PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of Pasta in the Context of Low Glycemic Index Dietary Patterns on Body Weight and Markers of Adiposity: A Systematic Review and Meta-analysis of Randomized Controlled Trials in Adults
AUTHORS	Chiavaroli, Laura; Kendall, Cyril; Braunstein, Catherine; Blanco Mejia, Sonia; Leiter, Lawrence; Jenkins, David; Sievenpiper, John

VERSION 1 – REVIEW

REVIEWER	Jennie Brand-Miller University of Sydney, Australia
REVIEW RETURNED	18-Sep-2017

GENERAL COMMENTS	This paper described a meta-analysis of the effect of pasta alone or pasta in a low GI diet on various measures of weight control. It has been conducted according to gold standard methods and interpreted carefully. The take home message is that pasta as a component of low GI diet has no negative effect on weight control. Indeed, it seems to assist with weight loss. This is topical area because carbohydrates are getting a bad rap in general (see Lancet September 2017) and refined carbohydrates in particular. Pasta is often called a refined food, but it actually has a good micronutrient nutrition profile, similar that of many wholegrain products. Strengths Uses meta-analysis gold standards Registered on clinicalrials.com Searches many databases Several outcomes related to weight gain were explored They found a large number of trials that included pasta n = 32 They assessed each study using the Cochrane bias tool Median follow up was 12 weeks Sensitivity tests were applied No evidence of heterogeneity Conducted various sub-group analyses eg study duration > or < 24 weeks Applied GRADE assessment to rate quality of studies The authors list both strengths and weakness of their analysis Weaknesses Studies as short as 3 weeks were included Quality of studies was on average moderate They found no of trials of pasta alone They found evidence of inconsistency

	There was evidence of unexplained heterogeneity in waist circumference There was evidence of indirectness Difficulty in quantifying the effect of pasta per se Comments to author 1. It would be good to include a reference to the higher micronutrient content of pasta vs white bread. Pasta is made with very hard wheats (eg durum wheat) that allow the aleurone layer to be preserved in the final semolina (hence the golden colour of pasta).

REVIEWER	Jordi Salas Salvadó Rovira i Virgili University Spain
REVIEW RETURNED	04-Oct-2017

GENERAL COMMENTS	The paper of Chiavaroli et al. is of great interest due to it is the first time that the effect of pasta alone or in the context of a low glycemic index diet on adiposity is evaluated in a systematic review and meta-analysis. Moreover, authors have evaluated the overall quality of the meta-analysis with the GRADE assessment. However, there are some minor issues that need to be addressed and clarified: 1. The main objective of the study was to assess the effect of pasta on adiposity. It is important to emphasize in the conclusion section that body weight and BMI were significantly reduced in the intervention group with pasta in the context of a low-GI dietary pattern compared with high-GI dietary patterns, even in the absence of effect on other measures of adiposity. 2. In the introduction section (lines 86-88) authors should add references when affirm that it is unclear whether pasta alone or in the context of a low-GI dietary pattern contributes to weight gain in order to better contextualize the readers. 3. In the main analysis of body weight, authors included the effect at 4 and 6 months. They should include only the results at 6 months because both are derived from the same study and therefore the long follow-up must to be included. 4. Because no studies were found evaluating the effect of pasta alone and only studies where pasta were included as a part of the low GI diet intervention were incorporated, it is important to indicate in the limitation section that it is impossible to rule out the possibility that the observed effects are due to the consumption of other healthy foods present in the low GI dietary pattern or due to the low GI per se. 5. Authors indicated in the methodology section that inter-study heterogeneity was considered significant if $p<0.10$. However, in the GRADE assessment explanation (line 197), it is indicated: "Substantial unexplained heterogeneity, $I2 <50\%$, $P<0.01$)." Please, clarify it. 6. It is a little bit confuse if p-value of lines 303, 305, 311, 317 and 319 and supplemental tables 6-10 refers to the pool effect or the inter-study heterogeneity. Please, change it in order to avoid misunderstandings.

REVIEWER	Aliki-Eleni Farmaki University of Leicester, UK
REVIEW RETURNED	09-Oct-2017

GENERAL COMMENTS	Abstract • Line 68: It should be clarified that the "treatment" is not an actual treatment or rephrase. Introduction • Lines 76-78: A more scientific background statement would be more appropriate. • Line 87: "in the context of a low-GI dietary pattern"- it should be expanded and clarified/explained better (maybe in the Study selection section- see next comment) as it is used though out the whole paper. Methods • Study selection section (lines 110-114): As requested in the previous comment, this sentence includes the rationale behind this meta-analysis. Consequently, it should be defined/ explained further focusing more on the specific phrase "in the context of a low-GI dietary pattern". • Data extraction section (line 130): Plot digitizer- I would like to express some doubts regarding the validity of the specific tool taking into account the fact that the Pubmed results were only 5. Maybe an article instead of a link would be more useful for checking the citations of this tool. • Statistical analysis section (lines 172-173): How the actual energy balance was assessed? It was taken somehow into account in the original studies?- A point/comment on this should be included in the discussion and limitations section as well as a point/comment regarding the energy intake adjustment wherever it is thought appropriate/relevant by the author. Discussion • Lines 358-362: It is questionable if this sentence about energy balance could apply based on the previous comment. It should be adjusted accordingly, depending on the way that the previous comment will be addressed.

REVIEWER	Antonio Palazón-Bru Miguel Hernández University, Spain.
REVIEW RETURNED	02-Dec-2017

GENERAL COMMENTS	1) In the abstract I would like to see the rationale to perform a meta-analysis (contradictory results in clinical trials, for example). 2) I do not understand why you registered this meta-analysis as a clinical trial. This is not correct. 3) In strengths and limitations of this study (after the abstract), you should indicated the rationale of your work. 4) "It remains unclear whether pasta alone or in the context of a low-GI dietary pattern contributes to weight gain.". What is the explanation for this statement? This is a key question in order to understand why you performed this meta-analysis. 5) What was your hypothesis for your research question? 6) Although you have indicated your search terms, to be able to replicate your results, you should write the search equations, indicating the fields to search and the connectors. 7) Could you explain the method of the Plot Digitizer program? 8) I do not understand why you analyzed heterogeneity if you used always random-effect models.

	On the other hand, in my opinion, the rest of the paper is well written and scientifically valid to be published in BMJ Open.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers
Reviewer: 4
Reviewer Name: Dr Palazón-Bru
Institution and Country: Miguel Hernández University, Spain.
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
My previos comments have not been applied to the text. I would need a letter to explain the reasons for not changing any phrase of the manuscript.
1) In the abstract I would like to see the rationale to perform a meta-analysis (contradictory results in clinical trials, for example).

We agree that a more explicit statement of rationale would be useful. Our rationale does not relate to contradictory results between randomized trials in the literature but rather to the absence of any syntheses of the available randomized trials to address the question whether pasta contributes to weight gain or like other low-glycemic index (GI) foods contributes to weight loss. We have revised the abstract (L30-33) and introduction (L83-87) to include statements to this effect.

2) I do not understand why you registered this meta-analysis as a clinical trial. This is not correct.

We apologize for any confusion. Our systematic review and meta-analysis is in fact registered as a "meta-analysis" and NOT as a clinical trial. The site clinicaltrials.gov allows for the registration of multiple study designs including observational studies and systematic reviews and meta-analyses of human evidence. It is NOT exclusively intended for the registration of clinical trials (https://clinicaltrials.gov/ct2/manage-recs/how-register). We have registered more than 25 protocols for systematic reviews and meta-analyses using the clinicaltrials.gov website and a search of the term "meta-analysis" on the clinicaltrials.gov website reveals 456 registrations of meta-analyses.

3) In strengths and limitations of this study (after the abstract), you should indicated the rationale of your work.

Although we again agree that a more explicit statement of the rationale for our work would be useful, it is not permitted for this section of the paper. As per the instructions to authors (http://bmjopen.bmj.com/pages/authors/), the "Strengths and Limitations of this Study" section is meant to relate only to the methods used…
"An Article Summary, placed after the abstract, consisting of the heading 'Strengths and limitations of this study', and containing up to five short bullet points, no longer than one sentence each, that relate specifically to the methods."

4) "It remains unclear whether pasta alone or in the context of a low-GI dietary pattern contributes to weight gain.". What is the explanation for this statement? This is a key question in order to understand why you performed this meta-analysis.

We agree that this statement requires some clarification. As part of including a more explicit statement of rationale, we have clarified why it is unclear whether pasta alone or in the context of low-GI dietary patterns contributes to weight gain in the abstract (L30-33) and introduction (L83-87).

5) What was your hypothesis for your research question?

Thank you for this question. We did not have a prespecified hypothesis. Unlike other forms of research interrogation, systematic reviews and meta-analyses do NOT need a hypothesis. An objective to synthesize or summarize the evidence on a given question is sufficient without preconceptions about the direction or magnitude of the relationship. A hypothesis per se is NOT a reporting requirement of the Cochrane Handbook (http://handbook-5-1.cochrane.org/), Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (http://prisma-statement.org/documents/PRISMA%202009%20checklist.pdf) or the PRISMA protocols (PRISMA-P) statement (http://www.prisma-statement.org/documents/PRISMA-P-checklist.pdf.

6) Although you have indicated your search terms, to be able to replicate your results, you should write the search equations, indicating the fields to search and the connectors.

We apologize for any confusion about our search strategy. Supplemental Tables S2 and S3 provide all the necessary information for a fully reproducible search. Supplemental Table S2 presents the full "search equations, fields, and connectors" used for each of the three database (Medline, Embase, and The Cochrane Library). The "equations" are represented by the order of the numbered search terms and symbols as shown; the "fields" are represented by the suffixes "tw" ("the Text Word (TW) index is an alias for all of the fields in a database which contain text words and which are appropriate for a subject search"[http://ospguides.ovid.com/OSPguides/medline.htm#TW]) ; and the "connectors" are represented by the final numbered lines shown for each database that connect numbers using "or", "and", "not", and "limit". Supplemental Table S3 provides the research question operationalized using the PICO framework.

7) Could you explain the method of the Plot Digitizer program?

Thank you again for this question. We agree that more information about Plot Digitizer would be useful. According to the website link (http://plotdigitizer.sourceforge.net/), Plot Digitizer is a JAVA program that digitizes scanned figures of X and Y plots from GIF, JPEG, or PNG image file formats and allows one to calibrate the X and Y axes for the estimation data points. We have provided this brief description and retained the website link (http://plotdigitizer.sourceforge.net/) in the methods section (L131-135).

8) I do not understand why you analyzed heterogeneity if you used always random-effect models.

We agree that it may seem odd to explore heterogeneity with sensitivity and a priori subgroup analyses when using random effects models. Although the pooled estimates from these models account for heterogeneity, they do not explain the heterogeneity. Even in the presence of heterogeneity estimates that are non-significant (P>0.10) with low I2¬values (<50%), residual unexplained heterogeneity may persist. As stated in the Cochrane handbook, "…random effects meta-analysis… is not a substitute for a thorough investigation of heterogeneity" (http://handbook-5-1.cochrane.org/). As a result it is incumbent on the investigator to pre-specify an analysis plan to explore sources of heterogeneity and test the robustness of the findings irrespective of the model used and whether heterogeneity is detected or not. The GRADE handbook (https://gdt.gradepro.org/app/handbook/handbook.html) explicitly recommends this approach, and we prespecified it in our own protocol (ClinicalTrials.gov Identifier, NCT02961088).

On the other hand, in my opinion, the rest of the paper is well written and scientifically valid to be published in BMJ Open.

Reviewer: 2
Reviewer Name: Jordi Salas-Salvadó
Institution and Country: Human Nutrition Unit, Hospital Universitari de Sant Joan de Reus, Rovira i Virgili University, Spain
Please state any competing interests or state 'None declared': No conflict of interest to declare

Please leave your comments for the authors below
Good work, congratulations
Many thanks for your support of the revised manuscript.

Reviewer: 1
Reviewer Name: Jennie Brand-Miller
Institution and Country: University of Sydney, Australia
Please state any competing interests or state 'None declared': Jennie Brand-Miller is a co-author of books about the glycemic index of foods. She is the Director of GI Foundation Limited, a non-profit company that administers the Australian 'GI Symbol' program, and oversees the Sydney University Glycemic Index Research Service (SUGiRS), a non-profit GI testing facility for the food industry. She has received honoraria for speaking engagements on the glycemic index of foods.

Please leave your comments for the authors below
The authors have adequately addressed the issues raised in my previous review. m
Many thanks for your support of the revised manuscript.

Reviewer: 3
Reviewer Name: Aliki-Eleni Farmaki
Institution and Country: University of Leicester, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
My minor comments have been adequately and satisfactorily addressed.
I do not have any further comments.
Many thanks for your support of the revised manuscript

VERSION 2 – REVIEW

REVIEWER	Jennie Brand-Miller University of Sydney, Australia Jennie Brand-Miller is a co-author of books about the glycemic index of foods. She is the Director of GI Foundation Limited, a non-profit company that administers the Australian 'GI Symbol' program, and oversees the Sydney University Glycemic Index Research Service (SUGiRS), a non-profit GI testing facility for the food industry. She has received honoraria for speaking engagements on the glycemic index of foods.
REVIEW RETURNED	17-Dec-2017

GENERAL COMMENTS	The authors have adequately addressed the issues raised in my previous review.

REVIEWER	Jordi Salas-Salvadó Human Nutrition Unit Hospital Universitari de Sant Joan de Reus Rovira i Virgili University Spain

REVIEW RETURNED	16-Dec-2017

GENERAL COMMENTS	Good work, congratulations

REVIEWER	Aliki-Eleni Farmaki University of Leicester, UK
REVIEW RETURNED	25-Dec-2017

GENERAL COMMENTS	My minor comments have been adequately and satisfactorily addressed. I do not have any further comments.

REVIEWER	Dr Palazón-Bru Miguel Hernández University, Spain.
REVIEW RETURNED	11-Dec-2017

GENERAL COMMENTS	My previos comments have not been applied to the text. I would need a letter to explain the reasons for not changing any phrase of the manuscript. 1) In the abstract I would like to see the rationale to perform a meta-analysis (contradictory results in clinical trials, for example). 2) I do not understand why you registered this meta-analysis as a clinical trial. This is not correct. 3) In strengths and limitations of this study (after the abstract), you should indicated the rationale of your work. 4) "It remains unclear whether pasta alone or in the context of a low-GI dietary pattern contributes to weight gain.". What is the explanation for this statement? This is a key question in order to understand why you performed this meta-analysis. 5) What was your hypothesis for your research question? 6) Although you have indicated your search terms, to be able to replicate your results, you should write the search equations, indicating the fields to search and the connectors. 7) Could you explain the method of the Plot Digitizer program? 8) I do not understand why you analyzed heterogeneity if you used always random-effect models. On the other hand, in my opinion, the rest of the paper is well written and scientifically valid to be published in BMJ Open.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3
Reviewer Name: Aliki-Eleni Farmaki
Institution and Country: University of Leicester, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Abstract

- Line 68: It should be clarified that the "treatment" is not an actual treatment or rephrase.

Thank you. We have revised to use the word "intervention" in this line instead (line 70).

Introduction

- Lines 76-78: A more scientific background statement would be more appropriate.

We have included statements from health advocacy groups (National Obesity Forum) and publications from BMJ as scientific references to support the background on the negative focus on carbohydrates.

- Line 87: "in the context of a low-GI dietary pattern"- it should be expanded and clarified/explained better (maybe in the Study selection section- see next comment) as it is used though out the whole paper.

Please see response to next comment.

Methods

- Study selection section (lines 110-114): As requested in the previous comment, this sentence includes the rationale behind this meta-analysis. Consequently, it should be defined/ explained further focusing more on the specific phrase "in the context of a low-GI dietary pattern".

We have added text to the study selection to help clarify. Please see lines 117-119.

- Data extraction section (line 130): Plot digitizer- I would like to express some doubts regarding the validity of the specific tool taking into account the fact that the Pubmed results were only 5. Maybe an article instead of a link would be more useful for checking the citations of this tool.

The use of Plot Digitizer to extract data from figures is recommended by the Cochrane Collaboration (http://training.cochrane.org/resource/extracting-data-figures-using-software-webinar). The website is the most appropriate reference since it is a program available online.

- Statistical analysis section (lines 172-173): How the actual energy balance was assessed? It was taken somehow into account in the original studies?- A point/comment on this should be included in the discussion and limitations section as well as a point/comment regarding the energy intake adjustment wherever it is thought appropriate/relevant by the author.

As written in brackets in the text, energy balance was assessed by comparing the energy recommendations provided to both the intervention and comparator arms. If both were recommended weight loss or caloric restriction, the study was considered negative energy balance; and if both were recommended weight maintaining diets. Energy intake was not adjusted for in our analyses since the objective was to assess the effect of the dietary advice as provided on body weight and adiposity changes. Part of the mechanism by which the dietary advice may achieve the greater weight loss may be through reduced overall caloric intake as a result of increased satiety as discussed (lines 423-432).

Discussion

- Lines 358-362: It is questionable if this sentence about energy balance could apply based on the previous comment. It should be adjusted accordingly, depending on the way that the previous comment will be addressed.

The statement regarding energy balance indicates that the weight loss was observed in the context of neutral energy balance which is when dietary advice is to consume the diets ad libitum. Since we are interested in assessing the effect based on the dietary advice as it was provided (whether in the context of negative or neutral energy balance), we do not want to adjust for energy intake. As mentioned, the mechanism of action behind the weight loss effect may be a result of increased satiety and decreased subsequent energy intake.

Reviewer: 4
Reviewer Name: Antonio Palazón-Bru
Institution and Country: Miguel Hernández University, Spain.
Please state any competing interests or state 'None declared': None.

Please leave your comments for the authors below
1) In the abstract I would like to see the rationale to perform a meta-analysis (contradictory results in clinical trials, for example).

The rationale for our study was to address the negative messages centered on pasta as a potential contributor to the epidemic of overweight and obesity which are not substantiated by any scientific evidence. Unfortunately we are limited in space in the abstract, thus this has been explained in the introduction (please see lines 78-93).

2) I do not understand why you registered this meta-analysis as a clinical trial. This is not correct.

Although we used the registration site clinicaltrials.gov, we did not register our systematic review and meta-analysis (SRMA) as a clinical trial. It is considered appropriate to use this registration database for SRMAs.

3) In strengths and limitations of this study (after the abstract), you should indicated the rationale of your work.

Since the instructions are to include up to 5 sentences which relate to the methods, the rationale would not be possible to add.

4) "It remains unclear whether pasta alone or in the context of a low-GI dietary pattern contributes to weight gain.". What is the explanation for this statement? This is a key question in order to understand why you performed this meta-analysis.

As discussed in the first paragraph of the introduction, pasta has been implicated in the epidemic of obesity, however it is also a low GI food and low GI diets have been demonstrated to have advantages for weight related outcomes. Therefore it is unclear whether pasta contributes to weight gain.

5) What was your hypothesis for your research question?

There is no hypothesis since we are pooling together existing evidence to determine the overall effect.

6) Although you have indicated your search terms, to be able to replicate your results, you should write the search equations, indicating the fields to search and the connectors.

Supplemental Table S1 includes the full description of how the search was performed and can be followed in order to replicate the results.

7) Could you explain the method of the Plot Digitizer program?

The Plot Digitizer program allows you to take a scanned image of a plot and easily digitize values off the plot. You calibrate the X and Y axis and then digitize the data points by clicking the mouse on each data point. The program is recommended by the Cochrane Collaboration.

8) I do not understand why you analyzed heterogeneity if you used always random-effect models.

Random effect models do not remove heterogeneity from meta-analyses. Heterogeneity may still exist, as we found in our analyses for waist circumference and body fat, which need to be explored through sensitivity and subgroup analyses, as described in the Cochrane Handbook for the conduct of SRMAs.

On the other hand, in my opinion, the rest of the paper is well written and scientifically valid to be published in BMJ Open.

VERSION 3 – REVIEW

REVIEWER	Dr Palazón-Bru Miguel Hernández University, Spain.
REVIEW RETURNED	30-Jan-2018

GENERAL COMMENTS	In my opinion your paper has high standards to be published in the BMJ Open in its current form.