

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Dietary factors and diabetes-related health outcomes in patients with type 2 diabetes: protocol for a systematic review and meta-analysis on prospective observational studies
AUTHORS	Barbaresko, Janett; Neuenschwander, Manuela; Schwingshackl, Lukas; Schlesinger, Sabrina

VERSION 1 - REVIEW

REVIEWER	Dr. Farzana Saleh Bangladesh University of Health Sciences Bangladesh
REVIEW RETURNED	24-Oct-2018

GENERAL COMMENTS	Accepted
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REVIEWER	Dr. V. Mohan Madras Diabetes Research Foundation & Dr. Mohan's Diabetes Specialities Centre, Chennai, India
REVIEW RETURNED	19-Dec-2018

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.
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REVIEWER	Jennie Brand-Miller University of Sydney. Australia I am the author of studies and books on the glycaemic index (GI) of foods. I manage a GI testing service at the University of Sydney and I am a Director of a food symbol program based on the GI.
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	Review of BMJ Open 2018-027298 Is the protocol scientifically valid? Yes Presented in an appropriate context? Yes Is the design ethical? Not sure Is it procedurally sound? Yes Does it include dates? No
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	<p>Do they need to clarify the rationale or methodology? I have a few questions</p> <p>Is there a major flaw that prevents sound interpretation of the data?</p> <p>No</p> <p>The authors claim this will be the first systematic review and meta-analysis to comprehensively summarise the available evidence and conduct meta-analyses on the association of dietary factors and diabetes-related outcomes in patients with T2D.</p> <p>To my knowledge, this is true – it will be the first. But this maybe because there are no studies of this nature!</p> <p>Questions for authors (clarification)</p> <ol style="list-style-type: none"> 1. They specify that only observational studies will be included. Does this mean that RCT such as LookAhead [1] will be excluded? Even the control group? 2. The authors should state explicitly that their systematic analysis of observational studies cannot imply cause-effect. 3. Are all endpoints specified in this protocol or will you add more as you explore the literature? For example, will age-related macular degeneration be included as an endpoint? 4. Why not include studies where the most well-established risk factor for all diabetes complications (HbA1c) is the endpoint? 5. Could the authors clarify whether they intend to use studies where a diet pattern is part of the original intention of the study, or whether the authors will generate the patterns themselves from dietary data? 6. Will they include vegetarian and vegan patterns? Plant-based diets is a silly term because sugar cane, palm oil, coconut fat are all plant-based. (This is ideology, not nutrition science). What if supplements are included (eg vitamin B12) in the vegetarian or vegan pattern? The authors state that they will exclude studies on supplements. 7. Will the authors include low glycaemic index and low glycemic load patterns? And whether findings will individual foods such as rice, pasta and potato can be ascribed to their glycaemic index? 8. Dose-response studies are planned. Will they will look at dose-response studies of fruit? Will they include fruit and vegetable juices under the umbrella term fruit? 9. Will they retrospectively categorise individuals to a score for DASH pattern or Med pattern etc? Or only if the original paper includes the terms? 10. The authors state that the systematic review will be based on published studies - hence, ethical considerations are not required. But they exclude studies in children with type 2 diabetes, pregnant women, women with GDM? Is this ethical? 11. The authors will exclude studies on biomarkers of dietary intake. Does that mean you'll exclude those that include both biomarkers
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	<p>and hard endpoints?</p> <p>12. Statistical significance is defined as $p < 0.05$ but there is robust discussion that this level leaves too much to chance so at best it is marginally significant. Perhaps the authors should specify $p < 0.01$ as their level of significance.</p> <p>References</p> <p>1. Look, A.R.G.; Wadden, T.A.; West, D.S.; Delahanty, L.; Jakicic, J.; Rejeski, J.; Williamson, D.; Berkowitz, R.I.; Kelley, D.E.; Tomchee, C., et al. The look ahead study: A description of the lifestyle intervention and the evidence supporting it. <i>Obesity</i> (Silver Spring, Md.) 2006, 14, 737-752.</p>
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REVIEWER	Grith Møller Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark
REVIEW RETURNED	15-Mar-2019

GENERAL COMMENTS	The study protocol is clear and the systematic review and meta-analysis well designed, and will provide a comprehensive overview of dietary patterns, foods and nutrients and their association with a range of diabetes-related outcomes. Consider rephrasing sentences 60-61 to improve clarity.
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REVIEWER	Francis Finucane HRB Clinical Research Facility Galway University Hospitals Galway Ireland
REVIEW RETURNED	20-Mar-2019

GENERAL COMMENTS	<p>This paper outlines a protocol for a systematic review and meta-analysis of dietary factors' influence on diabetes related complications in patients with type 2 diabetes. Overall this is a very well described and designed protocol which addresses an important clinical research question.</p> <p>The abstract is clear, as are the strengths and limitations of the study.</p> <p>Overall the introduction is very well written, though I would consider (3) a weak reference. The rationale for the study is otherwise well described. The authors ought to use the word "However" at the start of sentences rather than in the middle. Also the formatting in the references, particularly with the names of the journals, could be better and clearer.</p> <p>The methods are well described. The search strategy seems comprehensive. The statistical approach is robust as are the strategies to identify and minimise bias. Overall this is an excellent and worthwhile proposal.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 3

Reviewer Name: Jennie Brand-Miller

The authors claim this will be the first systematic review and meta-analysis to comprehensively summarise the available evidence and conduct meta-analyses on the association of dietary factors and diabetes-related outcomes in patients with T2D.

To my knowledge, this is true – it will be the first. But this maybe because there are no studies of this nature!

Response: We thank Prof Brand-Miller for her thoughts and valuable comments. We are aware of several studies that have been published on dietary factors and diabetes complications (e.g. fish intake and mortality (1, 2), dietary patterns and CVD (3), food groups and chronic kidney disease (4)). In addition, there are few systematic reviews looking at diet and retinopathy (5-7), however, these reviews have not conducted meta-analyses and included also cross-sectional and case-control studies.

Questions for authors (clarification)

1. They specify that only observational studies will be included. Does this mean that RCT such as LookAhead [1] will be excluded? Even the control group?

References

1. Look, A.R.G.; Wadden, T.A.; West, D.S.; Delahanty, L.; Jakicic, J.; Rejeski, J.; Williamson, D.; Berkowitz, R.I.; Kelley, D.E.; Tomchee, C., et al. The look ahead study: A description of the lifestyle intervention and the evidence supporting it. *Obesity* (Silver Spring, Md.) 2006, 14, 737-752.

Response: We thank Professor Brand-Miller for raising this interesting point. We also discussed this point earlier and decided to conduct a separate review on RCTs investigating diet and intermediates for diabetes complications as the current project is already quite comprehensive. We do not expect many intervention studies that investigated diet and hard endpoints listed in our protocol. In addition, most of the RCTs, including the LookAhead trial, focused on achieving weight loss through dietary modification (e.g. caloric restriction) in combination with the modification of physical activity. Thus, it is not possible to differentiate the effects of the different exposures (diet vs. physical activity). We added a statement to our eligibility criteria.

However, we will include follow-up studies of intervention studies/ randomized controlled studies, if they are in accordance with our in- and exclusion criteria. We have added a statement to the limitation section, that evidence will be derived from observational studies (compare comment 2). Finally, we added the information that we focus on prospective observational studies to the title.

Page 6, lines 134-136, Eligibility criteria: "Studies reporting on dietary factors in combination with other lifestyle factors (e.g. physical activity, lifestyle index) will be excluded."

Page 6, lines 142-146: "(4) Study design: We will include prospective observational studies (including cohort, nested case-control, case-cohort studies, and follow-up studies of intervention studies) published in a peer-reviewed journal. Cross-sectional, case only or case-control studies, conference abstracts, comments, letters and reviews will be excluded from the systematic review."

Title: "Dietary factors and diabetes-related health outcomes in patients with type 2 diabetes: protocol for a systematic review and meta-analysis on prospective observational studies"

2. The authors should state explicitly that their systematic analysis of observational studies cannot imply cause-effect.

Response: We included this issue in the limitations part: "Evidence will be derived from prospective observational studies, and thus a conclusive answer on causality cannot be provided." (page 3, lines 64-65)

3. Are all endpoints specified in this protocol or will you add more as you explore the literature? For example, will age-related macular degeneration be included as an endpoint?

Response: This is an interesting point. We included the most relevant and well-known diabetes-related outcomes. In addition, we considered the opinion of patients with diabetes mellitus regarding the selection of the outcomes. We have included a new statement of patient involvement in our protocol (page 12/13, lines 292-313).

Page 13, lines 301-308: "Moreover, patients also discussed about complications due to diabetes. One central point was the prevention of complications, especially cardiovascular diseases, polyneuropathy, diabetic foot pain and ulcer, nephropathy and retinopathy. Additionally, health-related quality of life and its predictors were mentioned as an important outcome regarding diabetes research. These findings underline that patients with diabetes are searching for clear and comprehensible information on dietary recommendations with regard to prevention of diabetes complications and health-related quality of life."

Furthermore, there is an ongoing survey on patients' needs and interests at our institution, and further patient-relevant outcomes will be identified, also during our project. Thus, we included the following statements:

Page 13, line 309-313: "Moreover, based on this survey,¹ a questionnaire was developed and tested in a pre-test. At the end of 2018, the questionnaire had been sent out to a representative study sample, including 3000 patients with diabetes registered at a local health insurance. These findings

will help us to focus on (further) patient-relevant outcomes, which we can incorporate in extensions of our systematic review and meta-analysis."

Page 14, lines 326-327: "Further research questions can be developed, e.g. dietary factors in association to further endpoints."

4. Why not include studies where the most well-established risk factor for all diabetes complications (HbA1c) is the endpoint?

Response: We agree with Professor Brand-Miller that HbA1c is an interesting endpoint. In the underlying project, we will focus only on "hard endpoints" in individuals with diabetes. In another project, we also plan to investigate associations between dietary factors and surrogate markers (Hba1c, blood glucose, blood lipids, inflammatory markers etc.).

(compare comment 1).

5. Could the authors clarify whether they intend to use studies where a diet pattern is part of the original intention of the study, or whether the authors will generate the patterns themselves from dietary data?

Response: We thank you for pointing this out. We will only include dietary patterns/habits that have been derived in the primary studies. We will not generate any dietary patterns based on the data available in the primary studies. For clarification, we rephrased the part in our manuscript:

Page 7, (lines 155-163): "Dietary patterns, dietary habits and diet quality: We will include dietary patterns generated in the primary study and derived by hypothesis-driven methods, namely dietary indices (e.g. Healthy Eating Index,17 18 DASH19), dietary scores (e.g. Mediterranean Diet Score20), exploratory-derived dietary patterns by e.g. principal component analysis, factor analysis or reduced rank regression, dietary habits (e.g. vegetarian or vegan diets), and diet quality (e.g. glycaemic index or glycaemic load)."

6. Will they include vegetarian and vegan patterns? Plant-based diets is a silly term because sugar cane, palm oil, coconut fat are all plant-based. (This is ideology, not nutrition science). What if supplements are included (eg vitamin B12) in the vegetarian or vegan pattern? The authors state that they will exclude studies on supplements.

Response: This is an interesting point. We will include studies that investigated vegetarian or vegan diets. We will also include studies on supplements. We have added a statement in our protocol.

Page 7, line 155-163: "Dietary patterns, dietary habits and diet quality: We will include dietary patterns generated in the primary study and derived by hypothesis-driven methods, namely dietary indices (e.g. Healthy Eating Index,17 18 DASH19), dietary scores (e.g. Mediterranean Diet Score20), exploratory-derived dietary patterns by e.g. principal component analysis, factor analysis or reduced

rank regression, dietary habits (e.g. vegetarian or vegan diets), and diet quality (e.g. glycaemic index or glycaemic load)."

Page 7, line 170-171: "Dietary supplements: vitamins (e.g. vitamin E or D), minerals (e.g. magnesium or calcium), or other products (e.g. fish oils)."

7. Will the authors include low glycaemic index and low glycaemic load patterns? And whether findings will individual foods such as rice, pasta and potato can be ascribed to their glycaemic index?

Response: We thank you for this interesting suggestion. We included glycaemic index and load to the exposure part (please compare response to comment 6). We will include these exposures only if the authors in the primary studies investigated glycaemic index/load, we will not ascribe foods to their glycaemic index, but we will discuss results of the food groups in relation to the results of dietary patterns or glycaemic index/load.

8. Dose-response studies are planned. Will they will look at dose-response studies of fruit? Will they include fruit and vegetable juices under the umbrella term fruit?

Response: Yes, we will also conduct linear and non-linear dose-response meta-analyses on fruit intake, if data are available. We will separately analyze fruit and vegetables as well as juices. We will not combine studies on fruit and studies on fruit and/or vegetable juices.

9. Will they retrospectively categorise individuals to a score for DASH pattern or Med pattern etc? Or only if the original paper includes the terms?

Response: We thank Professor Brand-Miller for pointing this out. As described in the response to your comment no. 5, we will only include studies that generated dietary patterns or that investigated dietary habits. Thus, we will not categorise individuals retrospectively. To clarify this in the manuscript we rephrased the part on dietary patterns (see lines 155-163, compare comment 5).

10. The authors state that the systematic review will be based on published studies - hence, ethical considerations are not required. But they exclude studies in children with type 2 diabetes, pregnant women, women with GDM? Is this ethical?

Response: We decided to exclude studies that solely investigated GDM or children as these study populations are expected to be different compared to the general adult population diagnosed with type 2 diabetes. Findings might be too heterogeneous to combine with each other. These procedure is very common, and has been applied in the past. Please compare with Li et al. (8), Avery et al. (9) or Schwingshackl et al. (10). We believe that this is not an issue of ethical considerations. However, future research question should focus on these specific populations.

11. The authors will exclude studies on biomarkers of dietary intake. Does that mean you'll exclude those that include both biomarkers and hard endpoints?

Response: We thank Professor Brand-Miller for this interesting point. According to her comment, we decided to include also studies on dietary biomarkers, if they investigated hard endpoints. However, findings on dietary intake and dietary biomarkers will be investigated separately. We included a sentence to the method section.

Page 7, lines 151-153: "We will evaluate the impact of different dietary factors assessed by established dietary assessment instruments such as food frequency questionnaires, diet history, 24h dietary recalls, dietary records, or biomarkers of dietary intake."

Page 11-12, lines 265-266: "We will separately investigate studies on dietary intake, dietary supplements, and biomarkers of dietary intake."

12. Statistical significance is defined as $p < 0.05$ but there is robust discussion that this level leaves too much to chance so at best it is marginally significant. Perhaps the authors should specify $p < 0.01$ as their level of significance.

Response: According to the recent discussion among well-known statisticians, we are grateful for raising this point. We will provide p-values, but according to the recent mentioned discussion in Nature, we will not interpret the results solely on the threshold of the p-value (3). We deleted the sentence on statistical significance from the manuscript and will focus on the strengths of effects, 95% confidence intervals as well as heterogeneity between studies.

Reviewer: 4

Reviewer Name: Grith Møller

1) The study protocol is clear and the systematic review and meta-analysis well designed, and will provide a comprehensive overview of dietary patterns, foods and nutrients and their association with a range of diabetes-related outcomes. Consider rephrasing sentences 60-61 to improve clarity.

Response: We thank Professor Møller for her positive feedback. We rephrased the sentence in the strengths and limitations section as follows:

Page 3, lines 64-65: "Evidence will be derived from prospective observational studies, and thus a conclusive answer on causality cannot be provided."

Reviewer: 5

Reviewer Name: Francis Finucane

1) This paper outlines a protocol for a systematic review and meta-analysis of dietary factors' influence on diabetes related complications in patients with type 2 diabetes. Overall this is a very well described and designed protocol which addresses an important clinical research question.

The abstract is clear, as are the strengths and limitations of the study.

Overall the introduction is very well written, though I would consider (3) a weak reference.

Response: We thank Professor Finucane for his careful review. We included a new reference for the risk factors of diabetes (Bellou et al. 2018 (11), page 4, line 81).

2) The rationale for the study is otherwise well described. The authors ought to use the word "However" at the start of sentences rather than in the middle.

Response: We rephrased the sentences accordingly.

Page 3, lines 64-65: "Evidence will be derived from prospective observational studies, and thus a conclusive answer on causality cannot be provided."

Page 5, lines 102-103: "However, a systematic review and meta-analysis on other health-related outcomes in patients with T2D is missing."

3) Also the formatting in the references, particularly with the names of the journals, could be better and clearer.

Response: We thank Professor Finucane for pointing this out. We checked the references again and formatted all references according to the journal guidelines.

4) The methods are well described. The search strategy seems comprehensive. The statistical approach is robust as are the strategies to identify and minimise bias. Overall this is an excellent and worthwhile proposal.

Response: We thank Professor Finucane for his positive feedback.

References

1. Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation*. 2003;107(14):1852-7.
2. Deng A, Pattanaik S, Bhattacharya A, Yin J, Ross L, Liu C, et al. Fish consumption is associated with a decreased risk of death among adults with diabetes: 18-year follow-up of a national cohort. *Nutr Metab Cardiovasc Dis*. 2018;28(10):1012-20.
3. Archundia Herrera MC, Subhan FB, Chan CB. Dietary Patterns and Cardiovascular Disease Risk in People with Type 2 Diabetes. *Curr Obes Rep*. 2017;6(4):405-13.

4. Dunkler D, Kohl M, Teo KK, Heinze G, Dehghan M, Clase CM, et al. Dietary risk factors for incidence or progression of chronic kidney disease in individuals with type 2 diabetes in the European Union. *Nephrol Dial Transplant*. 2015;30 Suppl 4:iv76-85.
5. Dow C, Mancini F, Rajaobelina K, Boutron-Ruault MC, Balkau B, Bonnet F, et al. Diet and risk of diabetic retinopathy: a systematic review. *Eur J Epidemiol*. 2018;33(2):141-56.
6. Lee CT, Gayton EL, Beulens JW, Flanagan DW, Adler AI. Micronutrients and diabetic retinopathy a systematic review. *Ophthalmology*. 2010;117(1):71-8.
7. Wong MYZ, Man REK, Fenwick EK, Gupta P, Li LJ, van Dam RM, et al. Dietary intake and diabetic retinopathy: A systematic review. *PLoS One*. 2018;13(1):e0186582.
8. Li L, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ*. 2014;348:g2366.
9. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care*. 2012;35(12):2681-9.
10. Schwingshackl L, Chaimani A, Hoffmann G, Schwedhelm C, Boeing H. Impact of different dietary approaches on glycemic control and cardiovascular risk factors in patients with type 2 diabetes: a protocol for a systematic review and network meta-analysis. *Syst Rev*. 2017;6(1):57.
11. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. *PLoS One*. 2018;13(3):e0194127.

VERSION 2 – REVIEW

REVIEWER	Jennie Brand-Miller University of Sydney, Australia I am President of the non-profit food endorsement company (The Glycemic Index Foundation, Ltd). I oversee a glycemic index testing service at the University of Sydney. I am the co-author of popular books on nutrition and the glycemic index.
REVIEW RETURNED	16-Apr-2019
GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.