PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Does high carbohydrate intake lead to increased risk of obesity? A systematic review and meta-analysis
AUTHORS	Sartorius, Kurt; Sartorius, Benn; Madiba, Thandinkosi; Stefan, Cristina

VERSION 1 – REVIEW

REVIEWER	Robert M West University of Leeds UK
REVIEW RETURNED	18-Jul-2017

GENERAL COMMENTS	There is need for a thorough SR in this area due to the controversy of the subject. This SR brings together evidence from 24 observational studies. The authors note the difficulties in synthesis of finds due to issues with the published literature, in particular lack of standardisation of definitions within the 24 studies, concentration of studies to certain ethnic groups. Figure 1 lacks some of the detail that I expected for an SR: specifically that there is no record of any studies discovered for example by hand searching - all are claimed from the databases. There is no mention of deduplication, and no details as to why studies have been excluded. Note that I have been confused. Figure 1 states there are 22 studies. I see 13 from Stratum 1 and 11 from Stratum 2 and no studies that are in both strata. Hence I cannot distinguish why there are only 22 and not 24. Figure 2 represents the size of studies in two ways: size of bubble as well as vertical position. Just the vertical axis would have been sufficient to capture this. Figures 3 and 4 provide forest plots with a restricted axis. As a result, the studies are not completely plotted, but have arrows. Would it not be better to increase the range of the horizontal axis to be 0.1 to 10 for example? The key points appear to be that the review reveals that studies are: (1) All observational - as expected (2) Few (3) Measures of carbohydrate content vary (4) There is variation by ethnicity, but the majority of publications address certain ethnic groups only.

	In the published protocol, the authors state that they will classify carbohydrates by sugars, starches, and fibre. There is no mention of this in the manuscript, but there is discussion that the identified publications do not distinguish refined and unrefined carbohydrates. So there is some inconsistency between the protocol and the report.

REVIEWER	José Pedro Lopes Nunes Faculdade de Medicina da Universidade do Porto, Portugal
REVIEW RETURNED	31-Jul-2017

GENERAL COMMENTS	I have read this manuscript with interest I recommend acceptance. The text is of interest, the study was carefully carried out and written. I would like to see some further discussion on possible cultural differences in carbohydrate intake across different countries/ continents but the present form of the text is acceptable in my view. The full bibliographic data of the selected studies that appear in Table 1 do not seem to be present in the text. For the benefit of the reader, I think it would be best to present such data,either in Table 1 or in the reference list. Regards.

REVIEWER	Prof Timothy Noakes University of Cape Town, South Africa I am an advocate of low carbohydrate diets and therefore have a strong bias in this matter. I do not however have any direct conflicts of interest in that I do not receive funding from any industry for my position. I do however write books about low carbohydrate diets. The proceeds from these books are donated to The Noakes Foundation which aims to promote research and understanding of the benefits of low carbohydrate diets. I have staked my professional reputation on low carbohydrate diets being healthy and important in the prevention and treatment of insulin resistance and type 2 diabetes.
REVIEW RETURNED	19-Sep-2017

GENERAL COMMENTS	This is a valuable contribution in that it brings into the open the possibility that high carbohydrate diets may be behind the modern obesity epidemic. Its weakness is that inherent in all epidemiological studies that it is difficult, perhaps impossible, to isolate diet as the sole difference between those who are fat and those who are thin. Furthermore we have the conundrum present in epidemiological studies of smoking. If there had not been a population of non-smokers, it might have been very difficult to show that cigarette smoking causes cancer. The same applies here. The clinical evidence is that not all "low" carbohydrate diets are biologically "low". The authors of this paper simply use the group eating the least carbohydrate in any study as their definition of "low". Which may be appropriate in the context of the analysis but might not be correct in terms of biology. For example, up to the 1960s a high carbohydrate diet would have been one containing more than about 38% carbohydrate (and less than about 45% fat) according to NHANES data for US citizens at the time.

	Today that diet would be called a low carbohydrate (high fat) diet whereas in the 1960s it might reasonably have been called a high carbohydrate low fat diet (especially when compared to carbohydrate and fat intakes in the Palaeolithic period). We have pretty good evidence that populations eating their historical low carbohydrate diets were lean; whereas modern populations eating more than 40% carbohydrate are (with one or two rare exceptions) becoming increasingly fatter since the adoption of the modern industrial diet. Thus the ideal control group to determine if carbohydrates are linked to obesity would be people eating biologically-low carbohydrate diets, that is below about 20% of total energy. Indeed the evidence from clinical work with obese patients is that diets providing less than 5-10% of total energy as carbohydrate are most effective suggesting that there is a critical cut off carbohydrate intake value, at least for the already obese, below which weight loss occurs but above which there is little or no effect. (This effect is likely linked to the increased satiation of high fat diets especially when the addictive effects of high sugar, high carbohydrate diets are also excluded). This is also compatible with the observation that reported weight losses in very large numbers of individuals following truly low carbohydrate diets is much greater (in some cases an order of magnitude) than is reported in clinical trials of dietary-induced weigh loss. My point is that the current study was not designed to test what most in the field of low carbohydrate diets would consider a reasonable hypothesis: That only truly low carbohydrate diets are protective against weight gain and obesity in the modern industrial food environment. Had the authors tested that hypothesis, they might have come up with a different conclusion. Furthermore it may indeed be that sugar is the real driver of obesity and this too needs to be considered. Again the only populations now not eating high sugar diets would be those that actively restart their carbohydrate intakes to below 10% of total calories. So perhaps I am making these points to encourage the authors to include these provisos in their conclusions and in their list of study limitations. I am certain this study will be widely reported as showing that carbohydrates do not cause obesity and it would be sad if the report is really a false-negative finding about the possibility of which the authors have not warned their readers. Specific comments: line comment 282-283 You did not study this since you did not report (as far as I can see) evidence for calorie intakes. So you cannot make that conclusion. This reflects your bias. Clearly obesity requires an intake of excess calories but the cause of the excessive intake is what is of real interest. Those promoting high fat low carbohydrate diets argue that these diets act by increasing satiety despite a lower total energy intake (first shown by Yudkin and colleagues in 1970). This point is repeatedly ignored by those promoting the calories in - calories out model of weight gain. If fat calories are more satiating and carbohydrate calories are more appetite stimulating, then it clearly matters from where the calories are coming. Appropriate discussion of this point is more helpful than the proposal that evidence supports the calories alone theory of obesity. 285-289 So what is your point? If other studies show this relationship but yours does not, surely you must try to explain why there is this discrepancy.

	Which study might be wrong, their's or your's? Do you believe your analysis or don't you? 302 You need to add the story about satiety here. You might also want to include ad libitum studies in which calorie intake is not restricted on the low carbohydrate leg of the diet but in which weight loss is still achieved. This begins to address the satiety issue. 306 This reference is now dated. The most recent meta-analysis Kelly SAM et al. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005051.pub3/abstract shows there has never been any evidence that cereals and grains improve human health. 310 Neither of these references supports the conclusion that "unrefined carbohydrates reduce CV disease". The sole studies showing reduced CV mortality in prospective studies have been when the fat intake is increased (PREDIMED and Lyon Diet Heart Study) and the PREDIMED study is fatally flawed since the greatest changes in dietary intake occurred in the "control" group who were told to reduce their fat intakes (which they did) wheres the dietary changes in the two intervention groups (increasing fat intake) were very modest by comparison and the outcomes showed benefits only in total stroke incidences (vs the "control" group"). 310 Reference 32 does not contain proof that unrefined carbohydrates protect against certain cancers and ulcerative colitis. The authors need to cite original studies (RCTs) only if such exist. 312 Whilst I have not yet read references 33-35, they would seem to have been nullified by the recent PURE study which needs to be included here. Also recall that association does not prove causation and this point needs to be re-iterated, over and over again. 315 It is extremely difficult to understand how "refined" carbohydrates should promote obesity, whereas "unrefined" carbohydrates should prevent it. For the ultimate product of carbohydrate whether from "refined" or "unrefined" sources is glucose, a metabolite for which the body has no essential requirement (since the liver can produce all the glucose the body requires regardless of dietary intake). When carbohydrate is ingested, the body must still cope with removing the excess glucose from the blood stream and in those with insulin resistance, this is very likely to induce obesity and type 2 diabetes in the long term. Also we need a proper definition of exactly what is a refined carbohydrate and what is an unrefined carbohydrate. For unless cereals and grains are refined, they cannot be digested by humans. So what truly is an unrefined cereal or grain? Clarification of this point would be welcomed. Again I refer to the recent meta-analysis showing that RCTs of increased cereal and grain intakes have NEVER shown any health benefits whereas I would argue that it would not really be difficult to show evidence for harm in those who are insulin resistant. 335 Please add that there are so many limitation in your study that you cannot make any conclusions about whether or not carbohydrates cause or prevent obesity. Then I suggest you add suggestions of how future meta-analyses might be improved. Perhaps the real problem is that meta-analyses do show that when the carbohydrate intake is low enough, low carbohydrate diets outperform low fat diets in terms of weight loss. If your studies are unable to show the corollary i.e. that carbohydrate intake is linked to obesity, then you have to think that perhaps you are reporting a false-negative finding. And you need to warn your readers that this is a real possibility.

	So in summary, the paper needs a major re-write to reflect the totality of what we know and to include the most recent findings including the PURE study and the negative outcomes of RCTs in which grain and cereal intakes are increased.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Robert M West
There is need for a thorough SR in this area due to the controversy of the subject. This SR brings together evidence from 24 observational studies. The authors note the difficulties in synthesis of finds due to issues with the published literature, in particular lack of standardisation of definitions within the 24 studies, concentration of studies to certain ethnic groups.

Response: We thank you for your review and have attempted to address your concerns. In general we expected (when developing the protocol) to use more than 22 studies and we expected more uniformity in the way carbohydrates would be accounted for in daily diets. In effect, there was insufficient evidence with regards to the different categories of carbohydrates so we concluded that total carbohydrates did not appear to increase relative risk of obesity fully recognizing that different categories of carbohydrates have higher or lower risk (e.g. sugars versus unrefined grains). We attempt to acknowledge this in the discussion re: 'good versus bad 'carbohydrates and prompt the need for more disaggregated meta studies.

Figure 1 lacks some of the detail that I expected for an SR: specifically that there is no record of any studies discovered for example by hand searching - all are claimed from the databases. There is no mention of deduplication, and no details as to why studies have been excluded.
Response: No studies were discovered by hand searching, all were retrieved from the databases. Agreed. The reasons for study exclusions in Figure 1 have now been included. We have also updated this figure as per the recommended PRISMA format:

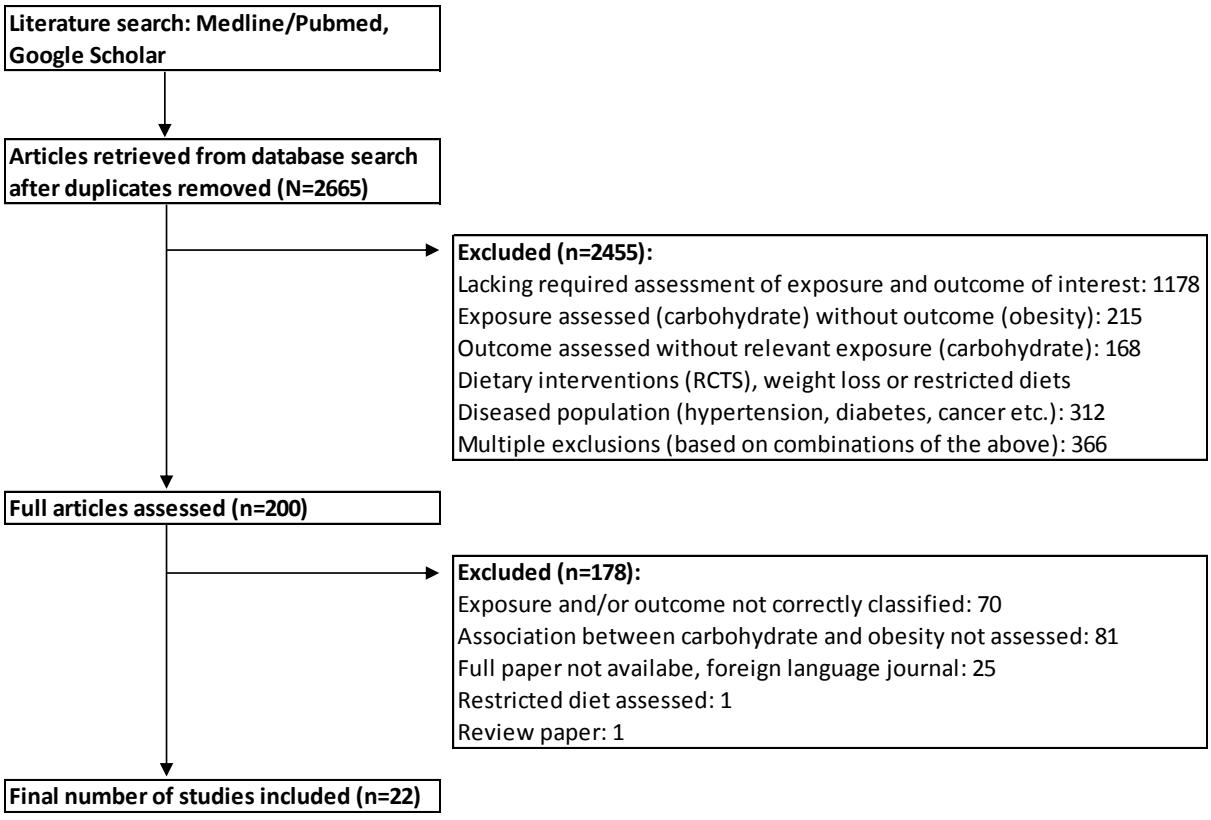

Figure 1: PRISMA flow diagram for study selection following search and selection/exclusion process Note that I have been confused. Figure 1 states there are 22 studies. I see 13 from Stratum 1 and 11 from Stratum 2 and no studies that are in both strata. Hence I cannot distinguish why there are only 22 and not 24.

Response: Apologies for the confusion. In effect we separated out results of two of the studies, namely 1634 (Murtaugh MA, Herrick JS, Sweeney C, Baumgartner KB, Guiliano AR, Byers T, Slattery ML. Diet composition and risk of overweight and obesity in women living in the southwestern United States. Journal of the American Dietetic Association. 2007 Aug 31;107(8):1311-21.) and 130 (Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971–2006. The American journal of clinical nutrition. 2011 Apr 1;93(4):836-43.) because they produced two sets of results for different population groups: - id 1634: Caucasian vs Hispanic and id 130: NHANES I baseline and 2005/2006 respectively.

Figure 2: represents the size of studies in two ways: size of bubble as well as vertical position. Just the vertical axis would have been sufficient to capture this.

Response: Given that there are multiple studies per year in later years we thought that the size bubble also effectively differentiated these studies in addition to the y-axis.

Figures 3 and 4: provide forest plots with a restricted axis. As a result, the studies are not completely plotted, but have arrows. Would it not be better to increase the range of the horizontal axis to be 0.1 to 10 for example?

Response: Agreed. We have revised the x-axis scale of these figure to remove the truncation arrows. Here are the revised figures (note we have also include log odds in Table 1):

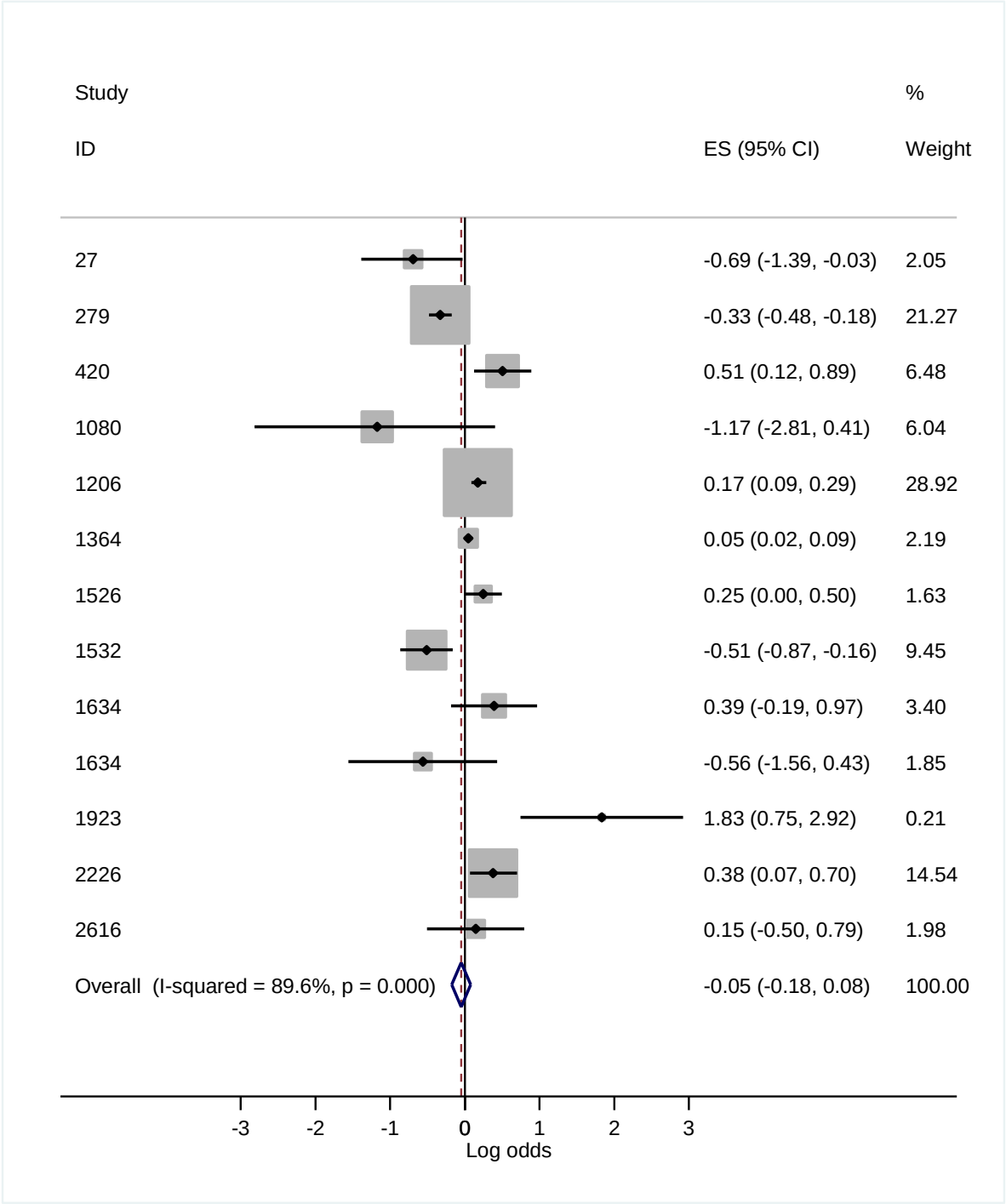

Figure 3: Forest plot of association (logs odds ratio) between high vs low carbohydrate intake and obesity

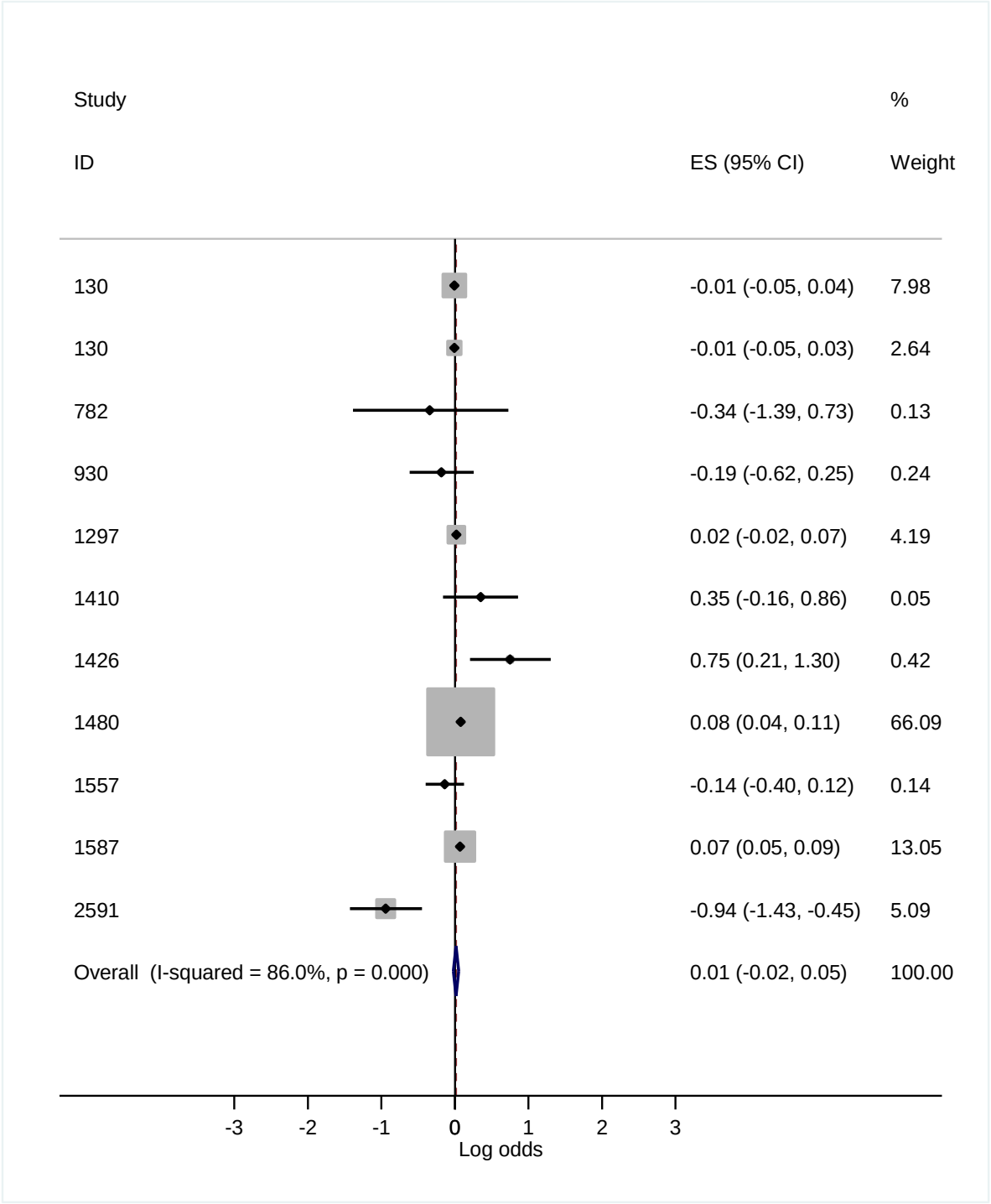

Figure 4: Forest plot of association (log odds ratio) between % carbohydrate intake of total energy and obesity

The key points appear to be that the review reveals that studies are:
(1) All observational - as expected
(2) Few
(3) Measures of carbohydrate content vary
(4) There is variation by ethnicity, but the majority of publications address certain ethnic groups only.

In the published protocol, the authors state that they will classify carbohydrates by sugars, starches, and fibre. There is no mention of this in the manuscript, but there is discussion that the identified publications do not distinguish refined and unrefined carbohydrates. So there is some inconsistency between the protocol and the report.

Response: We apologize for this discrepancy. When we developed the protocol we did indeed presume the selected studies that assessed/quantified the association between carbohydrate intake and obesity would provide disaggregated data re: types of carbohydrates, which proved NOT to be the case. We have added a line in the discussion/limitations because this is a crucial point as indicated by reviewer 3 as well. Please see discussion in lines 340-342 and 346-347.

Reviewer2: José Pedro Lopes Nunes

Comment: I have read this manuscript with interest I recommend acceptance. The text is of interest, the study was carefully carried out and written.

Response: We thank you for your review.

Comment: I would like to see some further discussion on possible cultural differences in carbohydrate intake across different countries/ continents but the present form of the text is acceptable in my view.

Response: Agreed. We include an additional comment with regards to the cultural/urban-rural differences in carbohydrate intake. Please see revised discussion on page 12.

Comment: The full bibliographic data of the selected studies that appear in Table 1 do not seem to be present in the text. For the benefit of the reader, I think it would be best to present such data, either in Table 1 or in the reference list.

Response: Agreed. The full citation for each study is now included in revised Table 1 as follows:

Strata	Id	Study	Exposure measured	Odds ratio	95% CI		Log odds ratio	95% CI		Sample size
1	27	Ahluwalia N, Ferrières J, Dallongeville J, Simon C, Ducimetière P, Amouyel P, Arveiler D, Ruidavets JB. Association of macronutrient intake patterns with being overweight in a population-based random sample of	Quartile 4 vs 1 (CHD per day)	0.50	0.25	0.97	-0.30	-0.60	-0.01	966

		men in France. Diabetes & metabolism. 2009 Apr 30;35(2):129-36.								
1	279	Bowman SA, Spence JT. A comparison of low-carbohydrate vs. high-carbohydrate diets: energy restriction, nutrient quality and correlation to body mass index. Journal of the American College of Nutrition. 2002 Jun 1;21(3):268-74.	Above 55% calories (High) vs 0% to 30% calories (Very low)	0.72	0.62	0.84	-0.14	-0.21	-0.08	10014
1	420	Choi J, Se-Young O, Lee D, Tak S, Hong M, Park SM, Cho B, Park M. Characteristics of diet patterns in metabolically obese, normal weight adults (Korean National Health and Nutrition Examination Survey III, 2005). Nutrition, Metabolism and Cardiovascular Diseases. 2012 Jul 31;22(7):567-74.	Quartile 4 vs 1	1.66	1.13	2.43	0.22	0.05	0.39	3050
1	1080	Jackson M, Walker S, Cruickshank JK, Sharma S, Cade J, Mbanya JC, Younger N, Forrester TF, Wilks R. Diet and overweight and obesity in populations of African origin: Cameroon, Jamaica and the UK. Public health nutrition. 2007 Feb;10(2):122-30.	Tertiale 3 vs 1 for CHD intake	0.31	0.06	1.50	-0.51	-1.22	0.18	2842
1	1206	Kim J, Jo I, Joung H. A rice-based traditional dietary pattern is associated with obesity in Korean adults. Journal of	Tertiale 3 vs 1 for white Rice and Kimchi	1.19	1.09	1.33	0.08	0.04	0.12	13618

		the Academy of Nutrition and Dietetics. 2012 Feb 29;112(2):246-53.								
1	1364	Lin H, Bermudez OI, Tucker KL. Dietary patterns of Hispanic elders are associated with acculturation and obesity. The Journal of nutrition. 2003 Nov 1;133(11):3651-7.	Rice dietary pattern	1.05	1.02	1.09	0.02	0.01	0.04	1030
1	1526	Meng P, Jia L, Gao X, Liao Z, Wu M, Li S, Chen B. Overweight and obesity in Shanghai adults and their associations with dietary patterns. Wei sheng yan jiu= Journal of hygiene research. 2014 Jul;43(4):567-72.	Staple food and vegetables higher obesity (Q4 vs Q1 higher proportion carb intake)	1.28	1.00	1.64	0.11	0.00	0.22	768
1	1532	Merchant AT, Vatanparast H, Barlas S, Dehghan M, Shah SM, De Koning L, Steck SE. Carbohydrate intake and overweight and obesity among healthy adults. Journal of the American Dietetic Association. 2009 Jul 31;109(7):1165-72.	Quartiles of carbohydrate intake compared to the lowest intake category (Q4 vs Q1)	0.60	0.42	0.85	-0.22	-0.38	-0.07	4451
1	1634	Murtaugh, M. A., Herrick, J. S., Sweeney, C., Baumgartner, K. B., Guiliano, A. R., Byers, T., & Slattery, M. L. (2007). Diet composition and risk of overweight and obesity in women living in the southwestern United States. Journal of the American Dietetic Association, 107(8), 1311-1321	High vs Low: Carbohydrate (% energy) - Non-Hispanic (White)	1.48	0.83	2.63	0.17	-0.08	0.42	1599
1	1634	Murtaugh, M. A.,	High vs Low:	0.57	0.21	1.54	-0.24	-	0.19	871

		Herrick, J. S., Sweeney, C., Baumgartner, K. B., Guiliano, A. R., Byers, T., & Slattery, M. L. (2007). Diet composition and risk of overweight and obesity in women living in the southwestern United States. Journal of the American Dietetic Association, 107(8), 1311-1321	Carbohydrate (% energy) - Hispanic					0.68		
1	1923	Rathnayake KM, Roopasingam T, Dibley MJ. High carbohydrate diet and physical inactivity associated with central obesity among premenopausal housewives in Sri Lanka. BMC research notes. 2014 Aug 23;7(1):564.	Percent of energy from carbohydrate: high (>=70%)	6.26	2.11	18.57	0.80	0.32	1.27	100
1	2226	Song, S., Lee, J. E., Song, W. O., Paik, H. Y., & Song, Y. (2014). Carbohydrate intake and refined-grain consumption are associated with metabolic syndrome in the Korean adult population. Journal of the Academy of Nutrition and Dietetics, 114(1), 54-62	Energy from CHD (Q5 vs Q1)	1.46	1.07	2.01	0.16	0.03	0.30	6845
1	2616	Youn, S., Woo, H. D., Cho, Y. A., Shin, A., Chang, N., & Kim, J. (2012). Association between dietary carbohydrate, glycemic index, glycemic load, and the prevalence of obesity in Korean men and women.	Q4 vs Q1 carbohydrate intake	1.16	0.60	2.21	0.06	-0.22	0.35	933

		Nutrition research, 32(3), 153-159								
2	130	Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971–2006. The American journal of clinical nutrition. 2011 Apr 1;93(4):836-43.	Carbohydrate intake (% of energy)-NHANES I	0.99	0.95	1.04	0.00	-0.02	0.02	12276
2	130	Austin GL, Ogden LG, Hill JO. Trends in carbohydrate, fat, and protein intakes and association with energy intake in normal-weight, overweight, and obese individuals: 1971–2006. The American journal of clinical nutrition. 2011 Apr 1;93(4):836-43.	Carbohydrate intake (% of energy)-NHANES 2005/2006	0.99	0.95	1.03	0.00	-0.02	0.01	4057
2	782	Garaulet M, Marin C, Perez-Llamas F, Canteras M, Tebar FJ, Zamora S. Adiposity and dietary intake in cardiovascular risk in an obese population from a Mediterranean area. Journal of physiology and biochemistry. 2004 Mar 1;60(1):39-49.	Carbohydrate intake (% of energy)	0.71	0.25	2.07	-0.15	-0.60	0.32	193
2	930	Hartline-Grafton HL, Rose D, Johnson CC, Rice JC, Webber LS. Are school employees role models of healthful eating? Dietary intake results from the ACTION worksite wellness trial. Journal of the American Dietetic Association. 2009 Sep	Carbohydrate intake (% of energy)	0.83	0.54	1.29	-0.08	-0.27	0.11	373

		30;109(9):1548-56.								
2	1297	Langlois K, Garriguet D, Findlay L. Diet composition and obesity among Canadian adults. Health Reports. 2009 Dec 1;20(4):11.	Carbohydrate intake (% of energy)	1.02	0.98	1.07	0.01	-0.01	0.03	6454
2	1410	Lyles III TE, Desmond R, Faulk LE, Henson S, Hubbert K, Heimburger DC, Ard JD. Diet variety based on macronutrient intake and its relationship with body mass index. Medscape General Medicine. 2006;8(3):39.	Carbohydrate DVS	1.42	0.85	2.36	0.15	-0.07	0.37	74
2	1426	Ma Y, Olendzki B, Chiriboga D, Hebert JR, Li Y, Li W, Campbell M, Gendreau K, Ockene IS. Association between dietary carbohydrates and body weight. American journal of epidemiology. 2005 Feb 15;161(4):359-67.	Daily dietary glycemic index vs BMI continuous	2.12	1.23	3.67	0.33	0.09	0.56	641
2	1480	Maskarinec G, Takata Y, Pagano I, Carlin L, Goodman MT, Marchand L, Nomura AM, Wilkens LR, Kolonel LN. Trends and dietary determinants of overweight and obesity in a multiethnic population. Obesity. 2006 Apr 1;14(4):717-26.	Carbohydrate (1 g/100 kcal)	1.08	1.04	1.12	0.03	0.02	0.05	101699
2	1557	Miller WC, Lindeman AK, Wallace J, Niederpruem M. Diet composition, energy intake, and exercise in relation	Lean vs obese subjects and energy derived from carbohydrates	0.87	0.67	1.13	-0.06	-0.18	0.05	216

		to body fat in men and women. The American journal of clinical nutrition. 1990 Sep 1;52(3):426-30.								
2	1587	Mokhtar N, Elati J, Chabir R, Bour A, Elkari K, Schlossman NP, Caballero B, Aguenaou H. Diet culture and obesity in northern Africa. The Journal of nutrition. 2001 Mar 1;131(3):887S-92S.	Carbohydrate mean daily energy intake	1.07	1.05	1.09	0.03	0.02	0.04	20080
2	2591	Yang, E. J., Chung, H. K., Kim, W. Y., Kerver, J. M., & Song, W. O. (2003). Carbohydrate intake is associated with diet quality and risk factors for cardiovascular disease in US adults: NHANES III. Journal of the American College of Nutrition, 22(1), 71-79	Carbohydrate intakes (% of energy)	0.39	0.24	0.64	-0.41	-0.62	-0.19	7828

Reviewer 3: Prof Timothy Noakes
Institution and Country: University of Cape Town, South Africa

Comment: (TN) Competing Interests: I am an advocate of low carbohydrate diets and therefore have a strong bias in this matter. I do not however have any direct conflicts of interest in that I do not receive funding from any industry for my position. I do however write books about low carbohydrate diets. The proceeds from these books are donated to The Noakes Foundation which aims to promote research and understanding of the benefits of low carbohydrate diets. I have staked my professional reputation on low carbohydrate diets being healthy and important in the prevention and treatment of insulin resistance and type 2 diabetes.

Response: Many thanks Tim, knowing that your position on low carbohydrate diets is built on emerging biology. We also believe that unrefined carbohydrates and sugars, combined with a sedentary lifestyle, stress and pollutants most likely underpin the epidemic of insulin resistance, type 2 diabetes.

Comment: (TN)This is a valuable contribution in that it brings into the open the possibility that high carbohydrate diets may be behind the modern obesity epidemic. Its weakness is that inherent in all epidemiological studies that it is difficult, perhaps impossible, to isolate diet as the sole difference between those who are fat and those who are thin. Furthermore we have the conundrum present in epidemiological studies of smoking. If there had not been a population of non-smokers, it might have been very difficult to show that cigarette smoking causes cancer.

Response: We fully acknowledge these limitations and that there are also cultural and evolutionary lifestyle changes in both developed and developing economies, as well as a rural-urban transition. See lines 335-339 e.g Finally, multiple confounding influences are nuanced across different populations, as well as age, gender and different ethnic groups in the same population, as well as differences between urban and rural populations [6 43 44]. See Lines 354-358 " A further limitation of our study was the concentration of a few countries in the two strata and the recognition that different populations/sub-populations consume varying proportions of different categories of carbohydrates in their daily diet [45]. This limitation is further nuanced by the nutrition transition experienced in industrializing countries in which higher a proportion of carbohydrates consumed consist of refined carbohydrates and sugars [46].

Comment: (TN)The same applies here. The clinical evidence is that not all "low" carbohydrate diets are biologically "low". The authors of this paper simply use the group eating the least carbohydrate in any study as their definition of "low". Which may be appropriate in the context of the analysis but might not be correct in terms of biology.
For example, up to the 1960s a high carbohydrate diet would have been one containing more than about 38% carbohydrate (and less than about 45% fat) according to NHANES data for US citizens at the time. Today that diet would be called a low carbohydrate (high fat) diet whereas in the 1960s it might reasonably have been called a high carbohydrate low fat diet (especially when compared to carbohydrate and fat intakes in the Palaeolithic period). We have pretty good evidence that populations eating their historical low carbohydrate diets were lean; whereas modern populations eating more than 40% carbohydrate are (with one or two rare exceptions) becoming increasingly fatter since the adoption of the modern industrial diet.

Response Agreed. These confounding influences are clearly acknowledged in the discussion and conclusions (see Page 12 where additional references have been included, and the conversation broadened). We think that (probably) the real trigger of increased level of obesity/type 2 diabetes/insulin resistance is (more) likely linked to the increased proportion of refined carbohydrates and sugars/changing lifestyle than unrefined grains and fibre. Due to the consolidated nature of the data regarding carbohydrates, however, we are unable to demonstrate this empirically.

Comment: (TN)Thus the ideal control group to determine if carbohydrates are linked to obesity would be people eating biologically-low carbohydrate diets that is below about 20% of total energy. Indeed the evidence from clinical work with obese patients is that diets providing less than 5-10% of total energy as carbohydrate are most effective suggesting that there is a critical cut off carbohydrate intake value, at least for the already obese, below which weight loss occurs but above which there is little or no effect. (This effect is likely linked to the increased satiation of high fat diets especially when the addictive effects of high sugar, high carbohydrate diets are also excluded).

Response: Agreed. From what we observed there is a need to standardize the collection of dietary carbohydrate data to show different categories over large sample sizes. We strongly support your arguments in our discussion and conclusion which acknowledges that the data only reflects a non-standard classification of high versus low carbohydrate intake (and percentage of intake), as well as does NOT show different categories of carbohydrate. Please see revised conclusion which warns readers of this (probability).

Comment: (TN)This is also compatible with the observation that reported weight losses in very large numbers of individuals following truly low carbohydrate diets is much greater (in some cases an order of magnitude) than is reported in clinical trials of dietary-induced weigh loss. My point is that the current study was not designed to test what most in the field of low carbohydrate diets would consider a reasonable hypothesis: That only truly low carbohydrate diets are protective against weight gain and obesity in the modern industrial food environment.

Had the authors tested that hypothesis, they might have come up with a different conclusion. Furthermore it may indeed be that sugar is the real driver of obesity and this too needs to be considered. Again the only populations now not eating high sugar diets would be those that actively restart their carbohydrate intakes to below 10% of total calories.

Response: Agreed. We think that future prospective type studies will be needed in this regard to provide stronger evidence as indicated in revised conclusion section. Clearly, the biology of appetite, obesity and eating related diseases appear to be ahead of the empirical data to support this.

Comment: So perhaps I am making these points to encourage the authors to include these provisos in their conclusions and in their list of study limitations. I am certain this study will be widely reported as showing that carbohydrates do not cause obesity and it would be sad if the report is really a false-negative finding about the possibility of which the authors have not warned their readers.
Response: Agreed. We strongly support your arguments in our discussion and conclusion which acknowledges that the data only reflects a non-standard classification of high versus low carbohydrate intake, as well as does NOT show different categories of carbohydrate. Please see revised conclusion which warns readers of this (probability).

Specific comments:
line comment
(TN) 282-283 You did not study this since you did not report (as far as I can see) evidence for calorie intakes. So you cannot make that conclusion. This reflects your bias. Clearly obesity requires an intake of excess calories but the cause of the excessive intake is what is of real interest. Those promoting high fat low carbohydrate diets argue that these diets act by increasing satiety despite a lower total energy intake (first shown by Yudkin and colleagues in 1970). This point is repeatedly ignored by those promoting the calories in - calories out model of weight gain. If fat calories are more satiating and carbohydrate calories are more appetite stimulating, then it clearly matters from where the calories are coming. Appropriate discussion of this point is more helpful than the proposal that evidence supports the calories alone theory of obesity.

Response: Agreed. We have reworded this section to ensure a lack of bias and clearly differentiate unrestricted versus restricted diets. See opening paragraph of discussion lines 281-291. We do not think the revised paper reflects bias. “Due to the nature of the data we were unable to consider satiety aspects (e.g. Yudkin et al, 1970). The results of this systematic review/meta study, only suggest that total carbohydrate proportion in an unrestricted diet is not positively (or negatively) related to obesity propensity. Our paper, therefore, cannot contradict the assumption that total energy intake/expenditure paradigm is the primary driver of body weight, modulated by an interaction of genetic, environmental and psychosocial factors [6-8].”

Comment: (TN) 285-289 So what is your point? If other studies show this relationship but yours does not, surely you must try to explain why there is this discrepancy. Which study might be wrong, their's or your's? Do you believe your analysis or don't you?

Response: Agreed. We have reworded the whole of the 1st paragraph in the discussion. See lines 281-291. We certainly believe our study was objective and that the pooled results are valid. Our point is that that the results of our systematic review/meta-study suggest no significant evidence of a relationship between total carbohydrate intake and body weight in a population level unrestricted diet. Nevertheless, we show no bias by indicating that other studies have indicated that certain dietary carbohydrates, like sugar sweetened beverages, are positively associated with weight gain [11 20], as well as indicate more studies are needed.

Comment: (TN)302 You need to add the story about satiety here. You might also want to include ad libitum studies in which calorie intake is not restricted on the low carbohydrate leg of the diet but in which weight loss is still achieved. This begins to address the satiety issue.

Response: Agreed. We have included satiety effect resulting in reduced hunger, calorie intake. See lines 304-305.

Comment: (TN)306 This reference is now dated. The most recent meta-analysis Kelly SAM et al. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005051.pub3/abstract
shows there has never been any evidence that cereals and grains improve human health.

Response: Agreed. We have added Kelly et al, 2017 and Clar et al (2017) (including SA Kelly) in the revised manuscript.

Comment: (TN) 310 Neither of these references supports the conclusion that "unrefined carbohydrates reduce CV disease". The sole studies showing reduced CV mortality in prospective studies have been when the fat intake is increased (PREDIMED and Lyon Diet Heart Study) and the PREDIMED study is fatally flawed since the greatest changes in dietary intake occurred in the "control" group who were told to reduce their fat intakes (which they did) whereas the dietary changes in the two intervention groups (increasing fat intake) were very modest by comparison and the outcomes showed benefits only in total stroke incidences (vs the "control" group").

Response Agreed. We have revised our wording to show that in a meta study (Mellen et al) there was a “consistent inverse relationship between unrefined grains and cardiovascular disease” (as opposed to mortality). In addition, the second reference is omitted (Burkitt et al). However, we maintain our viewpoint (that does not necessarily exclude your standpoint) but qualify our position by the need to consider confounding factors. Our conclusion with respect to the inverse relationship is based purely on the results of the paper. Our discussion (speculation) about the protective role of unrefined carbohydrates is referenced more conservatively. See Lines 312-316 “ Conversely, the protective role of unrefined carbohydrates is reflected in a ‘ consistent, inverse association between dietary whole grains and the incidence of cardiovascular disease’ [29]. In general, moreover, pooled meta-analyses have indicated a protective effect from the consumption of coarse grains [34 35].”

Comment: (TN) 310 Reference 32 does not contain proof that unrefined carbohydrates protect against certain cancers and ulcerative colitis. The authors need to cite original studies (RCTs) only if such exist.

Response: Agreed. We have removed this documented assumption rather than proof of this relationship. We have added that the results of pooled meta analyses to show that consistent epidemiological studies indicate the protective role of coarse grains. We accept that there are major confounders but feel the truth will out in due course but we maintain an argument that there are such things as ‘better’ and worse carbohydrates. The argument you have mounted (the biology) is not in dispute, neither your linking of the epidemic of type2 diabetes to sugars/unrefined carbohydrates.

Comment: (TN)312 Whilst I have not yet read references 33-35, they would seem to have been nullified by the recent PURE study which needs to be included here. Also recall that association does not prove causation and this point needs to be re-iterated, over and over again.

Response: We hope the discussion we mount (and now also revised) is very open-minded. Our only difference with you, as we indicated in our joint 'Sunday Times article" was that we maintained a distinction between good and bad carbohydrates rather than the notion of no carbohydrate is beneficial. Even if this was the case, a) some are better than others b) the world's population will continue to be reliant on carbohydrates as a staple in their daily diets given poverty and limited protein and other options in low and middle income countries.

Comment: (TN)315 It is extremely difficult to understand how "refined" carbohydrates should promote obesity, whereas "unrefined" carbohydrates should prevent it. For the ultimate product of carbohydrate whether from "refined" or "unrefined" sources is glucose, a metabolite for which the body has no essential requirement (since the liver can produce all the glucose the body requires regardless of dietary intake). When carbohydrate is ingested, the body must still cope with removing the excess glucose from the blood stream and in those with insulin resistance, this is very likely to induce obesity and type 2 diabetes in the long term.
Also we need a proper definition of exactly what is a refined carbohydrate and what is an unrefined carbohydrate. For unless cereals and grains are refined, they cannot be digested by humans. So what truly is an unrefined cereal or grain? Clarification of this point would be welcomed.
Again I refer to the recent meta-analysis showing that RCTs of increased cereal and grain intakes have NEVER shown any health benefits whereas I would argue that it would not really be difficult to show evidence for harm in those who are insulin resistant.

Response: Our study clearly does not say there is an inverse linear relationship between carbohydrate intake and obesity, merely, that higher carbohydrate diets (a category of diet) reveal no relationships with obesity. If indeed the reverse is true, the biology is ahead of the epidemiological evidence because it is distorted by confounding factors.

Comment: (TN)335 Please add that there are so many limitation in your study that you cannot make any conclusions about whether or not carbohydrates cause or prevent obesity. Then I suggest you add suggestions of how future meta-analyses might be improved. Perhaps the real problem is that meta-analyses do show that when the carbohydrate intake is low enough, low carbohydrate diets outperform low fat diets in terms of weight loss. If your studies are unable to show the corollary i.e. that carbohydrate intake is linked to obesity, then you have to think that perhaps you are reporting a false-negative finding. And you need to warn your readers that this is a real possibility.
So in summary, the paper needs a major re-write to reflect the totality of what we know and to include the most recent findings including the PURE study and the negative outcomes of RCTs in which grain and cereal intakes are increased.

Response: Agreed. Please see our revised conclusions.

VERSION 2 – REVIEW

REVIEWER	Robert West University of Leeds UK
REVIEW RETURNED	06-Nov-2017

GENERAL COMMENTS	This has been a difficult review due to the lack of definition of carbohydrate types by the authors in the texts selected. In particular conclusions are restricted and there are many 'caveats'. The value of this work is the identification that better distinction between carbohydrates is required for future research.

REVIEWER	Prof Timothy Noakes University of Cape Town, South Africa I am a promoter of low carbohydrate diets and an author of books promoting this eating plan.
REVIEW RETURNED	18-Nov-2017

GENERAL COMMENTS	The authors have properly and fully addressed all the issues I personally raised in the first review of this paper. The paper fairly represents the analysis of the papers that they included in the review. The important limitations inherent in this type of study are properly described.