assessed, although it has enabled key lifestyle variables relevant to cancer to be described. Estimating intakes of plant-based food is particularly challenging and a proxy value is an indicator only. Estimating a risk score is not a novel approach [28,29] (although never previously reported in high-risk patients) and there has been considerable discussion on how much weight to give each variable in the total score (e.g. if obesity is the most important item, should it be allocated 2 points instead of 1 point).

It is likely that there was a bias towards survey completion by people with a more favourable lifestyle, which has further implications for overall habits in this population group. The data are all self-reported and we have no validation of actual habits or measures, and such an approach often leads to under-reporting and socially biased results [30]. However, if these results reflect best practice, then there is clearly significant room for improvement.

Our previous work on lifestyle in people attending genetics clinics in Tayside [31] also highlighted that current behaviours were sub-optimal. In addition, qualitative data suggested that there were considerable doubts about the link between lifestyle and cancer and that fatalistic views were associated with poorer health behaviours. The findings of the present study show that, amongst people at higher risk of developing CRC, there are a number of health behaviours that are associated with CRC that could be targeted for risk reduction. Current evidence suggests [8] that the combined effect of lifestyle factors (examined by dietary risk score) and family history appears to be strongly related to increase CRC risk (risk estimates of between 2.7 and 14), suggesting that one or more risk factors act synergistically. These findings also highlight the importance of lifestyle advice versus discussion of single variables. Our recent pilot trial of a lifestyle intervention in patients referred to family history clinics [32], suggesting that a lifestyle programme for people with a family history of cancer is feasible to conduct and acceptable to participants, and the indicative results suggest favourable outcomes. However, post intervention interviews with participants highlighted the importance of providing a credible rationale for lifestyle change, which underlines the need for health professionals working in this area to introduce and endorse the importance of a range of risk factors in multicomponent interventions.

The generalisability of the current findings from one geographical area to others is unclear, although a number of studies have now reported that people with a family history from different countries do not have lifestyles consistent with current recommendations [33,34]. A recent review of nutritional and lifestyle factors in familial colorectal cancer makes a very strong case for providing effective lifestyle counselling for high-risk individuals [8]. In addition, such changes in lifestyle can help to decrease common comorbidities, including type 2 diabetes mellitus and cardiovascular disease [35]. The relatively uneven spread of lifestyle advice and interest suggests that opportunities and teachable moments could be developed for these patients. Such approaches might include brief verbal interventions by relevant staff, as supported by written material and signposting to web-based resources, community facilities and effective weight management programmes.

Being able to offer advice and guidance may also make it easier to alleviate the concerns of NHS staff that lifestyle topics are sensitive and difficult to raise and have the potential danger of impacting on professional relationships [36]. The development of a process for supporting lifestyle change in this patient group, who are already engaging in positive practice (regular colonoscopy screening), appears to be timely.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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ASA is principal investigator. ASA and RJS contributed to the conception and design of the study SC was responsible for data collection. ASA and SC contributed to data analyses. All authors contributed to the interpretation of data and the drafting of the paper. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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NUTRITION INTERVENTIONS

Calcium intake improvement after nutritional intervention in paediatric patients with osteogenesis imperfecta

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Abstract

Background: In several bone disorders, adequate calcium intake is a coadjuvant intervention to regular treatment. Osteogenesis imperfecta (OI) is a collagen disorder with a range of symptoms, ranging from fractures to minimum trauma, and it is typically treated with bisphosphonates. In the present study, we evaluate the impact of a nutritional intervention (NI) on dietary calcium intake and bone mineral density (BMD) in paediatric patients with OI.
Methods: A nonrandomised clinical trial was designed with a NI. Dietary calcium intake, anthropometry and clinical features were assessed at baseline, including anthropometry, basal metabolic rate (BMR), BMD. In addition, a food guidance form was developed and sent to patients by mail. After 12 months, clinical features of patients were reassessed and compared with the baseline data.
Results: Fifty-two children and adolescents were enrolled. Significant increases in total calcium intake (mg day^{-1}), percentage of adequate calcium intake (%) and number of cups of milk ingested were observed after NI. We detected a positive correlation between the variation of BMD and milk consumption in patients treated with bisphosphonate.
Conclusions: We observed an increase in calcium intake in patients with OI. This finding demonstrates the importance of nutrition therapy as part of a multidisciplinary treatment approach for bone health.

Introduction

Calcium is an important nutrient for bone health because it is directly related to the growth, development and maintenance of the skeleton, thereby providing structure and support [(1)]. Although calcium is present in many tissues, such as blood, muscle and extracellular fluids, bone comprises the largest reservoir in the body. Adequate calcium intake is crucial for maintaining a rigid skeleton, thus preventing osteoporosis and the occurrence of fractures [(1,2)].

Bone fragility is the main consequence for individuals with osteogenesis imperfecta (OI), an inherited disease characterised by low bone mineral density (BMD), bone deformity and most of cases repeated fracture [(3)]. The prevalence of OI ranges from on in 15 000 to one in 20 000 births, regardless of sex or ethnicity. Based on phenotype and clinical and radiological findings, the classification of OI is ordered into five subtypes (I–V) [(2)]. Considering the clinical features and order of severity, the types are I (classic, nondeforming OI with blue sclerae); IV (variable OI with normal sclerae); V (ossification in interosseous membranes); III (progressively deforming OI with normal sclerae); and II (perinatally lethal OI) [(3,4)]. Individuals with moderate and severe forms of OI (type III and IV) have skeletal deformities and reduced mobility [(4)]. A broad molecular classification of OI has been recognised in the last 10 years as a result of advances of genetic diagnosis with a variety of recessive, dominant and X-linked gene defects that encode proteins involved in type I collagen [(5,6)].

Our previous study had detected low dietary calcium intake in children with OI. Seventy-five percent of subjects had calcium intake below that recommended for their age [7]. Another study by our group that evaluated serum 25-hydroxyvitamin D concentrations and the correlation with other factors related to bone health, observing that more than 51.9% of the subject consumed only one or two glasses of milk day^{-1} [8]. An additional study showed that OI patients had a low dietary intake of calcium and vitamin D [9].

Considering these data, in the present study, we aimed to evaluate the impact of a nutritional intervention (NI), with emphasis on calcium intake in paediatric patients with OI.

Materials and methods

A nonrandomised clinical trial was designed and enrolled paediatric patients aged between 2 and 19 years who were diagnosed with all types of OI, based on clinical and radiological features [3]. Individuals were evaluated at the Reference Centre for Osteogenesis Imperfecta Treatment of Porto Alegre Clinical Hospital (HCPA-CROI), between March 2012 and December 2013. The study was approved by the Ethics Committee of the institution (#11-0585) and all individuals or their responsible caregivers provided their written informed consent.

Nutrition intervention

NI was performed at three nutritional visits (baseline, 6 and 12 months). Clinical features were evaluated at baseline, including anthropometric measurements, basal metabolic rate (BMR) and BMD. An indirect calorimetry test was performed to estimate the BMR of each participant. Dietary intake was assessed using a daily food intake report completed by participants on three nonconsecutive days. The frequency of consumption and amount of calcium intake were evaluated using a food frequency questionnaire (FFQ) with an emphasis on foods rich in calcium. Based on these data, the nutritional needs for each subject were calculated and personalised food guidance (including recipes rich in calcium) was delivered by mail.

In the second visit, at 6 months after baseline, adaptations were made to food guidance in accordance with the needs of each patient, doubts about feeding were clarified and the importance of a diet rich in calcium was reinforced.

On the third visit, at 12 months after baseline, dietary calcium intake, anthropometric measurements and BMD were re-evaluated.

Calcium intake

Calcium intake was assessed using an FFQ adapted to calcium intake [10] applied before and after the NI. In the present study, we focused on the consumption of foods high in calcium, such as milk, yogurt and cheese. To establish the percentage of the adequacy of intake, the values obtained from the FFQ were compared with the estimated average requirement (EAR) and recommended dietary allowance (RDA) [11].

The FFQ for calcium intake was composed of milk (1 cup = 175 mL), one carton of yogurt (120 mL) and cheese (1 medium slice = 30 g). These foods were classified according to the consumer (D, daily; W, weekly; M, monthly) and indicating the number of times (1–10) and the size of the corresponding portion, if greater, equal or less than the given portion (in accordance with a poster including colour photographs to illustrate the portion size of each food source of calcium).

The consumption of glasses of milk and soda was also evaluated according to quantity and frequency (For milk, 0 = does not consume; 1 = consume <1 cup day^{-1}, 2 = consume 1–2 cups day^{-1}, 3 = consume 3 or more cups of milk day^{-1}; for soda, 1 = consume daily, 2 = consume only on weekends or 2 times week^{-1}, 3 = consumes less than 1 day week^{-1} and 4 = does not consume).

Clinical data

Clinical data were obtained during the enrollment and included age, sex, OI type, use of bisphosphonates and calcium intake.

Anthropometric data and basal metabolic rate

Anthropometric measurements (weight and height) were measured and evaluated according to the *Z*-score proposed by the World Health Organization WHO (2006, 2007) [12]. The length was measured in the supine position in children smaller than 1 m and children who could not remain in the standing position. Patients over 1.04 m and unable to remain standing were measured in the supine position [13]. BMI was calculated and nutritional status was classified in accordance with the WHO (2006, 2007) [12]. The BMR was evaluated via indirect calorimetry and the data were published previously [14].

Bone mineral density

BMD was determined before and after the intervention using dual energy X-ray absorptiometry on a Lunar iDXA (GE Healthcare, San Francisco, CA, USA). Bone mineral

content (BMC) (g), lumbar spine BMD (L1–L4) and total body BMC were calculated and expressed as *Z*-scores. The *Z*-score was not obtained for children less than 5 years old as a result of a lack of values proposed by the manufacturer.

Statistical analysis

Descriptive analyses were represented by frequency and percentage. For parametric data, the mean (SD) was used and, to compare the pre- and post-NI values, paired *t*-tests were applied. For nonparametric data, medians and quartiles were used, and, for comparison of the pre- and post-intervention values of these ordinal qualitative variables, the Wilcoxon test was used. For nominal qualitative variables, we used the McNemar test. Pearson's and Spearman's correlation analyses were used for parametric and nonparametric data, respectively. Generalised estimating equations were applied for the stratification of the differences between the variables between pre- and post-NI.

Results

Table 1 shows the clinical features of patients at the baseline assessment. Fifty-two individuals were analysed, of whom 29 (55.9%) were female. The median age at the time of enrollment was 9 years (5.25; 12.7). OI patients were classified as 24 (46.2%) type I, 5 (9.6%) type III, 23 (44.2%) type IV and 1 (1.9%) type V. As a result of the small sample size, for analysis, type V was grouped together with type IV. Two subjects did not complete the evaluationat 12 months: one because of a fracture and the other as a result of convalescence following surgery for correction of deformities at the time of the third visit.

Considering bone mass, we observed a significant difference only in the pre- and post-NI in BMC and lumbar spine and total body BMD ($P < 0.005$) (Table 1).

Analysing dietary intake of calcium, there was a significant difference between pre- [706 (325) mg day^{-1}] and post- [885 (265) mg day^{-1}] NI in total calcium intake ($P < 0.001$). Regarding calcium intake adequacy, there was a significant difference ($P < 0.001$) from pre- to post-NI for both parameters: EAR (66% to 81%) and RDA (from 56% to 69%). Milk consumption also showed a significant difference after NI, with a decrease in the number of subjects who had no or poor intake and an increase in the number of cups day^{-1} ($P = 0.002$). The daily consumption of soft drinks decreased after NI ($P = 0.012$) (Table 2).

The correlation between variation of BMD and milk consumption showed that subjects who are treated with bisphosphonates reported a positive correlation, especially in the lumbar spine BMD ($r = 0.544$; $P = 0.029$) (Fig. 1).

Discussion

NIs provide the necessary knowledge to promote healthy eating habits [15]. Individuals with OI typically have a low calcium intake [7–9] and it is well-known that these nutrients are important for bone health, especially for children with bone disorders [2,10,16]. In our previous study addressing the calcium intake of children and adolescents, we found that 75% of subjects with OI had an adequacy percentage of calcium intake below 93.5% and detected an inverse correlation between age and calcium intake ($r = -0.527$) [5].

In the present study, we detected low a calcium intake at baseline. However, following the NI, we observed an increase in the consumption of rich calcium foods post-NI, as shown by the increase in the values of total calcium mg day^{-1}, EAR and RDA adequacy percentage and number of cups of milk day^{-1}, as well as a decrease in the daily consumption of soda.

To evaluate the intake of calcium, Cosenza *et al.* (2013) performed a randomised study in healthy children. Group 1 received only dietary counselling and Group 2 received dietary counselling plus supplementation of calcium and vitamin D. After 4 months of intervention, in both groups, significant improvements were observed for calcium intake. These data show that it is possible to increase calcium intake with dietary counselling [16], similar to the present study.

Previous studies have shown a decrease in BMD, particularly in the more severe forms of OI [6,17]. In the present study, we observed an increase in BMC values, lumbar spine BMD and total body BMD post-NI evaluation. A cohort study of 9 years with 52 children with OI observed a mean (SD) annual increase in BMD of 0.038 (0.024) g cm^{-2} year^{-1} and this annual increase in BMD was significantly higher in girls than in boys [18].

An important finding of the present study was the positive correlation between calcium intake and lumbar spine BMD in patients treated with bisphosphonates. We observed that individuals treated with bisphosphonates presented a positive correlation between variation in lumbar spine BMD and pre- and post-NI, as well as with the number of glasses of milk consumed (Fig. 1). Bisphosphonates comprise a group of drugs that inhibit osteoclast activity, thereby increasing BMD, as seen in the present study. The positive correlation of BMD and calcium intake in BP treated patients could be explained by an increased awareness with respect to the prevention of hypocalcaemia, which is a common side effect of BP therapy.

Table 1 Values variables of pre- and post-nutritional intervention

Variables	Pre-NI (n = 52)	Post-NI (n = 50)	P
Anthropometry			
Weight (kg)	25.5 (16.1–44.8)	30.6 (19.5–48.2)	<0.001
Stature (cm), mean (SD)	123 (25)	127.6 (24.2)	<0.001
Stature *Z*-score	−2.5 (−3.6 to −1.4)	−2.2 (−3.7 to −1.2)	0.287
BMI, mean (SD)	19.2 (5.4)	20 (5.7)	<0.001
BMI *Z*-score	0.2 (−0.8; 1.7)	0.2 (−1; 2)	0.115
Nutritional status, *n* (%)			
Underweight	5 (9.6)	3 (5.8)	
Eutrophic	29 (55.8)	32 (61.5)	0.540
Overweight	9 (17.3)	6 (11.5)	
Obesity	9 (17.3)	9 (17.3)	
Bone mineral density (BMD)			
BMD (g) dual energy X-ray absorptiometry	927.3 (523.7–1476.3)	1016.1 (604.3–1665.9)	<0.001
BMD spine (*N*)	51	44	
BMD spine (g cm^{-2})	0.62 (0.51–0.82)	0.66 (0.49–0.96)	<0.001
BMD *Z*-score spine (*N* g^{-1} cm^{-2})	46	39	
Z-score spine (g cm^{-2})	−1.35 (−2.07 to −0.52)	−1.3 (−2.1 to −0.3)	0.371
BMD total body (*N*)	46	44	
BMD total body (g cm^{-2})	0.7 (0.62–0.89)	−0.73(0.62–0.94)	0.007
BMD *Z*-score total body (*N* g cm^{-2})	46	39	
Z-score total body (g cm^{-2})	−0.75 (−1.7 to −0.3)	−1 (−1.8 to −0.4)	0.247

BMI, body mass index; NI, nutritional intervention. Data are the mean (range), except where indicated.

Table 2 Values of dietary intake and percentage of the adequacy of calcium at pre- and post-nutritional intervention according to the recommended dietary allowance (RDA) and estimated average requirement (EAR)

Variables	Pre (n = 52)	Post (n = 51)	P
Total calcium day^{-1} (mg)	706 (325.6)	885 (265.3)	<0.001
% EAR adequacy, mean (range)	66.3 (43.8–89.5)	81.9 (64.1–115.1)	<0.001
% RDA adequacy, mean (range)	56.1 (36.8–75.7)	69.1 (54.3–92.8)	<0.001
Consumption of a cup of milk			
Do not consume	4 (7.7)	–	
Less than 1 cup day^{-1}	9 (17.3)	4 (7.7)	0.002
Between 1 to 2 cup day^{-1}	28 (53.3)	30 (58.8)	
≥3 cup day^{-1}	11 (21.2)	19 (36.5)	
Consumption of soda			
Daily consumption	19 (36.5)	10 (19.6)	
Less than 1 day $week^{-1}$	27 (51.9)	30 (57.7)	
Only on weekends (2 day $week^{-1}$)	2 (3.8)	7 (13.5)	0.012
Do not consume	4 (7.7)	4 (7.7)	

Data are the mean (SD), except where indicated.

The association between short stature and OI has been well-described in the literature, especially in those with the most severe forms of OI [7–9,19,20]. In the present study, *Z*-score values for anthropometric measurements did not show a significant difference between the pre- and post-NI assessments, suggesting that patients grew into their own pattern according to the limitations of the disease. A study including the growth charts of patients with type I OI aged from 2 to 18 years old shows that subjects with type I OI are initially smaller than the healthy population, that development slows from 8 years old, and, ultimately, that body height is impaired. The body height/weight ratios are similar when comparing type I OI patients with healthy subjects. This finding is also reflected in the BMI data, which are similar when comparing OI patients with healthy children and adolescents [21].

Palomo *et al.* [22] have reported that BMI is not the best method for evaluating the body composition of these patients because BMI is a body height-related measure

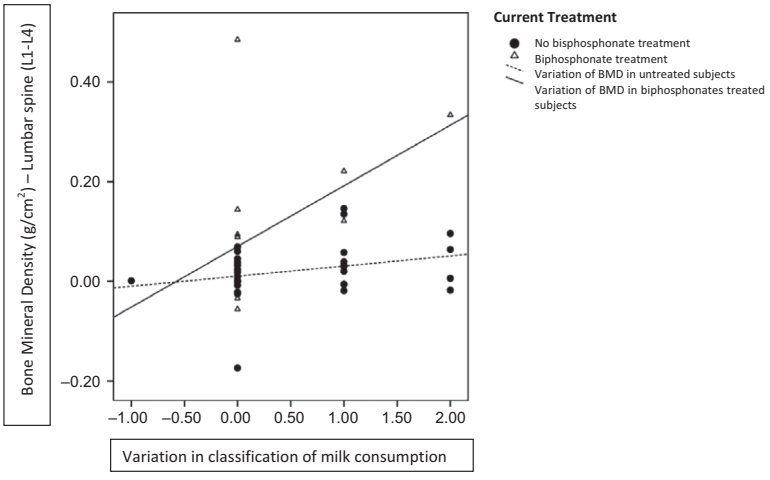

Figure 1 Correlation between variation in bone mineral density of the lumbar spine and variation in milk consumption classification.

and can be influenced by height loss as a result of leg deformities or scoliosis. Our previously published study showed a difference between the methods used to evaluate the body composition [14]. Several studies have reported an association between OI and a higher BMI and being overweight [7,9,19,20]. The present study did not detect a significant difference in the pre- and post-NI BMI *Z*-scores and the nutrition status of these patients. As well being described in the literature, and in addition to nutritional intervention according to metabolic rate, it is essential that physical activity is also practised. However, patients with OI, perform less physical activity because of the risk of fracture, making them and their parents more fearful. This causes them to decrease their energy expenditure and consequently, weight gain. Another consideration is that 12 months was not sufficient to show differences in the BMI *Z*-score of these patients. A meta-analysis performed by Vasques *et al.* [23] in 2014, aiming to evaluate the effects of NI and physical activity programmes on the BMI of children and adolescents, observed that several factors influenced the results, such as age, sex, NI duration, type of NI, frequency of physical activity and parental involvement, concluding that NI programmes have an effect on the prevention and reduction of obesity in children, even if this effect is of low magnitude.

Although the rate of adherence to treatment was not measured and we did not note a significant improvement of the BMI after NI, we did observe a significant increase in calcium intake, which was the main objective of the present study. These findings suggest adherence to the proposed recommendations of the nutritionist. According to the WHO, adherence is defined as the degree to which the behaviour of a person (e.g. ingestion of medication, following a diet and changes in lifestyle) correspond to and agrees with the recommendations of a physician or another health professional [24]. A study performed in 2010 evaluated adherence to treatment in patients with phenylketonuria and noted the importance with respect to both parents and patients understanding the diet [25]. We consider that this may have occurred in the present study because the nutritional counselling was carried out together with the parents/legal guardians of the children and adolescents, making them aware of the best way of achieving a diet rich in calcium.

The present study has some limitations. Two participants were lost to follow-up as a result of the presence of fractures or convalescent corrective surgery at the time of evaluation or hospitalisation for bisphosphonate treatment. In five children who were less than 5 years old, the *Z*-score for lumbar spine and total body BMD were not calculated because of a lack of values proposed by the manufacturer. We did not measure macronutrients at NI because this was beyond the scope of the present study. For ethical reasons, the study had no-intervention or placebo and control group, thus making it impossible to evaluate the real role of NI because individuals already have the answer conditioned to respond to evaluator that can lead to a information bias. Also, retrospective dietary surveys might underreport the eating of certain foods.

The present study aimed to evaluate the results of a NI with emphasis on calcium intake in children and adolescents with OI. Following the NI, we observed a significant increase in calcium intake (mg and relative to EAR and RDA). We also observed an increase in consumption of cups of milk and a decrease in the number of individuals who consumed soda daily. We also noted a positive correlation between lumbar spine BMD and milk consumption among those individuals receiving bisphosphonate treatment. Based on our findings, we emphasise the importance of nutrition therapy as part of a multidisciplinary treatment, helping to guide individuals with OI in relation to a rich, healthy calcium intake, thereby reducing the risks of morbidity, mortality and new fractures.

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 STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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TMF and EDM designed the experiment. MBZ collected and analysed the data. MBZ, TMF and EDM wrote the paper. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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CARDIOVASCULAR DISEASE

Usual dietary anthocyanin intake, sources and their association with blood pressure in a representative sample of Australian adults

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anthocyanins, Australia Health Survey, blood pressure, dietary intake, food sources.

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[Correction added on 14 May after first online publication: There were grammatical and typo errors in the abstract and these have been corrected in this version.]

Abstract

Background: Anthocyanins represent an important subgroup of non-nutritive components of food as evidence continues to build related to their beneficial bioactive effects. Using a recently developed Australian anthocyanin database, the present study aimed to estimate the intake of both total anthocyanins and their subclasses, identify food sources of anthocyanins, and determine associations between anthocyanin intake and measured blood pressure (BP).

Methods: The present study comprised a secondary analysis of the 2011–12 National Nutrition and Physical Activity component of the Australian Health Survey. Anthocyanin intake was estimated using an Australian anthocyanin database. Usual anthocyanin intake, as estimated from 24-h diet recall data, was computed using multiple source methods, whereas food sources were determined by calculating contribution of food groups to total anthocyanin intake. Regression analysis, adjusted for covariates (age, gender, body mass index, high BP diagnosis, smoking status and physical activity) assessed the relationship between anthocyanin intake and BP in adults aged ≥50 years.

Results: Mean anthocyanin intake was 24.17 ± 0.32 mg day^{-1}. Across age groups, berries were the top sources: blackberry (5–65%), cherry (2–24%), blueberry (2–13%) and raspberry (3–12%). There was a significant inverse association between anthocyanin intake and systolic BP ($\beta = -0.04$, $F = 16.8$, d.f. = 6, $r^2 = 0.05$, $P < 0.01$) and diastolic BP ($\beta = 0.01$, $F = 5.35$, d.f. = 6, $R^2 = 0.013$, $P < 0.01$), in models that adjusted for covariates.

Conclusions: In comparison with the world composite database, anthocyanin intake in the Australian population was above average [mean (SD): 24.17 (0.32) mg day^{-1} versus 18.05 (21.14) mg day^{-1}]. Berries were the primary source of anthocyanins. Anthocyanin intake in older adults aged ≥50 years was inversely associated with BP.

Introduction

Incorporating fruits and vegetables into the usual human diet has been shown to exert protective effects on health. These observed effects have been attributed to the presence of minerals, vitamins, phytochemicals and dietary fibre in these food groups [(1)]. Phytochemicals include phenols, terpenes, thiols, phytic acids, phytosterols and protease inhibitors. The phenols are the largest class of phytochemicals [(2)] and these bioactive compounds, independently and as a group in fruits and vegetables, have been associated with reduced mortality [(3)], weight loss [(4)], cardiovascular diseases [(5)] and some cancers [(6)].

Anthocyanins are a subgroup of polyaromatic phenols. They are one of the major subgroups. Epidemiological evidence has shown that anthocyanins, in addition to being responsible for the deep dark colours in fruits and vegetables, may also exert beneficial effects to health. To date, the most promising protective health effects of anthocyanins appear to be related to blood pressure (BP) regulation [5,7,8], vascular health [9] and cognitive function [10,11]. Chronic inflammation as a result of raised BP increases the risk of chronic diseases, including stroke, coronary heart disease, chronic kidney disease and heart failure [12,13]. Anthocyanins as part of the overall diet plays an integral role in the regulation of chronic inflammation [14]. Fruits such as berries, with high anthocyanin contents, amongst others, have been labelled as anti-inflammatory foods using the Dietary Inflammatory Index (DII) [15], which is a system used to assess the quality of foods based on their inflammatory potential [15].

Despite emerging evidence regarding the beneficial health effects of anthocyanins, inter-individual variability in their metabolism, which may be partly related to differing microbiota profiles [16,17], has hampered the identification of optimal intakes, as well as the clarification of their role in cardio-metabolic health. The food matrix in fruits and vegetables may contribute to the wide inter-individual variability with respect to metabolism and the subsequent effects of anthocyanins. Different cardiovascular and metabolic responses have been shown according to the food source of these compounds [18,19]. The synergistic effect of other diverse compounds and nutrients present in the source foods has also been explored [20,21].

Accurate measurement of nutrient intakes, in this case anthocyanins, tailored specifically to individual countries and regions is an important consideration in both epidemiological and experimental studies [22]. As a result of variations in climate, soil conditions and methods of plant harvesting, nutrient levels differ in foods produced across different regions [23,24]. This variation in nutrient content has led to the development of country/region specific food composition databases. Currently, the United States Department of Agriculture (USDA) Database for the Flavonoid Content of Selected Foods and the European Phenol-Explorer food composition databases exist for the measurement of polyphenol (including anthocyanin) intakes [25,26]. Comparing these two databases for the estimation of dietary polyphenol intake in Polish adults, Witkowska *et al.* [27] demonstrated significant discrepancies between the amount of flavonoid intake, estimated at 525 mg day^{-1} versus 403.5 mg day^{-1}, respectively ($P < 0.001$). This discrepancy led to the first-stage development of an Australian anthocyanin database aiming to determine the amount of anthocyanins consumed by Australians [28] as a result of differences in climate and agricultural practices in this region.

Following the development of an Australian anthocyanin database, the primary aim of the present study was to use this newly developed anthocyanin database to estimate the intake of both total anthocyanins and their subclasses in a nationally representative sample of the Australian population and to compare intakes with the world composite database and other population studies [29], as well as determine the top food contributors of anthocyanins in Australians.

Evidence from BP intervention studies has shown that more significant effects are observed in older adults [7,8] and elevated BP as part of metabolic syndrome is common in people aged 50+ years [30]. Therefore, a secondary aim of the present study was to determine whether there was an association between anthocyanin intakes and BP in Australians aged ≥50 years.

Materials and methods

The present study comprised a secondary data analysis of the 2011–12 National Nutrition and Physical Activity Survey (NNPAS) data from the Australian Bureau of Statistics (ABS) using Basic Confidentialised Unit Record Files. The NNPAS 2011–12 is a component survey of the 2011–13 Australian Health Survey (AHS), which involved a total of 12 153 persons carried out between 29 May 2011 and 9 June 2012 in approximately 9500 private dwellings selected throughout non-very remote areas of Australia.

The survey was conducted using a stratified multistage area sample of private dwellings. Survey aims were designed to provide detailed and broad level estimates for each state/territory and Australia, capital city/balance of state area, regions and subpopulations. Within selected households, a random subsample of residents was selected as follows:

- One adult (aged 18 years and older), and (where applicable)
- One child aged 0–17 years (AHS)
- One child aged 2–17 years (NNPAS) [31].

Data collection for NNPAS involved face-to-face interview (and by telephone for the second NNPAS interview) to collect data on general demographic information (including age, sex, marital status and country of birth) for all individuals, whereas detailed information was collected from one adult and one child aged 2–17 years. The survey sampling method covered about 97% of the people and households in Australia from which the study population was sampled.

A 24-h dietary recall method was used to collect information on food, beverages and dietary supplements consumed, as well as some general information on dietary behaviours.

All participants (n = 12 153) provided the first dietary recall via an interviewer-administered format using the Automated Multiple-Pass Method [32], as adapted to reflect the Australian food supply [33]. All respondents were invited to take part in a second 24-h dietary recall, conducted using computer assisted telephone interview. Data were collected from 63% of respondents (n = 7735). To account for seasonal changes in health and nutritional intake, the NNPAS data collection was randomly spread over a 12-month period. Calculation of the person weights adjusted for this seasonal variation.

No ethics approval was required for the present study because it comprised a secondary analysis. However, approval to carry out a secondary analysis with the NNPAS component of the AHS data was obtained by the researchers from the Australian Bureau of Statistics prior to conducting the study.

Estimation of anthocyanin intake

Estimation of anthocyanin intake occurred by applying a newly developed Australian anthocyanin database to the dietary records. The methods of the development of the database, including its strengths and weaknesses, are reported elsewhere [28]. Briefly, analytical values were systematically searched, and local researchers were contacted for unpublished data. Following compilation of the data, values were borrowed from the USDA flavonoid database for selected foods, as well as the European Phenol-Explorer database. Borrowed values were converted for Australian foods using a moisture conversion factor. There are a total of 5740 foods in the Australian Food and Nutrient Database (AUSNUT) 2011–13; of these, anthocyanin values were assigned to 318 individual foods.

The AUSNUT 2011–13 is a food composition database of food, dietary supplement and nutrient intake estimates that was compiled from participants' responses to the 2011–12 NNPAS. For the current analysis, the NNPAS data were expanded to include anthocyanin content of reported foods and total intakes were calculated based on the amount of food (g) consumed for each day of recall.

Using the two separate days of 24-h dietary recall data, usual anthocyanin intake was calculated using the multiple source method (MSM) [34,35]. The MSM comprises three steps. First, for each respondent in the study sample, the probability of consumption of the response variable on a randomly selected day was calculated. Second, the usual amount of food group intake on reported consumption days was estimated and, finally, the usual overall intakes were calculated by multiplying probability of consumption of the response variable with usual amount of intake on consumption days. Intake values were calculated within the MSM model assuming all of the participants were habitual consumers, given that anthocyanins are primarily found in fruit and vegetables, with age and gender included as covariates. Two variables were produced in the MSM output: usual daily intake of anthocyanins for all participants calculated by the MSM (e.g. measure of habitual intake) and the usual intake of anthocyanins in consumers from the 24-h dietary recall calculated by the MSM. Both of these variables were used in the statistical analysis (Fig. 1).

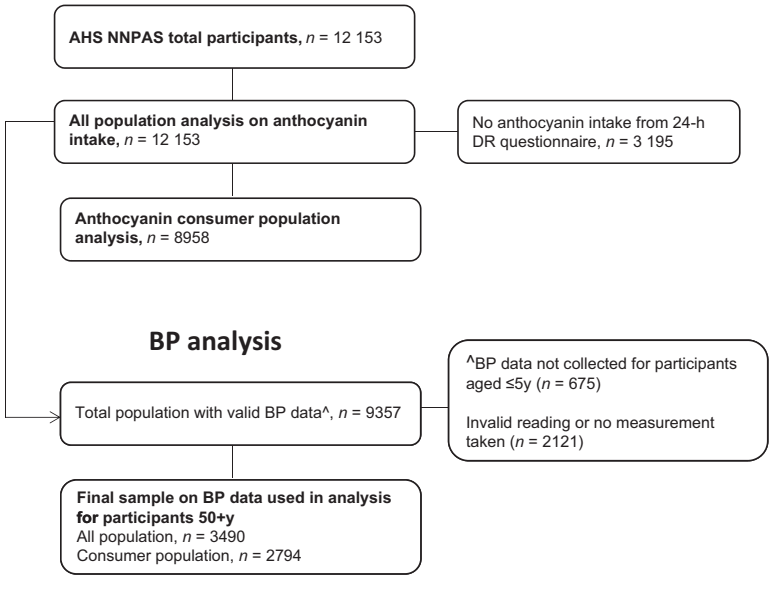

Figure 1 Participant flowchart for secondary analysis of the Australian Health Survey, National Nutrition and Physical Activity Survey (NNPAS) component. AHS, Australian Health Survey; BP, blood pressure; DR, dietary recall; y, years.

Statistical analysis

Statistical analysis was carried out using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). Daily anthocyanin intake was calculated and expressed as the mean (SE). The total population analysis was based on usual daily anthocyanin intake for all participants and the consumer population analysis was based on the usual intake of anthocyanins in consumers only. Intake of the major subclasses of anthocyanins (cyanidins, delphinidins, malvidins, pelargonidin, peonidins and petunidins) was also calculated. Weighting factors, including person weights and replicate weights produced by ABS [36], were applied to the data to generalise results to the total Australian population at the time the survey and to account for sampling discrepancies.

Mean anthocyanin intake for the total population and across subgroups [age groups, sex, body mass index (BMI) level of education, smoking status and level of physical activity] were calculated. Age groups were categorised according to those used in the National Health and Medical Research Council Nutrient Reference Values for Australia and New Zealand [37]. For the purpose of the analysis, categories of BMI, education, smoking and physical activity were grouped according to the ABS classifications, with similar classes grouped together (e.g. underweight Class 3, underweight Class 2 and underweight Class 1 grouped as 'underweight') and individuals aged <15 years were classified as 'not applicable' to maintain the integrity of the weighting factors applied [31].

Linear regression analysis was used to determine the relationship between anthocyanin intake and BP in adults aged ≥50 years (Fig. 1), with adjustment for age and gender (model 1) and adjustment for age, gender, BMI, physical activity, smoking status and whether diagnosed with high BP (by a health professional and/or measured BP ≥ 140/90 mmHg) (model 2). Inclusion criteria for this analysis were: (i) age ≥50 years and (ii) a valid BP measurement.

Level of significance was set at 0.05 and calculated from a *t*-test for pairwise comparisons or analysis of variance to determine whether there are differences in any of the subgroups, where appropriate.

Results

Dietary anthocyanin intake from the NNPAS was estimated at 24.17 (0.32) mg day^{-1} for the total population (n = 12 153) and 37.68 mg day^{-1} for the consumer population (n = 8958). Mean intakes for total and subclasses of anthocyanins according to sociodemographic (gender, age group, level of education) and lifestyle (BMI, smoking status and physical activity) are reported in Table 1. There were more adults than children (n = 9341 versus 2812) with no statistically significant difference in anthocyanin intake. Respondents who had high physical activity levels consumed more anthocyanins compared to those who had a sedentary lifestyle (30.04 mg day^{-1} versus 20.42 mg day^{-1}; $P < 0.001$). A similar trend was also observed for respondents with a Bachelor's degree compared to those with a diploma or lower (29 mg day^{-1} versus 24 mg day^{-1}, *t*-test: $P < 0.001$).

The top 10 food sources stratified by age are shown in Table 2. Berries are highly concentrated sources of anthocyanins [28, 38] and were the top contributors to total anthocyanin intake across all age groups. The top 10 food sources were reported as these comprised more than 50% of the total anthocyanin intake across all age groups.

There was a significant inverse association between measured systolic and diastolic BP and anthocyanin intake (Table 3). This was evident for both systolic ($\beta = -0.04$, $F = 7.77$, d.f. = 2, $r^2 = 0.01$, $P = 0.001$) and diastolic ($\beta = -0.01$, $F = 5.72$, d.f. = 2, $r^2 = 0.01$, $P = 0.005$) BP (Model 1: adjusted for age and gender). After controlling for further confounders (Model 2: age, gender, BMI, physical activity, high BP diagnosis, smoking status and physical activity), the association remained significant (systolic BP: $\beta = -0.04$, $F = 16.8$, d.f. = 6, $r^2 = 0.05$, $P < 0.01$; diastolic BP: $\beta = 0.01$, $F = 5.35$, d.f. = 6, $r^2 = 0.013$, $P < 0.01$).

Discussion

Using nationally representative dietary survey data, the present study reports an observed wide distribution of anthocyanin intake in the Australian population. The estimated mean (SE) intake was 24.17 (0.32) mg day^{-1}, which is midway between the estimates reported for other populations that range between 2.9 and 42.79 mg day^{-1} (Table 4) and above average in comparison with the world composite database [29]. There were variations in anthocyanin intake across subgroups analysed; for example, a higher anthocyanin intake in the 51–70 years age group [27.75 (0.65) mg day^{-1}] compared to the lowest consumption [18.56 (0.87) mg day^{-1}] in the 14–18 years age group ($P < 0.001$). Adults with a postgraduate qualification had higher anthocyanin intakes [30.09 (1.47) mg day^{-1}] compared to those without school qualifications [20.57 (0.43) mg day^{-1}] ($P < 0.001$), whereas highly active adults [30.04 (1.11) mg day^{-1}] had higher intakes compared to sedentary respondents [20.42 (0.73) mg day^{-1}] ($P < 0.001$). These results are consistent with previous reports on the significant association between sociodemographic and lifestyle factors and fruit and vegetable consumption [39–42]. Surprisingly, ex-smokers reportedly consumed significantly higher daily anthocyanins [27.68 (0.88 mg) day^{-1}] compared to both smokers [18.21 (0.68)

Table 1 Anthocyanin intakes by demographic and lifestyle factors for the Australian population (and consumer population) in the 2011–12 National Nutrition and Physical Activity Survey (NNPAS)

Stratification variable	*N*	Anthocyanins (mg day^{-1})			Cyanidins (mg day^{-1})			Delphinidin (mg day^{-1})		
		Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*
Total NNPAS population (consumer population)	12 153 (8958)	24.17 (37.68)	0.32 (0.41)		9.33 (15.22)	0.13 (0.23)		3.03 (5.07)	0.07 (0.12)	
Gender				<0.001 (<0.001)			<0.001			<0.001
Male	5702 (4030)	23.62 (38.27)	0.41 (0.63)		9.41 (16.04)	0.17 (0.33)		2.83 (4.89)	0.06 (0.11)	
Female	6451 (4928)	24.72 (37.14)	0.47 (0.67)		9.27 (14.49)	0.18 (0.29)		3.22 (5.24)	0.13 (0.22)	
Age group (years)				<0.001 (<0.001)			<0.001			<0.001
Children (≤18)	2812 (2071)	22.46 (35.25)	0.58 (0.90)		10.97 (17.96)	0.28 (0.45)		2.51 (4.04)	0.11 (0.18)	
2–3	464 (378)	21.51 (31.11)	1.40 (1.86)		7.54 (11.06)	0.43 (0.83)		3.45 (5.59)	0.28 (0.44)	
4–8	789 (633)	26.06 (37.04)	1.30 (1.78)		12.31 (18.60)	0.75 (1.17)		3.12 (4.59)	0.34 (0.52)	
9–13	787 (576)	22.92 (36.29)	0.91 (1.40)		12.02 (20.01)	0.53 (0.86)		2.11 (3.42)	0.12 (0.21)	
14–18	772 (484)	18.56 (33.69)	0.87 (1.74)		9.80 (18.13)	0.51 (1.09)		1.94 (3.29)	0.12 (0.22)	
Adults (≥19)	9341 (6887)	24.66 38.38	0.35 (0.44)		8.87 (14.43)	0.13 (0.23)		3.17 (5.37)	0.07 (0.13)	
19–30	1592 (1017)	19.24 (34.24)	0.68 (1.07)		8.48 (15.73)	0.29 (0.60)		2.42 (4.60)	0.13 (0.25)	
31–50	3565 (2543)	25.66 (40.55)	0.66 (0.91)		9.58 (15.79)	0.27 (0.45)		3.22 (5.48)	0.14 (0.25)	
51–70	2907 (2300)	27.75 (40.20)	0.65 (0.97)		8.88 (13.39)	0.24 (0.42)		3.55 (5.71)	0.13 (0.27)	
71+	1277 (1027)	24.61 (33.64)	1.15 (1.37)		7.29 (10.80)	0.32 (0.48)		3.64 (5.37)	0.22 (0.33)	
BMI (kg m^{-2})				<0.001 (<0.001)			<0.001			<0.001
< 25	4876 (3668)	24.38 (37.76)	0.59 (0.83)		9.91 (16.04)	0.21 (0.39)		3.02 (4.99)	0.14 (0.22)	
25 to <30	3044 (2274)	25.51 (39.10)	0.58 (0.87)		9.21 (14.92)	0.25 (0.41)		3.10 (5.24)	0.09 (0.19)	
≥30	2258 (1607)	23.23 (37.02)	0.76 (1.06)		8.53 (14.09)	0.30 (0.53)		3.08 (5.34)	0.15 (0.28)	
Measurement not taken	1975 (1409)	22.46 (35.68)	0.69 (1.09)		8.96 (14.74)	0.31 (0.56)		2.86 (4.71)	0.13 (0.27)	
Level of education				<0.001 (<0.001)			<0.001			<0.001
Not applicable	2180 (1676)	23.64 (35.87)	0.70 (1.08)		11.36 (18.06)	0.35 (0.61)		2.65 (4.21)	0.14 (0.22)	
Post-Grad	770 (629)	30.09 (44.42)	1.47 (1.92)		10.08 (15.66)	0.57 (0.81)		3.70 (5.88)	0.22 (0.40)	
Bachelors	1615 (1304)	29.90 (44.07)	1.22 (1.63)		10.84 (16.84)	0.35 (0.54)		3.75 (6.13)	0.27 (0.46)	
Diploma/TAFE Courses	3252 (2341)	24.61 (39.10)	0.56 (0.77)		8.74 (14.39)	0.21 (0.38)		3.07 (5.23)	0.12 (0.19)	
No non-school qualification	4190 (2893)	20.57 (32.99)	0.43 (0.71)		8.08 (13.54)	0.22 (0.44)		2.72 (4.68)	0.07 (0.17)	
Level not determined	146 (115)	29.06 (41.95)	2.40 (3.71)		9.32 (14.21)	1.04 (1.69)		4.43 (7.32)	0.67 (0.35)	
Smoking status				<0.001 (<0.001)			<0.001			<0.001
Not applicable	2180 (1676)	23.64 (35.87)	0.70 (1.08)		11.36 (18.06)	0.35 (0.61)		2.65 (4.21)	0.14 (0.22)	
Smoker	1813 (1073)	18.21 (32.61)	0.68 (1.10)		7.28 (13.38)	0.34 (0.68)		2.20 (4.14)	0.11 (0.25)	
Ex-smoker	3096 (2365)	27.68 (41.65)	0.88 (1.34)		9.40 (14.81)	0.28 (0.45)		3.38 (5.42)	0.12 (0.21)	
Never smoked	5064 (3844)	24.33 (37.41)	0.45 (0.70)		9.18 (14.79)	0.20 (0.33)		3.24 (5.46)	0.11 (0.20)	
Physical activity				<0.001 (<0.001)			<0.001			<0.001
Not applicable	2718 (2010)	22.64 (35.28)	0.60 (0.93)		10.99 (17.91)	0.28 (0.48)		2.54 (4.09)	0.11 (0.19)	
High	1328 (1066)	30.04 (43.83)	1.11 (1.24)		11.34 (17.63)	0.48 (0.67)		3.92 (6.33)	0.35 (0.53)	
Moderate	2574 (1950)	25.99 (39.50)	0.69 (0.96)		9.17 (14.55)	0.28 (0.43)		3.32 (5.53)	0.10 (0.20)	
Low	3351 (2461)	23.57 (37.13)	0.57 (0.83)		8.44 (13.92)	0.20 (0.37)		2.99 (5.06)	0.10 (0.19)	
Sedentary	2075 (1398)	20.42 (34.05)	0.73 (1.27)		7.40 (12.56)	0.27 (0.49)		2.68 (4.74)	0.15 (0.31)	
Not stated	107 (73)	26.59 (39.30)	4.93 (6.77)		12.55 (19.03)	3.28 (5.12)		3.28 (4.86)	0.67 (1.15)	

P values significant at < 0.05 using ANOVA. BP, blood pressure; BMI, body mass index; TAFE, Technical and further education.

mg day^{-1}] and nonsmokers [24.33 (0.45) mg day^{-1}]. Zamora-Ros *et al.* [43] similarly reported that ex-smokers consumed more anthocyanins (11.16 mg day^{-1}) than non-smokers (10.62 mg day^{-1}).

Estimation of anthocyanin intake in the Australian population is an important preliminary step in understanding anthocyanin–health relationships. Despite increased research interest on the observed health benefits of anthocyanins provided by food and beverages, the accompanying increased prevalence of consumption of processed foods translates to a reduced consumption of dietary anthocyanins [44]. In the 1970s, average daily

Malvidin (mg day^{-1})			Pelargonidin (mg day^{-1})			Peonidin (mg day^{-1})			Petunidin (mg day^{-1})		
Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*	Mean	SE	*P*
7.61 (14.14)	0.20 (0.42)		0.12 (0.21)	0.01 (0.02)		1.12 (1.99)	0.02 (0.05)		1.05 (1.98)	0.04 (0.08)	
		<0.001			<0.001			<0.001			<0.001
7.46 (14.46)	0.29 (0.67)		0.11 (0.21)	0.01 (0.03)		1.08 (1.98)	0.03 (0.07)		1.00 (1.97)	0.04 (0.09)	
7.76 (13.85)	0.23 (0.48)		0.13 (0.21)	0.01 (0.02)		1.16 (2.00)	0.04 (0.08)		1.10 (2.00)	0.06 (0.13)	
		<0.001			<0.001			<0.001			<0.001
4.86 (9.33)	0.33 (0.72)		0.11 (0.20)	0.01 (0.02)		0.89 (1.58)	0.05 (0.09)		0.57 (1.08)	0.07 (0.14)	
6.34 (11.18)	0.89 (1.53)		0.14 (0.27)	0.02 (0.04)		0.99 (1.67)	0.13 (0.21)		0.83 (1.49)	0.16 (0.27)	
6.51 (11.55)	0.67 (1.25)		0.16 (0.26)	0.02 (0.03)		1.51 (1.87)	0.11 (0.19)		0.83 (1.40)	0.19 (0.31)	
4.38 (8.54)	0.49 (1.14)		0.09 (0.16)	0.01 (0.02)		0.83 (1.50)	0.06 (0.11)		0.43 (0.87)	0.06 (0.15)	
3.06 (6.41)	0.44 (1.22)		0.07 (0.14)	0.01 (0.02)		0.64 (1.25)	0.06 (0.15)		0.36 (0.72)	0.07 (0.18)	
8.39 (15.52)	0.23 (0.47)		0.12 (0.21)	0.01 (0.02)		1.18 (2.11)	0.03 (0.06)		1.19 (2.24)	0.04 (0.08)	
4.62 (10.08)	0.45 (1.43)		0.16 (0.33)	0.04 (0.09)		0.78 (1.61)	0.05 (0.15)		0.57 (1.29)	0.06 (0.16)	
8.40 (15.84)	0.41 (0.85)		0.11 (0.17)	0.01 (0.01)		1.19 (2.13)	0.05 (0.09)		1.24 (2.35)	0.07 (0.15)	
10.97 (18.96)	0.49 (0.98)		0.11 (0.18)	0.01 (0.02)		1.46 (2.46)	0.06 (0.11)		1.54 (2.75)	0.08 (0.16)	
9.60 (14.16)	0.61 (0.99)		0.14 (0.23)	0.05 (0.09)		1.27 (1.91)	0.09 (0.16)		1.39 (2.14)	0.15 (0.24)	
		<0.001			<0.001			<0.001			<0.001
7.29 (13.73)	0.30 (0.64)		0.14 (0.24)	0.02 (0.03)		1.12 (1.99)	0.04 (0.08)		1.03 (1.96)	0.07 (0.13)	
8.96 (16.70)	0.45 (0.96)		0.12 (0.21)	0.02 (0.04)		1.25 (2.24)	0.05 (0.10)		1.24 (2.36)	0.06 (0.14)	
7.36 (13.36)	0.46 (0.99)		0.09 (0.17)	0.02 (0.04)		1.06 (1.91)	0.06 (0.12)		1.00 (1.90)	0.07 (0.18)	
6.51 (11.67)	0.43 (0.92)		0.09 (0.16)	0.01 (0.01)		0.97 (1.62)	0.05 (0.10)		0.82 (1.47)	0.06 (0.13)	
		<0.001			<0.001			<0.001			<0.001
5.39 (10.10)	0.38 (0.81)		0.12 (0.22)	0.01 (0.02)		0.96 (1.68)	0.06 (0.11)		0.62 (1.16)	0.09 (0.17)	
11.46 (20.61)	0.86 (1.68)		0.12 (0.20)	0.02 (0.02)		1.57 (2.69)	0.10 (0.20)		1.71 (3.09)	0.14 (0.28)	
10.07 (18.23)	0.65 (1.27)		0.17 (0.32)	0.04 (0.08)		1.46 (2.52)	0.09 (0.17)		1.54 (2.86)	0.13 (0.26)	
8.71 (16.56)	0.35 (0.74)		0.12 (0.19)	0.02 (0.03)		1.22 (2.24)	0.04 (0.10)		1.21 (2.35)	0.06 (0.14)	
6.07 (11.02)	0.25 (0.59)		0.10 (0.18)	0.02 (0.04)		0.89 (1.55)	0.03 (0.06)		0.80 (1.48)	0.04 (0.08)	
10.25 (17.42)	1.60 (3.00)		0.09 (0.15)	0.02 (0.04)		1.35 (2.15)	0.17 (0.31)		1.53 (2.70)	0.27 (0.53)	
		<0.001			<0.01			<0.001			<0.001
5.39 (10.10)	0.38 (0.81)		0.12 (0.22)	0.01 (0.02)		0.96 (1.68)	0.06 (0.11)		0.62 (1.16)	0.09 (0.17)	
5.27 (10.52)	0.33 (0.87)		0.15 (0.26)	0.05 (0.11)		0.78 (1.43)	0.04 (0.10)		0.73 (1.47)	0.05 (0.13)	
10.44 (18.77)	0.56 (1.10)		0.11 (0.17)	0.01 (0.01)		1.42 (2.48)	0.07 (0.13)		1.52 (2.82)	0.09 (0.18)	
7.65 (14.01)	0.27 (0.58)		0.12 (0.22)	0.01 (0.03)		1.12 (1.97)	0.03 (0.07		1.06 (1.96)	0.05 (0.10)	
		<0.001			ns			<0.001			<0.001
4.98 (9.53)	0.35 (0.75)		0.11 (0.20)	0.01 (0.02)		0.90 (1.60)	0.05 (0.10)		0.57 (1.09)	0.08 (0.15)	
9.58 (17.28)	0.72 (1.26)		0.11 (0.20)	0.01 (0.02)		1.45 (2.49)	0.09 (0.17)		1.47 (2.73)	0.14 (0.24)	
9.33 (17.07)	0.40 (0.83)		0.13 (0.21)	0.02 (0.04)		1.31 (2.30)	0.05 (0.10)		1.39 (2.62)	0.07 (0.15)	
8.12 (15.05)	0.38 (0.78)		0.10 (0.19)	0.01 (0.03)		1.13 (2.01)	0.05 (0.09)		1.08 (2.01)	0.06 (0.12)	
6.44 (12.04)	0.45 (1.04)		0.15 (0.25)	0.04 (0.08)		0.90 (1.63)	0.05 (0.13)		0.86 (1.62)	0.07 (0.17)	
7.15 (11.82)	1.54 (3.13)		0.21 (0.37)	0.12 (0.23)		0.99 (1.57)	0.17 (0.32)		1.00 (1.78)	0.22 (0.45)	

dietary anthocyanin intake in the USA was estimated at 215 mg day^{-1} in the summer and 180 mg day^{-1} during winter [45]. Current estimates show that dietary anthocyanin intake ranges between 3 and 43 mg day^{-1} across countries and tends to be higher in Southern compared to Northern European countries (Table 4).

The consumption of anthocyanin subclasses was also reported for the total and consumer populations. Cyanidins and malvidins were the most prevalent anthocyanins in both the general and consumer populations and across subgroups. In the 51–70 years age group, malvidins were the most prevalent anthocyanins. This could be explained

Table 2 Top 10 food sources of anthocyanins in the diet of the Australian population by age group

	Percentage total anthocyanin intake per age group																	
Age (years) *n*	2–3 464		4–8 789*		9–13 787		14–18 772†		19–30 1592		31–50 3565		51–70 2907		71 + 1277			
1	Blackberry, raw	36.6	Blackberry, raw	65.2	Blackberry, raw	37.5	Cherry, raw	23.9	Grape, raw‡	15.4	Eggplant§	8.1	Eggplant§	23.1	Eggplant§	26.4		
2	Raspberry, raw	12.8	Blueberry, raw	8.3	Blueberry, raw	12.7	Eggplant§	15.7	Cherry, raw	8.5	Blackberry, raw	7.4	Grape, raw‡	9.1	Wine, red,	10.3		
3	Blueberry, raw	10.3	Grape, raw‡	4.9	Grape, raw‡	11.2	Grape, raw‡	14.9	Cranberry, raw	8.2	Cherry, raw	5.7	Blackberry, raw	8.4	Cherry, raw	8.3		
4	Grape, raw‡	8.6	Cherry, raw	2.6	Cherry, raw	7.3	Raspberry, purchased frozen	8.9	Eggplant§	5.3	Blueberry, raw	5.1	Wine, red	7.8	Blueberry, raw	7.1		
5	Cabbage, red, raw	8.8	Raspberry, purchased frozen	2.4	Eggplant§	7.0	Blueberry, raw	8.5	Plum, unpeeled, raw	4.9	Raspberry, raw	4.9	Blueberry, raw	7.1	Blackberry, raw	5.1		
6	Cherry, raw	4.0	Plum, unpeeled, raw	2.4	Plum, unpeeled, raw	4.8	Cabbage, red, raw	5.9	Bean, black¶	4.5	Cranberry, raw	4.8	Cherry, raw	6.3	Plum, unpeeled, raw	4.9		
7	Raspberry, purchased frozen	3.4	Blueberry, purchased frozen	2.1	Raspberry, raw	3.2	Plum, unpeeled, raw	5.4	Raspberry, purchased frozen	3.9	Grape, black sultana, raw	4.6	Plum, unpeeled, raw	4.7	Raspberry, purchased frozen	4.7		
8	Plum, unpeeled, raw	3.2	Eggplant§	2.0	Raspberry, purchased frozen	2.6	Blueberry, purchased frozen	2.0	Blueberry, raw	3.8	Radish, peeled or unpeeled, raw	4.4	Raspberry, raw	2.9	Grape, Thompson,	3.4		
9	Eggplant§	2.7	Raspberry, raw	1.3	Apple, red skin, unpeeled, raw	1.6	Apple, red skin, unpeeled, raw	1.7	Wine, red	3.8	Raspberry, purchased frozen	4.3	Blueberry, purchased frozen	2.6	Radish, raw	3.2		
10	Blueberry, purchased frozen	1.4	Apple, pink lady, unpeeled, raw	0.9	Pear, unpeeled, raw, not further defined	1.3	Pear, unpeeled, raw, not further defined	1.5	Raspberry, raw	3.2	Wine, red, sparkling	4.1	Cabbage, red, raw	2.4	Raspberry, raw	2.9		
Sum		91.8		92.1		89.2		88.5		61.6		53.5		74.4		76.3		

*n = 2 excluded as a result of implausible dietary consumption data.
†n = 1 excluded as a result of implausible dietary consumption data.
‡Combination of Grape, raw, Grape, red, raw, and Grape, Thompson, seedless.
§Eggplant, peeled or unpeeled, fresh or frozen, raw.
¶Bean, black, dried, boiled, microwaved or steamed, drained.

Table 3 Association between anthocyanin intake and change in blood pressure in adults aged aged ≥50 years

	Anthocyanin intake in all population (consumer population) Effect size (regression coefficient and 95% CI) per unit (mg) increase					
	Model 1† *n* = 4184 (3327)			Model 2‡ *n* = 4184 (3327)		
BP parameters	Regression coefficient	95% CI	*P* value	Regression coefficient	95% CI	*P* value
Systolic BP	−0.04 (−0.03)	−0.06, −0.01 (−0.05, −0.01)	0.001* (0.002)*	−0.04 (−0.03)	−0.06, −0.01 (−0.05, −0.01)	<0.01* (<0.01)*
Gender	−2.50 (−2.51)	−4.28, −0.72 (−4.45, −0.58)	0.01 (0.01)	−2.67 (−2.68)	−4.40, −0.94 (−4.62, −0.74)	0.003* (0.01)*
BMI				0.06 (0.1)	−0.002, 0.12 (−0.004, 0.1)	0.06 (0.07)
High BP diagnosis				−7.92 (−7.38)	−9.80, −6.05 (−9.63, −5.12)	<0.001* (<0.001)*
Smoking status				0.70 (1.06)	−0.06, 1.46 (0.11, 2.01)	0.07 (0.03)*
Physical activity				0.09 (0.15)	−0.61, 0.78 (−0.63, 0.92)	0.80 (0.7)
Diastolic BP	0.01 (0.01)	−0.01, 0.02 (−0.01, 0.02)	0.005* (0.03)	0.01 (0.01)	−0.01, 0.03 (−0.01, 0.02)	<0.01* (0.02)*
Gender	−1.56 (−1.31)	−2.51, −0.62 (−2.40, −0.22)	0.002 (0.02)	−1.52 (−1.30)	−2.49, −0.54 (−2.42, −0.18)	0.002* (0.02)*
BMI				0.06 (0.06)	0.03, 0.09 (0.02, 0.11)	<0.001* (0.01)*
High BP diagnosis				−0.77 (−0.54)	−1.76, 0.22 (−1.64, 0.55)	0.12 (0.33)
Smoking status				−0.24 (−0.19)	−0.64, 0.16 (−0.68, 0.30)	0.24 (0.44)
Physical activity				−0.09 (−0.04)	−0.53, 0.35 (−0.49, 0.42)	0.68 (0.88)

†Model 1 covariates = age (included as a class variable) and gender.

‡Model 2 covariates = age (included as a class variable), gender, BMI, hypertension diagnosis, Physical activity and smoking status.

*Significant at $P < 0.05$; values in bracket represent analysis for consumer population.

BP, blood pressure; BMI, body mass index; CI, confidence interval.

by the difference in the consumption pattern of the major food contributor of anthocyanins in this age group, namely red wine, which has a high content of malvidins. A similar trend was also observed in other Australian population studies [46,47], with red wine being a major contributor of anthocyanins in older participants.

The highest contributing foods (top 10) of dietary anthocyanin in the Australian population were berries, principally blueberries, blackberries, raspberries and cherries. Berries are known to contain a very high concentration of anthocyanins [48]. Given this, anthocyanin research has generally focused on berries at the expense of other high anthocyanin foods, such as plums and eggplants, which also comprised some of the top 10 contributors of anthocyanins in the Australian population. Accordingly, further exploration aiming to gather epidemiological evidence of the health-related benefits related to these foods might be worthwhile.

The results obtained in the present study showed a significant association between anthocyanin intake in older adults and lower BP. This result is in agreement with current evidence from clinical and epidemiological studies on the effect of dietary anthocyanins on BP in acute settings and over the longer term [7,8,49]. Anthocyanins have also been classified as nutraceuticals with respect to their ability, as part of a food component, to provide health and medical benefits [50]. However, it is unlikely that these health benefits are the independent effects of anthocyanins instead a synergistic effect with other polyphenols [51]. This emphasises the importance of studying anthocyanin food sources, as is consistent with the present study, rather than isolated anthocyanins. A review by Pascual-Teresa *et al.* [52] observed that the evidence related to the protective effects of anthocyanins, as part of the diet, against cardiovascular disease risks has been consistent over the years. Dietary patterns with high intakes of fruits and vegetables (e.g. blueberries, apples and leafy greens) that are high in natural antioxidants and polyphenols (anthocyanins) have been shown to reduce the risk of high BP [53] and other chronic diseases evident in the DII [14]. This evidence has been consistent with similar dietary patterns. Using the DIII, Steck *et al.* [54] found that the Mediterranean diet showed anti-inflammatory potential based on the resulting DII scores. In addition, the Nordic diet significantly reduced 24-h ambulatory diastolic BP and mean arterial pressure compared to a control diet based on mean nutrient intakes in Nordic countries [55]. Other dietary patterns that emphasise a high fruit and vegetable intake (the Dietary Approach to

Table 4 Reported anthocyanin intake (mg day^{-1}) in population studies by country

Country (reference)	Sample size	Age/gender*	Dietary assessment	Total anthocyanin intake (mg day^{-1})
Australia (present study)	12 153	≥2 years	2 × 24-h DR (MSM method)	24.17
Australia[46]	10 851	≥2 years	24-h DR	1.4
Australia[47]	79	≥49 years	4-day WFR	7.0
China[62]	1393	35–75	FFQ	28†
Europe[57]		35–74 years	FFQ (GA^{2}LEN)	
Denmark	268			7.5
Finland	122			5.9
Sweden	1085			6.5
UK	139			9.8
Portugal	233			22.1
Belgium	107			10.5
Germany	305			5.5
The Netherlands Amsterdam	174			8.1
Poland	116			9.2
Europe[58]		35–74 years	24-h DR	
Greece	2687			31.82
Spain	3220			31.58
Italy	3953	35–74 years/F (1 out of 5 centres)		42.79
France	4735			37.42
Germany	4415	35–74 years/F		35.09
The Netherlands	3980			22.56
UK	1280	35–74 years/F (1 out of 2 centres)		26.12
Denmark	3917			28.21
Sweden	6050			20.96
Norway	1797	35–74 years/F		26.56
Finland[63]	1950	42–60 years/M	4-day food record	6.2
Finland[19]	2007	25–64 years	48 h diet recall	47
France[64]	4942	45–60 years	≥6 24-h diet recall	35
Spain[43]	40 683	35–64 years	Diet history questionnaire	18.88
UK[65]	1997	18–76 years/F	FFQ	18
USA[66]	8809	>19 years	24-h DR	3.1
USA[67]	5420	≥20	24-h DR	11.48

*Gender specified when sample size is gender specific

†Excludes malvidin and petunidin.

DR, dietary recall; F, female; GA^{2}LEN, Global Allergy and Asthma European Network of Excellence; M, male; MSM, multiple source method; FFQ, food frequency questionnaire; WFR, weighted food record.

Stop Hypertension), as well as low-carbohydrate, Palaeolithic, high-protein, low-glycaemic index, low-sodium and low-fat diets, were also found to significantly reduce BP (systolic BP: −8.73 to −2.32 mmHg; diastolic BP: −4.85 to −1.27 mmHg) compared to control/usual diets [56]. The attributable risk related to the polyphenols present in these diets (i.e. anthocyanins) cannot be disentangled from other health-promoting components of key foods included in these BP lowering dietary patterns.

Previous studies have estimated the dietary flavonoid intake in selected Australian populations using weighed food records [47] and from National Nutrition Survey (1995) data using a single 24-h dietary recall questionnaire [46]. The obtained in the present study using the latest nationally representative survey data differ significantly from earlier studies, with higher values than those reported in the present study. This is possibly a result of differences in the method of dietary assessments, as well as the use of the MSM to calculate usual daily intake from two repeated 24-h dietary recalls, it could also be as a result of difference/change in population characteristics. Our analysis indicates that the Australian population consumes intermediate quantities of anthocyanins compared to other populations (Table 4), although with quantities similar to estimates from some European countries including Belgium, Norway, Sweden and Denmark [57,58]. A need for tailored databases for nutritional epidemiological studies cannot be overemphasised. Following the development of the first Australian food composition database in the mid-1980s, comparative analysis showed that using the UK and

US databases overestimated specific nutrient contents by up to 60% [59]. As a result, it is imperative that databases be tailored to the specific food supply of the population under study. However, the development of nutrient databases is fraught with incomplete coverage of all nutrients and, hence, borrowing and calculating nutrient values is a known validated method in the absence of analytical values [60].

To our knowledge, the present study is the first to estimate dietary anthocyanin intake in the Australian population using an Australian-specific anthocyanin database, with this being a major methodological strength. Another notable strength is the use of a representative sample of the Australian population, as well as the validated method (MSM) of calculating usual nutrient intake from repeated 24-h dietary recalls [34]. Some of the limitations of the present study include the use of 24-h diet recall questionnaires in the NNPAS (1,2). The single 24-h diet recall has been considered insufficient because of the retrospective method of dietary assessment and an inability to describe the typical diet from a single day's intake. In addition, the recall is dependent on the memory and cooperation of the participant [61]. Four repeated 24-h diet recalls have been recommended as the most appropriate method for large surveys, [62], whereas two were applied in the NNPAS. The present study applied a regression model to these data to better represent usual intake, although no adjustments were made with respect to potential misreporting of the data. A further limitation relates to the effects of processing and storage [63], which was not taken into consideration for the borrowed data originating from the USDA and Phenol-Explorer food composition databases. Finally, the omission of anthocyanin intake from dietary supplements is a notable limitation of the present study. It is unlikely, however, that such supplements are widely used in Australia, and the composition of supplements and extracts in the AUSNUT food composition database did not include polyphenols (anthocyanins). Each of these elements could have led to both over- and underestimation of anthocyanin intake.

The cross-sectional nature of the present study limits interpretation of the inverse association found between anthocyanin intake and BP. However, evidence is beginning to emerge from experimental studies that supports a protective role of anthocyanins on the risk of cardiovascular disease in both young and older adults [19]. For two foods, plum and red cabbage, the Australian analytical data only reported total anthocyanins but not anthocyanin subclasses. Many fruits and vegetables that are high in anthocyanins are seasonal, being available only in summer and autumn in Australia; therefore, their contribution to total intake will depend on the time of year that the surveys are conducted. For example, red cabbage is a rich source of anthocyanins but accounted for <1% (0.2%) of total anthocyanin intake in the Australian population. This could also be as a result of not many people consuming red cabbage.

Although different methods have been described for estimating usual intake, the MSM method involves similar steps to the National Cancer Institute (NCI) method but uses different modelling procedures and the handling of nonconsumers [64]. Comparison of the different methods, including those from Iowa State University (ISU), NCI, MSM and Statistical Program to Assess Dietary Exposure (SPADE), showed that with small sample sizes (n = 150), the ISU, MSM and SPADE methods were more reliable and enabled more precise estimates than the NCI method, mainly for the 10th and 90th percentiles. The observed differences between methods became less significant with larger sample sizes (n = 300 and n = 500) [65].

Conclusions

In conclusion, the present study estimates for the first time, the mean daily intake of anthocyanin in the Australian population, according to sociodemographic characteristics, using an Australian-specific anthocyanin food composition database. Given the rapidly emerging evidence base related to the beneficial effects of anthocyanins on cardiovascular risk factors, the assessment of population-level intake of this flavonoid subgroup is well timed. Anthocyanin intake was similar to that reported in southern European countries, and higher than in Northern Europe and USA. Identification of major dietary sources of anthocyanins (blackberry, raspberry, blueberry, cherry, red cabbage, eggplant and red wine) allows for focused dietary messaging.

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 STROBE-nut guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

No funding is declared.

EI, KC and YP developed the anthocyanin database, which is part of a larger database development project led by YP. EI, KC and YP designed the current study. YP and KC advised on the statistical analysis. EI performed the statistical analysis and produced the first draft of the manuscript. All authors contributed to writing and editing the manuscript and approved of the final version of the paper submitted for publication.

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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. STROBE-nut: An extension of the STROBE statement for nutritional epidemiology.

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Journal of Human Nutrition and Dietetics

CARDIOVASCULAR DISEASE

Efficacy and safety of *Rhizoma curcumea longae* with respect to improving the glucose metabolism of patients at risk for cardiovascular disease: a meta-analysis of randomised controlled trials

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Keywords
curcumin, curcuminoids, glucose metabolism, cardiovascular risk, meta-analysis.

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Abstract

Background: Clinical evidence suggests that curcuminoids, as a natural polyphenol, can provide support for cardioprotection and glucose metabolism. This meta-analysis assessed the efficacy and safety of curcumin with respect to improving glucose metabolism in patients with cardiovascular risk factors.
Methods: Four databases (PubMed, Cochrane Library, Web of Science and Embase) were searched up to June 2018. The inclusion criteria included (i) randomised controlled trials (RCT) and (ii) subjects with risk factors for cardiovascular disease supplemented with curcumin and curcuminoids. A random-effects model and a standardised mean difference with a 95% confidence interval were used to perform quantitative data synthesis. Sensitivity and subgroup analyses were conducted to assess the effects.
Results: Fourteen eligible RCT with 1277 subjects were included. In the overall analyses, curcumin led to significant decreases in fasting blood glucose (FBG), glycated haemoglobin (HbA1c) and homeostatic model assessment of insulin resistance (HOMA-IR). The subgroup analyses suggested that curcumin or combined curcuminoids were more effective at reducing FBG and HbA1c in type 2 diabetes patients than in individuals with metabolic syndrome. Supplementation with curcuminoids at doses ≥300 mg day^{-1} showed significant decreases in FBG, HbA1c and HOMA-IR. The effects of supplementation on FBG, HbA1c and HOMA-IR were more significant over long periods (≥12 weeks) than short periods. Curcumin and curcuminoids were well tolerated, with no serious adverse events.
Conclusions: Curcumin or combined curcuminoids could exert cardioprotective effects in patients at risk for cardiovascular disease by improving glucose metabolism. However, further high-quality studies and larger sample sizes are required to confirm these results.

Introduction

Worldwide, the numbers of adults with metabolic syndrome (MetS) and diabetes mellitus (DM) continue to increase, generating a large healthcare and economic burden [1,2]. MetS and DM usually manifest as disturbed glucose metabolism (dysglycaemia) characterised by persistent abnormal blood glucose concentrations, including impaired fasting blood glucose (FBG) and impaired glucose tolerance [3,4]. Long-term hyperglycaemia leads to cardiovascular damage, impaired eyesight, renal failure and infectious diseases [5]. Recent findings have indicated

that hyperglycaemia leads to macro- and microvascular diseases, causes glycation of lipoproteins within the body, and potentiates atherosclerosis, which is the main cause of cardiovascular disease (CVD) [2]. Hyperglycaemia is now a well-established independent risk factor for CVD [6]. Major cardiovascular risk factors include age, sex, smoking, hypertension, dyslipidaemia, type 2 diabetes mellitus (T2DM) and MetS [7]. Thus, treatment of DM is of crucial importance for preventing CVD. Although some effective intervention programmes for T2DM have been designed in recent years [8–10], these interventions are usually uneconomical, and their drugs are poorly tolerated because of therapy-associated toxicities [9,10]. As a result of these concerns, the current goal is to develop powerful new drugs and identify natural therapeutic agents that control T2DM.

Plant polyphenols have been extensively researched as a result of their biological activity, and they play an important role in health benefits [11,12]. Among polyphenols, curcumin, a naturally occurring polyphenol, is the main curcuminoid present in the perennial plant *Rhizoma curcumea longae* (turmeric), which is widely used in cooking, dyes, cosmetic and medicines. Various studies have reported that curcumin can reduce FBG, glycated haemoglobin (HbA1c) and insulin resistance [13], thus improving glucose metabolism and reducing subsequent atherosclerosis [14–17]. However, the results have been inconsistent. Some studies have shown significant effects [18–28], whereas others have failed to report favourable effects [29,30]. The only previous meta-analysis on the topic had a limited sample size and significant publication bias and evaluated only the effects of curcumin on FBG and HbA1c concentrations in individuals with dysglycaemia [31]. Therefore, we performed a meta-analysis of 14 randomised controlled trials (RCT) aiming to estimate the efficacy and safety of curcumin or combined curcuminoids with respect to improving glucose metabolism among patients with cardiovascular risk factors.

Materials and methods

A systematic literature review was conducted according to recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist [32]. The review was registered on the PROSPERO database (ID number CRD42018104671) (https://www.crd.york.ac.uk/prospero).

Data sources and searches

We identified potentially relevant studies by performing a systematic computerised search of the following databases from inception to June 2018: PubMed, Cochrane Library, Web of Science and Embase. The search strategy used the following combination of key words and MeSH (medical subject heading) terms: (curcumin OR curcuminoid OR turmeric) AND (glucose metabolism OR fasting blood glucose OR oral glucose tolerance test OR glycated haemoglobin OR homeostatic model assessment of insulin resistance OR homeostatic model assessment of beta cell function OR insulin) and their abbreviations. Furthermore, we used multiple synonyms. The scope of the search was limited to human studies reported in English. The search was performed in June 2018 and the whole selection process was performed independently by two investigators (JH and SQ). Inconsistencies were resolved with the assistance of a third investigator (HDH) when necessary.

Inclusion and exclusion criteria

The following inclusion criteria were used for the studies in this meta-analysis: (i) an RCT design; (ii) subjects with risk factors for CVD, including age, sex, race, smoking, obesity, hypertension, dyslipidaemia, T2DM and MetS [7,33]; (iii) an intervention consisting of curcumin or combined curcuminoids, turmeric extract or turmeric powder, regardless of dose; interventions in the control group could be placebo or medication (if the control group was a medication, then the experimental group was treated with curcumin and this medication); (iv) a follow-up period of at least 4 weeks; and (v) adequate information provided about glucose metabolism [including at least FBG, HbA1c, homeostasis model assessment of insulin resistance (HOMA-IR) and insulin] at baseline and at the end of the trial or their net change values. The following categories were excluded: (i) studies including subjects who were children or pregnant; (ii) studies not reported in English; and (iii) subjects with type 1 diabetes. If there were several publications that used the same population, we selected the most recent and complete one.

Efficacy measures

The primary outcome measures were parameters of glucose metabolism. Specifically, we included FBG, HOMA-IR (fasting insulin μU mL^{-1} × fasting glucose mmol L^{-1} 22.5^{-1}) [34], insulin and the glycaemic control parameter HbA1c. The secondary outcome measure was the safety of treatment, assessed by side effects resulting from curcumin or curcuminoids.

Data extraction

The titles and summaries of studies retrieved from online databases were screened by two independent investigators

(JH and SQ) and all of the essential data were independently extracted from eligible articles. When possible, the calculations reported in the studies were checked twice. Data on the author and year of publication, study design, intervention information, baseline characteristics of subjects, and baseline and follow-up blood concentrations of glucose metabolism parameters were extracted. To avoid high heterogeneity, we included only those investigations with a study period of at least 4 weeks. In any study with more than two experimental groups, the most appropriate treatment group was chosen. When necessary, the authors were contacted by e-mail to obtain any missing data.

Risk of bias in the included studies

The risk of bias in eligible studies was evaluated by the same two independent reviewers (JH and QS) according to the 'Assessing risk of bias' table in the *Cochrane Handbook for Systematic Reviews of Interventions* [35]. Adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases were judged to be low, high or unclear in each of the included studies.

Statistical analysis

Meta-analysis was performed utilising STATA, version 12.0 (Stata Corporation, College Station, TX, USA). For the analysis, we extracted only continuous variables. When the units were not uniform, we used conversion factors. Mean (SD) values were calculated from mean values and standard errors using: mean = mean $_{\text{post-treatment}}$ − mean $_{\text{pretreatment}}$; SD = SE × $\sqrt{n}$ (where n is the number of participants); and SD = $\sqrt{[(\text{SD pretreatment})^2 + (\text{SD post-treatment})^2 - (2R \times \text{SD pretreatment} \times \text{SD post-treatment})]}$, assuming a correlation coefficient (r) = 0.5 [36]. If the resulting measurements were reported in medians and ranges, the mean (SD) values were estimated by the relevant formulas [37]. The effect sizes were measured using a Z-score, and a significant difference between experimental groups and control groups was defined as a $P < 0.05$. Chi-squared and I^2 tests were used to evaluate statistical heterogeneity. A random-effects model was chosen in the presence of significant heterogeneity. Because the included studies used continuous variables with large means and different units of the measurements, the standardised mean difference (SMD) with a 95% confidence interval (CI) was used. To explore heterogeneity among studies, we conducted subgroup analyses according to underlying disease, form of intervention, administered dose and duration of study. Sensitivity analyses were also performed by leave-one-out cross-validation (removing one study at a time and repeating the analysis). For the purpose of examining publication bias, Begg's test and Egger's test were performed.

Results

Search results and study characteristics

As illustrated by the search strategy (Fig. 1), 1417 relevant articles were identified, of which 704 were removed because they comprised duplicate documents retrieved from two or more databases. The remaining studies were further screened by scanning the titles and abstracts, resulting in the elimination of another 693 studies. After this elimination step, 20 full-text publications received detailed assessments, of which one was excluded [38] because it used the same patient groups as that employed in another study [23], and two additional papers were eliminated because of incomplete data [39,40]. Furthermore, one study was excluded for not being in English [41] and two were excluded for recruiting healthy subjects [42,43]. Ultimately, 14 RCTs with a total of 1277 subjects were included in the meta-analysis. The basic characteristics of the included RCT are shown in Table 1. Of the 14 eligible studies, six studies enrolled patients with T2DM, and eight studies included patients with MetS. Among these studies, five were conducted in Iran [21,23–25,44] and two were performed in Thailand [18,19]. The remaining studies were carried out in China [22,28], Pakistan [29], the Republic of Korea [30], Germany [20] and India [26,27]. Both the doses and the forms of curcumin varied among these studies. As specified by the inclusion criteria, each of these studies lasted at least 4 weeks. The study by Kocher *et al.* [20] used a cross-over design and the study by Maithili *et al.* [26] was performed in an open-label manner and was the only one with metformin in the intervention and control groups. The baseline characteristics of the subjects in the included studies are provided in Table 1 (see also the Supporting information, Table S1). In general, the study groups were comparable in terms of age, sex, weight, body mass index, blood pressure, serum lipids and proinflammatory cytokines at baseline. Table 2 lists the pre- and post-intervention glucose metabolism information from the included studies.

Risk of bias in the included studies

The risk of bias in the included RCT is shown in Fig. 2. In general, the risk of bias varied among these selected studies. Of the 14 RCT, nine were judged to have a low risk of bias and five were classified as having a high risk of bias [26,27,30,44]. Nine studies reported proper methods for randomising the subjects, such as computer-generated random numbers or a random number table, although

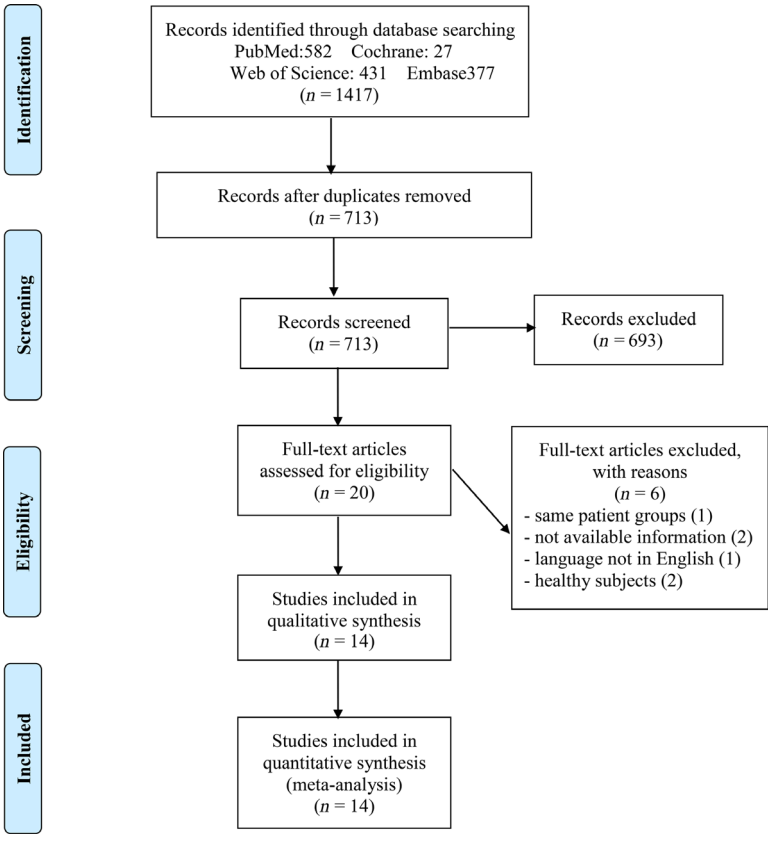

Figure 1 Flow diagram showing the study selection process.

the remaining studies did not describe how the subjects were randomly assigned [20,21,24,27,44]. Only seven of the studies used allocation concealment [18,19,22–24,29,30]. All of the included studies used double blinding of patients and practitioners, except for three studies [26,27,44]. All studies were judged to have a low risk of bias with regard to blinding of outcome assessment. Regarding the analysis of dropouts resulting in incomplete data reporting, two studies utilising per-protocol analysis were judged to have a high risk of bias [28,30], and other studies were categorised as having a low risk of bias because there were no drop outs [26], similar reasons and numbers of drop outs [21–23,25,27,44], or the use of intention-to-treat analysis [18–20,24,29].

Meta-analysis

Pooled data from 13 included studies with a total of 1064 subjects showed significant efficacy of curcumin treatment with respect to improving FBG (SMD = −0.382, 95% CI = −0.654 to −0.111 mg dL^{-1}, $P = 0.006$, $I^2 = 78\%$) (Fig. 3). To evaluate the sources of potential bias, we performed several subgroup analyses. First, the included trials were arranged into two subgroups according to the underlying diseases of the participants (Fig. 4a). Pooled data from eight studies that included patients with MetS showed no significant differences, whereas five studies with diabetes patients showed a significant decrease in FBG in the experimental group (SMD = −0.681, 95% CI = −1.067 to −0.294 mg dL^{-1}, $P = 0.001$). Second, we created three subgroups according to form of intervention: a curcumin subgroup, a curcuminoid subgroup and turmeric subgroup (Fig. 4b). Subjects in the experimental group with curcumin revealed a significant reduction in FBG concentration (SMD = −0.417, 95% CI = −0.765 to −0.069 mg dL^{-1}, $P = 0.019$). By contrast, pooled data from the curcuminoid subgroup and the turmeric subgroup showed no significant differences in the experimental group compared to the placebo group. Third, the analysis was stratified into two subgroups by administered dose. Patients receiving doses of curcuminoids ≥300 mg dL^{-1} showed a significant decrease in FBG (SMD = −0.577, 95% CI = −1.039 to −0.115 mg dL^{-1}, $P = 0.014$) compared to those taking <300 mg dL^{-1} (Fig. 4c). Fourth, two subgroups were created according to study duration. Patients who received the drug intervention for more than 12 weeks (≥12 weeks) showed a significant decrease in FBG (SMD = −0.551, 95%

Table 1 Characteristics of studies included in the meta-analysis

Study (year)	Region	Type	Target population	Duration (weeks)	Intervention	Curcumin source	*N*	Age (years)	Male/female	BMI (kg m^{-2})
Navekar *et al.* (2017) [23]	Iran	RCT, double-blind	NAFLD/MetS	12	Turmeric 3 g day^{-1}	Turmeric powder	21	42.09 (7.23)	10/11	31.81 (4.58)
					Placebo (contained starch)		21	40.38 (9.26)	8/13	32.92 (4.81)
Kocher *et al.* (2016) [20]	Germany	RCT, cross-over double-blind	Hyperlipidaemia	6	Curcuminoids 294 mg day^{-1}	Curcumin powder	42	51.19 (NA)	17/25	26.70 (4.60)
					Placebo (contained only Tween-80)		42	51.19 (NA)	17/25	26.80 (4.60)
Panahi *et al.* (2016) [44]	Iran	RCT	NAFLD/MetS	8	Curcumin complex 1 g day^{-1}	Curcumin complex	44	44.98 (12.59)	24/20	28.97 (3.42)
					Placebo (contained inert substance lactose)		43	47.21 (10.29)	27/16	29.07 (3.48)
Rahimi *et al.* (2016) [25]	Iran	RCT, double-blind	Type 2 diabetes	12	Nano-curcumin 80 mg day^{-1}	Nano-micelle curcumin	35	56.34 (11.17)	17/18	26.92 (2.71)
					Placebo		35	60.95 (10.77)	14/21	27.27 (3.59)
Rahmani *et al.* (2016) [24]	Iran	RCT, double-blind	NAFLD/MetS	8	Curcumin 70 mg day^{-1}	Curcuminoids	37	46.37 (11.57)	19/21	30.84 (4.45)
					Placebo		40	48.95 (9.78)	19/21	31.35 (5.67)
Amin *et al.* (2015) [29]	Pakistan	RCT, double-blind	MetS	8	Turmeric 2.4 g day^{-1}	Turmeric powder	63	42.40 (13.70)	63/0	28.10 (5.00)
					Placebo (contained Ispaghula)		63	41.57 (12.80)	63/0	27.50 (4.12)
Mirzabeigi *et al.* (2015) [21]	Iran	RCT, double-blind	CAD	8	Curcuminoids 2 g day^{-1}	Curcumin C3 complex	17	61.50 (8.70)	10/7	27.94 (3.62)
					Placebo		16	64.30 (8.42)	14/2	28.50 (3.67)
Maithili *et al.* (2014) [26]	Indian	RCT, open label	Type 2 diabetes	4	Metformin, turmeric 2 g day^{-1}	Turmeric powder	30	47.00 (7.17)	30/0	23.40 (3.03)
					Metformin		30	46.80 (6.10)	30/0	24.10 (3.26)
Yang *et al.* (2014) [28]	China	RCT, double-blind	MetS	12	Curcumin 1890 mg day^{-1}	Curcumin extract	33	59.03 (10.10)	12/21	30.61 (4.15)
					Placebo		32	59.61 (14.09)	17/15	28.78 (4.88)
Chuengsamarn *et al.* (2014) [19]	Thailand	RCT, double-blind	Type 2 diabetes	12	Curcuminoids 1.5 g day^{-1}	Turmeric powder	107	59.16 (1.07)	50/57	27.09 (0.52)
					Placebo (contained starch)		106	59.58 (1.04)	47/59	26.84 (0.42)
Kim *et al.* (2013) [30]	Korea	RCT, double-blind	High ALT	12	Turmeric 3 g day^{-1}	Fermented turmeric	30	39.00 (8.50)	28/2	26.80 (3.30)
					Placebo		30	36.20 (7.40)	28/2	27.40 (3.50)
Chuengsamarn *et al.* (2012) [18]	Thailand	RCT, double-blind	Type 2 diabetes	12	Curcuminoids 1.5 g day^{-1}	Turmeric powder	119	56.95 (12.00)	42/77	26.66 (5.24)
					Placebo		116	57.93 (12.70)	41/75	26.62 (5.50)
Na *et al.* (2012) [22]	China	RCT, double-blind	Type 2 diabetes	12	Curcuminoids 300 mg day^{-1}	Curcuminoids	50	55.42 (6.40)	24/26	27.12 (2.26)
					Placebo (contained starch)		50	54.72 (8.34)	25/25	27.42 (3.04)
Usharani *et al.* (2008) [27]	India	RCT	Type 2 diabetes	8	Curcumin 600 mg day^{-1}	C3 curcuminoids	23	55.52 (10.76)	12/11	24.66 (2.42)
					Placebo		21	49.75 (8.18)	11/10	23.98 (2.35)

ALT, alanine transaminase; CVD, cardiovascular diseases; MetS, metabolic syndrome; NA, not available; NAFLD, nonalcoholic fatty liver disease; RCT, randomised controlled trial.
Values are expressed as the mean (SD).

Table 2 The pre- and post-intervention glucose metabolism parameters in the included studies

			Experimental		Control	
Study	Outcome	Unit	Before	After	Before	After
Navekar *et al.* (2017) [23]	FBG	mg dL^{-1}	92.80 (22.98)	85.23 (13.44)	85.23 (10.06)	86.28 (9.34)
	HOMA-IR	no unit	3.12 (1.06)	2.48 (0.89)	2.97 (1.25)	3.08 (1.17)
	Insulin	μU mL^{-1}	13.83 (4.20)	11.82 (3.97)	14.08 (5.06)	14.36 (4.86)
Kocher *et al.* (2016) [20]	FBG	mg dL^{-1}	89.50 (9.10)	91.90 (10)	89.20 (9.40)	92.50 (9.50)
	HOMA-IR	no unit	2.00 (1.01)	2.00 (1.2)	1.70 (1.00)	1.90 (0.80)
	Insulin	μU mL^{-1}	9.00 (4.70)	8.90 (4.50)	7.80 (4.10)	8.50 (3.10)
Panahi *et al.* (2016) [44]	FBG	mg dL^{-1}	107.61 (30.26)	100.27 (11.92)	106.61 (25.67)	99.33 (10.27)
	HbA1c	%	6.17 (1.37)	5.95 (1.13)	6.06 (1.03)	5.77 (0.53)
	HOMA-IR	no unit	3.58 (2.75)	3.00 (1.15)	2.86 (1.42)	2.59 (0.74)
	Insulin	μU mL^{-1}	12.57 (4.16)	11.90 (3.37)	10.66 (2.98)	10.53 (2.64)
Rahimi *et al.* (2016) [25]	FBG	mg dL^{-1}	135.50 (51.33)	120.29 (38.01)	148.30 (76.41)	176.00 (61.56)
	HbA1c	%	7.59 (1.74)	7.31 (1.54)	7.49 (1.75)	9.00 (2.33)
Rahmani *et al.* (2016) [24]	FBG	mg dL^{-1}	111.65 (34.64)	107.57 (28.34)	116.90 (47.66)	118.18 (47.35)
	HbA1c	%	6.31 (1.62)	5.53 (1.27)	7.37 (1.33)	7.53 (1.43)
Amin *et al.* (2015) [29]	FBG	mg dL^{-1}	117.00 (12.7)0	116.10 (19.60)	119.10 (15.30)	116.10 (24.50)
Mirzabeigi *et al.* (2015) [21]	FBG	mg dL^{-1}	141.06 (55.20)	122.50 (35.68)	105.38 (32.27)	116.46 (24.96)
Maithili *et al.* (2014) [26]	FBG	mg dL^{-1}	116.00 (23.00)	95.00 (11.40)	111.00 (24.00)	102.00 (18.00)
	HbA1c	%	7.90 (1.30)	7.40 (0.90)	7.80 (0.50)	7.50 (0.70)
	HOMA-IR	no unit	5.10 (2.70)	4.00 (2.30)	6.40 (4.00)	4.70 (2.20)
	Insulin	μU mL^{-1}	18.00 (9.90)	22.00 (12.00)	23.00 (16.40)	19.00 (13.00)
Yang *et al.* (2014) [28]	FBG	mg dL^{-1}	112.75 (18.85)	114.82 (16.15)	117.53 (27.63)	124.32 (11.91)
	HbA1c	%	6.32 (0.91)	6.20 (0.73)	6.41 (1.03)	6.56 (1.06)
Chuengsamarn *et al.* (2014) [19]	HOMA-IR	no unit	6.12 (3.68)	4.05 (2.10)	5.63 (2.25)	5.92 (2.25)
Kim *et al.* (2013) [30]	FBG	mg dL^{-1}	91.90 (9.70)	93.00 (12.60)	90.10 (8.70)	89.60 (8.70)
Chuengsamarn *et al.* (2012) [18]	FBG	mg dL^{-1}	103.65 (10.80)	96.11 (7.00)	103.24 (10.55)	106.88 (8.17)
	HbA1c	%	5.86 (0.43)	5.77 (0.23)	5.83 (0.32)	5.92 (0.32)
	HOMA-IR	no unit	4.03 (2.51)	3.60 (1.87)	3.85 (2.25)	3.97 (2.17)
	Insulin	μU mL^{-1}	15.32 (9.50)	15.22 (1.30)	15.25 (9.13)	15.22 (1.34)
Na *et al.* (2012) [22]	FBG	mg dL^{-1}	154.44 (47.88)	131.04 (31.86)	151.38 (39.06)	147.06 (37.08)
	HbA1c	%	7.77 (1.82)	7.02 (2.04)	7.72 (2.12)	7.99 (2.86)
	HOMA-IR	no unit	5.80 (3.35)	4.14 (1.81)	5.82 (3.90)	5.49 (2.15)
Usharani *et al.* (2008) [27]	FBG	mg dL^{-1}	155.04 (17.94)	150.17 (18.84)	161.19 (19.97)	158.14 (17.38)
	HbA1c	%	8.04 (0.85)	8.03 (0.76)	7.82 (0.57)	7.80 (0.62)

FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance.
Data are shown as the mean (SD).

CI = −0.969 to −0.133 mg dL^{-1}, $P = 0.01$) compared to those receiving shorter interventions (Fig. 4d).

Eight of the 14 trials reported analyses of HbA1c ($n = 731$ cases and controls in total); these analyses indicated a significant reduction in HbA1c concentrations (SMD = −0.370, 95% CI = −0.631% to −0.110%, $P = 0.005$, $I^2 = 64.7\%$) (Fig. 5a). To explore the heterogeneity, we stratified the analysis into two subgroups on the basis of the underlying diseases (a MetS subgroup and a diabetes subgroup). Data analysis of five studies with diabetes patients showed a favourable effect on HbA1c (SMD = −0.455, 95% CI = −0.713% to −0.198%, $P = 0.001$). However, three studies with MetS patients showed no significant differences between the experimental and control groups. In addition, subgroup analysis according to form of treatment showed a significant effect of curcuminoids in lowering HbA1c concentrations in patients (SMD = −0.414, 95% CI = −0.665% to −0.164%, $P = 0.001$). Furthermore, subgroup analyses stratified by administered dose indicated that patients taking curcuminoids doses ≥300 mg day^{-1} showed a significant decrease in HbA1c (SMD = −0.322, 95% CI = −0.588% to −0.056%, $P = 0.018$) compared to those taking <300 mg day^{-1}. Another subgroup analysis by study duration revealed that patients who received drug interventions over long periods (≥12 weeks) showed a significant reduction in HbA1c (SMD = −0.488, 95% CI = −0.790% to −0.185%, $P = 0.002$). The complete outcomes of the subgroup analyses for HbA1c are shown in Table 3.

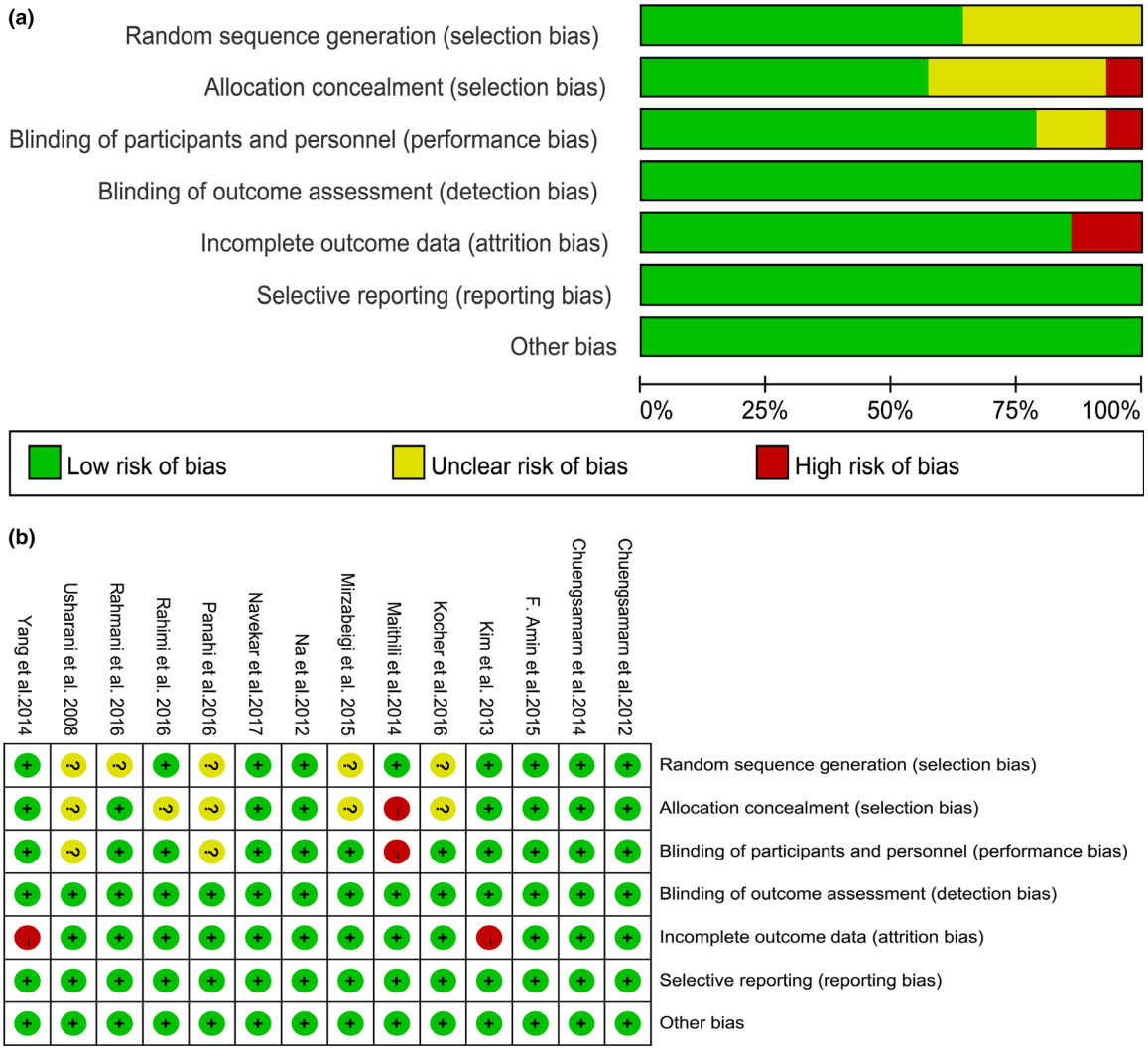

Figure 2 Risk of bias assessment for the included studies. (a) Risk of bias graph. (b) Risk of bias summary. The colour green and the plus (+) symbol represent a low risk of bias. The colour yellow and the question mark (?) symbol represent an unclear risk of bias. The colour red and the minus (−) symbol represent a high risk of bias.

A meta-analysis of seven trials, including 821 subjects, showed an obvious decrease in HOMA-IR in the experiment group compared to the control group (SMD = −0.351, 95% CI = −0.615 to −0.087, P = 0.009, I^2 = 68.9%) (Fig. 5b). To assess the sources of any underlying biases, we performed subgroup analyses by disease, form of treatment, administered dose and duration of intervention. First, we divided the included studies into two subgroups: the MetS subgroup and the diabetes subgroup. Patients in the MetS subgroup from three studies showed a significant change in HOMA-IR in the experimental group (SMD = −0.284, 95% CI = −0.554 to −0.013, P = 0.04) but not in the placebo group. Second, data analysis of four studies revealed an obvious effect of curcuminoid therapy on HOMA-IR (SMD = −0.44, 95% CI = −0.767 to −0.113, P = 0.008). Conversely, two studies showed no significant benefits of turmeric extract in the intervention group compared to the control group. Third, with regard to the administered dose, subjects supplemented with curcuminoid doses ≥300 mg day^{-1} showed a significant reduction in HOMA-IR (SMD = −0.508, 95% CI = −0.903 to −0.112, P = 0.012). Finally, we performed a meta-analysis with subgroups based on study duration. Significant treatment effects were observed in the subgroup of long-term studies (≥12 weeks) (SMD = −0.534, 95% CI = −0.864 to −0.203, P = 0.002) but not in the subgroup of short-term studies (<12 weeks). Table 3 shows the complete results of the subgroup analyses for HOMA-IR.

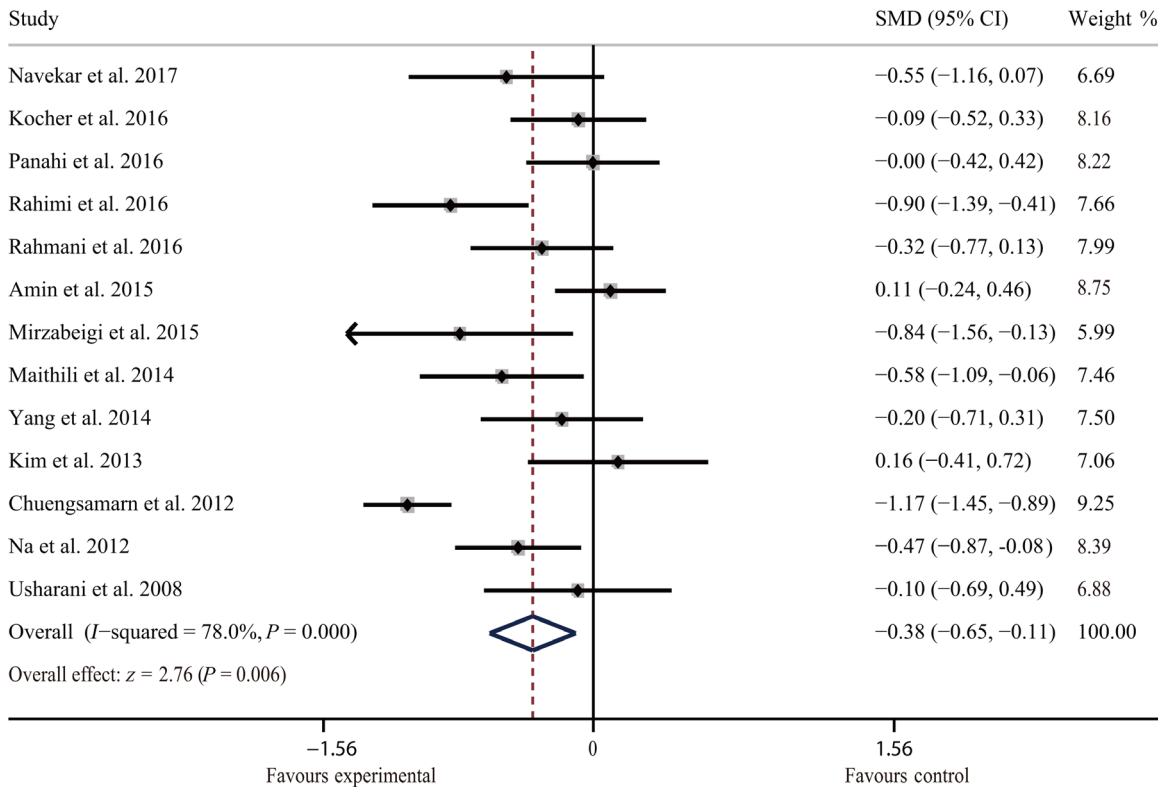

Figure 3 Forest plot of the meta-analysis for the comparison of fasting blood glucose concentrations between the experimental and control groups. CI, confidence interval; SMD, standardised mean difference.

Regarding insulin concentrations, the quantitative synthesis of data from five studies including 507 subjects failed to show any significant effect of the experimental treatment over the control treatment. The pooled estimate of the change in insulin after drug administration was −0.058 (95% CI = −0.352 to 0.235) μU mL^{-1}; $P = 0.697$ (see Supporting information, Figure S1).

Sensitivity analysis

The stability of the observed effect size was assessed by leave-one-out cross-validation. Removing each of the including RCT from the meta-analysis did not influence the robustness of the statistically significant combined effect size for the impact of supplemental curcumin or combined curcuminoids on glucose metabolism parameters. Heterogeneity was markedly reduced when the study by Chuengsamarn *et al.* [18] was removed, although the significant effect of supplementation on FBG concentrations did not change. Regarding the HbA1c analysis, when we excluded the studies by Panahi *et al.* [44] and Rahimi *et al.* [25], the heterogeneity was significantly reduced. However, the exclusions did not change the results of the quantitative data synthesis. With respect to the impact on HOMA-IR, the study by Chuengsamarn *et al.* [19] played a large role in the heterogeneity, although its exclusion did not change the result. When the study by Maithili *et al.* [26] was removed, the heterogeneity of the insulin analysis was significantly reduced without any change in the effect size.

Safety

Curcumin or combined curcuminoids were reported to be safe and well tolerated in the studies included in this meta-analysis. As shown in the Supporting information (Table S2), a small number of adverse events were reported in the treatment groups, and all of these effects were of mild intensity and short duration. The remaining studies reported no adverse effects in the experimental groups. No study in this meta-analysis reported any serious adverse reactions induced by curcumin or combined curcuminoids.

Publication bias

The overall potential publication bias for FBG among the included RCT was assessed by Begg's rank correlation test

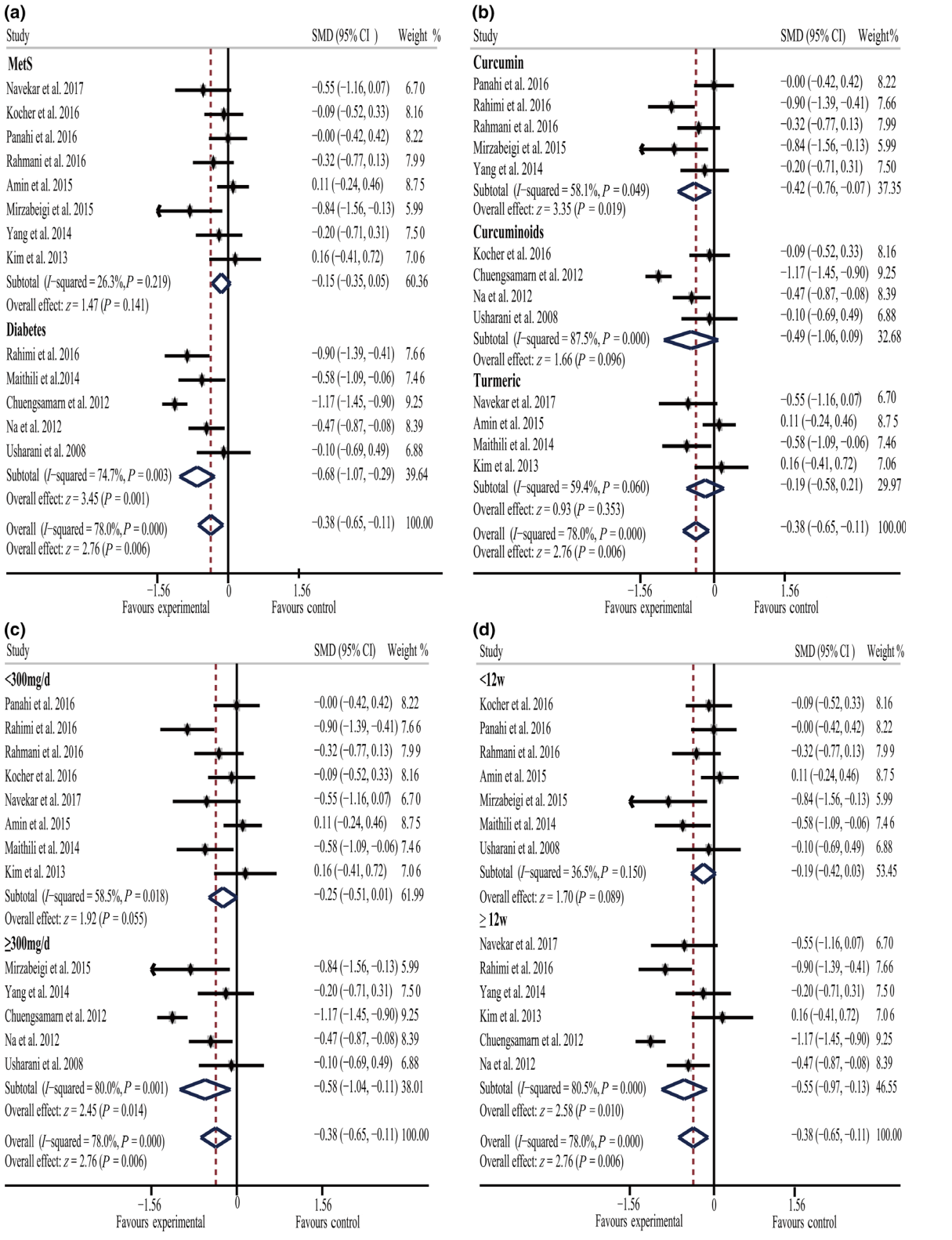

Figure 4 Forest plot of the subgroup analyses for fasting blood glucose stratified by (a) type of underlying disease, (b) Form of intervention, (c) administered dose and (d) duration of study. CI, confidence interval; SMD, standardised mean difference.

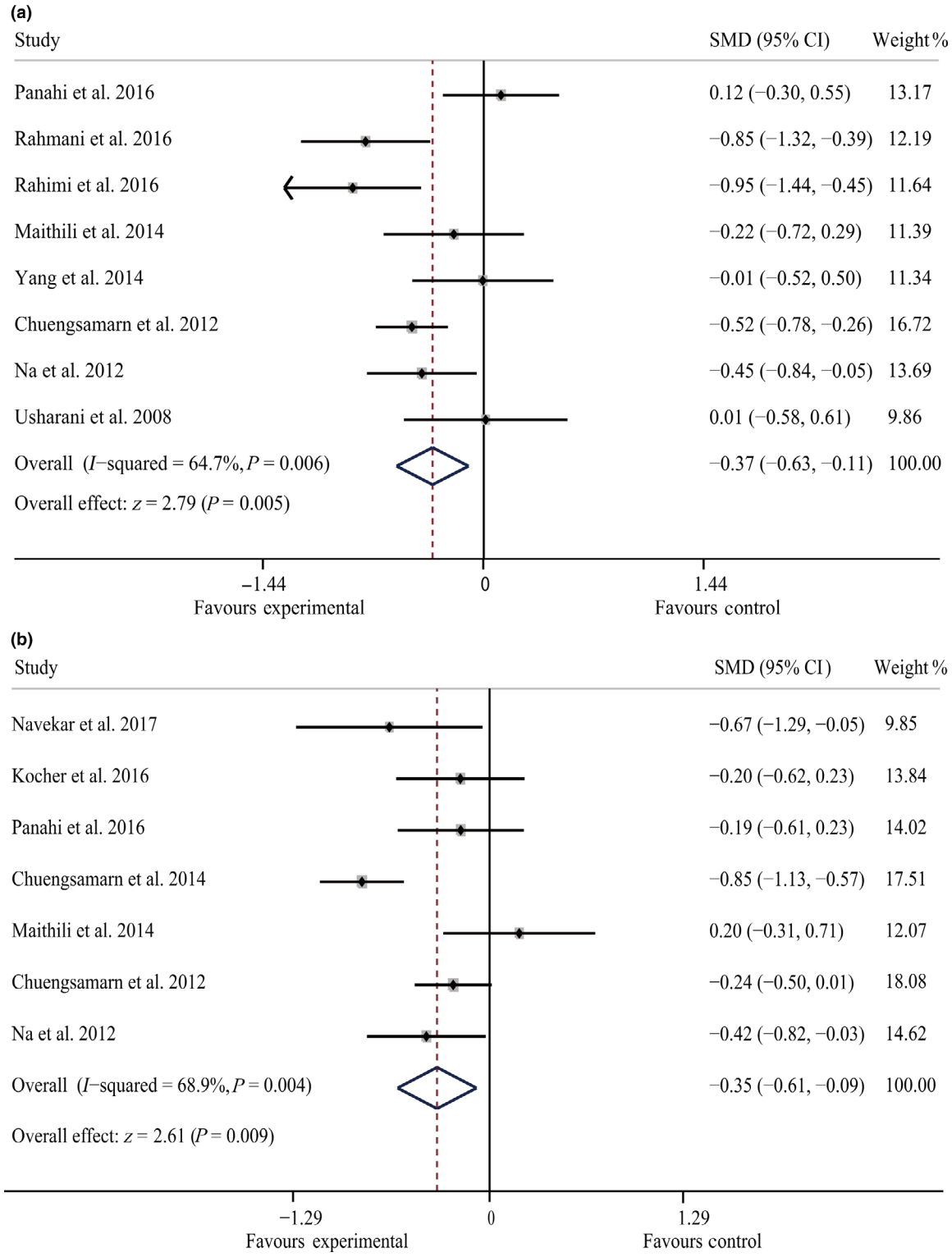

Figure 5 Forest plot of the meta-analysis for the comparison of glycated haemoglobin (HbA1c) and homeostatic model assessment of insulin resistance (HOMA-IR) between experimental and control groups. (a) HbA1c. (b) HOMA-IR. CI, confidence interval; SMD, standardised mean difference.

Table 3 The complete results of the subgroup analyses

Outcome of interest	Number of studies	Number of patients	SMD	95% CI	Overall effect		Heterogeneity	
					Z value	*P* value	I^2 (%)	*P* value
FBG								
Type of disease								
MetS	8	556	−0.149	−0.348 to 0.049	1.47	0.141	26.30%	0.219
Diabetes	5	509	−0.681	−1.067 to −0.294	3.45	0.001**	74.70%	0.003
Form of intervention								
Curcumin	5	326	−0.417	−0.765 to −0.069	2.35	0.019*	58.10%	0.049
Curcuminoids	4	463	−0.486	−1.058 to 0.086	1.66	0.096	87.50%	0.000
Turmeric	4	276	−0.187	−0.580 to 0.207	0.93	0.353	59.40%	0.060
Duration of study								
12 weeks	7	511	−0.195	−0.419 to 0.030	1.70	0.089	36.50%	0.150
≥12 weeks	6	554	−0.551	−0.969 to −0.133	2.58	0.010*	80.50%	0.000
Administered dose								
<300 mg day^{-1}	8	594	−0.252	−0.509 to 0.006	1.92	0.055	58.50%	0.018
≥300 mg day^{-1}	5	471	−0.577	−1.039 to −0.115	2.45	0.014*	80.0%	0.001
HbA1c								
Type of disease								
MetS	3	223	−0.244	−0.854 to 0.366	0.78	0.433	80.60%	0.006
Diabetes	5	478	−0.455	−0.713 to −0.198	3.47	0.001**	44.90%	0.120
Form of intervention								
Curcumin	4	293	−0.417	−0.972 to 0.138	1.47	0.141	81.90%	0.001
Curcuminoids	3	378	−0.414	−0.665 to −0.164	3.24	0.001**	23.80%	0.269
Duration of study								
<12 weeks	4	268	−0.237	−0.692 to 0.217	1.02	0.306	70.70%	0.017
≥12 weeks	4	463	−0.488	−0.790 to −0.185	3.16	0.002*	56.00%	0.078
Administered dose								
<300 mg day^{-1}	4	294	−0.467	−0.989 to 0.055	1.75	0.079	79.60%	0.002
≥300 mg day^{-1}	4	437	−0.322	−0.588 to −0.056	2.37	0.018*	39.70%	0.173
HOMA-IR								
Type of disease								
MetS	3	213	−0.284	−0.554 to −0.013	2.06	0.04*	0.00%	0.403
Diabetes	4	608	−0.360	−0.762 to 0.043	1.75	0.080	82.00%	0.001
Form of intervention								
Curcuminoids	4	632	−0.440	−0.767 to −0.113	2.64	0.008*	74.50%	0.008
Turmeric	2	102	−0.216	−1.065 to 0.633	0.50	0.618	77.70%	0.034
Duration of study								
<12 weeks	3	231	−0.092	−0.351 to 0.166	0.70	0.485	0.00%	0.428
≥12 weeks	4	590	−0.534	−0.864 to −0.203	3.16	0.002*	70.90%	0.016
Administered dose								
<300 mg day^{-1}	4	273	−0.185	−0.482 to 0.112	1.22	0.223	33.5%	0.211
≥300 mg day^{-1}	3	548	−0.508	−0.903 to −0.112	2.51	0.012*	80.1%	0.007

FBG, fasting blood glucose; HbA1c, glycated haemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; MetS, metabolic syndrome; SMD, standardised mean difference.
*$P < 0.05$; **$P < 0.001$; ***$P < 0.0001$.

($P_r > |z| = 0.464$) and Egger's linear regression ($P = 0.269$). As shown in Fig. 6, there was no obvious publication bias.

Discussion

MetS and DM (usually manifested as abnormal glucose metabolism) are closely related to morbidity and mortality from CVD [1]. Impaired glucose metabolism, including abnormal blood glucose concentrations, elevated HbA1c, decreased insulin concentrations and impaired glucose tolerance, is a strong risk factor for CVD [3]. Because of the inherent drawbacks of the currently available treatments for glycaemic abnormalities, it is crucial to concentrate on discovering natural therapies that improve glucose metabolism.

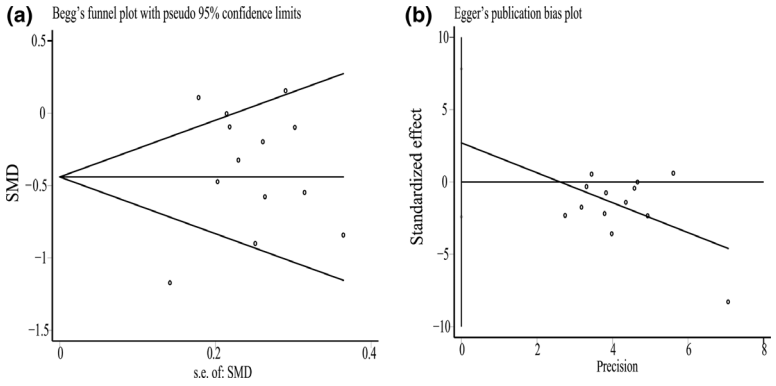

Figure 6 Overall publication bias among the included RCT for fasting blood glucose results. (a) Begg's rank correlation test. (b) Egger's linear regression. SMD, standardised mean difference.

In the present meta-analysis of RCT, we found significant reductions in FBG, HbA1c and HOMA-IR concentrations following supplementation with curcumin or combined curcuminoids, although there was no significant difference in insulin concentrations. Most of the included studies were of high quality, reinforcing the current findings. However, a number of problems in the analysis reduced the universality of these findings. First, significant heterogeneity was a major issue in the analysis of glucose metabolism. We performed sensitivity analysis and subgroup analyses to address this issue, and we also used a random-effects model to compensate for heterogeneity. Individuals with diabetes showed greater reductions than subjects with MetS in terms of FBG and HbA1c concentrations after the intervention. With regard to the administered agent, curcumin or combined curcuminoid supplementation had greater positive effects than turmeric supplementation among subjects with cardiovascular risk factors. It appears that turmeric will 'dilute' the results because it contains only 3%–5% curcumin(oids), [45] and both the profiles of active compounds and the administered doses were very diverse, likely demonstrating a dose effect. Subgroup analyses by administered dose were conducted to assess the effect. It is worth noting that a 300 mg day^{-1} supplementation of curcuminoids is the minimum effective dose that produces glycaemic control effects [46,47]. We found that patients receiving doses of curcuminoids ≥300 mg day^{-1} showed a significant decrease in FBG, HbA1c and HOMA-IR concentrations compared to those taking <300 mg day^{-1}. The glycaemic control effect of curcuminoids appears to be dose-dependent. As shown in the subgroup analysis stratified by the study duration, there was a significantly greater effect of supplementation on FBG, HbA1c and HOMA-IR concentrations in long studies (≥12 weeks) than in short studies. It appears that a long treatment period is needed to achieve changes in glucose metabolism within the safe range of doses. In addition, removing certain studies [18,19,25,26,44] led to a decrease in heterogeneity, although this did not influence the robustness of the statistically significant combined effect size.

A previous meta-analysis of 11 RCT evaluating the effects of curcumin on FBG and HbA1c concentrations was performed by Melo *et al.* [31]; this previous work was similar to the present meta-analysis in some respects and different in others. Similar to the results of the previous study, we reported that there was a significant decrease in the FBG and HbA1c concentrations of the individuals assigned to the curcumin experimental groups compared to the control groups. However, the data analysis by Melo *et al.* [31] found no significant changes in HOMA-IR among subjects who received curcumin, contradicting the results of the current meta-analysis. Because this previous data analysis was relatively small (including only three trials), it was underpowered to detect the effect of curcumin on HOMA-IR. Furthermore, we pooled data from five RCT to assess the effects of curcumin on insulin concentrations and found no significant improvements following curcumin supplementation. By contrast to the prior meta-analysis, subgroup analyses by administered dose indicated that the antidiabetic effect of curcuminoids appears to be dose-dependent (≥300 mg day^{-1}). We also stratified the included RCT into two subgroups according to study duration, which we found to be an important factor of treatment. Our results suggest that a long period (≥12 weeks) of curcumin treatment, within the safe range of doses, has greater positive effects than short treatment on glucose metabolism in patients at risk for CVD. In addition, Melo *et al.* [31] showed significant evidence of publication bias (Egger's coefficient = −3.53, 95% CI = −6.60 to −0.46, $P = 0.02$) as a result of several studies with small sample sizes. By contrast, there is no obvious publication bias (Begg's test, $P_r > |z| = 0.464$;

Egger's test, $P = 0.269$) in the present systematic analysis, and we included several additional studies of high quality and large size to increase the reliability of the results [21–23,26].

There are some possible molecular mechanisms that might explain these results. First, inflammation is a key factor in the development of insulin resistance and T2DM, and the effect of curcumin with respect to improving glucose metabolism is partly as result of the inhibition of inflammation by suppressing the nuclear factor-kappa B and c-Jun N-terminal kinase inflammatory signalling pathways [16,48]. In short, the anti-inflammatory activity of curcumin could play an important role in its anti-diabetic effect. Second, considerable studies have indicated that fat deposition in islets causes the deterioration of pancreatic beta cell functions (lipotoxicity) and insulin sensitivity has been associated with abnormal lipid metabolism [49,50]. Curcumin appears to improve insulin sensitivity and glucose metabolism by the amelioration of lipid metabolism via interaction with multiple targets, including peroxisome proliferator-activated receptor alpha, peroxisome proliferator-activated receptor gamma [51], cholesteryl ester transfer protein [52] and lipoprotein lipase [22]. Third, the hypoglycaemic effect of curcumin on T2DM is partly achieved by decreasing serum free fatty acids [53] because elevated free fatty acids lead to the accumulation of various lipid metabolites in the liver and skeletal muscle, which interfere with insulin signal transduction and inhibit insulin-stimulated glucose uptake and glycogen synthesis [54]. Fourth, curcumin also inhibits glucose production by increasing the activation of AMP kinase and inhibiting the activity of glucose-6-phosphatase and phospho-enolpyruvate carboxykinase [15,55]. Fifth, curcumin was shown to increase the electrical activity of pancreatic beta cells, resulting in insulin release [56]. Finally, curcumin can improve blood glucose and HbA1c by decreasing the production and synthesis of hepatic glucose and by stimulating glucose uptake [57]. In summary, these molecular mechanisms could explain the beneficial effects of curcumin on glucose metabolism.

Curcumin and combined curcuminoids were generally safe and well tolerated in this meta-analysis, consistent with the results of previous studies [58,59]. Dosages as high as 8000 mg day^{-1} have been shown to be well tolerated without obvious toxicity and can be used for at least 9 months with no serious adverse effects [18,60].

Some potential limitations of this meta-analysis must be discussed. First, the number of studies available on this topic was relatively small and most of the studies had very small sample sizes. The non-English literature should be included in future meta-analyses because some studies might have been excluded as a result of the language restriction. Second, we did not search the grey literature database and might have missed several unpublished studies. Third, some data were obtained indirectly, such as with formula transformations, using values in graphs and sending e-mails to authors, which might have influenced the accuracy of the results of the meta-analysis. Fourth, in some publications, the content of the placebo was not described. In one publication, the placebo was ispaghula, a fibre, which can also influence the blood sugar concentrations [61], causing unclear bias. Finally, the eligible articles were inhomogeneous in various ways, such as the diseases of the subjects, the dose and bioavailability of curcumin, the form of the intervention, and the study duration. Although the predefined subgroup analyses were performed, we should be cautious when interpreting some of the subgroup results as a result of the small number of subjects.

Conclusions

The findings of our meta-analysis suggested a promising effect of curcumin or combined curcuminoids on glucose metabolism in patients at risk for CVD. Individuals with diabetes showed greater benefits than subjects suffering from MetS in terms of reduced FBG and HbA1c concentrations following the intervention. Subjects who received curcumin showed a decrease in FBG concentrations compared to those who did not, and curcuminoid supplementation had reduced effects on HbA1c and HOMA-IR concentrations. Patients receiving doses of curcuminoids $\geq$300 mg day^{-1} showed a significant decrease in FBG, HbA1c and HOMA-IR concentrations compared to those taking <300 mg day^{-1}. Curcumin or curcuminoid supplementation had significantly greater effects on FBG, HbA1c and HOMA-IR concentrations over long periods ($\geq$12 weeks) compared to over short periods. No significant change in insulin concentrations was observed. Based on these results, curcumin could be a safe potential candidate for improving glucose metabolism. Nonetheless, further robust RCTs in larger populations are required to confirm the long-term stability of the clinical improvement.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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no influence on the research design, the data collection and analysis, the drafting of the manuscript or the decision to publish.
JH, RH and HDH conceived and designed the study. JH and SQ searched the literature and extracted the data. JH and SQ conducted statistical analysis. JH, SQ, LFH, YT and HDH wrote the manuscript; YXY, HR and HDH revised it. All authors read and approved the final manuscript.

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 the PRISMA statement and checklist [32]. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned (protocol has been registered with PROSPERO: ID number CRD42018104671) have been explained.

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Supporting information

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

Figure S1. Forest plot of the meta-analysis for comparison of insulin concentrations between the experimental and control groups.
Table S1. Baseline characteristics of the study subjects in the included studies.
Table S2. Number of subjects in the included studies reporting adverse events during supplementation with curcumin or combined curcuminoids.

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CARDIOVASCULAR DISEASE

Effectiveness and easiness of adherence to behavioural guidelines for diet and lifestyle changes for cholesterol-lowering: the Increasing Adherence of Consumers to Diet & Lifestyle Changes to Lower (LDL) Cholesterol (ACT) randomised controlled trial

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Keywords
adherence, cholesterol-lowering, dietary advise, easiness, lifestyle behaviour.

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Abstract

Background: The present study aimed to assess perceived effectiveness and easiness of behavioural diet and lifestyle changes related to dyslipidaemia given by physicians or dieticians as a result of diet and lifestyle modifications being difficult to maintain.
Methods: One-hundred hypercholesterolaemic individuals were enrolled in a parallel, randomised 6-week study. Fifty were advised by dietitians (dietitian group: DG) in six weekly face-to-face behavioural therapy sessions and 50 received standard advice from physicians (physician group: PG). All individuals were followed-up for another 6 weeks under real-life conditions. Questionnaires regarding perceived effectiveness, easiness of adhering, forecasted and actual adherence to specific cholesterol-lowering advice were completed.
Results: Scores of perceived effectiveness of advice for sufficient exercise, limiting saturated fat (SFA) intake, eating fish twice a week, consuming plenty of fresh fruit and vegetables, and limiting salt intake different scientifically (all $P < 0.05$) in PG and DG between study phases. Scores of the individuals' perception of effectiveness at all study phases were higher in the DG compared to PG for sufficient exercise, limiting SFA intake, eating fish twice a week, eating plenty of fruits and vegetables, and limiting salt intake, whereas scores of easiness were significant only for fish consumption ($P = 0.008$) and using foods with added plant sterols (all $P < 0.05$). DG and PG significantly differed in forecasted (week 6) versus actual adherence (week 12) to various chances, with DG reporting higher adherence.
Conclusions: Lifestyle and dietary changes related to dyslipidaemia can be achieved with continuous education, monitoring and follow-ups by dieticians, as well as potentially other trained healthcare professionals.

Introduction

Major modifiable risk factors, including obesity, poor dietary habits, physical inactivity, tobacco use and dyslipidaemia, increase the risk of cardiovascular disease (CVD) by 50–75% [1–3], underlying the need for effective intervention approaches that improve lifestyle and dietary behaviours [4].

In recent years, the effect of diet and lifestyle changes on blood lipid levels has been extensively reviewed [5]. Nutritional and behaviour changes have been shown to lower low-density lipoprotein-cholesterol (LDL-C) levels by up to 20% [6], and the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), in their joint ESC/EAS guidelines, have recently stated that dietary modifications should form the basis for dyslipidaemia management [6] and CVD prevention [7]. In their guidelines, they also emphasise the need to establish cognitive-behavioural strategies for lifestyle changes via the multidisciplinary involvement of healthcare professionals. However, although the benefits of diet and lifestyle changes, including regular physical exercise and intake of plant sterols for lowering or maintaining optimal LDL-C levels are clear [6,8], considerable debate remains in the scientific literature regarding the 'optimal' strategy for increasing compliance and adherence changes.

Interventions that provide education plus tailored or instructional components (e.g. feedback) to individuals have been shown to be more effective than education alone or nontailored advice [4,5]. According to Mannu *et al.* [9], the best approach appears to be clear patient communication in a professional healthcare setting. Brief dietary interventions are more cost-effective compared to longer multisession interventions as a result of the reduced time and expertise required for implementation [10,11]. On the other hand, the limited availability of time makes them unable to include a multitude of behaviour change techniques, hence limiting their long-term efficacy [4]. Low adherence rate in lifestyle changes, including diet and physical activity, therefore remains a major challenge in most studies [3,12,13].

The 'Increasing Adherence of Consumers to Diet & Lifestyle Changes to Lower (LDL) Cholesterol (ACT)' randomised controlled trial aimed to improve blood lipid levels in mildly-to-moderately hypercholesterolaemic individuals via structured dietary advice provided by either a dietician or physician, as well as to provide valuable information for healthcare professionals on methods of increasing patient's compliance to lifestyle and dietary changes. The findings concerning blood lipid changes and improvement of dietary habits and physical activity have been reported previously [14]. The aim of the present study was to assess the perceived effectiveness and easiness of the specific dietary and behavioural guidance given by physicians or dietitians at specific time intervals as part of the ACT study and also to examine actual and perceived (forecasted) compliance.

Materials and methods

Study design and study participants

The ACT study was a randomised controlled study for which the study design details have been reported previously [14]. In summary, the study included three phases: (i) a face-to-face consultation with a physician for screening and baseline serum lipid measurements (Phase 0); (ii) a 6-week intervention period under the supervision of a dietitian (dieticians group: DG) or physician (physicians group: PG) (Phase I); and (iii) a 6-week follow-up period under real life conditions (Phase II).

Physicians and dietitians were trained with respect to the study protocol procedures, toolkits and measurements. Dietitians were also trained to provide six face-to-face behavioural therapy sessions. Physicians provided usual care by standard advice based on national guidelines without any further counselling.

Briefly, study participants were recruited at the Centre for Cardiovascular Disease Prevention, Hygeias Melathron Infirmary, at the Department of Cardiology, Euroclinic and at Errikos Dunant, Hospital Centre (all in Athens, Greece). Recruitment of physicians and dietitians and the participants screening was conducted from September to December 2014. The intervention and follow-up periods lasted from January to August 2015. Individuals were recruited among inhabitants of Athens and surroundings via advertisements. In total, 100 study participants, (40% males) were allocated to the two intervention groups (PG and DG), each consisting of 50 individuals. Ethical approval for the study was obtained from the Bioethics Committee of the Agricultural University of Athens. All participants provided their written informed consent.

Key inclusion criteria were defined as age between 45 and 70 years, being of normal weight or overweight, having borderline to mildly elevated total cholesterol (TC) levels of between 200 and 250 mg dL^{-1} (5.18–6.47 mmol L^{-1}), triglycerides (TG) <300 mg dL^{-1} (<3.39 mmol L^{-1}) and systolic blood pressure <160 mmHg, as defined by the EAS/ESC guidelines for the management of dyslipidaemia [6], not taking cholesterol-lowering or anti-diabetic medication, and not consuming foods or supplements containing plant sterols (PS) or plant stanols. Major exclusion criteria were having a body mass index (BMI) <20 or >30 kg m^{-2}, having familial hypercholesterolaemia or a history of phytosterolaemia, the presence of severe concomitant diseases, and being

previously diagnosed with a coronary event. Other exclusion criteria included having food allergies or dietary restrictions, being smokers, following intense sport activities (>10 h week^{-1}) and being high alcohol consumers (female >21 units week^{-1}; male >28 units week^{-1}).

Dietary intervention and dietary advice

Participants were provided foods with added PS [choice of either three servings of spread (30 g) or two servings of spread (20 g) and one serving milk (250 mL) or two servings of spread (20 g) and one serving yoghurt (125 g) the 6-week intervention].

During the inclusion visit (Phase 0), physicians completed a health assessment questionnaire containing the participant's last available serum lipid parameters [TC, LDL-C, high-density lipoprotein (HDL-C) and TG] and the participant's record sheet comprising gender, age and baseline measurements of weight, height, BMI and blood pressure (BP). Physicians provided information about the study and randomly allocated them to either the PG or DG.

At the end of week 6, all participants completed a questionnaire (regarding consumption of foods with added PS (type, frequency, quantity) and visited the physician or the clinical laboratory to give another blood sample for lipids analysis [14].

Individuals in the PG group had only one face-to-face consultation with the physician during which they received standard advice, including brief information about cholesterol, PS use and food groups that should be avoided or consumed more frequently. Participants in the DG group received counselling in six face-to-face behavioural therapy sessions of 30 min on a weekly basis. Details concerning the content and advice given in these sessions are provided in Table 1.

A cholesterol-lowering information kit that included general information about cholesterol, PS and the different food products was further provided to participants in the DG, in addition to leaflets including practical advice on healthy eating, physical activity and goal setting.

In the 6-week follow-up period (Phase II), individuals were only encouraged to continue adhering to the diet and lifestyle advice including the consumption of PS-added foods as part of their daily diet.

Questionnaires

Participants in both groups, prior to study commencement, were asked to complete a basic cholesterol

Table 1 Description of session content provided to participants by the dieticians (DG group) in the six weekly 30-min face-to-face sessions

Session	Description/content
1	• Providing general advice on healthy eating including different foods as part of a healthy diet and information on portion sizes. • Informing on reading food labels and their use to make comparisons between packaged food and recognising more easily nutrients to avoid, such as salt, saturates fat and sugars. • Providing a 6-week diet and lifestyle plan based on the principles of a Mediterranean diet. The 6-week diet plan included the use of olive oil as exclusive source of added fat, unsalted nuts and soluble fibre found in foods such as oats, oat bran, beans, pulses and fruits and recommending 3 servings of plant sterol added foods (2 g day^{-1}). • Emphasising the Mediterranean diet pattern, referring to eating more beans and pulses, two portions of fish per week and less red and processed meat, being hydrated and physically active
2	• Advising on total dietary fat intake, on the three main types of fat (i.e. saturated, monounsaturated and polyunsaturated fatty acids) and on foods that contain these three types of fat. • Encouraging to eat less saturated and trans fats and to replace them with healthier unsaturated fats and omega-3 fatty acids. • Recommending two servings of fish per week
3	• Educating on reducing salt and recognising hidden salt in food groups, adding less salt during cooking and at the table, eating less processed foods and being aware of food labels and choosing lower salt options. • Educating on alcohol consumption and long-term health risks of a high regular alcohol consumption
4	• Advising on fruits and vegetables consumption and their health benefits. • Encouraging to meet the national five-a-day fruits and vegetables target. • Educating on the essential nutrients of fruits and vegetables, according to their colours, variety, seasonality and portion sizes
5	• Informing on whole grain products and their cholesterol-lowering benefits compared to refined cereals and grains. • Educating on specific components of soluble and insoluble fibres such as, B-vitamins, folic acid and antioxidants. • Handing out a list with whole grain products (whole oats, whole wheat cereals, brown rice, whole wheat pasta), their portion sizes and ideas for daily use
6	• Educating on the health benefits of being active daily. • Encouraging to increase physical activity to 150 min week^{-1} of moderate intensity activity or 75 min of vigorous intensity activity and to improve muscle strength on at least 2 days a week. • Providing practical tips on minimising sedentary behaviour by reducing time spent watching television, using the computer and on taking regular breaks at work

knowledge questionnaire, aiming to adjust for knowledge bias during analysis. Specifically, they were asked to report a healthy cholesterol level by selecting the correct cut-off for total cholesterol. More specifically, five different options were given (<190 mg dL^{-1}; 190–250 mg dL^{-1}; 251–304 mg dL^{-1}; >305 mg dL^{-1} and 'I do not know').

At baseline (Phase 0), upon being provided with the cholesterol-lowering advice by physicians or dietitians (according to group), participants were asked to report, using specific questionnaires, their primary perceived effectiveness of diet and lifestyle changes and the effort that it would require for them to adhere. At week 6 (Phase I) and week 12 (Phase II), upon actually adhering to the advised changes for 6 and 12 weeks, respectively, they were given the same questionnaires to assess 'actual perception' of easiness and effort required, as per the aim of the study.

A third questionnaire, evaluating forecasted (the individuals' perception of future adherence) and actual adherence to guidelines, was also given. The 'forecasted adherence' questionnaire was given at week 6 and week 12, including the same type of questions. The 'actual adherence' question was included in the perception questionnaires given at week 12. All questionnaires are provided in the Supporting infromation (Tables S1-S8).

Anthropometrics and other measurements

Weight and height were measured and used to calculate the BMI. Individuals were categorised as normal weight, overweight or obese based on their BMI (18–24.9; 25–29.9 and >30 kg m^{-2}, respectively).

Physical activity was evaluated using the International Activity Questionnaire – Short Form, at weeks 1 and 6 and individuals were categorised as low, moderate and highly active, according to guidelines. Details have already been reported elsewhere [14,15].

Blood sampling and blood lipid and blood pressure measurements

Study participants attended the Department of Cardiology and Lipids at 'Euroclinic Hospital' and a cooperating clinical laboratory on three occasions for blood collection. Venous blood samples were obtained at 8 h after a 12-h overnight fast. Serum was separated by centrifugation at 1500 ***g*** at 4 °C within 30 min of blood collection in a bench centrifuge. Aliquots of serum were stored at −80 °C until analysis in the clinical laboratory, at the Agricultural University of Athens. Serum TC, LDL-C, TG and HDL-C concentrations were determined by enzymatic colorimetric assays using a Cobas Integra 800 Analyzer (Roche, Basel, Switzerland). Supine BP measurements were performed in the right arm with a standard mercury sphygmomanometer (Baumanometer; WA Baum, Copiague, NY, USA) with an appropriate cuff size according to arm size (i.e. cuff with inflatable bladder width ≥40% and length ≥80% of the arm circumference at the midway point between the olecranon and acromion). Korotkoff phase I sounds were used for determination of systolic BP and phase V for diastolic BP. After a 5-min rest period, BP was measured three times to the nearest 2 mmHg with a 1-min interval between measurements, and the average of the last two measurements was used in the analysis.

Statistical analysis

Descriptive baseline characteristics of the study population are reported as the mean (SD) for continuous variables and as frequencies (%) for categorical variables. A Student's *t*-test or a nonparametric Mann–Whitney test was performed according to variable distribution to examine differences between the two study groups (PG versus DG). Chi-squared or Fisher's exact test was used to determine differences among categorical variables, based on total sample per group.

The Mann–Whitney *U*-test was performed for ordinal (scaled) variables, such as perception of easiness, as well as effectiveness and future adherence, to examine differences between the PG and DG groups in each study phase. Differences between all study phases and within study groups were tested using the Friedman test for ordinal repeated measures.

Post-hoc analyses were performed to derive actual study phase differences. A Wilcoxon signed rank sum test, with Bonferroni correction, was used to account for repeated individual measures (for effectiveness of cholesterol-lowering advice and adherence scaling scores) and repeated measures logistic regression for repeated binary variables [e.g. will you continue to adhere? (yes or no answers)].

Logistic regression for repeated measures was performed to assess differences within groups in total and per phase (forecasted adherence in week 6, actual and forecasted adherence in week 12), after adjusting for individuals' baseline BMI, cholesterol levels, age, gender, physical activity and cholesterol knowledge. The latter was used to decrease possible healthy-lifestyle bias.

Because there were no drop-outs during the study, losses to follow-up as well as from noncompliance were not considered in the analysis. The level of significance was set at 5% level ($\alpha = 0.05$). Data were analysed using STATA, version 14.0 (StataCorp LLC, College Station, Texas, USA).

Results

Baseline characteristics of the study population, including age, gender, body weight status, blood lipid levels, blood pressure, physical activity level based on IPAC questionnaire (short form) and knowledge about healthy blood cholesterol at the beginning of the study, are provided in Table 2. Although some participants had BMI >30 kg m^{-2}, the mean BMI in both groups was 28 (PG) and 29 (DG) (SD 3.2), with no statistical significance between the groups. Blood pressure levels were all within normal levels and, although statistically significant differences between the groups were found, these had no impact on the results. Statistical significant group differences were found only for knowledge of a healthy cholesterol level ($P = 0.006$), with a higher percentage of participants at baseline in the DG group compared to the PG group selecting the correct healthy cholesterol cut-off levels. At the end of Phase 1, 38 individuals (86%) in the PG group and 47 (94%) in the DG group knew the correct healthy total cholesterol levels ($P = 0.209$) (data not shown).

Of the 50 participants enrolled in both the PG and DG groups, 38 individuals (76%) from the PG group and 47 individuals (94%) from the DG group responded to the final questionnaires (Follow-up, Phase II). The final responders did not differ statistically from baseline per group for any of the variables (P for all < 0.05).

Effectiveness of dietary advice for blood lipid lowering

Within-physician group

The participants' perception of effectiveness for the cholesterol-lowering advice given by the physicians is shown in Table 3. Significant differences in scores were observed between the three study phases in the perceived effectiveness of advice for sufficient exercise, limiting saturated fat (SFA) intake, eating fish twice a week, and consuming plenty of fresh fruit and vegetables (for all,

Table 2 Baseline characteristics of study population

	Total study group, $n = 100$	Physician group (PG), $n = 50$	Dietician group (DG), $n = 50$	Between group P level[§]
Age, mean (SD), years	55.4 (7.0)	55 (6.3)	55.9 (7.6)	0.513
Males, *n*	40	21	19	0.683
Females, *n*	60	29	31	
Weight status, *n* (%)				
Healthy weight	12 (12)	8 (16)	4 (8)	0.143
Overweight	60 (60	32 (64)	28 (56)	
Obese	28 (28)	10 (20)	18 (36)	
BMI (kg m^{-2})	28 (3.2)	28 (3.2)	29 (3.2)	0.180
Systolic BP (mm Hg)	130 (120, 133)	130 (125, 130)	125 (120, 135)	0.033
Diastolic BP (mm Hg)	80 (78, 83)	80 (80, 85)	80 (75, 80)	0.002
Total cholesterol (mg dL^{-1})[††]	241 (222, 254)	241 (222, 252)	241 (221, 254)	0.612
LDL-C (mg dL^{-1})[††]	159 (147, 176)	159 (138, 176)	159 (149, 174)	0.994
HDL-C (mg dL^{-1})[††]	51 (44, 62)	51 (43, 62)	51 (44, 62)	0.918
TG (mg dL^{-1})[‡‡]	115 (92, 153)	117 (100, 159)	114 (87, 151)	0.261
Knowledge of healthy total cholesterol levels[†] at baseline (Phase 0) (*n*, %)	56 (56)	21 (42)	35 (70)	0.006
IPAQ[‡] level				
Low	100[¶]	1	1	0.369
Moderate		7	14	
High		40	34	

Results are presented as the mean (SD) or median (first quartile, third quartile).

BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

[†]Individuals selected the correct cut-off level for total cholesterol based on five different options <190 mg dL^{-1}; 190–250 mg dL^{-1}; 251–304 mg dL^{-1}; >305 mg dL^{-1} and 'I do not know'.

[‡]IPAQ: International Physical Activity (PA) Questionnaire.

[§]Independent-samples *t*-tests for normal distributed variables, Mann–Whitney *U*-tests for nonparametric variables and Pearson chi-squared tests for categorical variables.

[¶]Three extreme outliers (two in the PG group and one in the DG group) were excluded.

[††]Conversion factor to SI units: 0.0259 mmol L^{-1}.

[‡‡]Conversion factor to SI Units: 0.0113 mmol L^{-1}.

Table 3 Individual's perception of effectiveness of various diet and lifestyle factors for cholesterol lowering at baseline (Phase 0), week 6 (end of Phase 1) and week 12 (end of Phase 2) of the study based on a five-score system with 1 'not effective' to 5 'very effective'

	Perception of effectiveness on cholesterol lowering[§]										
	Baseline (Phase 0)			Phase I			Phase II				
	PG, $n = 50$	DG, $n = 50$	P^1	PG, $n = 50$	DG, $n = 50$	P^2	PG, $n = 38$	DG, $n = 47$	P^3	P^4	P^5
Sufficient exercise	3.7 (1.6)	4.8 (0.6)	**<0.001**	4.0 (1.7)[b]	4.9 (0.5)[b]	**0.002**	3.1 (1.8)[b]	4.4 (1.0)[b]	**<0.001**	**0.015**	**0.004**
Limiting saturated fat intake[†]	4 (1.4)	4.9 (0.4)	**<0.001**	4.1 (1.4)	5.0 (0.3)	**<0.001**	3.7 (1.7)	5.0 (0.3)	**<0.001**	**0.001**	0.097
Eating twice a week fish (1 × fatty fish)	3.9 (1.7)	4.8 (0.6)	**0.001**	3.8 (1.6)[b]	4.8 (0.6)	**<0.001**	3.1 (1.8)[b]	4.9 (0.5)	**<0.001**	**0.003**	**0.003**
Eating plenty fruit and vegetables[‡]	4.1 (1.5)	4.9 (0.4)	**0.004**	3.8 (1.4)	5.0 (0.3)	**<0.001**	3.9 (1.5)	4.9 (0.5)	**<0.001**	**0.013**	**0.039**
Limiting salt intake	3.4 (1.8)	4.6 (1.2)[c]	**<0.001**	3.4 (1.6)[b]	4.9 (0.6)[b]	**<0.001**	2.8 (1.4)[b]	3.7 (1.1)[b,c]	**0.009**	**0.01**	**0.001**
Including whole grain products in diet	3.5 (1.6)	4.6 (1.1)	**<0.001**	3.5 (1.7)	4.9 (0.4)[b]	**<0.001**	3.8 (1.6)	4.5 (1.0)[b]	0.060	0.931	**0.022**
Limiting alcohol consumption	3.4 (1.8)	4.6 (1.1)	**0.001**	3.4 (1.9)	4.8 (0.7)[b]	**<0.001**	3.9 (1.4)	4.4 (1.2)[b]	0.064	0.599	0.061
Using 30 g of plant sterol (PS) spread per day	4.4 (1.0)	4.7 (0.8)	0.083	4.5 (1.0)	4.7 (0.8)	0.641	4.5 (1.3)	4.4 (1.1)	0.466	0.144	0.775
Using 20 g PS spread and 1 glass PS milk per day[§]	4.5 (1.1)	4.8 (0.9)	**0.034**	4.4 (1.0)	4.7 (0.8)	0.533	4.5 (1.3)	4.4 (1.1)	0.914	0.223	0.072
Using 20 g PS spread and 1 pot PS yoghurt per day[§]	4.4 (1.1)	4.9 (1.0)	**0.034**	4.7 (1.2)	4.5 (1.2)	0.431	4.7 (0.7)	4.5 (0.9)	0.447	**0.03**	**0.015**

DG, dietitian group; PG, physician group. Significant levels at $P < 0.05$.

P^1, P^2, P^3: values derived from Mann–Whitney *U*-tests (between-group comparisons) for individuals' perception of factors effectiveness in cholesterol reduction at baseline (Phase 0) and end of Phase I and Phase II, respectively.

P^4, P^5: values derived from Friedman tests for PG and DG groups (within-individual comparisons at baseline, 6 weeks and 12 weeks), respectively. Superscript lowercase letters indicate values derived from a Wilcoxon signed rank sum test with Bonferroni correction for repeated measures: [a]within-individual comparisons at baseline and 6 weeks,[b]6 weeks and 12 weeks, [c]baseline and 12 weeks.

[†]Defined as limiting butter, hard margarine, fatty meat, full fat dairy products and snacks.

[‡]Defined as consuming 150 to 200 g of vegetables and 200 g of fruit.

[§]Because only a small percentage of the study population (overall <50%) responded to these questions, these they were not analysed *post hoc*.

P - values in bold denote statistically significant differences in each row.

$P < 0.001$; for limiting salt intake, $P = 0.009$). The perceived effectiveness of the other advice did not significantly differ between the three study phases. Post-hoc analysis showed that scores of perceived effectiveness for sufficient exercise, eating twice a week fish and limiting salt intake decreased significantly in week 12 (Phase II) compared to week 6 (Phase I).

Within-dietitian group

Significant differences in the participants' perception of effectiveness of the cholesterol-lowering advice of the dietitians between the three study phases were found for sufficient exercise ($P = 0.004$), eating fish twice a week ($P = 0.003$), eating fruits and vegetables ($P = 0.039$), limiting salt intake ($P = 0.001$) and including whole grain intake ($P = 0.022$) (Table 3). The other advice did not significantly differ between study phases. Post-hoc analysis revealed a significant decrease in the perceived effectiveness scores for whole grain intake and alcohol consumption between weeks 6 and 12, with these scores not differing from baseline levels. A large reduction of 1.2 ($P < 0.001$) in the score for the perceived effectiveness of limiting salt intake was found at the end of intervention at week 6 (Phase I) compared to end of follow-up period at week 12 (Phase II). The difference was also significant between baseline score and week 12 ($P = 0.001$).

Between-group comparison

Between-group comparisons of the perceived effectiveness of the specific diet and lifestyle advice provided by the physicians or dieticians for cholesterol-lowering are shown in Table 3. The scores of the individuals' perception of effectiveness for sufficient exercise, limiting SFA intake, eating fish twice a week, eating plenty of fruits and vegetables, and limiting salt intake significantly differed at the three study phases between individuals in the

PG and DG groups. Those in the DG group had higher scores in all cases.

The perceived effectiveness of consuming whole grain products and limiting alcohol consumption significantly differed between the groups at baseline and week 6, with scores being higher for individuals in the DG group. However, this was no longer the case at week 12 ($P = 0.06$), with a slight, nonsignificant increase in the scores seen in the PG group. The perceived effectiveness of consuming 30 g of PS-added spread per day did not differ in any phase, whereas the score for the use of combinations of PS-added products (i.e. spread with milk or yoghurt) was significantly different between the PG and DG groups only at baseline.

Effort required with respect to adhering to the cholesterol advice (perceived easiness)

The scores of the individuals' perception in the PG and DG groups for the effort needed to make the recommended changes (at baseline) compared to the actual perceived effort or easiness required to adhere to these changes in diet and lifestyle at weeks 6 (Phase I) and 12 (Phase II) are shown in Table 4.

Within-physician group

Scores of the effort of adhering to prescribed diet and lifestyle changes were significant only for fish consumption ($P = 0.008$), using 30 g of PS-added spread/day

Table 4 Individual's perception of effort required with respect to adhering to prescribed diet and lifestyle changes for cholesterol lowering at baseline (Phase 0), week 6 (end of Phase 1) and week 12 (end of Phase 2) of the study based on a five-score system with 1 'not easy at all' to 5 'very easy'

	Perception of effort/easiness[§]										
	Baseline			Phase I			Phase II				
	PG, $n = 50$	DG, $n = 50$	P^1	PG, $n = 50$	DG, $n = 50$	P^2	PG, $n = 38$	DG, $n = 47$	P^3	P^4	P^5
Sufficient exercise	3 (1.9)	3.5 (1.6)	0.203	2.6 (1.7)	3.4 (1.6)^{b}	**0.021**	2.8 (1.6)	4.2 (1.4)^{b}	**<0.001**	0.152	**0.022**
Limiting saturated fat intake[†]	4 (1.7)^{a}	3.9 (1.5)^{a,c}	0.500	3.2 (1.9)^{a,b}	4.8 (0.8)^{a}	**<0.001**	3.9 (1.5)^{b}	4.7 (0.9)^{c}	**0.001**	0.122	**0.005**
Eating twice a week fish (1 × fatty fish)	4.1 (1.5)^{a,c}	4.2 (1.3)^{c}	0.836	3.3 (1.6)^{a,b}	3.9 (1.2)^{b}	0.078	2.9 (1.8)^{b,c}	4.6 (0.9)^{b,c}	**<0.001**	**0.008**	**0.03**
Eating plenty fruit and vegetables[‡]	3.6 (1.8)	4.6 (1.0)^{a}	**0.006**	3.5 (1.7)	4.9 (0.5)^{a}	**<0.001**	3.2 (1.6)	4.8 (0.6)	**<0.001**	0.091	0.113
Limiting salt intake	2.6 (1.7)	4.1 (1.2)^{c}	**<0.001**	2.7 (1.6)	3.8 (1.1)^{b}	**<0.001**	2.8 (1.7)	4.5 (1.0)^{b,c}	**<0.001**	0.563	0.104
Including whole grain products in diet	3.1 (1.9)	4.2 (1.3)	**0.004**	3.3 (1.6)^{b}	4.6 (1.1)	**<0.001**	4.3 (1.3)^{b}	4.5 (1.1)	0.525	0.958	0.102
Limiting alcohol consumption	3.7 (1.5)	4.4 (1.2)^{c}	**0.017**	2.8 (1.9)^{b}	4.1 (1.1)^{b}	**<0.001**	4.0 (1.4)^{b}	4.9 (0.4)^{b,c}	**<0.001**	0.387	**0.007**
Using 30 g plant sterol (PS) spread per day	4.5 (1.2)^{c}	4.4 (1.0)^{a}	0.324	4.5 (1.0)^{b}	2.9 (1.9)	**<0.001**	3.1 (2.0)^{b,c}	3.8 (1.7)^{a}	0.156	**<0.001**	0.786
Using 20 g PS spread and 1 glass PS milk per day[§]	4.4 (1.4)	4.0 (1.4)	0.275	4.0 (1.3)	3.8 (1.8)	0.984	2.8 (1.9)	4.3 (1.4)	**0.043**	0.497	0.368
Using 20 g PS spread and 1 pot PS yoghurt per day[§]	4.7 (0.9)	4.5 (0.9)	0.189	4.4 (1.1)	4.4 (1.4)	0.550	2.5 (1.8)	3.8 (1.8)	0.059	**0.002**	0.125

DG, dietitian group; PG, physician group. Significant levels at $P < 0.05$.

P^1, P^2, P^3: Values derived from Mann–Whitney *U*-tests (between-group comparisons) for individuals perceived effort on adhering to these factors at baseline (Phase 0) and end of Phase I and Phase II, respectively); P^4, P^5: values derived from Friedman tests for PG and DG groups (within-individual comparisons at baseline, 6 weeks and 12 weeks), respectively. [a,b,c]Values derived from a Wilcoxon signed rank sum test with Bonferroni correction for repeated measures: [a]within-individual comparisons at baseline and 6 weeks,[b]6 weeks and 12 weeks and [c]baseline and 12 weeks.

[†]Defined as limiting butter, hard margarine, fatty meat, full fat dairy products and snacks.

[‡]Defined as consuming 150 to 200 g of vegetables and 200 g of fruit.

[§]Because only a small percentage of the study population (overall < 50%) responded to these questions, they were not analysed *post hoc*.

P - values in bold denote statistically significant differences in each row.

($P < 0.001$) and consuming 20 g PS-added spread and 1 pot PS-added yoghurt daily ($P = 0.002$), with lower scores after 12 weeks, hence showing reduced easiness (Table 4). Post-hoc analysis revealed significant differences in the effort of adhering with respect to limiting SFA intake between baseline and week 6, with the score being lower at 6 weeks compared to baseline but increasing again after 12 weeks to a score close to that at baseline. Scores for consuming fish twice a week differed between all phases, with perceived easiness decreasing at each phase. Scores for the perceived easiness of including whole grain products and limiting alcohol consumption significantly increased from week 6 to week 12. Scores for consuming 30 g day^{-1} of PS-added spread were the same at baseline and week 6 but were significantly decreased at week 12 (4.5 versus 3.1, $P < 0.001$). Similar effects were also observed for the combination of PS-added spread with either PS-added milk or yogurt.

Within-dietitian group

Significant differences in the scores of perceived efforts to adhere to diet and lifestyle changes were found between the study phases for sufficient exercise, limiting SFA intake, eating fish twice a week and limiting alcohol consumption (Table 4). Post-hoc analysis showed that the scores of the perceived/actual effort were higher after 12 weeks compared to baseline for limiting SFA intake, consuming fish twice a week, limiting salt intake and limiting alcohol consumption. The score for the effort on consuming 30 g of the PS-added spread daily and of sufficient exercise increased again from week 6 (Phase I) to week 12 (Phase II).

Between-group comparison

Overall significant differences between the PG and DG groups in the scores of perceived easiness were found for eating plenty of fruit and vegetables, limiting salt intake, including whole grain products in the diet and limiting alcohol consumption, with higher scores in the DG group at baseline and at the end of week 6 (Phase I). Differences in these scores remained significantly higher only for eating fruits and vegetables, limiting salt intake and limiting alcohol consumption at week 12 (Phase II).

Although no differences between the PG and DG group were found at baseline for the perceived effort that would be required for sufficient exercise, limiting SFA intake and eating fish twice a week, significant differences in the scores for the actual effort were found at weeks 6 and 12 (for eating fish only at week 12), suggesting that individuals in the DG group found it easier to adhere to these changes. Limiting alcohol consumption was the only lifestyle change found to be significantly different at all three study phases, with individuals in the DG group reporting higher scores and hence finding it easier to adhere. The score for using 30 g of PS-added spread was higher in the PG group at week 6; however, there was no significant difference in scores after 12 weeks between the groups.

Forecasted and actual adherence to cholesterol lowering advice

Table 5 shows the reported forecasted adherence at week 6, the actual adherence and the future forecasted adherence after 12 weeks (assessed at 12 weeks). The DG and PG groups significantly differed in various diet and lifestyle changes in forecasted (week 6) versus actual adherence (week 12), with the DG group reporting higher adherence. All advice was found to be significantly different for forecasted adherence (week 12), with the PG group reporting higher adherence only for PS-added spread consumption (PG: 87%, DG: 64%; $P = 0.004$). Repeated measured logistic regression showed a significantly higher actual adherence at week 12 compared to that forecasted at week 6 for eating fruits and vegetables and consuming PS-added spread (86% versus 58% and 76% versus 48%, respectively), whereas limiting alcohol was significantly lower (54% versus 66%).

At the week 12 forecast for future adherence, a significantly lower percentage of individuals in the PG group forecasted that they would continue to adhere to limiting salt intake and consuming whole grains, whereas consuming the PS-added spread was significantly higher and close to actual adherence.

In the DG group, a significantly lower actual (week 12) to forecasted (week 6) adherence was found only for consuming PS-added spread and yogurt (24% versus 60%). At the week 12 forecast, significantly more individuals responded that they would adhere to sufficient exercise and eating fish at least twice per week, whereas significantly less forecasted that they would continue to consume PS-added spread and milk, as well as PS-added spread and yogurt. These forecasts did not differ from the actual adherence at week 12.

Discussion

In the present study, we attempted to compare two different means of providing advice, including six weekly face-to-face sessions by dietitians compared to a single session by physicians, with respect to achieving compliance with diet and lifestyle changes in participants with mild to moderate hypercholesterolaemia. The main finding of the study was that a greater percentage of participants in the DG group adhered to the dietary and lifestyle recommendations and responded with higher perception scores concerning the effectiveness for cholesterol-lowering and

Table 5 Frequency of reported forecasted adherence at week 6 (until week 12), actual adherence at week 12 and future forecasted adherence after week 12 of participants by study groups (PG versus DG)

	Forecast (week 6)			Actual adherence (week 12*)			Future forecast adherence (week 12)		
Prescribed change	PG	DG	P^1	PG	DG	P^2	PG	DG	P^3
Sufficient exercise	0.44	0.60[c]	0.395	0.56	0.66	0.420	0.39	0.85[c]	**<0.001**
Limit saturated fat intake	0.62	0.94	**0.004**	0.90	0.94	-	0.68	0.98	**0.002**
Eat fish > 2 week^{-1}	0.40	0.78[c]	**0.039**	0.52	0.86	**0.004**	0.63	0.96[c]	**<0.001**
Eat plenty of fruit and vegetables	0.58[a]	1.00	**0.003**	0.86[a]	0.92	0.534	0.71	1.00	**0.002**
Limit salt	0.58[c]	0.84	0.186	0.52	0.86	**0.002**	0.32[c]	0.89	**<0.001**
Consume whole grains	0.64[c]	0.88	0.206	0.62	0.82	**0.023**	0.39[c]	0.85	**<0.001**
Limit alcohol	0.66[a]	0.94	0.086	0.54[a]	0.90	**<0.001**	0.82	0.98	**0.021**
30 g plant sterol (PS) spread per day	0.48[a,c]	0.58	0.688	0.76[a]	0.78	0.470	0.87[c]	0.64	**0.004**
20 g PS spread and 1 glass PS milk per day	0.14	0.50[c]	**0.029**	0.36	0.56	0.077	0.16	0.43[c]	**0.018**
20 g PS spread and 1 pot PS yoghurt per day	0.10	0.60[a,c]	**0.007**	0.30	0.24[a]	0.374	0.18	0.49[c]	**0.007**

DG, dietitian group; PG, physician group.

P^1, P^2, P^3: between-group comparisons. Values derived from Mann–Whitney *U*-tests with continuity correction (2 × 2 tables) or Fisher's exact test for forecasted adherence at week 6 (until week 12), for actual adherence at week 12 and for future forecasted adherence after week 12, respectively. [a,c]Within group comparisons. Values derived from repeated measures logistic regression [[a]denoting significant differences between forecasted adherence at week 6 (until week 12) and actual adherence at week 12; [c]denoting significant differences between forecasted adherence at week 6 (until week 12) and future forecasted adherence after week 12] for PG and DG groups, separately [adjusted for individuals' baseline weight category (body mass index), cholesterol levels, age, gender, physical activity and cholesterol knowledge].

*Individuals reporting that have adhered to advice given in the PG group and in the DG group. Significant level at $P < 0.05$.

P - values in bold denote statistically significant differences in each row.

easiness of following. Furthermore, participants in the DG group reported a significantly higher adherence to these guidelines in the future (week 12) compared to those in the PG group (forecasted perception). Therefore, a close and structure supervision from a dietitian (in our case, 30-min weekly sessions for 6 weeks) could ameliorate adherence to the advice after the end of the consultation period. This close supervision may not be feasible in a hospital setting but can be used in out-patient clinics, especially for high-risk patients.

The new goals set by the American Heart Association for 2020 for cardiovascular health directly incorporate metrics of lifestyle behaviours, including diet and physical activity habits, underlying their importance [5]. Even modest sustained diet and lifestyle changes can substantially reduce CVD morbidity and mortality. Because many of the beneficial effects of lifestyle changes accrue over time, long-term adherence maximises individual and population benefits [5,12].

The higher scores in the DG group for the individual's perception of the effort and easiness required with respect to adhering to the prescribed diet and lifestyle changes are reinforced by our former results [14]. Although structured advice on dietary changes from dietitians compared to common standard advice by physicians was equally effective for improving blood lipid levels during the 6-week intervention period, dietitians were more effective in the longer-term because the cholesterol-lowering effect was more pronounced at the end of the additional 6 weeks of follow-up [14]. In agreement with these findings, other studies showed that medium- and high-intensity counselling resulted in moderate to large changes in self-reported dietary and physical activity behaviours [5,16–20].

The higher score in the DG group for effectiveness and easiness with respect to eating plenty of fruit and vegetables is also in agreement with other studies [21,22]. More specifically, a meta-analysis found that dietary advice interventions (ranging from a single session to multi-sessions over 4 years) were effective in achieving an increase of fruit and vegetables intake by 1.18 servings day^{-1} compared to no or minimal advice interventions [21]. Similarly, in a systematic review and meta-analysis of nutrition interventions in primary care settings, Bhattarai *et al.* [22] reported that fruit and vegetable intake increased by 0.50 servings day^{-1}. Several meta-analyses also found a decrease in percentage energy intake from total dietary fat [21,22], especially from saturated fat [21]. This finding is not supported by the present study because no significant differences in SFA intake were reported in actual adherence. Differences were only found in the forecasted adherence, with a higher percentage of individuals in the DG group reporting to continue with limiting SFA intake, this remains to be confirmed by others studies with longer follow up period.

In a review analysing effective measures for lifestyle modification for hypercholesterolaemia, a number of

factors potentially affecting patient compliance with lifestyle advice included poor patient motivation, poor cognition, inaccurate health benefits, poorly perceived benefits of change, lack of clinical follow-up and complexity of regime [23]. The best approach appeared to be clear patient communication in a professional healthcare setting, which is in accordance with the findings of the present study. Based on findings, the use of evidence-based behavioural change strategies could increase the effectiveness of the technological interventions, and interaction with healthcare providers could increase the interventions success rate [24].

The effectiveness of dietitian counselling on sodium reduction compared to usual care (of guideline provision) was tested in a controlled trial resulting in a significant decrease in sodium intake at 3 months [25]. These results provided further evidence for the dietitian's role as part of the multidisciplinary team involved in hypercholesterolaemia treatment with respect to helping patients achieve and adhere to a healthy lifestyle approach [25].

According to the World Health Organization, all healthcare providers need to be made aware of the low rates of adherence to long-term therapies for patients with chronic diseases and should receive training on patient counselling [3]. These recommendations include physicians because prior studies have reported potential inadequate physician training in nutrition counselling, lack of behavioural intervention skills and a belief that chronic disease risk factor interventions are of low priority in acute care practice settings [26,27].

A major public health challenge is encouraging people increase physical activity on a regular basis for a healthy lifestyle and to maintain blood lipid levels within normal ranges. Evidence suggests that regular physical exercise is beneficial, although adherence remains a major hurdle, with a lack of time often being cited as a major barrier [28]. Although the present intervention was not specifically tailored to investigate any increase in physical activity, the improvement of dietary habits, including the increase in the consumption of PS, in combination with a shift in physical activity towards more moderate intensity levels, is suggested to have resulted in the observed beneficial effects on blood lipid profiles [14].

A considerable debate and confusion remains in the scientific literature regarding a potential 'gold standard' for enhancing adherence and positive feedback from interventions. Providing education plus individual-tailored or instructional components, such as those used in the present study, revealed a higher effectiveness than education alone or nontailored advice [4,29].

The present study was relatively short in duration. It has been argued that an intervention with a shorter time frame presents some limitations. Because brief interventions involve less exposure, they may be unable to include a multitude of behaviour change techniques, thus limiting their long-term efficacy. Therefore, the actual effectiveness of brief nutritional interventions warrants further investigation, especially for individuals with hypercholesterolaemia because their treatment must be lifelong. [4]. Noticeably, in a Cochrane review, most studies reporting a dietary adherence outcome favour the intervention group compared to the control/usual care group in the short-term. Also, no significant effects at later time points were reported [13]. Generally, it is difficult to extract clear results because the studies were generally of short duration and low quality and the adherence measures varied widely [13].

Conclusions

Lifestyle and dietary changes related to dyslipidaemia can be achieved with continuous education, monitoring and follow-up by dieticians, and potentially other trained healthcare professionals, in various areas, including outpatient clinics, for specific short-term time periods, such as 6 weeks, as reported in the present study.

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 CONSORT guidelines (see Supporting Information). The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest. EAT is employed by Unilever R&D. Before divesting its spreads business (now owned by KKR and operating since 2 July 2018 under the name Upfield™), Unilever marketed food products with added plant sterols.

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EM performed the statistical analysis, interpreted the results and wrote the paper. EAT and AZ designed the research, interpreted the data and co-wrote the paper.

TES designed the research, carried out the field work and co-wrote the paper. AP, ID KP and TES conducted research and were part of the Dietitian Group. SPE, GG and AK conducted research and were part of the Physician Group. All authors reviewed the manuscript and approved the final version submitted for publication.

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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. Questionnaire for perceived effectiveness of adhering to guidelines, used at week 0.

Table S2. Questionnaire for perceived easiness with respect to adhering to guidelines, used at week 0.

Table S3. Questionnaire for effectiveness with respect to adhering to guidelines, used at week 6.

Table S4. Questionnaire for easiness with respect to adhering to guidelines, used at week 6.

Table S5. Questionnaire for reported forecasted adherence used at week 6.

Table S6. Questionnaire for effectiveness of adhering to guidelines, used at week 12 (including a question for actual adherence – column 2).

Table S7. Questionnaire for easiness with respect to adhering to guidelines, used at week 12 (including a question for actual adherence – column 2).

Table S8. Questionnaire for reported future forecasted adherence used at week 12.

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NUTRITION INTERVENTIONS

Calcium intake improvement after nutritional intervention in paediatric patients with osteogenesis imperfecta

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Abstract

Background: In several bone disorders, adequate calcium intake is a coadjuvant intervention to regular treatment. Osteogenesis imperfecta (OI) is a collagen disorder with a range of symptoms, ranging from fractures to minimum trauma, and it is typically treated with bisphosphonates. In the present study, we evaluate the impact of a nutritional intervention (NI) on dietary calcium intake and bone mineral density (BMD) in paediatric patients with OI.
Methods: A nonrandomised clinical trial was designed with a NI. Dietary calcium intake, anthropometry and clinical features were assessed at baseline, including anthropometry, basal metabolic rate (BMR), BMD. In addition, a food guidance form was developed and sent to patients by mail. After 12 months, clinical features of patients were reassessed and compared with the baseline data.
Results: Fifty-two children and adolescents were enrolled. Significant increases in total calcium intake (mg day^{-1}), percentage of adequate calcium intake (%) and number of cups of milk ingested were observed after NI. We detected a positive correlation between the variation of BMD and milk consumption in patients treated with bisphosphonate.
Conclusions: We observed an increase in calcium intake in patients with OI. This finding demonstrates the importance of nutrition therapy as part of a multidisciplinary treatment approach for bone health.

Introduction

Calcium is an important nutrient for bone health because it is directly related to the growth, development and maintenance of the skeleton, thereby providing structure and support [(1)]. Although calcium is present in many tissues, such as blood, muscle and extracellular fluids, bone comprises the largest reservoir in the body. Adequate calcium intake is crucial for maintaining a rigid skeleton, thus preventing osteoporosis and the occurrence of fractures [(1,2)].

Bone fragility is the main consequence for individuals with osteogenesis imperfecta (OI), an inherited disease characterised by low bone mineral density (BMD), bone deformity and most of cases repeated fracture [(3)]. The prevalence of OI ranges from on in 15 000 to one in 20 000 births, regardless of sex or ethnicity. Based on phenotype and clinical and radiological findings, the classification of OI is ordered into five subtypes (I–V) [(2)]. Considering the clinical features and order of severity, the types are I (classic, nondeforming OI with blue sclerae); IV (variable OI with normal sclerae); V (ossification in interosseous membranes); III (progressively deforming OI with normal sclerae); and II (perinatally lethal OI) [(3,4)]. Individuals with moderate and severe forms of OI (type III and IV) have skeletal deformities and reduced mobility [(4)]. A broad molecular classification of OI has been recognised in the last 10 years as a result of advances of genetic diagnosis with a variety of recessive, dominant and X-linked gene defects that encode proteins involved in type I collagen [(5,6)].

Our previous study had detected low dietary calcium intake in children with OI. Seventy-five percent of subjects had calcium intake below that recommended for their age [7]. Another study by our group that evaluated serum 25-hydroxyvitamin D concentrations and the correlation with other factors related to bone health, observing that more than 51.9% of the subject consumed only one or two glasses of milk day^{-1} [8]. An additional study showed that OI patients had a low dietary intake of calcium and vitamin D [9].

Considering these data, in the present study, we aimed to evaluate the impact of a nutritional intervention (NI), with emphasis on calcium intake in paediatric patients with OI.

Materials and methods

A nonrandomised clinical trial was designed and enrolled paediatric patients aged between 2 and 19 years who were diagnosed with all types of OI, based on clinical and radiological features [3]. Individuals were evaluated at the Reference Centre for Osteogenesis Imperfecta Treatment of Porto Alegre Clinical Hospital (HCPA-CROI), between March 2012 and December 2013. The study was approved by the Ethics Committee of the institution (#11-0585) and all individuals or their responsible caregivers provided their written informed consent.

Nutrition intervention

NI was performed at three nutritional visits (baseline, 6 and 12 months). Clinical features were evaluated at baseline, including anthropometric measurements, basal metabolic rate (BMR) and BMD. An indirect calorimetry test was performed to estimate the BMR of each participant. Dietary intake was assessed using a daily food intake report completed by participants on three nonconsecutive days. The frequency of consumption and amount of calcium intake were evaluated using a food frequency questionnaire (FFQ) with an emphasis on foods rich in calcium. Based on these data, the nutritional needs for each subject were calculated and personalised food guidance (including recipes rich in calcium) was delivered by mail.

In the second visit, at 6 months after baseline, adaptations were made to food guidance in accordance with the needs of each patient, doubts about feeding were clarified and the importance of a diet rich in calcium was reinforced.

On the third visit, at 12 months after baseline, dietary calcium intake, anthropometric measurements and BMD were re-evaluated.

Calcium intake

Calcium intake was assessed using an FFQ adapted to calcium intake [10] applied before and after the NI. In the present study, we focused on the consumption of foods high in calcium, such as milk, yogurt and cheese. To establish the percentage of the adequacy of intake, the values obtained from the FFQ were compared with the estimated average requirement (EAR) and recommended dietary allowance (RDA) [11].

The FFQ for calcium intake was composed of milk (1 cup = 175 mL), one carton of yogurt (120 mL) and cheese (1 medium slice = 30 g). These foods were classified according to the consumer (D, daily; W, weekly; M, monthly) and indicating the number of times (1–10) and the size of the corresponding portion, if greater, equal or less than the given portion (in accordance with a poster including colour photographs to illustrate the portion size of each food source of calcium).

The consumption of glasses of milk and soda was also evaluated according to quantity and frequency (For milk, 0 = does not consume; 1 = consume <1 cup day^{-1}, 2 = consume 1–2 cups day^{-1}, 3 = consume 3 or more cups of milk day^{-1}; for soda, 1 = consume daily, 2 = consume only on weekends or 2 times week^{-1}, 3 = consumes less than 1 day week^{-1} and 4 = does not consume).

Clinical data

Clinical data were obtained during the enrollment and included age, sex, OI type, use of bisphosphonates and calcium intake.

Anthropometric data and basal metabolic rate

Anthropometric measurements (weight and height) were measured and evaluated according to the *Z*-score proposed by the World Health Organization WHO (2006, 2007) [12]. The length was measured in the supine position in children smaller than 1 m and children who could not remain in the standing position. Patients over 1.04 m and unable to remain standing were measured in the supine position [13]. BMI was calculated and nutritional status was classified in accordance with the WHO (2006, 2007) [12]. The BMR was evaluated via indirect calorimetry and the data were published previously [14].

Bone mineral density

BMD was determined before and after the intervention using dual energy X-ray absorptiometry on a Lunar iDXA (GE Healthcare, San Francisco, CA, USA). Bone mineral

content (BMC) (g), lumbar spine BMD (L1–L4) and total body BMC were calculated and expressed as *Z*-scores. The *Z*-score was not obtained for children less than 5 years old as a result of a lack of values proposed by the manufacturer.

Statistical analysis

Descriptive analyses were represented by frequency and percentage. For parametric data, the mean (SD) was used and, to compare the pre- and post-NI values, paired *t*-tests were applied. For nonparametric data, medians and quartiles were used, and, for comparison of the pre- and post-intervention values of these ordinal qualitative variables, the Wilcoxon test was used. For nominal qualitative variables, we used the McNemar test. Pearson's and Spearman's correlation analyses were used for parametric and nonparametric data, respectively. Generalised estimating equations were applied for the stratification of the differences between the variables between pre- and post-NI.

Results

Table 1 shows the clinical features of patients at the baseline assessment. Fifty-two individuals were analysed, of whom 29 (55.9%) were female. The median age at the time of enrollment was 9 years (5.25; 12.7). OI patients were classified as 24 (46.2%) type I, 5 (9.6%) type III, 23 (44.2%) type IV and 1 (1.9%) type V. As a result of the small sample size, for analysis, type V was grouped together with type IV. Two subjects did not complete the evaluationat 12 months: one because of a fracture and the other as a result of convalescence following surgery for correction of deformities at the time of the third visit.

Considering bone mass, we observed a significant difference only in the pre- and post-NI in BMC and lumbar spine and total body BMD ($P < 0.005$) (Table 1).

Analysing dietary intake of calcium, there was a significant difference between pre- [706 (325) mg day^{-1}] and post- [885 (265) mg day^{-1}] NI in total calcium intake ($P < 0.001$). Regarding calcium intake adequacy, there was a significant difference ($P < 0.001$) from pre- to post-NI for both parameters: EAR (66% to 81%) and RDA (from 56% to 69%). Milk consumption also showed a significant difference after NI, with a decrease in the number of subjects who had no or poor intake and an increase in the number of cups day^{-1} ($P = 0.002$). The daily consumption of soft drinks decreased after NI ($P = 0.012$) (Table 2).

The correlation between variation of BMD and milk consumption showed that subjects who are treated with bisphosphonates reported a positive correlation, especially in the lumbar spine BMD ($r = 0.544$; $P = 0.029$) (Fig. 1).

Discussion

NIs provide the necessary knowledge to promote healthy eating habits [15]. Individuals with OI typically have a low calcium intake [7–9] and it is well-known that these nutrients are important for bone health, especially for children with bone disorders [2,10,16]. In our previous study addressing the calcium intake of children and adolescents, we found that 75% of subjects with OI had an adequacy percentage of calcium intake below 93.5% and detected an inverse correlation between age and calcium intake ($r = -0.527$) [5].

In the present study, we detected low a calcium intake at baseline. However, following the NI, we observed an increase in the consumption of rich calcium foods post-NI, as shown by the increase in the values of total calcium mg day^{-1}, EAR and RDA adequacy percentage and number of cups of milk day^{-1}, as well as a decrease in the daily consumption of soda.

To evaluate the intake of calcium, Cosenza *et al.* (2013) performed a randomised study in healthy children. Group 1 received only dietary counselling and Group 2 received dietary counselling plus supplementation of calcium and vitamin D. After 4 months of intervention, in both groups, significant improvements were observed for calcium intake. These data show that it is possible to increase calcium intake with dietary counselling [16], similar to the present study.

Previous studies have shown a decrease in BMD, particularly in the more severe forms of OI [6,17]. In the present study, we observed an increase in BMC values, lumbar spine BMD and total body BMD post-NI evaluation. A cohort study of 9 years with 52 children with OI observed a mean (SD) annual increase in BMD of 0.038 (0.024) g cm^{-2} year^{-1} and this annual increase in BMD was significantly higher in girls than in boys [18].

An important finding of the present study was the positive correlation between calcium intake and lumbar spine BMD in patients treated with bisphosphonates. We observed that individuals treated with bisphosphonates presented a positive correlation between variation in lumbar spine BMD and pre- and post-NI, as well as with the number of glasses of milk consumed (Fig. 1). Bisphosphonates comprise a group of drugs that inhibit osteoclast activity, thereby increasing BMD, as seen in the present study. The positive correlation of BMD and calcium intake in BP treated patients could be explained by an increased awareness with respect to the prevention of hypocalcaemia, which is a common side effect of BP therapy.

Table 1 Values variables of pre- and post-nutritional intervention

Variables	Pre-NI (n = 52)	Post-NI (n = 50)	P
Anthropometry			
Weight (kg)	25.5 (16.1–44.8)	30.6 (19.5–48.2)	<0.001
Stature (cm), mean (SD)	123 (25)	127.6 (24.2)	<0.001
Stature *Z*-score	−2.5 (−3.6 to −1.4)	−2.2 (−3.7 to −1.2)	0.287
BMI, mean (SD)	19.2 (5.4)	20 (5.7)	<0.001
BMI *Z*-score	0.2 (−0.8; 1.7)	0.2 (−1; 2)	0.115
Nutritional status, *n* (%)			
Underweight	5 (9.6)	3 (5.8)	
Eutrophic	29 (55.8)	32 (61.5)	0.540
Overweight	9 (17.3)	6 (11.5)	
Obesity	9 (17.3)	9 (17.3)	
Bone mineral density (BMD)			
BMD (g) dual energy X-ray absorptiometry	927.3 (523.7–1476.3)	1016.1 (604.3–1665.9)	<0.001
BMD spine (*N*)	51	44	
BMD spine (g cm^{-2})	0.62 (0.51–0.82)	0.66 (0.49–0.96)	<0.001
BMD *Z*-score spine (*N* g^{-1} cm^{-2})	46	39	
Z-score spine (g cm^{-2})	−1.35 (−2.07 to −0.52)	−1.3 (−2.1 to −0.3)	0.371
BMD total body (*N*)	46	44	
BMD total body (g cm^{-2})	0.7 (0.62–0.89)	−0.73(0.62–0.94)	0.007
BMD *Z*-score total body (*N* g cm^{-2})	46	39	
Z-score total body (g cm^{-2})	−0.75 (−1.7 to −0.3)	−1 (−1.8 to −0.4)	0.247

BMI, body mass index; NI, nutritional intervention. Data are the mean (range), except where indicated.

Table 2 Values of dietary intake and percentage of the adequacy of calcium at pre- and post-nutritional intervention according to the recommended dietary allowance (RDA) and estimated average requirement (EAR)

Variables	Pre (n = 52)	Post (n = 51)	P
Total calcium day^{-1} (mg)	706 (325.6)	885 (265.3)	<0.001
% EAR adequacy, mean (range)	66.3 (43.8–89.5)	81.9 (64.1–115.1)	<0.001
% RDA adequacy, mean (range)	56.1 (36.8–75.7)	69.1 (54.3–92.8)	<0.001
Consumption of a cup of milk			
Do not consume	4 (7.7)	–	
Less than 1 cup day^{-1}	9 (17.3)	4 (7.7)	0.002
Between 1 to 2 cup day^{-1}	28 (53.3)	30 (58.8)	
≥3 cup day^{-1}	11 (21.2)	19 (36.5)	
Consumption of soda			
Daily consumption	19 (36.5)	10 (19.6)	
Less than 1 day $week^{-1}$	27 (51.9)	30 (57.7)	
Only on weekends (2 day $week^{-1}$)	2 (3.8)	7 (13.5)	0.012
Do not consume	4 (7.7)	4 (7.7)	

Data are the mean (SD), except where indicated.

The association between short stature and OI has been well-described in the literature, especially in those with the most severe forms of OI [7–9,19,20]. In the present study, *Z*-score values for anthropometric measurements did not show a significant difference between the pre- and post-NI assessments, suggesting that patients grew into their own pattern according to the limitations of the disease. A study including the growth charts of patients with type I OI aged from 2 to 18 years old shows that subjects with type I OI are initially smaller than the healthy population, that development slows from 8 years old, and, ultimately, that body height is impaired. The body height/weight ratios are similar when comparing type I OI patients with healthy subjects. This finding is also reflected in the BMI data, which are similar when comparing OI patients with healthy children and adolescents [21].

Palomo *et al.* [22] have reported that BMI is not the best method for evaluating the body composition of these patients because BMI is a body height-related measure

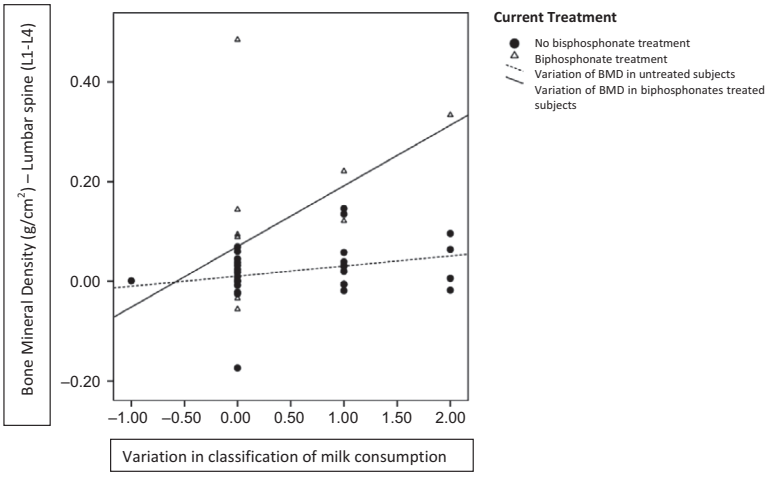

Figure 1 Correlation between variation in bone mineral density of the lumbar spine and variation in milk consumption classification.

and can be influenced by height loss as a result of leg deformities or scoliosis. Our previously published study showed a difference between the methods used to evaluate the body composition [14]. Several studies have reported an association between OI and a higher BMI and being overweight [7,9,19,20]. The present study did not detect a significant difference in the pre- and post-NI BMI *Z*-scores and the nutrition status of these patients. As well being described in the literature, and in addition to nutritional intervention according to metabolic rate, it is essential that physical activity is also practised. However, patients with OI, perform less physical activity because of the risk of fracture, making them and their parents more fearful. This causes them to decrease their energy expenditure and consequently, weight gain. Another consideration is that 12 months was not sufficient to show differences in the BMI *Z*-score of these patients. A meta-analysis performed by Vasques *et al.* [23] in 2014, aiming to evaluate the effects of NI and physical activity programmes on the BMI of children and adolescents, observed that several factors influenced the results, such as age, sex, NI duration, type of NI, frequency of physical activity and parental involvement, concluding that NI programmes have an effect on the prevention and reduction of obesity in children, even if this effect is of low magnitude.

Although the rate of adherence to treatment was not measured and we did not note a significant improvement of the BMI after NI, we did observe a significant increase in calcium intake, which was the main objective of the present study. These findings suggest adherence to the proposed recommendations of the nutritionist. According to the WHO, adherence is defined as the degree to which the behaviour of a person (e.g. ingestion of medication, following a diet and changes in lifestyle) correspond to and agrees with the recommendations of a physician or another health professional [24]. A study performed in 2010 evaluated adherence to treatment in patients with phenylketonuria and noted the importance with respect to both parents and patients understanding the diet [25]. We consider that this may have occurred in the present study because the nutritional counselling was carried out together with the parents/legal guardians of the children and adolescents, making them aware of the best way of achieving a diet rich in calcium.

The present study has some limitations. Two participants were lost to follow-up as a result of the presence of fractures or convalescent corrective surgery at the time of evaluation or hospitalisation for bisphosphonate treatment. In five children who were less than 5 years old, the *Z*-score for lumbar spine and total body BMD were not calculated because of a lack of values proposed by the manufacturer. We did not measure macronutrients at NI because this was beyond the scope of the present study. For ethical reasons, the study had no-intervention or placebo and control group, thus making it impossible to evaluate the real role of NI because individuals already have the answer conditioned to respond to evaluator that can lead to a information bias. Also, retrospective dietary surveys might underreport the eating of certain foods.

The present study aimed to evaluate the results of a NI with emphasis on calcium intake in children and adolescents with OI. Following the NI, we observed a significant increase in calcium intake (mg and relative to EAR and RDA). We also observed an increase in consumption of cups of milk and a decrease in the number of individuals who consumed soda daily. We also noted a positive correlation between lumbar spine BMD and milk consumption among those individuals receiving bisphosphonate treatment. Based on our findings, we emphasise the importance of nutrition therapy as part of a multidisciplinary treatment, helping to guide individuals with OI in relation to a rich, healthy calcium intake, thereby reducing the risks of morbidity, mortality and new fractures.

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 STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted.

Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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TMF and EDM designed the experiment. MBZ collected and analysed the data. MBZ, TMF and EDM wrote the paper. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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NUTRITION INTERVENTIONS

Food-basket intervention to reduce micronutrient deficiencies among Maasai-pregnant women in Tanzania: a quasi-experimental study

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Abstract

Background: Micronutrients comprised of vitamin and mineral nutrients that are needed during pregnancy for foetal growth, development and maturation, as well as for reducing/preventing maternal complications. However, micronutrient-rich foods (vegetables and fruits) are lacking in the Ngorongoro Conservation Area as a result of restrictions on cultivation in conservation areas and the unavailability of vegetables and fruits in local markets. The present study introduced a food basket intervention and assessed the effectiveness of the food baskets with respect to addressing anaemia, vitamin A and iron deficiencies among pregnant Maasai women within the Ngorongoro Conservation Area.
Methods: The quasi-experimental study included Misigiyo ward as a control group (provided education only) and Olbalbal ward as an intervention group (provided food baskets and education). The study assessed haemoglobin, serum ferritin and retinol at baseline and during follow-up. Haemoglobin, serum ferritin and retinol were quantitatively (duplicate) measured with HemoCue™ (HemoCue AB, Ängelholm, Sweden), Maglumi 800 (Snibe Diagnostic, Shenzhen, China) and vitamin A enzyme-linked immunosorbent assay, respectively. Dependent and independent *t*-tests were used to compare the micronutrient blood levels between and within the groups.
Results: The present study found a statistically significant increase in serum retinol ($P < 0.001$) in the intervention group compared to the control group; moreover, baseline serum retinol was positively associated with the follow-up serum retinol, whereas baseline haemoglobin and serum ferritin were negatively associated.
Conclusions: The food basket intervention holds promise with repect to reducing micronutrient deficiency, especially in communities where micronutrient-rich foods are scarce.

Introduction

Micronutrient malnutrition is a prevalent global health problem, especially in mother–child dyads [(1)]. In developing countries, maternal micronutrient deficiencies have been associated with short- and long-term effects, such as miscarriage, low-birth weight, stillbirth, preterm birth, congenital disabilities, poor neurological development, delayed growth, decreased cognitive development, and infant and/or maternal death [(2–4)]. The present study focuses on vitamin A and iron as micronutrients of significant public health concern for pregnant women.

Vitamin A is a fat-soluble vitamin. It plays a major role in cell division, growth and maturation (foetal organ and

skeletons), upkeep of the immune system to fight against infections, development of vision in the foetus, maintenance of maternal eye health and prevention of night blindness during pregnancy [5]. The prevalence of night blindness (a consequence of vitamin A deficiency) among pregnant women is approximately eight million worldwide [6]. In low- and middle-income countries, 15% of pregnant women have gross vitamin A deficiency, whereas 8% of pregnant women have vitamin A deficiency at a sufficient level to cause night blindness. Moreover, 39% of Tanzanian pregnant women were found to be vitamin A deficient [7].

Iron is a mineral found naturally in select foods. It plays a major role in formation of haemoglobin that aids in transportation of oxygen throughout the body [8]. When there is a chronic lack of iron in the diet, infection (parasitic infection) and infestation (worms), and iron-deficiency anaemia can result, contributing to maternal mortality and morbidity. Maternal mortality can be caused by increased blood loss during delivery, pre-eclampsia and miscarriage [9]. Iron-deficient mothers are at risk of delivering low birth weight, preterm and/or iron-deficient babies [10]. The prevalence of prenatal iron deficiency anaemia is 15%–20% worldwide and is estimated to be as high as 35%–75% in developing countries [11]. In Tanzania, 45% of women of reproductive age (15–49 years) are anaemic [7].

Maternal anaemia, as well as iron and vitamin A deficiencies, are increasing across the African continent as a result of poverty, lack of micronutrient knowledge and food insecurity [12]. To address this situation, the Food Agriculture Organization and the United Nations recommend micronutrient supplementation, fortification and food-based approaches as potential strategies for combating micronutrient deficiency [13]. Although this triad of solutions is noted, the food-based approach offers the most sustainable solution for both poverty and micronutrient malnutrition reduction in developing countries [13–16].

The food basket, as a food-based approach, consists of different foods gathered from local farmers specialising in the cultivation of certain foods. The purpose of the food basket intervention is to provide diverse micronutrient-rich foods to each individual or household depending on food aid/external needs, with the aim of improving nutrition status [17]. Little is known about the effectiveness of the food baskets with respect to combating maternal micronutrient deficiencies. The available studies have suggested that the food baskets are often aimed at providing the least costly array of foods without considering micronutrient density and cultural acceptability [18,19].

The food basket intervention consisted of micronutrient-rich foods (vegetables and fruits) that were supplied to pregnant women participants because this group is often identified as at risk for micronutrient deficiency. The food basket composition was based on the reported high prevalence of vitamin A deficiency (100%) and anaemia (29%) in this community [20]. High levels of vitamin A and iron deficiency were associated with the restrictions for cultivation in the Ngorongoro Conservation Area (NCA), cultural dietary restrictions, and inaccessibility/unavailability/unaffordability of fresh vegetables and fruits in local markets [21,22]. Previous work shows that this population had good knowledge about the need for iron in the diet; however, it also showed that this knowledge did not translate to good dietary practices (Mshanga N, Martin H & Petrucka P, Unpublished data).

The rationale of the present study was to consider the impact of the food basket intervention with respect to reducing micronutrient deficiency in a resource-poor setting, as well as the implications for the health status of the mother and unborn child. To achieve the stated objective, the study assessed the effectiveness of the food basket intervention with respect to reducing anaemia, vitamin A and iron deficiency by measuring the vitamin A and iron status of select Maasai pregnant women before and after a food basket intervention.

Materials and methods

Study area, participants and design

The study was conducted in NCA, comprising a unique protected area where the conservation of natural resources (animal and vegetation) is integrated with human activities. NCA is located 180 km west of Arusha in the crater highlands area of Tanzania. The majority of residents are Maasai pastoralists who have, in recent times, started to shift from animal-based diets to cereal-based diets because of the depletion of animal stocks as a result of diseases, droughts and famine.

The present study used a quasi-experimental (pre-post) design. Participants were recruited within two geographical locations, specifically in Misigiyo village (10 km from NCA gate) and Olbalbal village (42 km from the gate). Furthermore, Olbalbal ward was purposively selected as the ward where the Agri-health Cooperative project was implemented, whereas Misigiyo ward was selected based on its similar characteristics to the Olbalbal ward. To assess the effectiveness of the project implemented in Olbalbal ward, the Olbalbal group was categorised as an intervention group and Misigiyo as the control group. Thus, the intervention group received the food basket and nutrition education, whereas the control group received nutrition education only. Maasai pregnant women who were 1–12 weeks pregnant (to allow for follow-up) were recruited from antenatal and mobile clinics in both Olbalbal and Misigiyo wards, with those

experiencing maternal complications being excluded from the study.

Nutrition education

Nutrition education was provided by the nutritionist to the intervention and control group. The lessons were explained in Swahili language and translated into Maa language by a research assistant used vegetable and fruit models. The participants were divided into two groups (containing either 12 or 13 participants), with one group first attending the nutrition education class when the other collected the food baskets and attended ANC clinics, then reversing the roles. Nutrition education was divided into three parts: (i) role of vegetables and fruits in our body and during pregnancy; (ii) good preparation, cooking and storage methods of vegetables and fruits; and (iii) foods that hinder or affect the absorption of certain micronutrients (e.g. tea and iron; zinc and iron). Furthermore, study participants from the intervention group were encouraged to diversify their diets (i.e. to consume at least three different vegetables per day) and all of the study participants (from control and intervention groups) were advised to continue consuming wild Indigenous vegetable (i.e. African nightshade).

To preserve the vegetables and fruits (i.e. because refrigeration is not an option), participants who had clay pots (large and small) in their households were advised to put the smaller pot in the larger pot and put sand in the space between the two pots. Furthermore, they were instructed to keep the sand moist by adding water (daily), when placing the vegetables (packed in plastic bags) in the smaller pot. Both pots were then covered with a wet sack to keep the produce cool. For those who did not have clay pots, they were advised to sprinkle the vegetables with water and put them in a plastic bag. With the clay method, the green leafy vegetables stayed fresh for 4–6 days, whereas those using the plastic bag method found that freshness was retained for 3–4 days. The storage lessons were adopted from the Technical Centre for Agriculture and Rural Cooperation [23].

Food basket intervention

Traditional birth attendants (TBAs) were responsible to distribute the food basket for the project primarily as a result of their cultural role as influencers of pregnant women with respect to the consumption of vegetables and fruits. We recognise that there are both formal and informal providers within the health sector and, within the communities of interest, the cultural and/or traditional practices often dominate. The vegetables and fruits contained in the food basket were cultivated in Karatu district (a nearby district) and transported to Olbalbal (intervention group). The food basket contents and micronutrient contributions are shown in Table 1. The food basket contents were selected based on the participants' preferences, existing micronutrient deficiencies identified during baseline testing, plus the nutritional quality and quantity of the available vegetables and fruits. The nutritional content of the vegetables and fruits in the food basket was obtained from previous studies [24–28].

One food basket contained the core elements of one bunch of sweet potato leaves, amaranth, pumpkin leaves, onions, oranges, carrots and pumpkins. Dependent on availability, Chinese cabbage (*Brassica rapa*) was added to one supply, and spinach was supplied in the next distribution followed by saro because these were highly preferred vegetables in the community, although they were difficult to obtain on a consistent basis.

As a result of the dispersed settlement patterns in these two communities, the food baskets (four or five food baskets for each participant) were provided twice per month, on market days, because there was reliable public transport that enabled the target population to go to the market, visit the antenatal clinic and collect their food baskets. More importantly, the study was conducted during the rainy season, which enabled the participants to continue consuming wild vegetables (African nightshade) as reported in a prior study (Mshanga N, Martin H & Petrucka P, Unpublished data). The food baskets were provided for a period of 6 months.

Recruitment

At the beginning of the study, in the intervention group, the TBAs announced the presence of this study during religious gatherings, village meetings and markets, as well as to their neighbours. Interested participants were instructed to contact any TBA who would then take the participant to the clinic for the recruitment process. There were no mobile clinics at the intervention area as a result of the presence of markets, which resulted in participants relying on public transport to reach the clinic. At the control group site, announcements were made at church gatherings by the health personnel and village leaders also made announcements to each household, instructing interested participants to attend the clinic, as well as mobile clinics as a result of a lack of markets in this community. Upon recruitment, standard measurements, such as last normal menstruation calculations and positive results for pregnancy testing, confirmed pregnancy, whereas fundal height measurement estimated pregnancy age in weeks.

At the beginning of the study, all of the recruited participants to both the control and intervention groups

Table 1 Micronutrient content of vegetables present in one food basket

Vegetable	Botanical names	Fe (mg)	Vitamin A	Retinol equivalent	Vitamin C	Zn (mg)
Sweet potato (20 leaves)	*Ipomoea batatas* (L)	152	5340	455	436	12
Amaranth (12 leaves)	*Amaranthus*	157.2	2052	171	534	7.2
Pumpkin (12 leaves)	*Cucurbita pepo* (L)	78	4992	416	294	19.2
Onion (20)	*Allium cepa* (shallot)	4	0	0	148	4
Orange (10)	*Citrus aurantium*	1	80	6.6	530	1
Pumpkin (3)	*Cucurbita*	2.4	603	50.25	15	0.6
Carrots (10 pieces)	*Daucus carota*	3	8410	700.8	59	2
Spinach (12 leaves)	*Spinacia oleracea*	32.4	9828	819	120	9.6
Chinese cabbage (12 leaves)	*Brassica rapa* (bok choy)	3.6	1440	120	300	2.4
Saro (12 leaves)	NA	151.2	22.92	1.91	241.2	7.2
African nightshade (12 leaves)	*Solonumnigrum*	190.8	47.64	3.97	20	3.4
WHO recommended daily intake during pregnancy.	NA	31–61	-	600	50	20

Sources: Lyimo *et al*. [24]; Weinberger and Msuya [25]; Lukmanji *et al*. [26]; WHO [30]; Kamga *et al*. [27]; Mamboleo *et al*. [28]. NA, not applicable.

were tested for malaria (and this was repeated on every clinic visit for food basket collection/nutrition education) and provided with long lasting insecticide nets for the prevention of malaria. For the participants who were diagnosed with malaria, they were prescribed with malaria tablets (quinine plus clindamycin) for 7 days. Furthermore, participants were given deworming tables (mebendazole) on their next clinic visit (after 2 weeks) and this treatment was repeated every 3 months. Moreover, sulphadoxine-pyrimethamine was given twice, at week 20 of pregnancy and, again, 4 weeks after the first dose as an intermittent preventive treatment for malaria. In addition, participants were physically assessed for any symptoms of infection and advised to practice good water, hygiene and sanitation (WASH) practices, such as avoiding unpasteurised foods, aiming to prevent infections. All medications were provided free of charge.

Follow-up

During the study period, each TBA was responsible for attending two to three participants based on their residential proximity. TBAs and the researcher filled the baskets with the selected vegetables and fruits and each TBA distributed the food baskets to the pregnant women who they were attending. For those women who were unable to visit the clinic on each occasion, the responsible TBAs supplied the food basket to their home place.

After supplying food baskets, the TBAs made unscheduled home visits to evaluate compliance on the dietary intake of vegetables and fruits supplied in the food basket and to encourage the participants to continue attending their ANC appointments to access the next food supplies. Attendance at ANC clinic was not a prerequisite for them to receive the food basket but comprised a convenient way of meeting the study participants.

Data collection and laboratory analysis

A qualified and experienced nurse collected blood samples from each participant during baseline and follow-up in the study. A 5-mL syringe was used to draw blood from the median cubital vein. A few drops were used for haemoglobin analysis on a HemoCue™ (HemoCue AB, Ängelholm, Sweden) machine and the remaining blood was stored in a vacutainer tube and left to clot for 30 min. Afterwards, the blood was centrifuged at a spin rate of 145–202 $\times$ ***g*** for 15 min. The serum was pipetted from the clotted blood and stored in a 2-mL Eppendorf tube. Then, the serum was transported in a liquid nitrogen jar to the laboratory where it was stored at −40 °C until analysis.

Laboratory analysis was conducted at the Safe Focus Laboratory in Arusha, Tanzania, where serum ferritin and retinol blood serums were quantitatively analysed in duplicate using the Maglumi 800™ machine (Snibe Diagnostic, Shenzhen, China) (employing a chemo-luminescence immunoassay system) and the Human Reader™ (HUMAN Diagnostics, Magdeburg, Germany) machine (via a vitamin A enzyme-linked immunosorbent assay). Serum ferritin is an iron store that releases its iron when there is iron depletion [29]; therefore, low levels of serum ferritin confirm iron deficiency. Serum retinol is the predominant circulating form of vitamin A, with vitamin A deficiency being diagnosed when the serum retinol count is less than 0.07 μmol L^{-1} [30].The analysis of serum retinol by enzyme-linked immunosorbent assay and serum ferritin by a chemo-luminescence immunoassay was based on techniques previously described by Yalow & Benson [31] and Woodhead & Weeks [32], respectively.

Statistical analysis

Descriptive statistics, such as frequency distribution, were used to assess the socio-demographic characteristic data

of the study participants. The chi-squared test was used to compare the categorical variables, such as vitamin A deficiency, anaemia status (haemoglobin < 11 g dL^{-1}) and iron depletion status (ferritin < 12 ng L^{-1}) between groups (control and intervention). A dependent *t*-test was computed to determine changes in the continuous variables, such as serum retinol, ferritin and haemoglobin concentrations, which occurred within control and intervention groups. An independent *t*-test was used to determine the changes in serum retinol, ferritin and haemoglobin between the groups from baseline and after intervention. Lastly, stepwise multiple regression analysis was carried out to identify factors associated with serum retinol increase at the end of the study. SPSS, version 25 (IBM Corp., Armonk, NY, USA)™ and PRISM, version 7 (GraphPad Software Inc., San Diego, CA, USA) were used to perform statistical analysis. $P < 0.05$ was considered statistically significant.

Ethical approval

Ethical clearance from National Institute for Medical Research (NIMR/HQ/R. 8a/Vol. 1X/2708) was obtained along with a permit from NCA Authority. The ethical committee approved a written consent, parental/guardian assent forms (for minor participants) and the use of verbal consent for the case of illiteracy. After explanation to the study participants, those willing to participate signed informed consent forms. For the participants who did not know how to read and write, consent was provided orally in Maa with an impartial (nonresearch associated) witness to acknowledge the individual's verbal consent, and a thumb print signature was used.

Results

Socio-demographic characteristics of the study participants

There were 77 participants who volunteered to join the study and, based on the inclusion and exclusion criteria, 50 participants (25 in the control and in the intervention group) were eligible and consented to participate in the study (Fig. 1). Of those enrolled participants, two mothers delivered before follow-up and one miscarried; therefore, 47 participants remained at follow-up assessment. Over half (64% and 56% in the intervention and control groups, respectively) of the study participants were between 25 and 29 years of age. Most of the participants (92% and 96% in the intervention and control groups respectively) reported being married, and 72% listed their mothers-in-law as the nearest female supporter (Table 2).

Haemoglobin and anaemia

During baseline, study participants had a mean haemoglobin level of 12 and 11 g dL^{-1} in the intervention and control groups, respectively, showing no statistical difference of the haemoglobin levels between the groups ($P = 0.74$) (Fig. 2). There was no significant difference in the level of haemoglobin after 6 months between the intervention and control groups ($P = 0.06$). Moreover, 76.2% of the participants were anaemic during baseline with no significant difference between the groups ($P = 0.27$); however, there was a significant decrease in the proportion of anaemic women in the intervention group ($P < 0.02$) compared to the control group at follow-up.

Serum ferritin and iron deficiency

At the beginning of the study, participants across both groups had a mean ferritin of <7 ng mL^{-1}. However, after the food basket intervention, the ferritin levels were seen to slightly increase in the intervention group and further decrease in the control group (Fig. 3), whereas there was no statistical difference of pre- and post-intervention ferritin ($P = 0.10$). Although there was no significant difference in the proportion of iron-deficient women in both groups ($P = 0.44$) at the beginning and end of the study, the control group had a higher prevalence of iron-deficient women than the intervention group at the end of the study.

Serum retinol and vitamin A deficiency

Both groups had a serum retinol of less than 0.70 μmol L^{-1} during baseline and the difference was statistically insignificant between the groups ($P = 0.32$). After 6 months of the food basket intervention, there was a significant increase of serum retinol of 20 μmol L^{-1} in the intervention group ($P < 0.001$), whereas there was an insignificant increase of 3 μmol L^{-1} in the control group ($P = 0.07$) (Fig. 4). All of the study participants were vitamin A deficient and there was no statistically significant difference between the two groups at baseline ($P = 0.28$). Both groups experienced a decrease in the proportion of vitamin A deficient women over the course of the study, although the control group remained with a higher proportion of vitamin A deficient women after 6 months.

A stepwise multivariable analysis was performed to calculate the contributions made by the geographic location (ward), baseline haemoglobin, serum ferritin and serum retinol changes. The findings showed that, at baseline, vitamin A status of the participants was positively

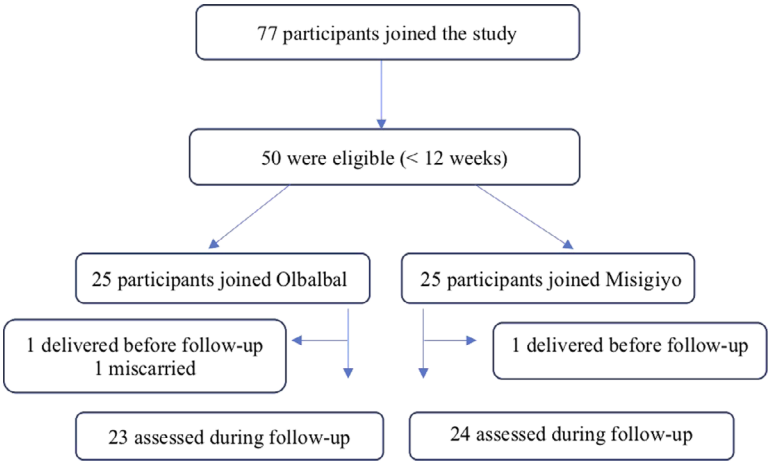

Figure 1 Distribution of study participants and loss to follow-up. At the beginning of the study, 77 participants joined the study but only 50 (25 each ward) were eligible for enrolment. At the end of the study, there were three dropouts caused by miscarriage and early delivery (before 6 months of intervention).

associated with the increase of serum retinol during follow-up. Conversely, wards, baseline haemoglobin and serum ferritin were negatively associated with serum retinol levels (Table 3). In addition, independent variables were able to predict 69% of the serum retinol changes.

Discussion

The food basket, together with nutrition education interventions, significantly increased serum retinol in pregnant women in the intervention group; however, there was an insignificant increase of serum retinol in the education only group (control). The present study is one of only a few showing the usefulness of fruits and vegetables with respect to reducing maternal vitamin A and iron deficiency, especially in pastoral societies.

The significant increase of serum retinol may be associated with the dietary intake of vegetables and fruits present in the food basket. These findings were in contrast to the findings of Mulokozi *et al.* [33] who found no significant difference between vegetable intake and retinol status of Tanzanian pregnant women. The difference between the results of the present study and those of Mulokozi *et al.* [33] may be attributed to the different study designs because the latter study assessed the participants' retinol level and related it to the vegetable intake, whereas the present study measured the retinol levels of vegetable intake and nonvegetable intake participants for a period of time. Moreover, the reason for this shift may relate to the findings of the study by Tanumihardjo *et al.* [34], who reported that supplying vitamin A rich foods to deficient patients results in high cleavage rates of provitamin A, which contributes to the increased bio-efficacy of serum retinol.

The presence of small amounts of zinc in the food supplied may have contributed to the increase of serum retinol. Hess *et al.* [35] reported that zinc acts as a cofactor of β,β-carotene 15-15′- dioxygenase 1 (BCO1) enzyme, which plays an important role in breaking the provitamin A from plant foods to the form that is easily absorbed (retinol) in the body. Dietary intake of wild vegetables (i.e. African nightshade), as reported in a previous study, may have contributed to the small increase of serum retinol in the control group (Mshanga N, Martin H & Petrucka P, Unpublished data). Moreover, the nutrition/health education provided during the present study might have contributed to the increase of serum retinol in both groups. As suggested by Howson *et al.* [16], providing nutrition education together with food interventions improves dietary intake because the educated population would have acquired a certain knowledge (e.g. green leafy vegetable intake prevents night blindness) that influences their dietary practices. The results were similar to the quasi-experimental findings of Kidala *et al.* [36] reporting a high increase of serum retinol in Tanzanian mothers who received nutrition education.

Arinola *et al.* [37] suggested an intake of deworming pills to reduce micronutrient deficiency among pregnant women; therefore, the increase of serum retinol in both groups may be attributed to the intake of deworming pills, malaria prevention interventions and the provision of WASH education. The findings of the present study are similar to a study carried out in Benin, which found an increase in haemoglobin after the provision of sulphadoxine-pyrimethamine and deworming tables to pregnant women who had low haemoglobin at the beginning of the study [38]. All of the participants were given the same care regarding the prevention of diseases (parasitic, infectious and infestation), controlling for artefacts in haemoglobin and serum ferritin levels. Hence, the changes seen in the present study may be attributable to the impact of the food baskets as a result of diversification and micronutrient redress. As suggested by Thompson and Amoroso [13], a combination of different sources of micronutrient rich foods (i.e. different vegetables per

Table 2 Socio-demographic characteristics of study participants

Variable	Intervention group		Control group	
	n	%	*n*	%
Number of participants				
Baseline	25	100	25	100
Follow-up	23	92	24	96
Age (years)				
15–20	2	8	1	4
21–24	1	4	2	8
25–29	16	64	14	56
≥30	6	24	8	32
Nearest female supporter				
Mother in law	17	68	19	76
Co-wife	5	20	2	8
Mother	3	12	4	16
Marital status				
Single	2	8	1	4
Married	23	92	24	96
Education status				
No formal education	8	32	6	24
Primary	12	48	16	64
Secondary	5	20	2	8
Gravidity				
0	0	0	0	0
1–3	14	56	17	68
4–6	3	12	7	28
≥7	8	32	1	4
Parity				
0	5	20	4	16
1–3	12	48	16	64
4–6	3	12	5	20
≥7	5	20	0	0
Occupation				
Pastoralist	23	92	24	96
Business women	2	8	1	4

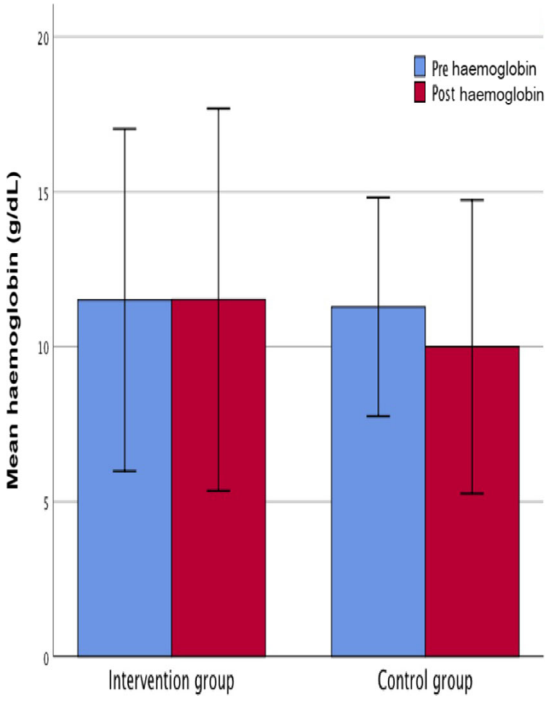

Figure 2 Pre- and post-haemoglobin. The study participants from both wards had a mean haemoglobin of less than 11 g dL^{-1} at the beginning of the study, whereas the haemoglobin level dropped in the control group and remained constant in the intervention group. The results were obtained from independent and dependent *t*-tests.

meal) may help to reduce and prevent different types of micronutrient deficiencies.

Although this is a pastoralist society, pregnant women were restricted in their consumption of milk, animal protein, rice and other carbohydrates, protein and fat foods [22], and there was also a lack of micronutrient supplements in NCA health centres [39]. The different vegetables provided contained a nonhaeme iron (low absorbable iron). This situation may explain the statistically insignificant increase of haemoglobin and ferritin after food basket intervention, which may be attributed by the supply of nonhaeme-rich vegetables and highly perishable vegetables (i.e. they cannot store for longer periods of time). Moreover, the small increase of serum ferritin and haemoglobin may be attributed to the haemo-dilution (increase of blood volume (approximately 1.5 L) that occurs in the last trimester, hence clinically reducing the amount of ferritin and haemoglobin [40,41].

Furthermore, the minor increase of serum ferritin may be triggered by the increased use of ferritin (stored iron) in haemoglobin synthesis. These findings are similar to those of the study by Milman [42], who found a decrease in ferritin when haemoglobin increases and associated this with the increased use of ferritin during haemoglobin formation. These results are in line with a study conducted by Makola *et al.* [43], which reported low ferritin levels after an 8-week supply of dietary supplements in Tanzanian pregnant women. The increase of haemoglobin and ferritin may be attributed to the reduced consumption of calcium-rich foods (i.e. milk) as one of their cultural restricted foods during pregnancy because calcium tends to hinder the absorption of iron in the body. A study by Bivolarska *et al.* [44] found a significant reduction in maternal serum ferritin with dietary intake of fish and cow's milk.

Study limitations included a failure to control consumption by the target participants, although the TBAs undertook intermittent home-based visits to evaluate dietary intake and to advise the study participants to continue using the vegetables and fruits. Although the study participants used traditional storage methods (i.e. clay pots), some of the green leafy vegetables could not survive the 2-week period because of a lack of power and/or cold storage

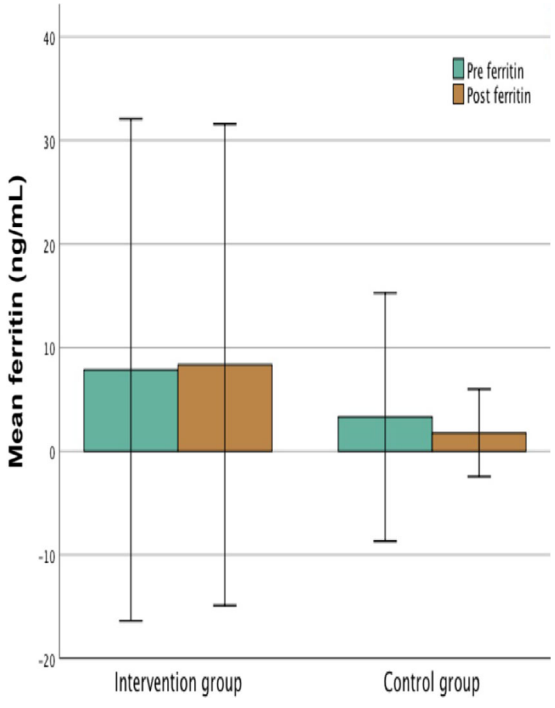

Figure 3 Pre- and post-ferritin. At the beginning of the study, participants across both groups had a mean ferritin of <7 ng mL^{-1}. However, after the food basket supply, the ferritin levels were seen to slightly increase in the intervention group and further decrease in the control group. The results were obtained from independent and dependent *t*-tests.

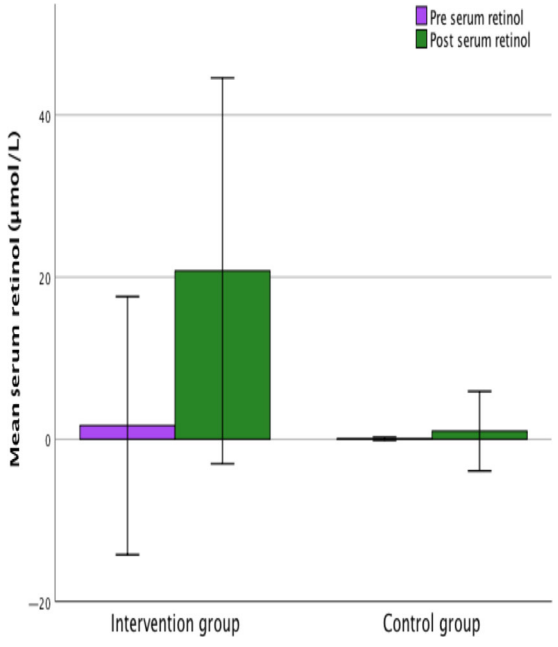

Figure 4 Pre- and post-serum retinol. Both groups had a serum retinol of less than 1 µmol L^{-1} during baseline, whereas, after 6 months of the food basket intervention, there was an increase of mean serum retinol of 20 mcg dL^{-1} in the intervention group and 3 mcg dL^{-1} in the control group. The results were obtained from independent and dependent *t*-tests.

in this community which was the resuilt of a lack of electricity in the conservation area. Because of budget constraints, the study failed to assess creatinine levels for detecting infection among participants; however, the study participants were advised to practice WASH and other hygienic practices (i.e. food pasteurisation) to prevent infections. Lastly, the majority of study participants joined the study during weeks 6–12 of pregnancy, and so we may have missed a crucial period where there is high need for micronutrients (such as folic acid, which is highly needed before conception and during the first trimester).

Overall, the evidence obtained from the present study indicates that, when used together, food basket and nutrition education interventions may reduce micronutrient deficiency amongst pregnant women in developing contexts. Moreover, the present study shows the importance of treating vitamin A deficiency by advocating for the consumption of vegetables and fruits, especially in pregnant women, because they are being advised to consume provitamin A (β-carotene) as a result of its low likelihood of causing vitamin A toxicity. Therefore, the NCA could allocate farming areas in nearby districts to enable the availability of vegetables and fruits. Furthermore, the community/traditional/religious leaders (e.g. Laigwanan, elders) should be trained and advised on the importance of the intake of vegetables/fruits among pregnant, lactating women, as well as women of reproductive age, because they are the most influential persons in the community.

Table 3 Factors predicting the vitamin A levels during follow-up

	β^2	*P*	Confidence interval
Constant	49.18, 8.31	0.000	32.40 to 65.95
Wards	−19.78, 2.330	0.000	−24.49 to −15.08
Pre-haemoglobin (g dL^{-1})	−0.15, 0.62	0.805	−1.41 to 1.10
Pre-ferritin (ng mL^{-1})	−0.21, 0.15	0.166	−0.52 to 0.09
Pre-serum retinol (µmol L^{-1})	0.578, 0.21	0.009	0.15 to 1.007

$r = 0.83$, $r^2 = 0.69$, adjusted $r^2 = 0.65$.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

The Creates and Green Hope Organization funded this research through the Maasai Agri-Health Cooperative project. CREATES funded data analysis, interpretation and manuscript writing for parts of the study, whereas Green Hope Org. financed all of the data collection activities.

NM and PP were responsible for conceiving the study. NM was responsible for data curation, formal analysis, methodology and writing the original draft. PP was responsible for resources. HM and PP were responsible for study supervision. NM, HM and PP were responsible for writing, reviewing and editing. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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 CONSORT guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned [National Institute of Medical Research (NIMR/HQ/R. 8a/Vol. 1X/2708)] have been explained.

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NUTRITION INTERVENTIONS

Effectiveness and safety of selenium supplementation for type 2 diabetes mellitus in adults: a systematic review of randomised controlled trials

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Keywords
selenium, type 2 diabetes mellitus, adult, insulin resistance.

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Abstract

Background: The role of selenium (Se) in the management of type 2 diabetes mellitus (T2DM) remains unclear. We systematically assessed the effectiveness and safety of Se supplementation in adults with T2DM.
Methods: MEDLINE, EMBASE and the Cochrane Library were searched up to April 2018 for randomised controlled trials (RCTs) evaluating the effectiveness of Se against a comparator on DM-related outcomes.
Results: Four RCTs (241 participants) were included. In individual RCTs, Se supplementation significantly reduced fasting insulin levels [mean difference (MD) = −3.6 μIU mL^{-1}; 95% confidence interval (CI) = −6.36 to −0.84; MD = −5.8 μIU mL^{-1}; 95% CI = −9.23 to −2.37], homeostasis model of assessment-estimated insulin resistance (HOMA-IR) (MD = −1; 95% CI = −1.79 to −0.21; MD = −1.6; 95% CI, −2.58 to −0.62) and homeostasis model of assessment-estimated B cell function (HOMA-B) (MD = −13.6; 95% CI = −23.4 to −3.8; MD = −22.6; 95% CI = −36.39 to −8.81). No effects of Se were noted on most of the other outcomes of interest. None of the RCTs assessed the mortality, diabetes-related complications, non-high-density lipoprotein (non-HDL), blood pressure and health-related quality of life. The impact on HDL and fasting plasma glucose (FPG) was ambiguous. Only one adverse event (nausea) was reported as a reason for discontinuing the intervention; however, among the studies, the reporting was not accurate. Furthermore, only one RCT reported increase in FPG level in the Se group (MD = 36.38 mg dL^{-1}; 95% CI = 15.39–57.37).
Conclusions: Currently, there is no evidence to support the effectiveness of Se supplementation in the T2DM population.

Introduction

Diabetes mellitus (DM) has become a global burden of health care, currently affecting more than 425 million people [(1)]. By the year 2045, its prevalence is anticipated to increase to 629 million [(1)]. Type 2 diabetes mellitus (T2DM) is the most prevalent form of DM, accounting for 90% of all diabetic cases. Due to chronic hyperglycaemia, DM leads to multifaceted complications, such as retinopathy, atherosclerosis, nephropathy, polyneuropathy and diabetic foot ulcers [(1,2)]. For the first-line of therapy, long-term lifestyle changes are recommended, such as the establishment of a healthy diet, physical activity and optimisation of body weight. If these changes are not sufficient to control the glycaemic profile, oral medication is prescribed [(1)]. Given the rising worldwide prevalence and the fact that up to 50% of patients have developed complications even at the time of diagnosis [(3)], research into

effective methods of primary and secondary prevention of T2DM has imposed a massive strain on scientists.

Selenium (Se) is a trace element that is substantial for the maintenance of thyroid and immune-endocrine function [4]. However, its effect on glucose metabolism has not been well established. As a chronic hyperglycaemia can cause a substantial increase of reactive oxygen species (ROS) and oxidative stress, leading to diabetes-related complications [5] and a decreased Se level [6], it was hypothesised that, in patients diagnosed with T2DM, Se supplementation may be beneficial. However, a number of studies indicate that it may act adversely on glucose homeostasis and insulin sensitivity and even increase the risk of T2DM [7–11]. This can be partially explained by the impact of Se on selenoproteins and insulin signalling [12]. The antioxidants can prevent oxidative cell damage by scavenging ROS; however, their overexpression may impair insulin sensitivity because ROS are also essential for insulin sensitisation [5]. There is also growing evidence from animal [13,14] and human studies on the potential procancerogenic effect of Se supplementation [15]. Therefore, the potential benefits of Se need to be balanced with possible harms. Recently, in 2018, two systematic reviews of randomised controlled trials (RCTs) showed equivocally the effect of selenium on T2DM development [10,11].

Although a 2017 systematic review [16] evaluated the effects of different antioxidants on diabetic kidney disease progression, no RCT with Se supplementation was included. In the last few years, a number of relevant interventional studies have been published that showed the ambiguous effects of Se supplementation on glycaemic control, insulin resistance and the lipid profile [7,17]. Although inconsistent data suggest that Se influences the course of T2DM, the direction of the effect remains unclear. More recently, Tabrizi *et al.* [6] concluded that Se supplementation reduced insulin concentrations and increased the quantitative insulin sensitivity check index (QUICKI) compared to placebo, with no beneficial effects of the intervention on the other outcomes of interest.

Given the conflicting data from recently published RCTs [7,17,18], the scarcity of valuable conclusions from systematic reviews [16,19] and the lack of registration of ongoing studies, the present review aimed to systematically evaluate the effectiveness and safety of Se supplementation in the management of T2DM in adults.

Materials and methods

This systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Intervention [20] and in accordance with the PRISMA Statement [21] (for the PRISMA Checklist, see the Supporting information, Table S1).

The methods were specified in advance and documented in a protocol published in PROSPERO with registration number CRD42017078657 [22], which was followed at each stage of this review.

Eligibility criteria

All relevant RCTs, including those of crossover design, were eligible for inclusion. No restrictions on the lengths of trials, interventions and follow-up of outcomes were imposed. Participants were adults with T2DM (defined by standard diagnostic criteria valid at the time of commencing the study) [22], regardless of the presence of diabetes-related complications. To increase the homogeneity, studies performed only in a population with type 1 diabetes mellitus (due to a distinct aetiology and clinical course) [23] or gestational and/or pregestational diabetes mellitus (due to disparities in functions of the endocrine system leading to significant alterations in maternal metabolism) [24] were excluded.

Studies were included regardless of Se dose/duration/frequency. Studies that assessed Se as a part of a complex drug/supplement were excluded. Subjects in the control group received either placebo/standard care or no intervention. The *primary* outcomes were all-cause/diabetes-related mortality; body weight (BW)/body mass index (BMI) change; diabetes-related complications; and adverse events (AEs). The *secondary* outcomes were insulin sensitivity/resistance; glycaemic control; blood pressure (BP); lipid profile; and health-related quality of life (HRQoL) (measured and calculated as change from baseline at the end of the study with validated instruments).

Literature search

MEDLINE (through PubMed), The Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) and EMBASE were searched for relevant studies published up to August 2017 (and updated in April 2018). The weekly e-mail update of new search results in PubMed was performed. Three other databases (http://apps.who.int/trialsearch; http://www.ukctg.nihr.ac.uk/default.aspx; https://www.tripdatabase.com) were also screened to identify unpublished and ongoing trials. The main Medical Subject Headings (MeSH) and text keywords used in the search strategy were as follows: diabetic; diabetes mellitus, type 2; diabet*; selenium; selenium compounds. No language restriction or other filters were imposed. Only the Cochrane Collaboration's validated filters (http://work.cochrane.org/rct-filters-different-databases) for identifying RCTs in PubMed and

EMBASE were used [20]. For full search strategy, see the Supporting information (Table S2).

Five of the reviewers (AS, ZO, JDP, BMZ, MK) independently screened titles and abstracts of identified articles and evaluated them for eligibility. The full texts of studies assessed as potentially relevant were retrieved and checked against eligibility criteria. The references of identified studies, key review articles and systematic reviews were also screened for any additional relevant papers.

Data extraction and quality assessment

Data extraction was performed, using a data extraction form designed by the reviewers, independently by two groups (AS, ZO and JDP; BMZ and MK) and then crossly assessed to identify any discrepancies. Data were extracted as complete (available) case analyses. Differences were resolved by discussion. All extracted data were entered into REVIEW MANAGER (REVMAN), version 5.2 (The Cochrane Collaboration, The Nordich Cochrane Center, Copenhagen, Denmark) by one group (AS, ZO and JDP) and checked for accuracy by an independent group (BMZ and MK).

The same two groups of the reviewers independently assessed methodological quality of the included trials using the Cochrane Collaboration's tool for assessing risk of bias, including random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other bias. All data with support for judgment were entered into REVMAN, and risk was classified as 'high', 'low' or 'unclear'. A consensus was achieved through discussion; in case of disagreement, another reviewer (HS or BMR) was consulted.

All available supplementary sources of relevant data were checked during the process of data extraction and risk of bias assessment to ensure the highest possible completeness and reliability of the analysis. Attempts were made to contact the authors to access additional relevant data or clarification of methods, as required; however, with no response.

Data analysis

Heterogeneity was determined by chi-squared and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. For the chi-squared test, χ^2 greater than the degrees of freedom and $P < 0.05$ indicate substantial heterogeneity; for the Higgins I^2 statistic [25], a value of 75% is defined as considerable heterogeneity [20]. The visual inspection of forest plots was also performed. Identification of substantial heterogeneity of the included studies (>50%) was planned to be followed by analysis based on the random-effects model. If substantial heterogeneity was not revealed, the fixed-effects model was planned to be used. However, as a result of substantial clinical heterogeneity (variability in the included populations), a meta-analysis was not performed.

The data were analysed using the REVMAN, version 5.2 (The Cochrane Collaboration, The Nordich Cochrane Center, Copenhagen, Denmark). For continuous outcomes, the mean difference (MD) with 95% confidence interval (CI) between the experimental and control groups is reported to show the difference. If data were presented as means, the MDs were obtained by subtracting the final mean from the baseline value; missing SDs were estimated with the correlation coefficient quantified for each outcome using available data from included studies [20]. The analyses were based on the available case analysis.

Due to an insufficient number of eligible trials (<10) included, the publication bias (using a test for asymmetry of the funnel plots as proposed by Egger *et al.* [26] was not assessed [20,26].

A number of subgroup analyses were planned based on factors that may potentially influence the results, such as: the age of participants, sex of participants, type of supplement (a type of Se compound), dosage, duration of intervention, comparators, concomitant medications and presence of diabetes-related complications. However, due to the limited data available, these analyses were not performed. After primary analysis, we considered the additional post-hoc subgroup analysis to assess how the study quality affected the effect of Se; however, there were insufficient data to draw any meaningful insights from the analysis. The RCTs were poorly reported, all having at least one high and one unclear risk of bias in the risk of bias domain.

Results

For a flow diagram documenting the study selection process, see Fig. 1. All identified eligible trials were published in English. Two full-text studies by Bahmani *et al.* [17,27] were thoroughly assessed and judged as one trial. Table 1 summarises the key characteristics of the four included studies. For the characteristics of excluded trials, with reasons for their exclusion, see the Supporting information (Table S3). Moreover, two registered RCTs were identified (one RCT completed, with published study protocol) [28], although the results were not available (see the Supporting information, Table S4).

Summary of included studies

The four included studies randomised a total of 241 participants (age range 18–85 years) [7,17,18,27,29]. All

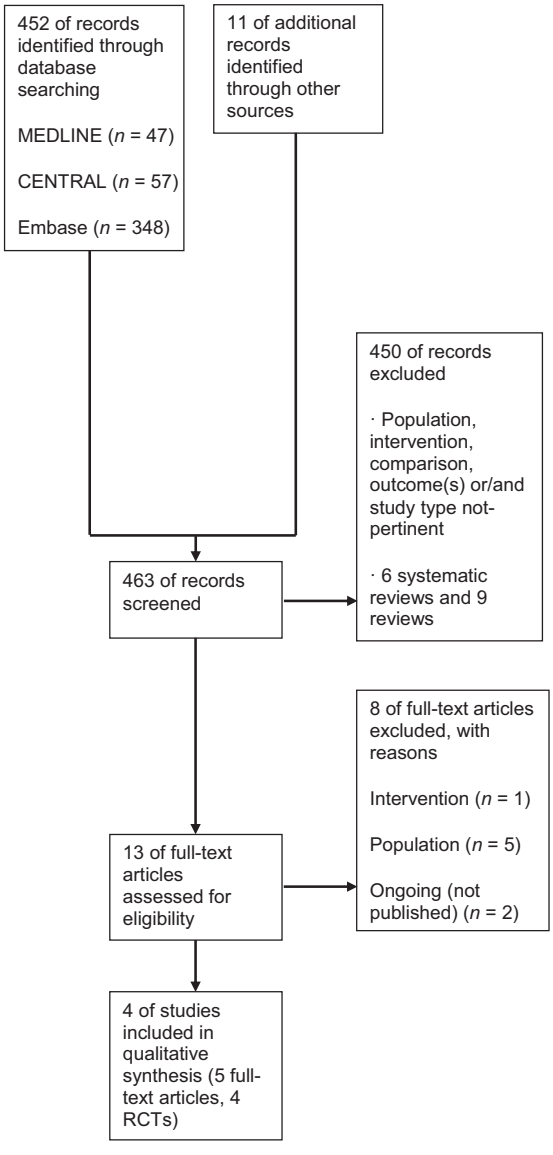


Figure 1 Flow diagram of the study selection process. RCT, randomised controlled trial.

selected studies were randomised, placebo-controlled, superiority, single-centre trials of parallel design with two arms [7,17,18,27,29]. Except for one study, performed in France [29], all studies [7,17,18,27] were undertaken in Iran. Sample size calculations were only available in two trials [17,18,27].

With the exception of one RCT by Faure *et al.* [29] (0.96 mg day^{-1}), the daily dose of Se was 0.2 mg [7,17,18,27]. The type of Se supplementation was consistent across the studies (capsules, tablets, or ampoules; via the oral route). The RCTs were heterogeneous with respect to Se compounds received (Se, sodium selenite, Se yeast). The studies were inconsistent in regard to the duration of the intervention, which ranged from 8 weeks [18] to 12 weeks [7,17,27]; for one RCT, the follow-up period was reported as 3 months (90 days) [29]. No concomitant intervention was imposed in any of the evaluated trials. In all included trials, standard antidiabetic therapy was maintained; in two RCTs, the preservation of antilipidemic treatment was also mentioned [17,27,29]. The authors of three RCTs [7,17,18,27] encouraged study participants to follow their routine diet and not to change regular levels of physical activity throughout the trial period. Only two RCTs reported baseline Se level (reported by authors as within normal and below laboratory range) [7,29]. The daily intake of Se throughout the study was evaluated exclusively by Bahmani *et al.* [17] and Faure *et al.* [29] (53.2 to 54.9 μg day^{-1}). Apart from one trial [29], where financial support from industry was declared, all other studies were supported by grants [7,17,18,27].

The methodological quality assessment of the four included trials is presented in Fig. 2, as well as in the Supporting information (Fig. S1). Intention-to-treat analysis was performed in two RCTs [17,18,27]. All included trials had a number of methodological limitations, including unclear sequence generation (two RCTs) [17,27,29], unclear allocation concealment (three RCTs) [7,17,27,29] and selective or unclear reporting (four RCTs) [7,17,18,27,29]. The risk of attrition bias was high or unclear in three RCTs [17,18,27,29]. Three RCTs were evaluated as having a high risk of other bias [7,17,27,29]. An adequate number of participants for final analysis (≥80%) was achieved in all of the studies [7,17,18,27,29]. Only two RCTs provided an adequate description of the compliance assessment method [17,18,27].

Due to the high heterogeneity of groups of patients in the included studies (T2DM with different complications, such as: retinopathy, nephropathy and stable coronary heart disease), a narrative summary was performed instead of pooling data in the form of meta-analyses. A summary of all numerical data is provided in Fig. 2.

Selenium supplementation and body weight/body mass index change

Only two RCTs (n = 120; Se 0.2 mg day^{-1}) reported data on these outcomes; no differences between groups were noted at any time point (8 and 12 weeks) for BW and BMI change [17,18,27].

Selenium supplementation and glycaemic control

Glycated haemoglobin (HbA1c)

Two RCTs (one RCT, n = 60; Se 0.2 mg day^{-1}; and one RCT, n = 48; Se 0.96 mg day^{-1}) reported this outcome at the same time point (12 weeks) [17,27,29]. Regarding another RCT (n = 60; Se 0.2 mg day^{-1}), based on the

Table 1 Characteristics of the included studies

Reference, year (country)	Participants, age (years) at enrolment	Intervention	Comparison	Duration of intervention (follow-up)	Analysis [*n/N*; follow-up (%)]	Sample size calculation
Farrokhian *et al.* 2016 (Iran) [18]	*n/N* 54/60; females 66.6%;40–85 years [mean (SD) age: 57.85 (10.74)]; type 2 diabetic patients with stable coronary heart disease	Se yeast 0.2 mg day^{-1} (tablets) (*n/N* 27/30)	Placebo (cellulose, not specified) (*n/N* 27/30)	8 weeks (8 weeks)	ITT for each outcome (60/60; 90%)	Yes
Bahmani *et al.* 2016 (Iran) [17]; Bahmani *et al.* 2016 (Iran) [27]	*n/N* 52/60; males 50%; 45–85 years [mean (SD) age: 62.25 (11.01)]; patients with diabetic nephropathy and proteinuria; 10% of patients with diabetes mellitus type 1	Se yeast 0.2 mg day^{-1} (capsules) (*n/N* 26/30)	Placebo (capsules, starch) (*n/N* 26/30)	12 weeks (12 weeks)	ITT for each outcome (60/60; 87%)	Yes
Faghihi *et al.* 2014 (Iran) [7]	*n/N* 60/65; males 56.6% (*n* 60); 18–70 years [mean (SD) age: 54.54 (7.65); *n* 60]; type 2 diabetic patients	Sodium selenite 0.2 mg day^{-1} (tablets) (*n/N* 33/34)	Placebo (tablets, not specified) (*n/N* 27/31)	3 months (12 weeks)	ACA for each outcome (60/65; 92%)	Not reported [in protocol (60); calculation not specified]
Faure *et al.* 2004 (France) [29]	*n/N* 48/56; percentage of males not specified; 49–58 years (range; mean not specified); type 2 diabetic patients; 51/56 diabetic retinopathy	Se 0.96 mg day^{-1} (Granions de Selenium, ampoules) (*n/N* 21/not specified)	Placebo (not specified) (*n/N* 27/not specified)	3 months (90 days)	PP for each outcome (48/56; 86%)	Not reported

ACA, available case analysis; ITT, intention-to-treat; PP, per protocol.

available data, MD and SDs were calculated [7]. In none of these RCTs did Se supplementation lead to a significant reduction in HbA1c compared to placebo.

Fasting plasma glucose (FPG)

Three of four RCTs (two RCTs at week 12: $n = 60$; Se 0.2 mg day^{-1} and $n = 48$; Se 0.96 mg day^{-1}, and one RCT at week 8; $n = 60$; Se 0.2 mg day^{-1}) reported no significant difference with respect to this outcome between groups at different time points [17,18,27,29]. In only one RCT ($n = 60$; Se 0.2 mg day^{-1}; 12 weeks) was a significant change (increase) in FPG (mg dL^{-1}) found in the Se group (calculations were made based on available data) [7].

Selenium supplementation and insulin resistance

Fasting insulin

In two RCTs (total $n = 120$; Se 0.2 mg day^{-1}) that assessed this effect, Se supplementation resulted in a significant decrease in fasting insulin levels at different time points (one after 8 weeks and the other after 12 weeks) [17,18,27]. In the remaining two RCTs ($n = 60$; Se 0.2 mg day^{-1}; and $n = 48$; Se 0.96 mg day^{-1}), no necessary data were available to calculate SDs and MDs between groups [7,29]. Additionally, the authors of the latter study have apparently reported the wrong units for insulin concentration (mmol L^{-1} instead of μIU mL^{-1}, with the latter being more biologically plausible).

Homeostasis model of assessment-estimated insulin resistance (HOMA-IR)

Consistent with the results of our analysis, two RCTs (total $n = 120$; Se 0.2 mg day^{-1}) reported a slight decrease in this insulin resistance marker with Se supplementation, both at 8 [18] and 12 weeks [17,27]. In another study ($n = 60$; Se 0.2 mg day^{-1}), the authors did not report the accurate data; therefore, a lack of data did not allow us to assess this outcome in terms of the MD between groups [7].

Homeostasis model of assessment-estimated B cell function (HOMA-B)

Consistent with our analysis, two RCTs (total $n = 120$; Se 0.2 mg day^{-1}) reported a significant decrease in HOMA-B with Se supplementation, after 8 [18] and 12 weeks of study [17,27].

Quantitative insulin sensitivity check index (QUICKI)

Only two RCTs (total $n = 120$; Se 0.2 mg day^{-1}) reported this outcome. Neither of studies, after 8 [18] and 12 weeks of intervention [17,27], reported a significant difference in QUICKI between groups.

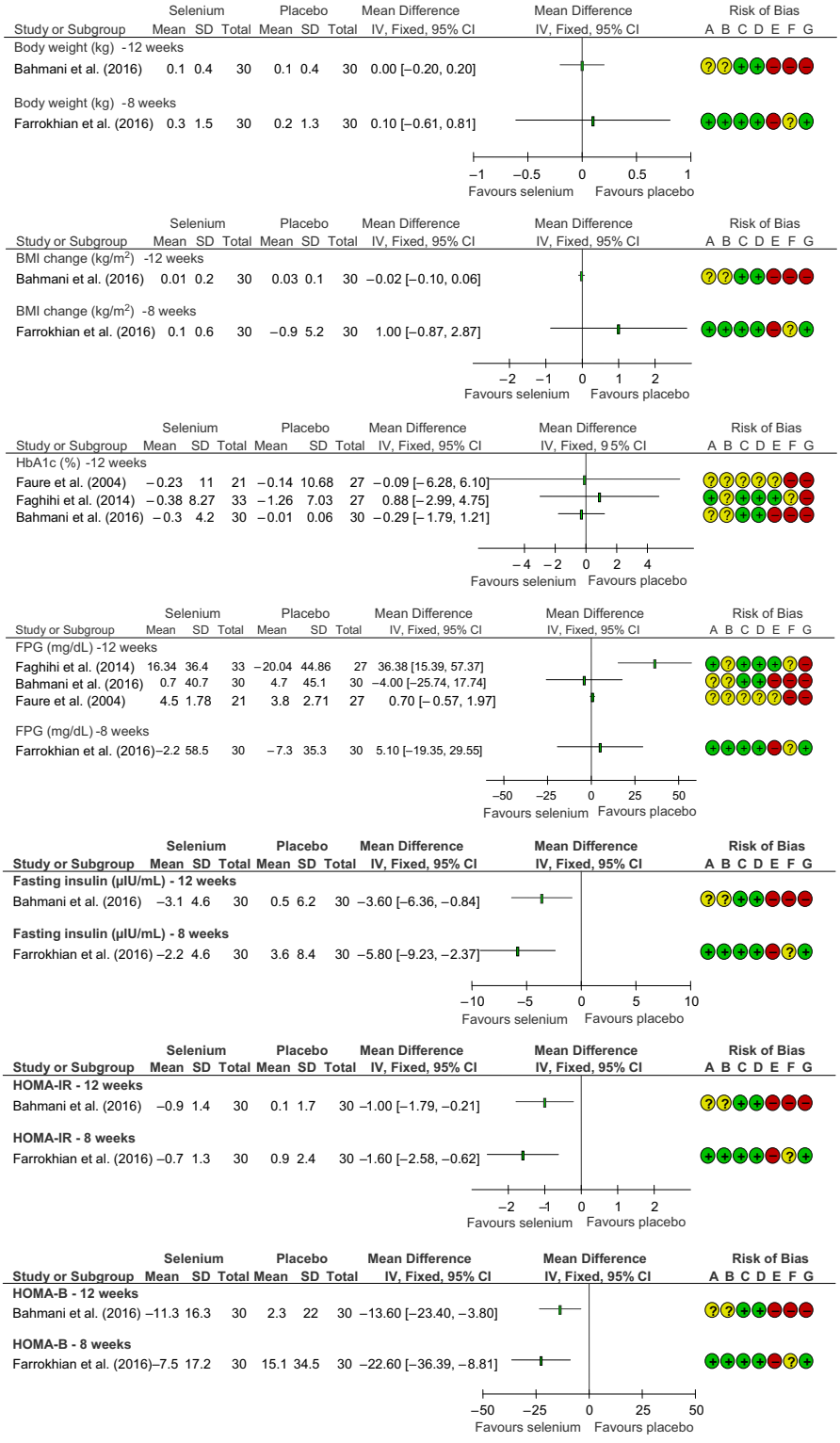
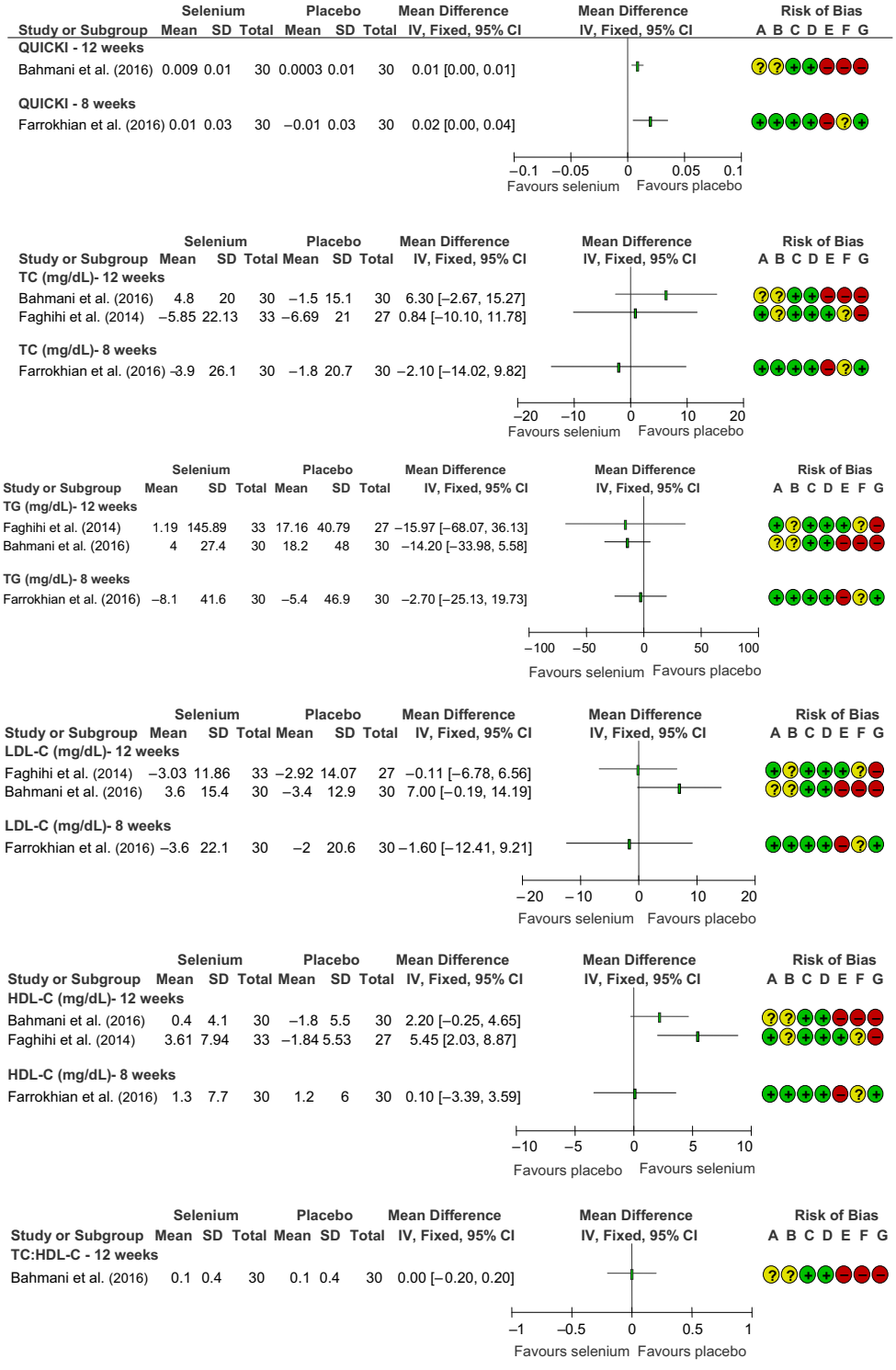


Figure 2 Effect of selenium supplementation on the management of type 2 diabetes mellitus: primary and secondary outcomes at different time points. BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein-cholesterol; HOMA-B, homeostasis model of assessment-estimated B cell function; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; LDL-C, low-density lipoprotein-cholesterol; QUICKI, quantitative insulin sensitivity check index; TC, total cholesterol; TG, triglycerides.



Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 2 Continued

Selenium supplementation and lipid profile

Total cholesterol (TC)

One RCT (n = 60; Se 0.2 mg day^{-1}) assessed change in TC after 8 weeks and found no effect of Se supplementation [18]. Also, two other RCTs (total n = 120, Se 0.2 mg day^{-1}) reported no differences between groups with respect to this outcome at week 12 [7,17,27].

Triglycerides

No difference in triglyceride levels was noted between groups after 8 weeks (one RCT, n = 60; Se 0.2 mg day^{-1}) [18] and 12 weeks (two RCTs, total n = 120; Se 0.2 mg day^{-1}) [7,17,27] of study.

Low-density lipoproteins (LDL)

Three RCTs evaluated the effect of Se supplementation compared to placebo on the change in LDL level. No difference was noted after 8 weeks (n = 60; Se 0.2 mg day^{-1}) [18] and 12 weeks (two RCTs; n = 120; Se 0.2 mg day^{-1}) [7,17,27] of study.

High-density lipoproteins (HDL)

There were conflicting data in regard to the effects of Se supplementation on the HDL level. A higher MD for HDL in favour of the Se group was found for only one RCT (n = 60; Se 0.2 mg day^{-1}) after a 12-week intervention (calculations based on available data) [7]. However, no effect of Se supplementation was reported in another two RCTs after 8 weeks (n = 60; Se 0.2 mg day^{-1}) [18] and 12 weeks (n = 60; Se 0.2 mg day^{-1}) [17,27] of study.

Total cholesterol/high-density lipoprotein ratio (TC:HDL ratio)

Only one RCT (n = 60; Se 0.2 mg day^{-1}) assessed the effect of this intervention on the TC:HDL ratio; however, no difference with respect to this outcome between the experimental and control groups was observed after 12 weeks of follow-up [17,27]. For two RCTs that did not report this outcome, an attempt to calculate MDs for the Se and placebo groups based on the data from the original studies was made; however, insufficient data were available to obtain SDs for both groups and MDs between groups [7,18].

Selenium supplementation and other diabetes-related outcomes

None of the included RCTs reported non-HDL levels, all-cause and diabetes-related mortality, diabetes-related complications, BP and HRQoL outcomes.

Safety of selenium supplementation in type 2 diabetic patients

Data regarding intervention-related AEs were available from all of the included RCTs (total n = 241) [7,17,18,27,29]. The AE rates were similar in the experimental and control groups. In two of the four RCTs, no AEs were observed [17,18,27]. In one RCT having an unclear risk of reporting bias, one patient reported nausea as a reason for discontinuation [7]. However, in three of the four RCTs, this outcome was poorly reported [7,17,27,29]. The authors of one RCT (n = 56; Se 0.96 mg day^{-1}) did not provide specific data to make an assessment of a difference between groups in the AE rate possible; the reasons for study discontinuation were pooled for both groups (one AE was noted but not specified; one stroke was also reported, although it was probably not assessed properly as a serious AE) [29].

Discussion

The present systematic review of current evidence showed that, compared to placebo, there is no effect of the supplementation of Se on most of the primary outcomes of interest in the population of adults with T2DM. Two out of four clinically important, prespecified endpoints (all-cause/diabetes-related mortality and diabetes-related complications) were not found in any of the included RCTs. No differences were observed with respect to BW and BMI change between the experimental and control groups. The overall AE rate was similar between groups; only once was a specified AE (nausea) reported as a reason for intervention discontinuation. However, the reporting of side effects was not adequate in three out of four RCTs; therefore, the evidence is limited. Regarding most of the secondary outcomes, no significant differences were found between the Se and control groups. However, the ambiguous results regarding the HDL levels (RCTs at different timepoints) and the adverse effect of Se supplementation on the FPG was reported. With regard to insulin resistance reduced fasting insulin, HOMA-IR and HOMA-B, but not QUICKI, were observed.

Although our systematic review focused on the TD2M subjects only to increase the homogeneity of the studied population, the population within the included trials were notably different, which might have influenced the consistency of findings. Moreover, three out of four RCTs included were performed in the same country (risk of *population bias*), limiting the generalisability of the results [7,17,18,27].

None of two RCTs [17,18,27] evaluating the Se yeast, assessed the baseline Se level of participants, as well the change at the end of intervention period. Despite the absorption of sodium selenite possibly being limited compared to Se yeast [30], Faghihi *et al.* [7] noted the significant increase of Se serum concentration from a status of deficiency to the optimal level. Only one author [29] assessed the red-cell Se GSH peroxidase activity, a

biomarker of Se redox function [31], which increased with the supplementation of elemental Se compared to placebo. A proper assessment of baseline Se status (deficiency *versus* normal), optimal level or change after the intervention, as well as the bioavailability of analysed Se form, should be considered, because these differences may misestimate the effects of the intervention.

Of note, Se is suggested to have a narrow therapeutic window with a possible adverse effect below and above the optimal range [32]; however, for subjects with T2DM, this range has not yet been established. The dietary reference intake (DRI) varies across the regulatory and scientific societies (25–70 μg for adults) and the optimal level of Se depends on the laboratory [10,33–35]. The daily intake should not exceed 400 μg L^{-1}; however, the recently reported toxicity suggested a lower dosage, which has been already included in the lower Japanese DRI [15,36]. The optimal dosage of Se for selenoproteins synthesis is in the range 50–75 μg L^{-1} [34]; however, due to the two-faced impact of selenoproteins on human health, this should be treated with caution [5,37]. The daily intake of Se throughout the study was evaluated in only two of four RCTs (53.2–54.9 μg day^{-1}) [17,18,27]. Apart from one RCT [29], all trials used standard, pharmacological doses (0.2 mg Se day^{-1}) [7,17,18,27]. Only one AE (nausea) was reported in the study by Faure *et al.* [29]. As Se may act dose-dependently, it should therefore be considered whether individuals are deficient or within normal or high Se levels, because the safety and effectiveness of its supplementation may vary across deficiency, adequacy, supranutritional and toxic levels [38]. The supranutritional level (estimated as >200% recommended dietary allowance) ranges between the adequate and toxic levels for a nutrient. The intake of Se from other dietary sources should also be estimated. Only two out of four RCTs assessed the baseline Se level [7,29], which was reported by the authors as being below and within the normal range. According to Faure *et al.* [29], the baseline plasma Se status and the activity of Se-related enzymes were within the normal laboratory range; however, after 90 days of intervention (0.96 mg Se day^{-1}), the Se level slightly exceeded the optimal value (from 1.04 to 1.27 μmol L^{-1}). Moreover, Faghihi *et al.* [7] found an adverse effect of Se on glucose homeostasis. Participants were noted with a baseline Se serum concentration in the normal laboratory range and supplementation led to an increase of Se level (from 42.69 to 71.98 μg L^{-1}) [7]. The authors indicated that a correlation between a rise of Se level and simultaneous FPG increase may exist. Moreover, the duration and timing (diet *versus* supplements) of exposure, the chemical form of Se, and genetic factors may all exert effects. It is possible that lifelong consumption of Se may be associated with more adverse effects (whereas the follow-up period in all of the included RCTs did not exceed 3 months) [11].

A systematic review can be only as good as the studies that it includes. Important limitations of the present review include the methodological quality of the included studies, the relatively short durations of the intervention periods (not more than 12 weeks), a lack of compliance assessment and/or its results, and the provision of sample size calculations in only two RCTs.

No similar protocols of systematic reviews had been published at the stage of commencing this work. However, during the completion of our review, another systematic review by Tabrizi *et al.* [6] concerning Se intervention was identified. Compared to our systematic review, numerous limitations were identified. The PICOS frame and the eligibility criteria for inclusion of RCTs in the other review were not precisely defined and, combined with the lack of a preregistered protocol, this increase the risk of a reporting bias. Furthermore, the search described by the authors was completed in May 2017 and did not include two RCTs published in 2004 and 2016 [27,29], which were included and evaluated in the present systematic review. Additionally, one RCT fulfilling the other review eligibility criteria was also omitted, which further increases the risk of bias [39]. The main limitation of the recently published systematic review is the decision to combine the available data into a meta-analysis, despite the populations' heterogeneity (a mixed population of patients with T2DM, polycystic ovary syndrome, gestational diabetes and diabetic nephropathy) and the different time frames for RCT interventions (6–12 weeks), which may be incorrect and misleading. Finally, the authors indicated that there was no significant publication bias based on the results of Egger's test. However, use of the test itself, when fewer than 10 RCTs are included in a systematic review, may be inappropriate, as suggested by the Cochrane Collaboration [20].

By contrast, a major strength of the present systematic review is the use of a rigorous methodology according to the Cochrane Handbook [20]. Moreover, several methods were employed to reduce the possible risk of bias (e.g. prespecified methods in the previously registered protocol in PROSPERO, a comprehensive study search). An additional advantage of this review is the focus on a well-defined population of patients with T2DM, aiming to increase the credibility of the results and make the findings available for direct application into clinical practice. No restrictions by language, year or length of the trial were imposed.

Due to high heterogeneity of study populations and interventions, the results obtained in the present review were not pooled in the form of a meta-analysis because it was judged to be inappropriate. We have shown inconsistent effects of Se supplementation on insulin and FPG.

By contrast, Tabrizi *et al.* [6] noted the positive effect of Se on QUICKI outcome, and no impact on FPG [6]. As a result of these and other abovementioned limitations, our conclusions differ.

Conclusions

The currently available evidence shows no consistent and positive effect of Se supplementation in adult patients with T2DM for most of the studied outcomes.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interests.

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All authors initially conceptualised the study and study design. AS, ZO, JDP, BMZ, and MK performed data collection and interpretation. AS, ZO, and JDP drafted the first version of the manuscript. HS, BMZ, MK, and BMR supervised the project. All authors read and approved the final version of the manuscript.

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 (protocol published in PROSPERO, ID number CRD42017078657) have been explained.

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Supporting information

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

Figure S1. Quality assessments of included studies (risk of bias summary and graph).

Table S1. PRISMA 2009 checklist.

Table S2. Search strategy for MEDLINE (via PubMed).

Table S3. Characteristics of the excluded studies.

Table S4. Characteristics of the ongoing studies.

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NUTRITIONAL SUPPORT

The experiences and support needs of people living at home with an enteral tube: a qualitative interview study

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Abstract

Background: The number of people with an enteral tube (ET) living at home is increasing globally and services to support them to manage this complex and life-changing intervention vary across regions. The present study aimed to gain an understanding of the experiences of people living at home with an ET and their carers, as well as to explore their views of supporting services and ET-related hospital admissions.
Methods: A qualitative inductive descriptive design was employed. Semi-structured, face-to-face interviews with a purposive sample of people with an ET living at home and carers were undertaken. Interviews were transcribed, initial codes were assigned for salient constructs, and these were then grouped and developed into themes and sub-themes.
Results: Nineteen people with ETs and 15 carers of people with ETs were interviewed. Five themes were generated: home better than hospital, feelings about the tube, living with the tube, help when you need it and cost for health service. Participants indicated the ET significantly influenced daily life. Participants described becoming used to coping with the ET at home over time and developing strategies to manage problems, avoid hospital admission and reduce resource waste. Variation in supporting services was described.
Conclusions: People with ETs and their carers need considerable support from knowledgeable, responsive healthcare practitioners during the weeks following initial placement of the ET. Twenty-four hour services to support people with ETs should be designed in partnership with the aim of reducing burden, negative experience, waste and hospital admissions. National frameworks for home enteral nutrition could set the standard for support for people with ETs.

Introduction

Enteral tubes (ETs) enable the delivery of food, fluid and medication for people who are unable to swallow sufficient to meet their needs. The number of people receiving ET feeding at home has increased globally over recent years, although the exact prevalence is difficult to determine [(1)]. The increase is a result of the trend for more complex care needs being managed in primary care, as well as increasing numbers of people having ET placed to manage long-term conditions or to support a long recovery from illness or surgical intervention. Gastrostomy tubes are commonly placed for long-term nutritional support [(2)]. In addition, people may be discharged from hospital with a jejunostomy and nasoenteric tubes [(2)].

Discharge from hospital of a person receiving ET feeding has enormous implications for both the person and their relatives or carers. It is a complex therapy, requiring the development of knowledge and skills and lifestyle adaptations. People with a gastrostomy tube report it to

be time-consuming and disruptive to their lives [3–7]. Furthermore, the relatives of people living at home with an ET have described managing the new life situation that it presents as a struggle [8,9]. Others have described ET feeding as an appreciable burden of treatment [10]. Appropriate education, training and support are required both to ensure a smooth transition between care settings and safe and effective management within the primary care setting [11–13].

Lack of support to manage ET feeding in the community has been reported to lead to complications, such as tube blockage, increased hospital admissions [14] and dissatisfaction with care provided [9]. Acute care hospitalisations have been reported to be common in some groups receiving enteral nutrition [15], with many visits to the emergency department being described as potentially avoidable [16]. Avoiding hospital attendance is important because the cost of hospital care is high and it has the potential to negatively impact on the person with an ET [10,16].

The presence of nutrition support teams in clinical settings varies from country to country and co-ordinated support for people receiving home enteral nutrition (HEN) can be lacking [2,17]. A recent systematic review by Majka *et al.* [18] highlighted a reduction in hospital costs with team interventions to support people with long-term enteral feeding. Interventions were described as multifaceted and included education, auditing and feedback methods [18]. There are several ways in which services can be organised to support people receiving enteral feeding at home [18,19]. Standards or guidelines for HEN services have been developed in some areas [20], although they are lacking in others [2]. However, there have been few published reports on patients or carers views on what could support them to manage ETs at home and their experiences of admission for tube-related problems. This is crucial to inform the design of services aiming to support people so that they develop confidence and techniques to self-manage ETs and prevent avoidable hospital admissions.

The overall aims of the present study were to gain understanding of the experiences of people with ETs and their carers concerning hospital admission for ET-related issues and to explore their views of services that could support the management of ETs at home and avoid hospital admission. The purpose of this study was to provide data to underpin the design of patient-focused ET services.

Materials and methods

Study design

A qualitative inductive descriptive design was employed to allow participants to voice their opinions and share their experience [21]. Semi-structured, face-to-face interviews were undertaken with people with ETs and their carers, enabling the interviewer to discover the participants own 'framework of meanings' [22].

Sample size

A purposive sample of people with ETs living at home in UK southern counties and their carers participated. The services provided for people with ETs living at home vary across the region, giving a sample with a range of experiences. Sample size was determined during analysis when it was considered that data saturation had been achieved (i.e. when no new information or themes emerged from the interviews) [23]. Participant characteristics were collected to 'ground' the findings [24]. Carers included unsalaried carers (i.e. family members) or employed carers for the person because both provide support for ET issues.

Eligibility criteria

Eligibility criteria included: adults (over 18 years) with ETs living at home; adult carers of people (over 18 years) with ETs at home; ability to give informed consent; and ability to understand and converse in English language.

Recruitment

Participants were recruited though several routes to increase the range and diversity of experience. Methods included:

- Advertisement through a support group (Patients on Intravenous and Nasogastric Nutrition).
- Contact of eligible people in general practitioner (GP) practices via a Trust Research Nurse and the local National Institite for Health Research (NIHR) Clinical Research Network. A researcher contacted those who expressed an interest and supplied a contact number via the Research Nurse or potential participants were invited to contact the lead researcher directly via letter from the practice.
- Three dietitians provided verbal information about the study during planned clinical visits if considered appropriate. People who expressed an interest and provided their contact details were contacted by a researcher.
- Advertisement and Participant Information Sheet (PIS) available at local events for people with ETs.

At first contact with the researcher, the study was explained, eligibility checked and, if interest expressed, a PIS was sent. A follow-up telephone call within 1 week confirmed receipt of the PIS and an interview date was arranged.

Interviews were conducted between October 2015 and March 2018 by two researchers who were trained in qualitative interview techniques. Thirty-one people were interviewed in their home, two people were interviewed in a private room in a healthcare location (with reimbursement of transport costs) and one person was interviewed at the home of the person for whom they cared. People with ETs and carers who agreed to participate chose to be interviewed together rather than separately. This enabled those who had difficulty in expressing themselves verbally to 'voice' their views. Both interviewers were registered nurses (RN) but introduced themselves as researchers. However, some participants knew one in her capacity as an RN in a HEN Team.

At the start of the interview, the PIS was reviewed with the participant(s) and a consent form was signed. Interviews were recorded digitally [21] and guided by an interview guide [25]. The guide contained six closed questions about participant characteristics in relation to their ET to allow description of the context of the findings and the main open-ended questions (Table 1) with associated prompts relating to the aim of the study [22].

Participants were informed the interview could be stopped and their consent withdrawn at any point without giving a reason, until the study findings were published. The interviewer explored topics raised by the participant in detail and checked understanding by summarising. At the end of the interview, participants were thanked and asked if they have any further comments. The interview was complete when the participant had nothing further to add.

Interviews were transcribed verbatim by a professional transcription service. The recorded interview was deleted following transcription. Transcription and analysis took place concurrently with the interviews. Initially, six transcripts were checked for accuracy against the recording by one researcher. This allowed the researcher to ensure that the transcription was verbatim and to immerse themselves in the data at the start of data analysis [26].

Table 1 Main open ended questions in semi-structured interview guide

- Tell me a bit about why and when the tube was put in.
- Could you talk about any sort of problems (if any) you have had with the tube?
- What helped you to deal with any of the problems that you had with the tube?
- Could you talk about any hospital admission that you have had experience of for problems related to the tube?
- Could you tell me how you think this admission/any of these admissions for tube problems could have been avoided?
- Can you describe to me what you would like in the community to help you to manage the tube?

Data handling

Research data were managed according to University policy. A unique anonymised number was allocated to individual participants' audio recordings and electronic files, which were stored on a password-protected University system. Paper records containing personal information (e.g. signed consent) were stored in a locked cabinet in a locked University office separately from the interview data.

Data analysis

Transcripts were imported into the software package NVIVO, version 12 (QSR International Pty Ltd, Melbourne, VIC, Australia) and analysed in accordance with the phases of thematic analysis outlined by Braun and Clarke [27]. Transcripts were read and reread to develop a general understanding, initial semantic codes were assigned to key attributes, and then expanded, and revised as required. The initial codes described important features of the data of relevance to the broad research question. Codes were then refined by grouping and a thematic list was developed [21,28]. Themes represented coherent groups of codes. Similar clusters of codes within each theme formed subthemes. Interviews were analysed separately for each person even when the interview of a carer and person with an ET took place together. A proportion of the scripts were independently analysed by two other researchers with the aim of identifying whether the codes and themes generated were robust and unbiased, and any disputes were resolved by discussion. Potential themes were reviewed and finalised to ensure that they presented the main concepts relating common, recurring patterns within interviews [27]. Subthemes focused on specific elements of the themes and provide a rich description of each theme. Quotations were selected to illustrate the essence of a theme [29] and the selection of quotes aimed to give a clear example from a wide range of participants. Quotes are *verbatim* but edited to provide a fluent account [omissions are indicated by (. . .)] and punctuation added to aid clarity [30]. Participants were referred to as C (carer) or P (person with ET) followed by an anonymous number.

Credibility

Standards for Reporting Qualitative Research [31] were used to ensure transparency. Dependability of the data and analysis were enhanced by conducting the research rigorously by adhering to the protocol to guide the systematic conduct of the study and allow for transparency of methods. An interview topic guide was used to ensure that questions were relevant to the research question. The

audio recording of the interviews was transcribed verbatim by an experienced transcriber and checked to ensure that participants' views were accurately represented in the dataset. Credibility was enhanced by the use of multiple analysts. The process of identifying participants, data collection and the analysis are reported accurately to enable the confirmability and context of the findings to be considered [26]. Although the issues described were context-specific, commonalities with other reports are discussed to enable consideration of transferability.

Research governance and ethics

Research ethics approval (15/LO/1359) was obtained via the National Integrated Research Application System (IRAS project ID: 185295). Approval to undertake the study in a Trust was given by the Trust Research Office and NHS Permission/PIC Authorisation was granted by the local CRN to undertake the study in the related primary care region. Informed consent was obtained from all participants.

Results

Nineteen people with ET and 15 carers of people with ET participated. The interview length was between 15 min and 82 min [mean (SD) 43 (16) min]. People interviewed together described the management of the tube as a joint venture, often with clearly defined roles for each person, as illustrated by the following:

> 'I look after the tube and she maintains it' to which his wife replied, 'You're the host, aren't you!' and he replied, 'I keep it safe' (PO15 and CO14)

The age of the person who carers supported ranged from 3 to 83 years [(mean (SD) 41 (27) years]. Only one carer was salaried. Four people with ETs lived alone, with the rest living with family (grandchildren, children or spouses). All reported living in their own homes. Table 2 shows the participant characteristics.

Five themes and 10 associated subthemes were generated (Fig. 1) and these are described with selected quotes to illustrate salient points. There was great similarity between the experience of carers and people with ETs and so themes were generated from both groups together.

Home better than hospital

This central theme described participants' experience and views of hospital admission for ET-related issues. Almost all of the participants stated that they preferred management of ET-related issues to be undertaken in their own home. Participants with balloon gastrostomy tubes (BGT) expected their tubes to be changed at home rather than hospital. One participant who had had his tube changed at home voiced his opinion about having it changed in hospital:

> 'I don't want to have to do that. Go up the [hospital name], are you joking? This way, suits me down to the ground' (P002)

Two subthemes within this theme related to hospital attendance avoidance and experiences of hospital admission.

Avoid hospital

A number of participants expressed that they would actively avoid hospital admission, as illustrated by one person with an ET stating:

> 'If we can avoid hospital we will' (P011)

Reasons for hospital admission avoidance included the time and discomfort taken to travel to hospital and the experience of hospital admission. As one person with a tube stated when describing why she liked to stay at home:

> 'Being at home is a hundred times better even if I'm still just as ill (. . .) because I've got the comfy chair that I can be hoisted into – we've got all the facilities here' (P004)

Several described strategies used to avoid hospital admission, ranging from replacing displaced BGTs to managing without feed over the weekend until routine community services could be accessed. This is illustrated by one carer describing how she reinserted a tube that had fallen out and then administered only water (contrary to good practice guidelines [32]) until the ET could be replaced by community staff:

> 'So, I put it back in and I phoned the helpline (. . .). But it was a case of if you really want anything done you've got to go to hospital. (. . .) so I thought he isn't going to go into the hospital, we don't have good experiences of [hospital name] (. . .) I said to her "well he's still having fluids so he'll be alright without his feeds until Monday morning"' (C005)

However, a few participants did not have strong views about avoiding attending hospital, as one carer said:

> 'I don't mind, I'm quite happy to take her if there was an issue or I'm quite happy for people to come here. I haven't got a problem either way . . .' (C009)

If admitted to hospital, many participants outlined that they were very keen to be discharged quickly.

Table 2 Participant and interview characteristics

Group	Interviewed	Mean (SD) age (years)	Age range (years)	Gender	Type of tube (one person had experience of two types)	Length of time with tube (months)	Tube management	Relationship to person with ET
Carers (n = 15)	Alone (n = 3) With person they cared for (n = 8) With another carer (spouse/partner) (n = 4)	51 (16)	22–77	Female: 13 Male: 2	RIG: 7 Button: 6 PEG: 2 Tube with JEJ extension: 3	2–240 (mean 76 ± 90)	Without support from other carers (n = 5) With support of salaried carers (n = 7) With support of family members (n = 3)	Mother (n = 5) Father (n = 2) Sister (n = 1) Wife/partner (n = 6)
People with enteral tubes (n = 19)	Alone (n = 11) With a carer (n = 8)	64 (9)	47–83	Female: 8 Male: 11	RIG: 11 PEG: 3 NG: 1 Tube with JEJ extension: 4	2–240 (mean 35 ± 53)	Primarily without support of carers (n = 5) With support from spouse/partner or salaried carer daily or at times (n = 9) Entirely managed by carers (n = 5)	NA

ET, enteral tube; PEG, percutaneous endoscopic gastrostomy; RIG, radiologically inserted gastrostomy.
Button: low profile gastrostomy; Tube with JEJ extension: tube with jejunal extension. NA, not available.

Hospital admission

Many participants related experiences of hospital admission for ET-related issues attributable to a variety of causes, such as ET dislodgement, stoma infection and complications with a routine BGT change. Some participants described the admissions as avoidable; for example, one carer participant who had experienced multiple admissions for tube dislodgement and considered hospital admission could be avoided by more frequent changes stated:

> 'Yes most of them, nearly all of them I think could be avoided' (C003)

Some participants described how their inability to contact a community healthcare professional able to provide support resulted in admission. This was often described as occurring out of usual office hours, for example one carer stated:

> 'if it happened to be out of hours you (...) talk to somebody who doesn't know anything but is just reading a script. Then because it's always low priority you end up with hours and hours and hours before they get back to you. And then they say take him up to A and E. He doesn't belong in A and E, we just need some help with this' (C010)

Others had experience of being admitted over one or more nights because the required procedure could not be scheduled in the hospital on the day they attended:

> 'When the tube came out and the new one wouldn't go in we were sent to the hospital about 11 AM. Went up there, they said they couldn't refit it until the next day' (C005)

Experiences of hospital admission ranged from being portrayed as positive to experiences that had left the person with the tube or the carer frustrated and fearful. The positive experiences were described as admissions where the issue was resolved quickly because of the presence of a healthcare professional experienced in tube management or where it was considered the issue was complex and admission inevitable. One carer described how a community professional had arranged for the person they cared for to be seen by the appropriate department which had led to a satisfactory experience:

> 'We've gone up a couple of times. Because you have to check for acid when you put the [type of] button in now, and a couple of times I haven't been able to get an acid reading. And I phoned [name of nurse] and [name of nurse] arranges for us to go up for an ultrasound to check the PEG is in place and things.

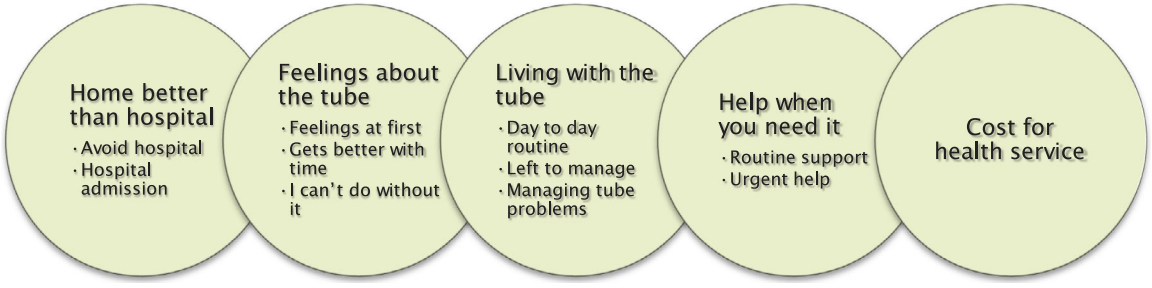

Figure 1 Themes and subthemes generated.

> But that's the only time and you'll just literally go in, have the x-ray and back out again. It's never been a major problem for us' (C009)

One of the reasons for a poor experience appeared to arise from hospital healthcare practitioners' lack of knowledge about ET placement and management. Furthermore, variation in the availability of staff able to manage tube problems impacted on the experience of hospital admission. One participant described his view having experienced tube displacement:

> '. . . the thing that I'd like you to note is that you go to Accident and Emergency and I don't think they are always ready and able to look after a PEG that has fallen out' (P006)

Another aspect of hospital admission described related to the hospital environment and the detrimental effect this could potentially have on the person with the tube. For some people the busy hospital environment caused confusion and the change in routine affected ET management. Several others described not being supported to self-manage their enteral nutrition, for example, one person with a tube reported:

> 'I got told off for touching the pump, while I was in hospital. They said I mustn't do anything even though I do it at home all the time (. . .) I thought oh well they can do it then!' (P012)

A few described not being able to meet their care needs. For example one participant with limited mobility stated:

> 'I was really, really thirsty and I said "Excuse me could someone help me to have a drink please?" (. . .) And I called and I called and I called, and in the end someone came and said "what do you want?", I said "Could you please pass me my drink?". So they passed my drink but they put it rested it on my arm (. . .) so I couldn't get it because my arm was still bad (. . .) So then when the consultant came round and said "we'd like to keep you in and do some surgery to hopefully stop it doing that again" I said "no thank you I want to go home"' (P004)

Several participants described their journey and hospital experience as time consuming and problematic. For example one carer stated:

> 'This one time we had to go to the day ward because there was no actual slot for us to get it done. So, obviously the ambulance that we went in couldn't stay there for hours, so they had to come back (. . .) We were there at 9 AM and we didn't get seen until 2 PM that afternoon and then [hospital worker] turned around and said "we can't arrange transfer you'll have to get a taxi and sort your own way back"' (C004)

A few participants and their carers described how food and drink offered was unsuitable for their dysphagia management. For example, one carer stated:

> 'That's what annoyed him as well. "What would you like to eat, what would you like to drink?" He's nil by mouth!' (C007)

This gave rise to feelings of frustration and anxiety.

Feelings about the tube

All of the participants described their feelings about the ET, both in terms of both physical sensations and emotional experience, giving rise to the second central theme. Participants described their feelings changing over time as they adapted to living with the tube and coping with issues that arose.

Feelings at first

Participants talked about their initial experience and feelings about having an ET inserted and coping in the immediate period following discharge from hospital, as illustrated by one participant:

> 'It's a huge shock to the system, when you actually get the tube put in and you stop eating. Immediately you are in a pickle anyway because it all seems very odd, your whole life seems very strange suddenly. That's bad enough having to deal with that (. . .) it's

very isolating and very odd, so to have something else go wrong with the tube' (P018)

The decision to have the tube inserted was described as difficult to cope with by several. This was either because it would impact on their eating habits or, for carers, because they were unable to provide food and drink for the person for whom they cared. As one carer stated:

'It made me feel awful as a mum that I couldn't even get basic food and medication to her and it was taken out of my hands. It wasn't great' (C003)

The period before initial tube placement was described as frightening by some, partly as a result of a fear of the unknown. One participant verbalised her feelings waiting for the tube insertion on the day of the procedure:

'I kept thinking, "where are my clothes?", because I was just going to run away and not be there. But obviously I did [stay] in the end and actually having it put in was fine, in the end' (P018)

The procedure to place the tube was commented on by a few with only one person reporting a distressing experience:

'And I wouldn't want to go through; I wouldn't go through it again' (P007)

However, the need to have the tube placed appeared to be accepted, as one carer participant stated:

'But then to be honest, when we found out that we will have to put the tube in, although it was a scary thing (. . .) the way the situation was, I thought, you know what, you can only get better' (C011)

Many participants reported receiving some training in managing the tube in hospital prior to discharge, although some would have liked more opportunity to learn the procedures required to care for the tube. As one participant indicated:

'I would have preferred someone to say "now do you understand?" and I could have said "could you go through that again". But she did it so quickly and spoke so quickly, which young ones do now, I couldn't take it all in' (C014)

Some participants identified that learning opportunities could be missed in hospital and suggested that they would have like to have been involved in tube management in the acute care setting. One participant stated:

'It would be nice to say "well this is what you can do at home", because there wasn't really much of that' (C002)

The complexity of the therapy was recognised, as one participant stated:

'But in the hospital people had come from University and they'd had weeks of training' (C012)

This lead to feelings of anxiety on discharge, as one participant described:

'You feel at a loss to begin with, and it's a bit worrying for family as well' (P009)

Some felt that they needed more time and support to learn the care required at home:

'I think it would have been better if she had done it the first time – "this is how it's done". And then come in another week, the next week, and say "right now you do it and I'll see where you go wrong"' (P015)

The first few weeks following discharge after initial insertion required people to learn and adapt to life with the ET.

Gets better with time

Many described becoming used to the tube and adapting their lifestyle to accommodate the tube. For example, one carer spoke about her initial feelings and how over time, through experience, she became used to managing the tube:

'I was petrified quite frankly. I never said anything but inside I was all tensed up all the time. So, yes it was very, very scary. But I've got it off pat now. I'm quite organised and once I knew what I had to do I was fine' (CO12)

Participants described the process of becoming used to the tube as a learning process that required time, as one indicated:

'It takes time to learn everything' (CO15)

Some participants stated that they were supported to learn ET management by observing a nurse undertake it and then doing it a few times observed until they felt confident. For many, the learning was described as a process both the person with an ET and their carer went through together. As one participant carer stated:

'We both learnt together, didn't we?' (C013)

Over time, the intervention was described as becoming a part of normal lifestyle, as one participant said:

'Like with most things when you start anything complex it is a bit of a worry how to deal with it. When you do it all the time you think everybody else does it' (P015)

Participants who had managed their tubes for years described getting to know the system and learning whom to contact when help was needed. As one participant indicated:

> '... now I have the confidence that I've got enough phone numbers and I know enough contacts, but I know how to get things done and make things happen' (P001)

Further, participants indicated little need for support to manage:

> 'I'm so used to doing it on my own now; I don't really know that anyone could give me any help as such' (P008)

And considered themselves experts by experience:

> 'As our GP will say to other health professionals "Mrs X is the expert, talk to her, she knows what she's doing"' (C010)

I can't do without it

The final subtheme illustrates how many participants viewed the ET as a positive intervention, reducing the risk of choking and improving nutritional intake, as exemplified by one carer statement:

> '... when people ask "oh when do you think he'll get rid of the tube", I say "I don't worry about the tube at all (...), it's like a blessing" (C011)

However, one participant divulged the presence of the tube was a negative influence on life, stating:

> 'Living with that it's like having a ball and chain right. It ruins your life' (P003)

A number expressed how they considered the tube crucial to maintain life as without it the person with the ET would be unable to eat and drink sufficient to stay well, as one participant stated:

> 'Without that tube she's not going to survive and I don't think anyone ever sees it as that much of an issue where to us it's a big issue' (C003)

Living with the tube

The theme 'living with the tube' describes how participants managed day-to-day life to accommodate the tube and associated management. As one participant indicated:

> 'It is a huge life changing thing' (P018)

Participants explained the need to adapt their lifestyle to accommodate the tube and associated interventions.

Day-to-day routine

All participants described the impact of the tube on day-to-day life. Significant changes to activities of daily living were outlined and how participants planned holidays and managed work were described. Social activities were reported to present a challenge. One participant carer explained how she felt when administering enteral feed outside of the home:

> 'I'm so conscious if I'm outside and if I have to feed him I have to cover everything and do it like I am doing something wrong' (CO11)

Managing tube problems

As well as managing the day-to-day routine with the tube, all participants revealed the need to deal with tube problems and the strategies that they adopted to do this and to avoid a problem arising in the future. The range of tube problems related was wide and included dislodgement, stoma infection and overgranulating tissue. Multiple strategies were described to manage issues. At times strategies did not adhere to practice guidelines, for example, using wire to unblock a tube. Pain was a significant issue for many participants particularly when the tube was pulled.

Two participants identified a solution to the repeated problems of the BGT falling out that they experienced, indicating that a more frequent change could result in less emergency admissions. However, this request was reported to have been refused by their healthcare providers. One participant considered that this was a result of the cost of the tube, stating:

> 'It's expense isn't it, but it was 8 months and then slowly they brought it forward to the seven and then obviously it got to six but then no change other than an emergency' (C004)

Some participants described not having problems with the tube and managing well with it.

> 'Yes, I am quite happy. I don't have any problems' (P002)

Left to manage

A number of participants related that they felt that they were left to manage their tube, illustrated by one carer stating:

> 'You are kind of left to it (...) you don't see anybody' (C001)

Support from healthcare practitioners was described as very limited by some participants with little contact with healthcare professionals experienced in ET management reported.

Help when you need it

Many participants stated that they wanted help when they considered that they needed it and outlined the type of help they wanted. Others articulated that the support they received was sufficient to address their needs. Support from a variety of healthcare practitioners was described and included dietitians, nutrition nurses (Company and NHS), district nurses and GPs. The need for routine support was indicated and this was outlined as particularly important in the time period immediately following tube placement. As participants became 'experts' in their tube management, less need for routine support was described.

Routine support

All of the participants described the need for regular contact with a healthcare worker with knowledge of ETs, described by one participant as:

> 'Someone who knew the ins and outs of how that thing works (. . .) and could organise and arrange, it seems to be all over the place' (C004)

Some described the routine support they had in positive terms, for example:

> 'I just have to phone her and say I've got a problem and she either comes out or she'll call me back and we'll deal with it. She is supportive' (C009)

Others indicated that they lacked sufficient routine support. One person with a tube talked about how the community nurse provided support when requested but regular visits were not scheduled:

> 'The district nurse comes out but only, mainly, if you've got a problem. Simply because they've got other workloads so there is no point coming out and saying hello – it's not a chat show! This is where you get left and if you've got a problem you don't really know who to speak to because you don't see these on a regular basis' (P015)

The need to have support to train carers was indicated by some. A few participants considered the use of virtual support rather than face to face or telephone support as potentially helpful but this did not feature strongly in many interviews.

Urgent help

In addition to the need for routine support, a requirement for some to help when urgent issues arose was described. Participants described varying experiences, with some knowing and having access to knowledge healthcare practitioners when an issue arose with the tube and some describing a chaotic and uncoordinated response to urgent issues. As described above, of particular concern for many participants was support out of office hours, as one participant described:

> 'It's such a turmoil when it's out of hours' (C010)

Cost for health service

This theme related to some participant's concern about waste of both time and resource. It was a very prominent theme in a few interviews but, unlike the other themes, did not feature in many interviews. Several participants outlined that the equipment that they received was in excess of that required. As one carer stated:

> 'And we ended up with boxes and boxes of stuff. I've still got some sterile water and syringes' (C013)

At times participants reported that had explicitly stated they did not require a resource but it was still delivered to them. One participant reported that despite indicating no feed was required they continued to receive deliveries of feed:

> 'They just kept on sending it, even though my partner was phoning up saying we don't need it, can you not send it?' (P014)

One participant described how he had tried to give the excess resource to the local hospital and his pharmacy to avoid waste but they had been unable to accept the excess feed.

Other participants stated that what they considered avoidable hospital admissions used considerable resource, for example, the carer of a person with a tube who had experienced several admissions for problems with their tube stated:

> 'The amount of money it costs to do out of hours, do the district nurse coming out, do an ambulance call, do the A and E, do the switch to AMU for 2 days to wait for them to figure out what to do – how much is that costing the NHS? It's ridiculous, it's wasteful and it's not patient centred' (C010)

Other areas participants described as wasteful included the cost of supplying equipment and feed to travel abroad when it was considered local supplies in the country visited could be used.

Discussion

The present study provides an understanding of the experiences of people with ETs and their carers regarding hospital admission for ET-related issues in one UK region.

The findings highlight the potential for some hospital admissions to be prevented by the presence of supportive services in the community. Although access to healthcare practitioners or services during traditional office hours was often described, support to manage urgent problems at evenings and weekends was considered particularly limited. Other factors that were strongly considered to avoid hospital admission included changing BGTs according to requirements, even if this was more frequently than usual practice.

People with ETs and their carers described varied experiences of hospital admission for ET-related issues that were influenced by the availability of healthcare personal experienced in ET management. They generally wanted to avoid hospital and, if admitted, wanted to go home as quickly as possible. When people with ETs did attend hospital admission, they considered that an overnight stay could potentially be avoided by prompt management in the emergency department or acute medical admissions unit.

The interviews enabled participants to describe their situation and voice their views on issues of particular relevance to them, as well as explore the topics driven by the interview schedule and study aims. As a result, participants all described their feelings about adapting to and living with the ET. Although the burden of treatment is recognised [5,33–36], similar to other studies, many participants in the present study described the ET in positive terms emphasising how important it was for life [7,8,37,38]. Participants described the tube as part of the context of their life and expressed how they managed day-to-day, including for some taking a vacation and working.

The findings of the present study have also enhanced our understanding of people's experience of managing an enteral feeding tube at home from the perspective of both the carer and the person with an ET. The insertion and management of an enteral feeding tube has a huge impact on day-to-day life at home. People with ET require much more support in the initial weeks and months following tube insertion to support them so that they develop confidence and the techniques to self-manage. Training on tube management undertaken in the busy hospital environment prior to discharge may be forgotten on discharge. As other studies have highlighted [8], the first few days following discharge can be frightening as people learn to manage the tube and complications that can arise. Bjuresater *et al.* [5] highlighted that a lack of preparation before discharge in terms of support at home will result in insecurity and uncertainty. Following the initial period, people appear to adapt to the presence of the tube and learn to manage the intervention and common complications, gradually becoming proficient. The findings stress the need for comprehensive preparation and support from health practitioners when the therapy is introduced and to continue with this support. A recent study by Jukic *et al.* [8] explored the experience of carers who supported older patients with HEN in Italy and outlined the importance of supporting caregivers. MacDonald *et al.* [39] describe the concept of 'wayfinding', where carers actively learn and develop over time as a response to their lived experience. This is supported by the findings of the present study.

In accordance with other studies [3,6,7,16,40,41], participants described a variety of problems associated with the ET and strategies that they employed to manage them. The qualitative approach of the present study enabled participants to freely describe issues with their enteral nutrition, although there are well documented limitations with an interview approach [42]. Participants with tubes in the present study often described managing the tube themselves and most described receiving dietetic input. In contrast, Lim *et al.* [43] identified most people with tubes as bed-bound and not receiving dietetic follow-up. One interesting finding is that some participants described how cost savings could potentially be realised. HEN is a costly therapy [17] and, in common with a another recent study [7], people with ETs at home in the present study identified areas of potential cost savings.

The present study highlighted variation in local services available to provide support, leading to differences in people's experiences. The need to review regularly people with ET in the community setting is well recognised [44], with the emphasis on a multidisciplinary team approach [13,45,46]. The participants in the present study did not express a strong preference for a team approach or the type of healthcare professional that could support them. They described a range of different practitioners from whom they sought advice. Their main requirement appeared to be someone who listened to them and was knowledgeable. Regular support by knowledgeable practitioners has previously been suggested to improve experience and may reduce hospital admission [5]. Support could be provided by a HEN team or other established community services, such as community nurses or a combination of services. The availability of a HEN team may lead to improved clinical outcomes for people with tubes and can save costs [17,47]. Gramlich *et al.* [2] have made the case for a standardised approach to HEN and Boland *et al.* [6] described the need to develop national guidelines for HEN service provision to inform local policy. A regional or national strategic approach to HEN informed by people with ETs and their carers, and similar to that of the national framework for home parenteral nutrition, could address some of the unwarranted variation in

services and patient experience described in the present study.

Limitations

The findings of the present study may not be transferable to other regions. Regional variations in service delivery are well documented [44]; however, the findings do generate insights, which have relevance to similar settings. The context of the research has been carefully described to enable others to understand the findings [26] and relate them to their practice setting. Participants were self-selected and may have had views different from those who did not participate. Many of the participants had a BGT, which are more likely to become displaced as a result of balloon failure than other types of ET [48]. One of the researchers was a member of a service that supported a few of the participants with their ET management, which could have influenced the content of the interview and biased the findings. For example, a more in-depth interview could have been achieved because a relationship was already formed with the participant, or an interview focussed less on the research question because the participant expected the researcher to take a therapeutic role [43]. This was addressed by the inclusion of participants from areas not covered by the service and also by using analysts independent of the service.

Conclusions

Participants in the present study emphasised the need for knowledgeable healthcare practitioners to provide routine support, particularly in the initial discharge period when adapting to the tube, and to manage urgent issues beyond traditional office hours. Organisation of HEN services should be guided by national standards for the provision of services for people with ETs, informed by people with ETs and their carers and the regional context, aiming to ensure an equitable and supportive experience. The presence of a responsive community service with the knowledge and skills to support people with ETs is likely to reduce hospital admission for ET-related problems, particularly if a service is available during the evenings or overnight. Economic evaluation would inform the development and viability of such services.

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 SRQR guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.

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SG was responsible for the conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, and writing (original draft, review and editing). KT and NJ contributed to the formal analysis, validation and writing (review and editing). MF contributed to the conceptualization, funding acquisition and writing (review and editing). MF contributed to funding acquisition. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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NUTRITIONAL SUPPORT

Malnourished adults' receipt of hospital discharge nutrition care instructions: a pilot study

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Abstract

Background: Malnutrition remains an important yet under-recognised problem among hospitalised adults. Although interventions exist aiming to improve nutritional status beyond hospitalisation, few studies examine how often and what type of nutrition care instructions are given at discharge. The present study sought to review nutrition-focused discharge care provided to malnourished adults.
Methods: We reviewed the electronic medical record for discharge nutrition care instructions provided to adult patients identified by dietitians as malnourished over a 4-month period.
Results: Seventy-six eligible patients were identified during the study period. More than half of malnutrition cases (64.5%) were attributed to chronic illness. According to electronic medical record documentation, 6.6% received discharge instructions to consume oral nutrition supplements and 30.3% received new or changed prescriptions for vitamins/noncaloric supplements. Almost half of patients (47.4%) received general diet instructions that did not address malnutrition and 44.8% received inappropriate instructions to limit caloric intake.
Conclusions: A majority of malnourished adult patients receive inappropriate or inadequate nutrition care instructions at the time of discharge. Clinician education and redesign of nutrition care options in the electronic medical record may improve the provision of post-discharge nutrition care instructions.

Introduction

Malnutrition, defined as overnutrition or undernutrition leading to changes in body composition and diminished function [(1)], is a common problem in hospitals. Malnutrition can be caused by starvation, chronic disease-related inflammation and acute disease-related inflammation [(2)]. The prevalence of malnutrition varies widely among hospitalised adults, with estimates ranging from 4% to 45% [(3–8)]. Multiple studies report adverse effects of malnutrition, which include a prolonged length of stay [(5–7)], increased overall and in-hospital mortality [(5–7)], increased risk of readmission [(6,7,9,10)] and higher hospitalisation costs [(6,10)].

The majority of malnourished patients become malnourished as a result of chronic disease, suggesting that interventions need to continue well beyond the hospitalisation to be successful [(3)]. Despite physician support for performing nutrition assessments at discharge, a Canadian task force survey found that this is not achieved on a regular basis [(11)]. Several barriers prevent effective discharge nutrition care planning, including insufficient nutrition knowledge among clinicians [(12,13)], as well as the amount of time and resources associated with discharge education [(13)]. Case managers also use inconsistent strategies for nutrition-related discharge plans and experience discrepancies in the perceived availability of, and access to, community food resources [(14)].

Nutrition-focused interventions, such as dietary counselling and oral nutrition supplementation (ONS), have demonstrated success in improving outcomes after discharge [15–17]. Systematic reviews/meta-analyses have found that dietary counselling and ONS improve energy intake and weight gain, although they have a limited impact on mortality [18–24]. It is likely that these interventions are valuable components of post-discharge care that includes additional intervention such as discharge planning and care management.

Despite the benefits of such nutrition-focused interventions, few studies examine how often patients receive instructions to consume ONS or adapt their food intake after discharge. Young *et al.* [25] described nutrition care prescribed to elderly patients at risk of malnutrition who were discharged to independent living in the community. Only 14% (six of 42) of patients received nutrition-focused discharge planning from a registered dietitian (RD) or a nurse and only 19% (eight of 42) received practical nutrition supports, such as meal delivery or shopping assistance [25]. Laur *et al.* [26] examined the nutrition care of adult patients 30 days after discharge. They found that only 42% (110 of 249) of patients received nutrition recommendations at discharge, and only 65% of these patients (71 of 110) followed the recommendations. The most common discharge instructions related to food intake, community food services and use of ONS. Approximately 27% (66 of 249) consumed ONS post-discharge, although it was unknown whether patients received instructions from hospital staff to do so [26]. These studies suggest that patients who are malnourished or nutritionally at risk may not consistently receive and follow discharge care instructions that could improve outcomes.

Because the successful treatment of malnutrition depends on continuing to meet patients' nutritional needs beyond the hospital stay, there is a need to describe the standard of post-discharge nutrition care provided to malnourished adults. We conducted a pilot study to characterise the discharge nutrition instructions provided to malnourished patients.

Materials and methods

Setting

Christiana Hospital, part of the Christiana Care Health System, is a 913-bed community-based tertiary care centre in northern Delaware. The study was reviewed and approved by the Christiana Care Institutional Review Board.

Population

We reviewed the nutrition-focused discharge instructions for adult (aged ≥18 years), English-speaking patients who were identified as malnourished by an RD during an index hospitalisation at Christiana Hospital between 15 November 2017 and 15 March 2018. Patients were excluded if they were on maternity, psychiatric or hospice/comfort care; not on a hospitalist service; or experiencing active withdrawal from substance abuse. These inclusion/exclusion criteria were intended to identify patients who could be expected to continue their nutritional care at home with appropriate instruction. Patients were identified based on their inclusion in a quality improvement database of malnourished patients. This database consists of all patients identified by RDs as meeting criteria for malnutrition.

Identification of malnutrition

Nursing staff screen all patients with the following five questions: (i) have you had <50% of usual intake for >7 days prior to admission; (ii) have you had unintentional weight loss of >10 pounds in 6 months; (iii) have you received enteral or parenteral nutrition in the past 3 months; (iv) do you have difficulty swallowing; and (v) do you have any cultural or religious food preferences? RDs perform an evaluation of any patient with a positive response to any of the above questions, any patient on enteral or parenteral nutrition, any patient without a diet for more than 5 days, any patient ordered supplements, any patient with a body mass index (BMI) <17 kg m^{-2} or > 40 kg m^{-2}, all patients over age 80 years, and any patient for whom a physician or nurse requests consultation. RDs identify malnutrition using a modified version of criteria recommended by the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition (ASPEN). ASPEN guidelines recommend at least two of the following six criteria to be met for a diagnosis of malnutrition: (i) ≤50–75% of estimated energy requirement for a given time period based on illness type or social/environmental circumstances; (ii) interpretation of weight loss by a clinician, assessed by percentage of weight lost from baseline; (iii) mild, moderate or severe loss of subcutaneous fat; (iv) mild, moderate or severe loss of muscle mass; (v) mild, moderate or severe generalised or localised fluid accumulation; and (vi) reduced handgrip strength, compared to normative standards supplied by the manufacturer of a handgrip measurement device [27]. In our institution, RDs routinely perform the physical examinations necessary to assess for fluid accumulation and fat and muscle loss [28]. Because of known difficulties in obtaining handgrip strength measurement [29,30], Christiana Care created a practice guideline substituting underweight BMI (BMI <18.5 kg m^{-2}). Based on the degree of the reduction in energy intake, weight loss, muscle loss, fat loss or fluid accumulation, we classified malnutrition as moderate or severe as described by White *et al.* [27]. Vest

et al. [3] further describe the methods used at Christiana Care to identify malnutrition.

Data collection

Descriptive demographic and health variables for patients were extracted from the quality improvement database of malnourished patients. If a variable was unavailable in the database, it was obtained from review of the electronic medical record (EMR). Patients were classified into the weight categories based on their BMI at the time of RD evaluation: underweight (BMI < 18.5 kg m^{-2}), normal weight (BMI = 18.5–24.9 kg m^{-2}), overweight (BMI = 25–29.9 kg m^{-2}) and obese (BMI ≥ 30 kg m^{-2}). The Elixhauser Comorbidity Index, a validated tool for use with administrative databases, was used to classify the medical comorbidities of patients [31].

Each patient's record was reviewed to identify any post-discharge nutrition care instructions in the 'Discharge Instructions' or 'Discharge Summary' sections of the EMR. Post-discharge nutrition care instructions were (i) instructions to consume ONS; (ii) new or existing prescriptions for vitamins/noncaloric supplements; or (iii) dietary instructions, which are drawn from an automated checkbox list of more than 40 common options. All standardised and free-text dietary instructions were grouped into nine categories for analysis. For the purposes of these chart reviews, ONS included any nutritional shakes, puddings, powders or similar products. Vitamins/noncaloric supplements included multivitamins, vitamins, minerals, herbal supplements, fish oils or similar products.

Statistical analysis

Descriptive statistics were used to examine the characteristics of the study population and the nutrition instructions that they received at discharge. Categorical variables were reported using frequencies and percentages, and continuous variables were reported using the mean (SD).

Results

Characteristics of the study population

During the 4-month study period, 76 unique malnourished patients were identified in accordance with the study's inclusion/exclusion criteria. The characteristics of the study population are listed in Table 1. The mean (SD) age was 64.6 (16.9) years and patients were predominantly white (73.7%). Their mean (SD) BMI at index admission was 21.7 (5.3); 28.9% were underweight, 51.3% were normal weight, 13.2% were overweight and 6.6% were obese. Patients had a mean (SD) of 9.3 (4.0) comorbidities, as classified using the Elixhauser Comorbidity Index. The majority of patients (81.5%) were identified as having severe malnutrition and 64.5% of all malnutrition cases were attributed to chronic illness. The most frequently recommended in-hospital nutrition intervention was ONS (given to 88.2% of patients). Finally, more than one-third (34.2%) of patients were

Table 1 Characteristics of the study population

	Study population (n = 76)
Age, mean (SD)	64.6 (16.9)
Age 80 and over, *n* (%)	12 (15.8)
Male, *n* (%)	39 (51.3)
Race, *n* (%)	
White	56 (73.7)
Black	17 (22.4)
Other	3 (3.9)
Body mass index (BMI), mean (SD)	21.7 (5.3)
Underweight (BMI <18.5), *n* (%)	22 (28.9)
Normal weight (BMI = 18.5–24.9), *n* (%)	39 (51.3)
Overweight (BMI = 25–29.9), *n* (%)	10 (13.2)
Obese (BMI ≥30), *n* (%)	5 (6.6)
Elixhauser Comorbidity Index,* mean (SD)	9.3 (4.0)
Admitting diagnosis, *n* (%)	
Surgical disease	–
Trauma	–
Respiratory disease	14 (18.4)
Cardiac disease	3 (3.9)
Infectious disease	6 (7.9)
Gastrointestinal	20 (26.3)
Endocrine	–
Renal	7 (9.2)
Peripheral vascular disease	1 (1.3)
Neurologic	1 (1.3)
Other	24 (31.6)
Type of malnutrition, *n* (%)	
Moderate as a result of acute illness or injury	4 (5.3)
Moderate as a result of chronic illness	10 (13.2)
Moderate as a result of social or environmental circumstances	–
Severe as a result of acute illness or injury	22 (28.9)
Severe as a result of chronic illness	39 (51.3)
Severe as a result of social or environmental circumstances	1 (1.3)
Recommended in-hospital intervention, *n* (%)	
Tube feedings	4 (5.3)
Total parenteral nutrition	7 (9.2)
Oral nutrition supplements	67 (88.2)
Diet education	–
Liberalised diet	4 (5.3)
None/continue current diet/monitor patient	2 (2.6)
Other	2 (2.6)
Discharge location, *n* (%)	
Home or home with health care	37 (48.7)
Health care facility	26 (34.2)
Death or discharge to hospice	13 (17.1)

*Based on data available for 75 patients.

Table 2 Diet instruction categories

General information		
• Okay to return to your normal eating habits • Eat lightly at first meal • Drink lots of water every day	• Alcohol abuse and nutrition guide • 'Avoid alcohol'* • 'No restrictions'*	• 'Oral intake as tolerated, primarily for comfort'* • 'Regular diet; dehydration, adult'*
Cardiac diet		
• Refer to heart healthy meal guide • Low sodium eating plan/meal guide	• Eat meals low in salt • DASH eating plan • Refer to heart healthy and low carb meal guide	• 'Avoid extra salt'* • 'Mechanical soft diet; cardiac diet'*
Consistency modified/texture modified/small meals		
• Refer to ground food meal guide for dysphagia 2 • Eat six small meals a day • Eat soft foods • Refer to easy to chew meal guide (dysphagia 3) • Refer to honey thick fluids meal guide	• Refer to nectar thick fluids meal guide • Refer to puree meal guide (dysphagia 1) • Thickening liquids for dysphagia diet • Soft food meal plan	• 'Aspiration precautions, dysphagia to advance later based on speech eval'* • 'Avoid any food that is difficult to swallow'* • 'Dysphagia 2 diet; nectar thick liquids'* • 'Soft/bland diet'*
Gastrointestinal diet		
• Eat bland foods • Avoid spicy and fried food • Refer to low fibre meal guide • Low fibre and residue diet	• Low fat diet for pancreatitis or gallbladder conditions • Food choices to help relieve diarrhea	• 'BRAT diet (bananas, rice, applesauce and toast)'* • 'Increase fibre'* • 'Low residue diet'*
Renal diet		
• Limit fluids each day • Refer to healthy kidney meal guide • Refer to low phosphorus meal guide	• Refer to low potassium meal guide • Dialysis diet • Potassium content of foods	• 'Low salt, low fat, low potassium diet'* • 'Maintain fluid restriction 1500 mL day^{-1}'*
Malnutrition		
• Malnutrition guide	• Refer to high protein and high calorie meal guide	• Failure to thrive
Education related to tube feeding/total parenteral nutrition		
• 'Continue tube feeds at night; Percutaneous Endoscopic Gastrostomy Tube Home Guide; Care of a Feeding Tube'*	• 'Continue with at least six cans daily of tube feeding regimen at home'*	• 'Total parenteral nutrition at night; high fat diet if possible'* • 'Tube feeds; resume previous diet'*
Low carbohydrate diet		
• Refer to low carb meal guide		
Miscellaneous		
• Iron deficiency/anaemia guide		

*Quotation marks indicate free-text instructions. DASH, Dietary Approaches to Stop Hypertension.

discharged to a nursing home or other health care facility and 17.1% died or were discharged to hospice.

Chart review of post-discharge nutrition care instructions

The EMR was reviewed for documentation of nutrition care instructions, including standardised and free-text dietary instructions, which were grouped into nine categories. Table 2 shows examples of instructions in each of these categories. Many of these instructions are either inappropriate or difficult to understand. For example, it is unlikely that the average malnourished patient derives much benefit from being told to 'eat meals low in salt' or to 'return to their normal eating habits'. Some of these patients may be harmed from instructions to follow a low carbohydrate or cardiac diet. Table 3 shows the proportion of patients who received each category of instruction and the proportion of patients who were asked to take ONS or vitamins/noncaloric supplements. Five patients (6.6%) received EMR-documented discharge instructions to consume ONS. Twenty-three (30.3%) received new or

Table 3 Electronic medical record (EMR) documentation of post-discharge nutrition care instructions

	Study population (N = 76)
Received EMR-documented instructions to consume oral nutrition supplements, *n* (%)	5 (6.6)
Received EMR-documented new or changed prescription(s) for vitamins/noncaloric supplements, *n* (%)	23 (30.3)
Received EMR-documented diet discharge instruction(s), *n* (%)	66 (86.8)
General information	36 (47.4)
Cardiac diet	19 (25.0)
Consistency modified/texture modified/small meals	16 (21.1)
Gastrointestinal diet	12 (15.8)
Renal diet	11 (14.5)
Malnutrition	9 (11.8)
Education related to tube feeding/total parenteral nutrition	4 (5.3)
Low carbohydrate diet	4 (5.3)
Miscellaneous	1 (1.3)

changed prescriptions for vitamins/noncaloric supplements. Finally, 10 patients (13.2%) did not have any diet discharge instructions documented in the EMR. The most commonly provided diet discharge instructions included general information (given to 47.4% of patients), cardiac diet information (given to 25.0% of patients) and modified consistency/texture diet information (given to 21.1% of patients). Only nine (11.8%) received diet instructions specific to malnutrition. Almost half (44.8%) received cardiac, renal or low carbohydrate diet instructions that are inappropriate for malnourished patients because they limit the intake of energy- and nutrient-dense foods.

Discussion

We found that most malnourished patients either received no discharge instruction on malnutrition or received inappropriate discharge instructions. This is concerning because efforts to improve the identification of malnourished patients may not translate into clinical benefits if interventions are not continued beyond the acute care hospitalisation. Even though malnutrition is often associated with being underweight, the mean BMI of this population was in the normal weight range and the majority of patients (71.1%) were normal weight, overweight or obese. Malnutrition is a complex condition that can be identified in both underweight and overweight/obese patients and it is vital to ensure that clinicians diagnose and provide appropriate treatment to malnourished patients regardless of their BMI. Two-thirds of malnutrition cases were attributed to chronic illness, emphasising the importance of nutritional care for chronically ill patients.

Our population did not receive optimal post-discharge nutrition care instructions. Table 2 shows the limited quality and quantity of instructions for malnourished patients, often simply referring them to prepopulated education guides. Almost half (44.8%) of patients who were identified as malnourished during index admission received harmful diet instructions to limit caloric intake at discharge and 47.4% received general diet instructions that did not address malnutrition. Even the few patients who received diet instructions specific to malnutrition did not receive adequate instructions because the malnutrition guide they received was determined to be of poor quality. This guide came from an external provider of patient education materials and does not contain appropriate instruction for our population. The guide identifies pregnancy and lactation as the first potential risk factors for malnutrition and also singles out specific diets that can be complete and adequate (e.g. vegetarian diets) as causes of potential vitamin deficiencies and thus malnutrition. Most importantly, there is no mechanism to individualise this diet guide to meet the unique and varied needs of a patient suffering from malnutrition. The treatments listed by the guide are vague and simplistic and therefore they are of little value to an individual patient. Christiana Care RDs choose not to use the guide in light of these concerns and, instead, instruct patients on the specifics of a high-protein, high-calorie diet tailored to their individual issues. However, RDs are not typically involved in preparing discharge instructions for a patient. Physicians such as hospitalists are primarily responsible for preparing discharge instructions and may be unaware of the inaccuracies in the malnutrition guide.

There are multiple potential causes for inadequate nutrition discharge instructions, including a lack of physician education on nutrition and communication. However, it is likely that EMR itself is a source of systematic error. Although EMRs have solved some problems such as illegible medical records, they have created new problems as well, such as inaccurate clinical information resulting from the copying and pasting of data in notes [32–34]. EMRs may offer dietary instructions of varying quality and require additional effort from clinicians to individually tailor instructions. Clinicians may erroneously assume that dietary instructions prepopulated in the EMR are appropriate for their patients. At Christiana Hospital, the EMR includes more than 40 different diet education guides created by clinical staff or obtained from an external provider of patient education materials. This automation is intended to streamline care and ensure that all patients receive some form of dietary education at discharge. In practice, however, it may reduce diet education to a perfunctory task. The availability of diet instructions and the

ease with which they are selected may disincentivise the individual tailoring of these instructions and prevent a more thoughtful consideration of the unique dietary needs of malnourished patients.

Few malnourished patients received discharge instructions to consume ONS, an intervention that could be used to treat and prevent malnutrition after they return home. Although the majority (88.2%) of malnourished patients were recommended and received ONS during their hospital stay, fewer than 7% received documented instructions to continue ONS after discharge. This is likely not a result of clinicians doubting the therapeutic effectiveness of ONS but rather stems from a discharge process that promotes this systematic error. Perhaps if ONS were part of a nutrition reconciliation process required at discharge [35], a higher percentage of patients would receive appropriate instruction for ONS.

Malnutrition may persist if patients return home with the same chronic illnesses and social circumstances that contributed to their original case of malnutrition. These findings suggest the need for further provider education with respect to providing appropriate dietary education, as well as multidisciplinary collaboration between providers and RDs both during and after hospitalisation. Future work should examine the impact of referrals to community-based nutrition resources such as meal delivery programmes on long-term outcomes and incidence of malnutrition on subsequent evaluations in this population.

Finally, the present study highlights issues in prospectively following the discharge disposition and nutrition care of malnourished patients. Although the investigation sought to describe the nutrition instructions provided to patients who would likely return home, more than half were discharged to a nonhome location or died. Future investigations should extend the study period, loosen inclusion/exclusion criteria or use a retrospective design to obtain a larger sample.

Limitations

The present study reviewed only those nutrition-focused discharge care instructions that were documented in the EMR. It is unknown what, if any, nutrition instruction was provided to patients by RDs during their hospital stay but remained undocumented in the record. It is possible that, even though the discharge paperwork provided inadequate education on malnutrition, patients may have received better than adequate education from the RDs prior to discharge, thus making the discharge instructions less important. However, the receipt of conflicting instructions from the discharge paperwork and RDs would still constitute suboptimal care. Additionally, we reviewed the documentation of any new or changed prescriptions for vitamins/noncaloric supplements as part of the patients' post-discharge nutrition care. However, we were unable to determine whether such prescriptions were made specifically to treat the effects of malnutrition.

Conclusions

A majority of malnourished adult patients receive inappropriate or inadequate nutrition care instructions at the time of discharge. Almost half of these patients return to the home environment, which highlights the need for discharge care that addresses their long-term nutritional needs. Clinician education and redesign of nutrition care options and workflow in the EMR may aid in the provision of discharge instructions to treat and prevent malnutrition after patients leave the hospital.

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 STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

The authors declare that they have no conflicts of interest.
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All authors contributed to the design of the study. MB acquired and analysed the data. All authors interpreted the data and drafted and revised the manuscript. All authors approved the final version of the manuscript submitted for publication.

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NUTRITIONAL SUPPORT

A laboratory-based evaluation of tube blocking and microbial risks associated with one blended enteral feed recipe

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Abstract

Background: Concerns associated with blended enteral feeds include the risk of blocked tubes and microbial contamination, although the available evidence is limited. The present laboratory-based investigation aimed to examine these risks in a blended feed providing a nutritionally adequate intake for a hypothetical patient.

Methods: A one-blended feed recipe was made using three different methods (professional, jug and stick blenders) and three storage procedures. Feed samples were syringed via 10-, 12- and 14-French (Fr) enteral feeding tubes and both blockages and the time taken were recorded. Feed samples were diluted, plated on agars, incubated and bacterial colony-forming units (CFU) counted. After storage at −80 °C, identification was undertaken using 16S rRNA polymerase chain reaction sequencing.

Results: Two blockages occurred during 27 administrations of feed made using a professional blender, although they were resolved with a water flush. No blockages occurred with the 14-Fr tube and administration was quicker with wider tubes ($P < 0.00001$). There was no significant difference between the total bacterial CFU of feeds prepared using different methods ($P = 0.771$) or stored differently. The genus of bacteria identified included *Enterococcus*, *Bacillus*, lactose-fermenting *Enterobacteriaceae*, *Pseudomonas* and *Staphylococcus*. Pathogens, such as *Clostridium* spp., *Salmonella* spp. and *Vibrio* spp., were not identified by phenotypic tests used. Sequencing identified *Escherichia coli*, *Shigella* spp., *Streptococcus lutetiensis* and *Staphylococcus epidermidis*.

Conclusions: The present study found no risk of tube blockages when one blended feed recipe made using three methods was delivered via a 14-Fr tube. There is concern about bacterial contamination, although this was not influenced by the methods of preparation or storage used in the present study.

Introduction

Usual practice in enteral tube feeding is to provide nutrition through commercially prepared, nutritionally-complete liquid feeds [(1)]. However, there is increasing patient and carer-led interest in providing nutrition using blended or liquidised food that is prepared and administered at home [(2,3)]. Reported benefits associated with blended diets include improvements in reflux and bowel problems and empowering patients and carers without

'medicalising' feeding [4–6]. A number of concerns about the health risks associated with blended diets have been described [1,7–10] and these include nutritional inadequacy, blocked feeding tubes and food-borne infection [1,11].

However, there is little systematically reported evidence to support or refute these concerns [5,8,9,12]. Peer-reviewed guidance on how blended diets should be prepared or administered is available but acknowledges the limited evidence [13–15]. Advice from patient and carer-led websites is also available [2,3]. However, there is little evidence that guidance or advice has been evaluated in terms of risk of tube blocking or microbiological load.

The primary aims of this series of laboratory-based studies were to examine the risk of blockage of feeding tubes and the microbiological load associated with a blended feeding regime providing a nutritionally adequate intake for a hypothetical patient. Secondary aims included evaluating practicalities such as time to deliver the feed and food waste associated with blending food. Different terminology, including liquidised, blenderised and pureed, is used to describe these feeds, although the term 'blended feeds' is used in the present study because this is commonly used by patients and carers.

Materials and methods

Blended feed recipe

A recipe for a blended diet was developed based on ideas for ingredients shared by patients and carers [2,3] and designed to meet the estimated nutritional requirements [16–23] for a hypothetical man aged 70 years weighing 68 kg, with body mass index of 22.5 kg m^{-2} and low physical activity (Table 1). This person was arbitrarily chosen because home enteral feeding is more prevalent in those aged ≥60 years and ≤5 years [24] and producing a larger volume of feed for a hypothetical adult was more practical for the procedures described below. It was assumed that, apart from requiring tube feeding, the man was otherwise in good health and had no other clinical conditions that might impact on his intake (i.e. able to tolerate lactose, cow's milk protein, etc.). Where possible, ingredients that were considered lower risk from a food hygiene perspective were used (i.e. not raw meat, fish or eggs). Providing estimated energy and macronutrient requirements in the feed recipe was prioritised because micronutrients could be more easily supplemented if needed. Nutritional composition was determined using the web-based nutrient analysis software NUTRITICS (https://www.nutritics.com).

Blending procedures

The blended feed was made by combining all the ingredients using one of three different methods using (A) a professional blender (Vitamix Professional Series 750; Vitamix, Olmsted Falls, OH, USA) and an extra fine sieve, cleaned using a solution from sterilising tablets (Milton Pharmaceutical UK Limited, Cheltenham, UK); (B) a jug blender (Kenwood Series BL430; Kenwood Appliances Plc, Havant, UK) and a standard sieve, cleaned with cold water; and (C) a stick blender (Kenwood Series HB6600; Kenwood Appliances Plc) without sieving, cleaned with hot water and supermarket regular washing up liquid. The feeds were made by students studying nutrition and dietetics, who had passed a level two food safety certificate, and production was undertaken in a diet laboratory adhering to strict hygiene procedures and under staff supervision. Once made, the feeds were divided into three samples which were treated to mimic possible home storage scenarios: (X) no storage, transferred immediately to the microbiology lab for analysis; (Y) stored in a domestic fridge at approximately 4 °C for 24 h followed by 2 h at ambient temperature; and (Z) stored in a domestic fridge at approximately 4 °C for 48 h followed by 4 h at ambient temperature. These procedures were designed to reflect optimum practice with minimal opportunity for microbial growth (X), an approach suggested as good practice [15] (Y) and a high-risk procedure (Z) that deviated from this [15]. The residue remaining on all utensils for feeds A, B and C and the unsieved fraction (i.e. waste) from feeds A and B were weighed to determine total waste. The nutritional composition of the remaining feed [i.e. total recipe – (residue remaining on utensils + unsieved fraction)] was then compared with the estimated nutritional requirements making an assumption that the proportions lost would be comparable for all nutrients.

Tube blockages and feeding time

Immediately after making, 60-mL samples from each of the three feeds, ABC, were administered in triplicate using a 60-mL enteral compatible syringe through three different sized clean enteral feeding tubes [10, 12 and 14 French (Fr); Corpak MedSystems, Buffalo Grove, IL, USA] into an empty container. Twenty millilitres of water was administered after every 60 mL of feed and a 10-s break was given after every 20 mL of feed to mimic the effect of chewing and swallowing in normal eating. The number of blockages, attempts to unblock, time taken to administer the feed and the researcher's observations of the process were recorded. The administration was repeated with a standard 1 kcal mL^{-1} formula feed

Table 1 Recipe and calculated nutritional composition of blended diet and comparison with estimated requirements for hypothetical man

Ingredients and weight			
Whole fat milk (g)	855	Avocado (g)	133
Cooked brown wholegrain rice (g)	570	Water (g)	95
Raw tomatoes (g)	532	Feta cheese, regular not low fat (g)	55
Lettuce (g)	342	Red wine vinegar (g)	8
Chick peas, canned, drained (g)	312		

Nutrient	Quantity in feed	Estimated requirement (ER)*	Adequacy of total recipe (% ER)	Adequacy after deducting 32% waste (% ER)†
Energy (kcal)	2142	2151	100	68
Protein (g)	90	53	>100	>100
Carbohydrate (g)	259 [48% energy]	50% energy	96	96
Fat (g)	83 [35% energy]	35% energy	100	100
Fibre (g)	38	30	>100	86
Sodium (mg)	982	<2359	Within target	Within target
Calcium (mg)	1595	700	>100	>100
Magnesium (mg)	560	300	>100	>100
Iron (mg)	10	8.7	>100	78
Zinc (mg)	13	9.5	>100	93
Selenium (μg)	37	75	49	34
Iodine (μg)	282	140	>100	>100
Vitamin A (μg)	805‡	700	>100	78
Vitamin D (μg)	0.3	10	3	2
Vitamin E (mg)	16	13§	>100	84
Vitamin K_1 (μg)	478	70¶	>100	>100
Thiamin (mg)	1.9	0.9	>100	>100
Riboflavin (mg)	2.6	1.3	>100	>100
Niacin** (mg)	39	16	>100	>100
Vitamin B_6 (mg)	1.8	1.4	>100	87
Folic acid (μg)	497	200	>100	>100
Vitamin B_{12} (μg)	8.3	1.5	>100	>100
Vitamin C (mg)	146	40	>100	>100
Water (g)	2404	2500	96	65

*Estimated requirements based on: energy, estimated average requirement using physical activity level of 1.49 [16]; macronutrients and most micronutrients, reference nutrient intake [17]; fibre [18]; sodium based on <6 g of salt [19]; vitamin D [20]; vitamin E [21]; vitamin K [22]; fluid [23].
†Estimated by deducting 32% from quantity in feed to account for sieved losses from feeds A and B.
‡Retinol equivalents.
§α-tocopherol.
¶Phylloquinone only.
**Nicotinic acid equivalents.

(Nutrison; Nutricia, Dublin, Ireland). To consider the physical strength required to administer the bolus feeds, the left and right handgrip strength of two researchers were measured using a digital grip-strength dynamometer (TKK Takei 5501 Grip-D; Takei Scientific Instruments Co.,Ltd, Tokyo, Japan) in accordance with the method of España-Romero *et al.* [25] and compared against normative values [26].

Microbial load

Samples from each of the three feeds, ABC, at each of the three storage timepoints, XYZ, were diluted, spread on seven types of agar and incubated aerobically (except Columbia blood agar: anaerobically) at 37 °C (except mannitol yolk polymyxin at 30 °C) (Table 2). Total colony-forming units (CFU) were counted in triplicate with 10% blind checked for accuracy by a second researcher. Using CFU g^{-1} determined during presumptive testing, the microbial load in each feed of (i) *Bacillus cereus* was compared with guidelines for interpreting results for enumeration of bacterial pathogens and (ii) *Enterobacteriaceae* was compared with guidance on the interpretation of results for hygiene indicator organisms in ready-to-eat foods [27].

Table 2 Impact of storage time on log colony forming units per g of blended feeds prepared using different methods and grown on seven agar types after incubation

			Storage		
Agar and presumptive bacteria selected	Incubation	Method	X	Y	Z
Baird Parker: *Staphylococcus aureus*	Aerobic at 37 °C	A	3.52	4.07	4.30
		B	3.45	2.22	2.52
		C	2.70	2.22	2.22
Cetrimide: *Pseudomonas aeruginosa*	Aerobic at 37 °C	A	4.39	4.81	4.51
		B	2.52	4.12	3.89
		C	3.71	4.74	5.30
Columbia blood: Nonselective	Anaerobic at 37 °C	A	4.25	4.46	5.41
		B	4.43	5.19	5.39
		C	5.67	5.50	5.38
Kanamycin: *Enterococci species*	Aerobic at 37 °C	A	3.54	4.53	4.64
		B	3.58	3.50	3.22
		C	3.43	3.56	4.39
MacConkey A: *Non-lactose-fermenting Enterobacteriaceae*	Aerobic at 37 °C	A	3.92	4.46	5.24
		B	4.11	4.36	3.12
		C	ND	4.10	5.43
MacConkey B: *Lactose-fermenting Enterobacteriaceae*	Aerobic at 37 °C	A	3.22	3.26	3.58
		B	4.41	3.12	4.19
		C	ND	3.79	3.86
Mannitol yolk polymyxin: *Bacillus cereus*	Aerobic at 30 °C	A	4.61	4.49	4.50
		B	3.18	4.02	4.63
		C	4.61	4.52	4.79
Nutrient: Nonfastidious organisms	Aerobic at 37 °C	A	4.60	5.68	5.70
		B	3.68	4.37	4.91
		C	5.73	5.27	4.50
Mean (SD)		A	4.01 (0.53)	4.47 (0.68)	4.74 (0.69)
		B	3.67 (0.65)	3.87 (0.91)	3.99 (0.98)
		C	3.23 (2.25)	4.21 (1.05)	4.48 (1.07)

Storage: X = plated immediately; Y = 24 h in fridge + 2 h at ambient temperature; Z = 48 h in fridge and 4 h at ambient temperature. Method: A = professional blender; B = jug blender; C = stick blender. Analysis of variance across three storage times: method A, $P = 0.091$; method B, $P = 0.764$; method C, $P = 0.263$.
ND, not detected (zero used for statistical analyses).

Microbial identification

Bacterial colonies of unique morphologies were randomly selected for identification by Gram staining, oxidase test, catalase test and API 20NE strips (bioMerieux, Marcy-l'Étoile, France), as well as re-streaked onto nutrient agar plates (Oxoid, Basingstoke, UK) for pure culture and stored at −80 °C. Resuscitated pure cultures on nutrient agar were subcultured in 10 mL of nutrient broth (Oxoid) and incubated at 37 °C for 24–48 h for genomic DNA extraction using the GenElute Bacterial DNA Kit (Sigma-Aldrich, Gillingham, UK). Each polymerase chain reaction (PCR) was carried out with 10–100 ng of DNA template, 0.5 μM each of 16S rRNA universal primers 27F (5'-AGAGTTTGATCMTGGCTCAG-3') and 1492R (5'-TACG-GYTACCTTGTTACGACTT-3'), 200 μM of each dNTP, 0.02 U of Phusion DNA polymerase and 1 × Phusion Green HF buffer (New England Biolabs, Hitchin, UK). Amplicons with an expected amplicon size of 1.4 kb, sized by gel electrophoresis, were column purified with Monarch PCR & DNA Cleanup Kit (New England Biolabs) and sequenced using the same 16S rRNA universal primers. Sequence analysis was carried out with CLC WORKBENCH (Qiagen, Valancia, CA, USA) and BLASTn [28].

Statistical analysis

The effect of the preparation method and tube size on blockages was analysed descriptively. After testing for normality, multivariate two-way analysis of variance (ANOVA) was used to examine differences in time taken to deliver (i) the blended feeds delivered via tubes of different diameter; (ii) the blended feeds prepared using the three different methods; and (iii) the three blended feeds and standard formula feed. ANOVA was also used to compare CFU across groups for differences associated with

preparation method and storage time. $P < 0.05$ was considered statistically significant.

Ethical approval

Ethical permission was not required for the present study.

Results

Nutritional analysis and waste

The feed recipe provided >95% of the estimated requirements for energy and all nutrients except for selenium and vitamin D (Table 1). The total waste was 942 g (32%) for feed A (extra fine sieve), 891 g (31%) for feed B (standard sieve) and 29 g (1%) for feed C (unsieved). After deducting 32% for the total waste, the remaining feed provided <95% of the estimated requirements for energy, fibre, iron, zinc, selenium, vitamins A, D, E and B_6 and fluid (Table 1).

Tube blockages and feeding time

Two tube blockages occurred during 27 feed administrations and both were associated with feed A (i.e. prepared using the professional blender and extra fine sieve). The blockages occurred once each with 10- and 12-French tubes but a single 10-mL water flush was sufficient to resolve both blockages. No blockages occurred with feeds B or C or when using a 14-Fr tube. The time taken to deliver one 60-mL bolus varied between 46 and 137 s, excluding the 20 s rests. There was no significant difference between the time taken to deliver feeds prepared using different methods ($P = 0.987$), although the time decreased significantly as tube size increased ($P < 0.00001$) (Table 3). No blockages occurred with the standard formula feed for any tube diameter and it was significantly quicker to deliver the standard feed via the three tubes than the blended feeds ($P = 0.00001$) (Table 3). It was found that substantial force was required to deliver the bolus feeds using the syringe, especially with the smaller tubes. Their mean handgrip strength was 17.7 and 18.3 kg (left) and 18.9 and 18.1 kg (right), respectively; all values were <10% for age and gender normative values [26].

Microbial load and identification

There was no significant difference between total bacterial CFU of blended feeds prepared using different methods with values [mean (SD)] varying widely [A = 46.6 (48.3); B = 53.5 (49.3); C = 36.3 (31.8); $P = 0.771$]. The impact of storage time on bacterial CFU varied with an increase in colonies on some agars but, overall, this was not significantly different (feed A, $P = 0.091$; B, $P = 0.764$; C, $P = 0.263$) (Table 2). The genus of bacteria identified included *Enterococcus*, *Bacillus*, lactose-fermenting *Enterobacteriaceae*, *Pseudomonas* and *Staphylococcus* and these were similar for all three methods of feed preparation (Table 4). Pathogens, such as *Clostridium* spp., *Salmonella* spp. and *Vibrio* spp., were not identified by the phenotypic tests used. Potentially clinically significant Gram negative, non-Enterobacteriaceae taxa identified using API 20NE strips included *Pseudomonas alicaligenes* from feed prepared using method A and *Pseudomonas luteolin*, *Pseudomonas fluorescens* and *Pseudomonas putida* from feed prepared using method C. Of 16 cryogenically preserved cultures, only 10 were viable and genomic DNA could be extracted for PCR. Sequencing of 16S rRNA gene identified *Escherichia coli*, *Shigella* spp., *Streptococcus lutetiensis*, *Staphylococcus epidermidis*, *Staphylococcus warneri* and *Lactobacillus paracasei* subsp. tolerans. For additional details, please see supplementary information (Table S1). The presumptive bacterial load of *Bacillus cereus* of all blended feed samples was within the borderline category defined by the

Table 3 Time taken to deliver one 60-mL bolus of feed prepared using three different blending methods and a standard formula feed through tubes of different diameter

Tube size in French* gauge (external diameter)	Method of feed preparation†			Standard formula feed‡ (1 kcal mL^{-1})
	A: Professional blender + extra fine sieve	B: Jug blender + standard sieve	C: Stick blender + no sieve	
10 (3.3) mm	95.7 (10.5)	107.7 (8.5)	105.3 (10.7)	40.3 (0.6)
12 (4.0) mm	105.7 (14.4)	114.0 (21.0)	107.3 (10.7)	35.3 (2.5)
14 (4.6) mm	65.0 (4.8)	50.2 (10.2)	57.9 (3.3)	27.3 (2.1)

Data are the mean (SD).

Values exclude rest time during bolus delivery.

*Analysis of variance (ANOVA) across three tube sizes for three blended feeds, $P < 0.00001$.

†ANOVA across three methods of blended feed preparation, $P = 0.987$.

‡ANOVA across three blended feeds and standard formula feed, $P = 0.00001$.

Table 4 Genus of bacteria identified in blended feeds prepared using three methods

Genus	Method of feed preparation and cleaning		
	A: Professional blender + extra fine sieve + solution from sterilising tablets	B: Jug blender + standard sieve + cold water wash	C: Stick blender + no sieve + hot soapy water
Enterococcus	3	3	2
LA fermenting Enterobacteriaceae	1	1	3
Staphylococcus	2	3	3
Pseudomonas	1	3	1
Bacillus	2	2	0

Health Protection Agency [27] (i.e. CFU g^{-1} between 10^3 and $\leq 10^5$), regardless of preparation or storage procedure. However, a bacterial load of *Enterobacteriaceae* of approximately half the blended feeds was categorised as unsatisfactory (i.e. CFU g^{-1} $>10^4$), with no clear pattern of association with preparation or storage method.

Discussion

This laboratory-based evaluation is the first known systematic examination of the combined risks of tube blocking and microbial load of a blended feed. Only one recipe, based on low microbial risk, was examined and different results would be anticipated if different ingredients were used. However, the results provide useful information that is relevant to service users and healthcare professionals working in this field.

The total recipe met the estimated nutrient requirements of the hypothetical man who it was designed for, except for selenium and vitamin D, although this deficit could easily be made up with supplementation. However, the process of sieving resulted in almost one-third of the total recipe weight being lost despite determined efforts, including repeat blending, to sieve the feeds. Interestingly, the weight of feed lost using different blenders and sieves was comparable. The estimation of nutritional adequacy of the feed remaining after sieving (Table 1) makes an assumption that the losses of all nutrients are equivalent to the sieved weight loss, which is probably incorrect. Reports on the effects of sieving on individual dry ingredients (e.g. grains and legumes) indicate that this is associated with loss of micronutrients [29], although comparable data are not available for blended feeds. Selecting ingredients that would provide less fibre may reduce sieved losses and requires exploration. Although sieving has been recommended for blended feeds [10,13], this practice was not reported by patients and carers participating in a qualitative study [6].

The results from the present study indicate that the risk of blocking a 14-Fr enteral feeding tube when administering this blended feed recipe prepared using all three methods, including the stick blender without sieving, is low. This is compatible with anecdotal comments posted on social media by carers who routinely use blended feeds without major problems associated with blockages [30]. The findings may not be transferrable to a clinical situation and are limited to the recipe investigated because other foods may increase the risk of tube blocking. However, the ability for the feed made using a stick blender to be successfully delivered by syringe bolus without blocking the tubes is important because a high-powered professional blender is frequently described as necessary or desirable [2,3,30], although this equipment is considerably more expensive than a stick blender: approximately £400/€459/$510 compared to £30/€33/$38 (2019 prices). The consistency of feed produced using the three methods varied, with the thickest being produced using the professional blender, and the colour also varied the with production method, suggesting that the blending processes resulted in different levels of plant cell breakdown; this may have implications for intestinal absorption of micronutrients. Although the time associated with administering the feed via the 14-Fr tube was significantly quicker than for narrower tubes, extrapolating to delivering the feed for a whole day, in addition to making it, would be considerably more time-consuming for carers than using a standard formula. This additional time commitment has been reported by carers but accepted as necessary to enable blended feeding [6,31]. In addition, the force required to empty the syringe may be challenging for frail carers. Both these issues require further investigation so that carers can be best supported.

The bacteria genera identified were expected as a result of the use of nonsterile food even though low-risk ingredients were used and the feeds were made in an area with strict hygiene procedures, as well as by researchers with a certificate in food hygiene. Although the enumeration of *Bacillus cereus* was categorised as borderline using Health Protection Agency [27] criteria, that of *Enterobacteriaceae* was unsatisfactory in approximately half of the blended feeds with no clear picture emerging of safer or less risky preparation or storage procedures. This raises concern

about the microbial safety of the feeds overall because *Enterobacteriaceae* is considered an indicator organism (i.e. suggesting an overall poor hygiene status). Comparable microbial loads of blended feeds have been reported previously [10,32–34] and are inevitable in blended feeds made from nonsterile ingredients and in nonsterile conditions. Carvalho *et al.* [35] identified blenders, work surfaces, jugs and sieves as 'dirty zones' with potential for microbial contamination in an evaluation of enteral feeding in hospital. These are also likely to be a source of contamination in domestic kitchens which, in addition, may also be the site of nonfood practices [36,37], which have the potential to further increase risk. Although the identification of bacterial species from a limited selection of culturable colonies was helpful for gauging the presence of pathogens, a more comprehensive screen will be needed to accurately determine pathogen load and transmission in blended feeds. Culture of bacterial species with fastidious growth requirements (e.g. strict anaerobes) should also be considered. Further genetic analyses will be needed with respect to the consideration of antibiotic-resistant bacteria.

Although sterile formula feeds are associated with least microbial risk, sterile production of blended feeds would be hard to achieve in a domestic setting. In addition, complex procedures need to be reconciled with the concept of home blended feeding being 'just food' [31] and the social benefits of being included in a family meal [6], which are considered as highly important by those choosing to use this method of feeding. Feed sterility may not be an appropriate goal for those who required enteral tube feeding but are otherwise physically stable and not immunocompromised. It should be noted that 433 parents of blended-fed children reported their children had fewer gastrointestinal symptoms with blended feeds than with standard formula and, when these occurred, attributed them to the child's medical condition rather than food-borne illness associated with feeding [38]. Similarly, improvements in bowel habits associated with receiving blended feeds have been reported [6,39]. The positive role of microbes in gastrointestinal health [40] needs consideration because these may be contributing to some of the improvements reported by those using or preparing blended feeds. This needs to be balanced against potentially life-threatening risks associated with food-borne illness [41]. Although randomised controlled trials of blended diets may be ethically challenging because of these risks, future studies based on systematic clinical observations and risk-benefit modelling are needed.

The present study is limited to one hypothetical blended feed recipe, its laboratory-based design and the absence of testing for *Listeria* spp. The study only tested a bolus method of administering the feed and did not investigate the use of continuous feeding using a pump. A more extensive study design that allowed preparation method, equipment cleaning regime and storage to be independently tested, as well as including a wider range of microbial evaluations (e.g. identifying at genus level using a matrix-assisted laser desorption/ionization mass spectrometer), might provide more useful information that could inform guidelines for those patients and carers who decide to proceed with blended feeding.

In conclusion, this small laboratory-based evaluation of one-blended feed recipe found little risk of tube blockages associated with delivery via a 14-Fr tube and this was not influenced by the method of feed preparation. The findings raise potential concerns about the microbial load of blended feeds, although this was not influenced by the method of preparation or storage used in this study. The time taken to deliver blended feeds via enteral tubes was significantly longer than for a standard 1 kcal mL^{-1} formula feed and this needs to be considered by carers. Sieving feeds was associated with considerable food waste and, for the recipe evaluated, this was unnecessary because the risk of tube blockage was not increased with unsieved feeds.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Conflict of interests, source of funding and authorship

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AM conceived the idea, designed and supervised the overall study, contributed to data collection and led the writing of the manuscript. SB and SG designed and supervised the microbial evaluation, undertook the PCR sequencing and co-wrote the manuscript. SB, CS-N and MS designed the recipe, made the feeds, undertook the initial microbial evaluation and contributed to the manuscript. EC and LJ made the feeds, evaluated feed waste, undertook the

tube blockage evaluation and contributed to the manuscript. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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Supporting information

Table S1. Bacterial species identified in blended feeds using polymerase chain reaction sequencing.

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NUTRITIONAL SUPPORT

The impact of living with home enteral feeding: perspectives of people who have had a diagnosis of head and neck cancer

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Abstract

Background: The number of people with head and neck cancer who are home enterally fed continues to grow each year. Insertion of a feeding tube is common place in these patients and is considered to have a detrimental effect on quality of life. The present study aimed to investigate the daily impact of home enteral feeding (HEF) from the perspective of people who have had a diagnosis of head and neck cancer.
Methods: The methodology aligned with interpretative phenomenology analysis. People who were home enterally fed, with head and neck cancer, and aged ≥18 years were recruited. Data were collected using semi-structured interviews and analysis focused on what the daily impact of HEF meant for participants.
Results: Data saturation was achieved after interviewing 15 participants. Five cluster themes were identified. 'Deviation from the norm' encompassed change and loss of normality. 'Regaining control leading to empowerment' encompassed participant empowerment through development of new skills and adjusting the feeding regime. 'Creating a new normal' involved making adjustments to facilitate inclusion and participation. 'External modifiers of the HEF experience' and 'internal modifiers of the HEF experience' encompassed the identification of external and internal HEF factors that influenced HEF adaptation.
Conclusions: HEF was found to influence peoples' daily lives substantially and required extensive adjustments for individuals to find a new normal. A greater level of interpretation was provided beyond the current evidence-base for this group. Policymakers and clinicians should recognise the wider impact of HEF and ensure that this awareness is embedded in clinical practice.

Introduction

Malnutrition is a major concern in people with head and neck cancer (HNC) [(1)]. Up to 40% of people with HNC are malnourished at the point of diagnosis and 80% suffer significant weight loss during their cancer treatment [(1,2)]. Side effects of cancer treatment can be long-lasting, which means that enteral feeding is often required in community settings up to or even beyond 1 year post-treatment [(3)].

Home enteral feeding (HEF) can constitute an additional burden for people living after HNC [(4)]. A considerable amount of time needs to be dedicated to managing HEF [(4)]. Time is often spent undertaking tube care, managing stock levels of feed and equipment, administering feed, and giving medications via the tube.

Additionally, 8–30% of people have tube-related complications, comprising tube site leakage, infections, blockage or inadvertent tube removal [5]. People with HNC who have a feeding tube report a poorer quality of life compared to those who have never had a feeding tube or those who have had a feeding tube removed [6]. HEF may therefore have an impact beyond influencing nutritional and clinical status.

HEF may impact on the wider aspects of peoples' daily lives, including their social or psychological well-being [6]. Current nutritional guidance fails to recognise this impact [7–9] and lacks any acknowledgement regarding the importance of supporting people holistically [7–9].

The research examining how enteral feeding impacts on peoples' lives [6,10–17] consistently reports negative experiences on social eating [10–12,14,17]. Participants were reported feeling uncomfortable watching others eat [10] or self-conscious of the feeding tube when eating out [11]. A sense of loss was described by some participants because activities centred around food were previously key leisure or pleasure life events [10]. There is a lack of consensus on how HEF impacts on other aspects of peoples' lives, including hobbies, socialising and relationships [6,10–17]. Variation between studies exists regarding the impact of HEF on social functioning, with two studies reporting no impact [10,14] and, conversely, others stating that social functioning was hindered [6,15,17].

Additionally, there are contradictory results concerning the impact of HEF on daily activities. No differences in physical state or role functioning, 10–12 months after cancer treatment [14,16] were found when comparing people with and without a feeding tube, and one study found that discreet g-tubes lessen impact [17]. By contrast, other studies found that HEF impacted negatively on daily activities, including role functioning, hobbies or leisure activities [6,15]. The effects of HEF on intimacy has been reported to vary from minimal [13,14,16] to substantial [6,17], and the frequency of tube-related complications was found to fluctuate between studies [6,11,13]. However, studies investigating how tube-related complications impact on participants' lives are lacking in the literature.

Most studies have highlighted that HEF does impact on multiple aspects of peoples' lives [6,10–12,15,17]. However, there is a paucity of data regarding how important this impact is for participants and what it means in context of their daily lives. These questions are not explored in the current evidence-base. Understanding the lived experience of HEF amongst people with a diagnosis of HNC would enable clinicians to support an ever-growing cohort of people more holistically within clinical settings [18].

The present study therefore aimed to investigate the impact of HEF from the perspective of people who have had a diagnosis of HNC.

Materials and methods

Theoretical orientation

The study was framed within the interpretivist paradigm, meaning that participant and researcher subjectivity was a central focus, in addition to recognising the existence of multiple, valid realities [19]. Use of interpretative phenomenological analysis (IPA) aligned with this theoretical orientation [18]. Our research questions aligned with the aims of IPA by asking, 'how do people with a feeding tube in place make sense of living with a feeding tube?' and 'what does having a feeding tube in place mean for people in the context of their daily lives?' [18]. Furthermore, analysis adhered to IPA principles with regards to its idiographic, inductive and grounded nature, in addition to its commitment to divergent cases [18].

Sampling and recruitment

Purposive sampling was undertaken through the use of a sampling frame (see Supporting information, Appendix S1). Inclusion criteria comprised individuals who were: home enterally fed, diagnosed with HNC ≤2.5 years ago, aged ≥18 years, able to speak English and able to provide informed consent. Participants were excluded if they no longer had a feeding tube, or if they had recently received or were imminently due to cancer treatment (≤3 weeks).

The tube feeding dietitian from two National Health Service (NHS) sites identified eligible participants and managed recruitment at their own site. Eligible participants received a participant information sheet and covering letter from their clinical dietitian either face-to-face or in the post (see Supporting information, Appendix S1). Data collection continued until data saturation was reached.

Data collection

Data were collected through face-to-face, semi-structured interviews. Interviews were audio-recorded and transcribed verbatim. An interview schedule was developed based on a review of the current evidence-base as well as clinical experience (see Supporting information, Appendix S1). The interview guide was not pilot tested.

The researcher conducted each interview. All participants were aware that the researcher was working part time as an advanced HEF dietitian. Many participants already knew the researcher in her clinical role. The researcher had previously conducted qualitative interviews during a research internship at The University of Manchester.

Data analysis

Analysis focused on experiences of HEF, what this meant for participants and the impact of HEF on individuals' lives [18]. Each transcript was analysed in depth before moving onto the next. First, the researcher reviewed the audio-recording and transcript multiple times. The next stage involved line-by-line analysis of each participant's transcript in turn. Comments summarised the participant's responses at face-value and also provided a review of their use of language [18]. Conceptual comments drew upon both descriptive and linguistic comments to give an interpretation of the participant's perception of their experience [18].

Sub-themes and overarching themes were then generated (see Supporting information, Appendix S1). Divergent sub-themes were noted separately and were taken forward to the inter-participant stage of analysis.

Full inter-participant analysis only took place after each participant's account had been analysed individually. At this stage, each sub-theme was listed in a table starting from the first participant's transcript. Moving through subsequent participants' transcripts and by comparing with previously analysed transcripts, similar sub-themes were grouped together and new or divergent sub-themes were added to the sub-theme list within the data analysis table. Overarching themes linked similar sub-themes together.

In the final analytic stage, themes common between multiple participants were grouped into 'cluster' themes (see Supporting information, Appendix S1) [18]. Despite this, contrasting accounts were viewed with equal importance to accounts that showed similarities. An example illustrating the generation of a cluster theme is provided in the Supporting information (Appendix S1).

Rigour

Rigour was enhanced by data collection across multiple NHS sites, the double-coding of five transcripts and the random selection of five participants to undertake member checking [20]. There was agreement with the researcher and second coder with regards to the double-coded transcripts.

The researcher's epistemological position meant that she recognised she was not neutral in the research process. The researcher continually reflected on how her underlying assumptions originating from her role as a HEF dietitian may influence the research process. The appreciation of researcher subjectivity enabled the researcher to approach the study from a more open and reflective stance.

Throughout the research process, the researcher also reflected on the impact of the research context. For example, participants could choose the location for their interview in an attempt to reduce participant–researcher power imbalances related to the interview setting. The researcher also aimed to enhance participant–researcher rapport through the use of open, nonleading questions, gentle probing and active listening [18,21].

Ethical approval

Ethical approval was obtained from the Central Greater Manchester Ethics committee (REC reference: 17/NW/0505) on 23rd October 2017.

Member checking

One participant felt that his vomiting episodes were secondary to excess phlegm, in addition to the feed, and so the relevant sub-theme was amended accordingly. None of the other participants ($n = 4$) wanted to make any amendments.

Results

Participant and interview characteristics

Data saturation was reached by the fifteenth interview because no further information or themes were generated at this point. Most participants (93%) were recruited from site one. Recruitment at site two was limited because there were fewer than expected eligible participants. All participants chose to be interviewed in their own home. Mean interview duration was 44.5 min. Participant characteristics are summarised in Table 1.

Thematic analysis

Five cluster themes were identified: 'deviation from the norm', 'regaining control leading to empowerment', 'creating a new normal', 'external modifiers of the HEF experience' and 'internal modifiers of the HEF experience'. Participants have been given pseudonyms. Additional participant quotations are presented in the Supporting information (Appendix S1).

Change: 'Deviation from the norm'

Many participants described the physical, social and emotional impact of HEF on their daily lives. In many cases, these changes were associated with a negatively perceived shift from participants' previous normality.

Table 1 Participant characteristics

Participant characteristic	Number of participants
Total number of participants	15
Gender	
Female	5
Male	10
Age (years)	
>40 to ≤50	2
>50 to ≤60	3
>60 to ≤70	9
>70 to ≤80	1
Mean (SD) age (years)	61.3 (7.55)
Ethnicity	
White British	13
Non-white British	2
Time since diagnosis (months)	
<1 to ≤6	8
>6 to ≤12	4
>12 to ≤18	2
>18 to ≤24	0
>24 to ≤30	1
Mean (SD) time since diagnosis (months)	8.9 (7.22)
Time since treatment (months)	
<1 to ≤6	10
>6 to ≤12	3
>12 to ≤18	1
>18 to ≤24	0
>24 to ≤30	1
Mean (SD) time since treatment (months)	6.9 (6.90)
Time since tube insertion (months)	
<1 to ≤6	10
>6 to ≤12	3
>12 to ≤18	1
>18 to ≤24	0
>24 to ≤30	1
Mean (SD) time since tube insertion (months)	8.1 (7.14)
Type of feeding tube	
Balloon gastrostomy tube	13
Low profile button	2
Percutaneous endoscopic gastrostomy	0
Jejunostomy/PEG-J/nasogastric	0
Type of feeding method	
Continuous (pump) feeding	6
Bolus feeding	6
Mixture of continuous and bolus feeding	3

PEG-J, percutaneous endoscopic gastro-jejunostomy.

Physical impact

HEF disturbed meal times, sleep, daily activities, physical contact, work and travel.

Disturbed sleep led to increased tiredness and restricted daytime activities:

> 'As soon as I finish feeding, normally it's like daytime 6 o'clock . . . I lie down flat and go to sleep in the morning, yeah. Yes, definitely, I lose hours on the daytime activity then' (Nicholas, 60 years)

Tube-related complications led to practical implications including accessing input from health professionals, cleaning up after tube site leakage, and delayed feeding:

> 'I've had the occasional accident where I've forgotten to undo the clamp and it's gone all over the room and it is very thick and difficult to get off the walls, it's awful honestly' (Emily, 71 years)

Social impact

Being tube fed led to participants feeling socially excluded in many circumstances. Participants felt distanced from others at mealtimes as they could not eat. To deal with this, some would physically isolate themselves at meal times:

> 'The thing I miss most is sitting down to a meal with other people, because I can't partake of the meal, so I tend to go into a different room and feed myself with feed. So I miss that social aspect of eating ' (Emily, 71 years)

Social activities outside the home were curtailed as a result of the time tube feeding took and anxieties regarding the feeding tube being damaged:

> To get anywhere ready to go out, you have to make sure you've had your feed, you've had your medicine, whatever, you're done, and then you're alright. You have a three-hour window, so you can go out and get back' (Arnold, 65 years)

> 'Getting on a bus wasn't really an option in case you were scared it might fall out or get pulled out or you fell over' (Jean, 54 years)

Feed-related side effects including nausea and vomiting, also contributed to reduced social interactions:

> 'I've kept certain people away from the house because of being sick. . . so I didn't want people to see me' (Connor, 66 years)

Tube feeding impacted on participants' relationships as they could no longer take part in shared activities if they involved food. Friends and family could feel guilty about eating in front of the participant. Alternatively, they may not understand that the participant could not eat reinforcing feelings of being different:

> 'My husband and I would quite often, on the way home from work, not have dinner at home, we'd eat on the way in . . . I haven't done that now for . . . well, yeah . . . it's changed our life, the way

we live. I try not to think about it. Sometimes it does bother me' (Lilian, 61 years)

'They feel terrible because they're eating a big meal and I'm eating a mouthful, especially when I've cooked it as well' (Jean, 54 years)

'People say, do you want another one, and I say, no, I'm alright thanks. Are you sure? And you say, yeah. And I am. People can't understand you don't need to have a load' (Frank, 61 years)

Emotional impact

Tube feeding led to many negative emotions for participants. Participants felt out of control of their daily lives secondary to restrictions imposed by the feeding regime. There was a sense of feeling chained and trapped: '*my total life is like taken over by this pump feeding at night*' *(Nicholas, 60 years)*. Many participants felt embarrassed exposing their tube in front of others due to what they might think: '*I used to do a lot of swimming . . . oh, I don't think people would like to see that hanging down in the pool and stuff like that*' *(Harry, 67 years)*. A number of participants were fearful about inadvertently triggering tube-related complications or feed-related side effects:

'There's always the fear that something might go wrong and it might leak and that's quite a big fear' (Emily, 71 years)

'And I'm always aware of it being there or if anybody hugs me, I'm always careful of it' (Connor, 66 years)

Many participants also described how HEF had resulted in a loss of social or household identity. Loss of identity gave rise to feelings of exclusion and frustration:

'I used to do a lot of DIY and quite a bit of gardening . . . but constantly wife will be saying, oh your tube, your tube, you can't lift that' (Christopher, 70 years)

Participants were disappointed and saddened by the losses entailed with their disease:'All I wanted was a cup of tea' (Jean, 54 years)

Adaptation: 'Regaining control leading to empowerment'

Regaining independence and control facilitated HEF adaptation. Empowerment was achieved through knowledge and skill development, increasing flexibility in the feeding regime and minimising side-effects related to the feed:

'Rather than the district nurse, they said, we'll be here between 8 and 5, you were stuck in the house. But we'd rather do it ourselves, then you can manage your time better' (Arnold, 65 years)

'My stomach was too tiny, everything that I was trying to fit in with the drinks (bolused) just bloated me all the time, but now it seems settled, especially with the pump feed' (Vera, 48 years)

Participants' sense of freedom was increased by introducing flexibility in the feeding location and being comfortable to feed in front of family and friends:

'I'll take it (feed) with me . . . so it doesn't matter where I go, as long as I have my fresh water to flush it' (Adam, 68 years)

'It was one of my brothers, and I just said can I borrow a cup and explained what I was doing, and I just did it where I was in the living room. They understood. I didn't feel embarrassed or anything' (Craig, 64 years)

Creating a new normal

Adapting daily activities around HEF worked towards restoring a feeling of normality and inclusion. Some had learnt to adapt food choices when eating out, others had adapted to using the feeding tube around others to join in with meal times:

'Now I'm starting to be able to eat a bit more, then I would have, say, soup with everybody rather than have a feed, and stuff like that . . . yeah, I enjoy it . . . socialising and being part of human life again I think' (Emily, 71 years)

'Like my wife's thing with me when she has breakfast, I have two bottles of feed. And then we both have lunch in the afternoon. And then when she has dinner, I have two bottles of feed. So I'm living with her like a normal person. We're both eating the same food, the similar food at least, and sitting on the table eating together' (Nicholas, 60 years)

Some participants felt adapted to HEF by becoming accustomed to the feeding tube and the feeding regime over time: '*It's part of me*' *(Francesca, 62 years; Lilian, 61 years; Frank, 61 years)*.

External modifiers of the home enteral feeding experience

Support from family, friends or the public was encouraging and reassuring for participants. Support positively impacted on the HEF experience and facilitated HEF adaptation:

> 'A bit strange at first because they used to say would you like a cup of tea, Mum, but now it's like, would you like a flush, Mum? ' (Vera, 48 years)

By contrast, negative input from family, friends or the public hindered HEF adaptation.

> 'It took a long while for him (husband) to understand that I was poorly, and I couldn't eat. He'd still come in and say what are we having for tea? It took a long, long time. In fact, we fell out over it, big time' (Jean, 54 years)

Internal modifiers of the home enteral feeding experience

Internal modifiers of the HEF experience included participants' own coping mechanisms and internal conflict. Having a positive and resilient attitude facilitated adaptation to HEF: '*I am totally thankful, grateful, that I've got it because it's helping me, it's helping me a lot, so you've got to be positive*' *(Craig, 64 years)*.

Many participants recognised a conflict between the tube being a necessity and their perception of the feed being unnatural: '*a necessary evil*' *(Christopher, 70 years; Lilian, 61 years)*. Internal conflict hindered HEF adaptation. Participants recognised that by taking the pressure off eating the feeding tube hindered their progress with oral intake:

> 'I don't want porridge or something like that because I'm fed as far as I can see' (Francesca, 62 years)

Discussion

Despite HEF causing an initial feeling of change and disruption, many participants eventually adapted at least one aspect of their daily life to fit around the enteral feed. This HEF adaptation was facilitated by participants developing ways to restore power, independence, freedom, flexibility, participation and inclusion. Internal and external modifiers of the HEF experience influenced HEF adaptation.

In line with previous research, having a feeding tube in place triggered a sense of loss for many participants, including a loss of their ability to undertake daily activities [6,10,17,22,23], a loss of feeling connected to others [10,17,22,23] and a loss of their sense of self [24]. We found that family relationships can become fractured through the guilt of eating in front of loved ones receiving HEF, and through participants feeling isolated by family members not understanding their struggle to eat and drink. Attempting to partake in previously enjoyed activities or social interactions often led to anxiety about the feeding tube being damaged, as well as embarrassment about others' perceptions of the feeding tube. Our findings add to the existing literature by identifying how anxiety related to tube-complications can hinder participation in daily activities and socialising.

Despite HEF initially causing considerable disturbances to participants' daily lives, as found in previous research, many participants felt adapted to at least some aspects of HEF over time [10,11]. Increasing flexibility in the feeding regime made participants feel empowered, more in control and independent. This mirrors the wider literature with respect to living with a long-term condition in that regaining a sense of being in control can enable people to feel like they are restoring normality in their daily lives [25]. Furthermore, adapting at least one of their usual activities around HEF facilitated a sense of participation. Similarly, the wider literature also shows that people with long-term conditions often adjust daily activities to facilitate participation [26–28].

Support from family, friends and the public facilitated this journey to HEF adaptation and promoted participants' sense of acceptance and inclusion. The importance of feeling supported has also been identified previously [17,22,23]. In line with the data reported in the present study, Bjuresater *et al.* (2015) described how support encouraged feelings of 'safety and security', whereas a lack of support led to feelings of 'loneliness and vulnerability'.

Although not investigated in the present study, previous research has identified that parallels can be drawn between the experiences of both people receiving HEF as a result of HNC and their family caregivers [4,29]. Both parties can experience a sense of loss, isolation and emotional distress as a result of HEF [4,29,30]. Equally, both have to make substantial adjustments to create their new normal [4]. Supporting people receiving HEF should therefore also encompass supporting the physical and emotional well-being of their family caregivers [4,29,31]. Information and training should be tailored to the needs of both the patient and their family caregiver, and both parties should have the opportunity to express their feeling and concerns [4,29,31]. This in turn can facilitate positive HEF adaptation for both the patient and family caregiver [4].

As well as external influences, participants' own internal coping mechanisms and internal conflict also impacted on HEF adaptation. Our data added to the current literature by identifying that, even though participants recognised the importance of the feed, some were uncomfortable with the feed being unnatural. Participants recognised that these thought processes were not helpful.

By contrast to our findings, it has been reported in some of the previous quantitative literature that HEF has only a minimal impact on daily activities, hobbies and socialising [13,14,16]. Because the impact of HEF can vary day-to-day and week-to-week, restricting participants' responses to a single answer on a questionnaire can be difficult to interpret and of limited value [32]. Having set questions with predefined options may have meant that some aspects of the HEF experience were missed in these studies. Furthermore, Veldhuis *et al.* [32] asked participants to only recall their experiences during the previous week, which does not give a comprehensive reflection of their entire HEF experience.

A limitation of the present study was that most sampling targets were not achieved (see Supporting information, Appendix S1). Although data saturation was reached based on the included participants, having a more heterogeneous sample may have generated additional, more diverse themes [33]. Furthermore, drawing upon more than one type of data collection method would have increased rigour [20,34]. Despite these limitations, rigour was enhanced through member checking, the use of a second coder, comprehensive reflexivity and commitment to idiographic analysis [18,20].

Knowing the researcher in advance could have been a limitation. However, this appeared to encourage positive interactions as a result of the established mutual trust and rapport, and enabled the researcher to tailor interactions and more greatly understand their underlying context [35,36].

The present study adds to the current evidence-base by exploring not only how HEF impacted on participants' daily lives, but also what this impact means to participants. Understanding the wider impact of HEF on each patient's daily life, and identifying barriers to them achieving a sense of normality, can assist people making the transition to establishing their new normality. Tailored skill and knowledge development empowers patients and this supports them with adapting to HEF. Educating patients on how they can adjust the volume, rate or timing of the feeding regime to fit around different activities enables inclusion and participation, and this encourages patients to regain a sense of control and freedom into their daily lives.

The ultimate aim of future research will be to develop a patient-reported outcome measure for people who have had a diagnosis of HNC and are tube fed, using the information gained from the interviews. As a result of the limited sample diversity in the present study, future research could also explore the impact of HEF amongst people from ethnic minority groups or those that are aged ≤50 years.

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Conflict of interests, sources of funding and authorship

The authors declare that they have no conflicts of interest.
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AT was the lead author and undertook the study. SB was the academic supervisor, advised on the study design and methods, and was responsible for the data analysis and the proofreading of the manuscript submitted for publication. AS provided support for the data analysis, as well as the drafting of the manuscript and proofreading.

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Supporting information

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

Appendix S1. Supplementary material to support the article above

