Comments of the SACN draft Report on Carbohydrates and Health

Arne Astrup and the International Carbohydrate Quality Consortium (ICQC)*

Introduction

The draft Report is welcome in its scope, though is lacking in execution. Overall, it appears the review activity has been too extensive for reviewers to attend to essential details, and will largely be 3 (possibly 4) years out of date by the time of publication, Here the authors have limited their attention to two aspects that leave them surprised about the execution and analyses conducted (**Methodology**) and about an aspect of diet that is often handled particularly poorly, as is the case in the draft Report (i.e. **Glycaemic index and load**).

We detected a lack of clear definition of the study population used. It is stated that included are studies of “healthy or with an intermediate stage of ill health” but the authors excluded type 2 diabetes, those on statins or anti-hypertensive drugs or those who are hypertensive at baseline and even pregnant women. Failure to assess the effects of dietary carbohydrates including glycemic index and load in specific states with a high prevalence of insulin resistance such as those with diabetes, hypertension, central adiposity, the metabolic syndrome, pregnant women etc. is a major mistake for good biological reasons. We are heading towards an age when the numbers of such individuals free living in the community has grown rapidly. To make guidelines based on results in the slim and healthy who can tolerate all sorts of dietary indiscretions is the classic approach. However failure to provide for the "walking wounded" (the insulin resistant with or without frank disease) is a major error since this group suffers the majority of the misfortunes and requires major financial assistance as they consume most of the health care resources. For those conditions included it is difficult from the SACN draft report alone to know about the context or condition of persons, age, duration of treatment, dose etc. No cut-offs for

hyperglycemia, hypertension or hyperlipidemia were specified (was hypertension >140/90mmHg?). Furthermore, it is not clear whether the authors combined metabolic syndrome studies with the completely healthy. If the two were combined it is no wonder that a significantly high heterogeneity resulted. In our opinion it would be relevant to include all studies and assess also vulnerable (disease) groups. The days of designing public health messages for a healthy population are gone. The healthy have a lot of latitude in what they do, the less healthy not so much. It is therefore advised to include all health/disease states, do a spline analysis for the break point to determine who needs to exercise caution.

Why including diabetes in your report is important

Diabetes affects 382 million people worldwide with a prevalence of 1 in 10 people expected in 2035, and current estimates for the UK indicated a prevalence of 8-10% of the population already when including those without diagnosis. Almost half of the population with diabetes or 175 million people worldwide are undiagnosed (IDF data) and most of these have type 2 diabetes. Diabetes complications are a major cause of disability and it is one of the major risk factors for CVD. Furthermore it is being diagnosed at earlier ages, which means it is widespread throughout the population and the health care costs per person over a lifetime are therefore growing. With such a large social and economic burden diabetes is the target of much dietary advice hence dietary reviews and meta-analyses on carbohydrates and health which include cardiometabolic outcomes should include diabetes. Regarding glycemic index and diabetes there is convincing evidence from meta-analyses of prospective cohort studies that low glycemic index diets reduce the risk of developing type 2 diabetes (Barclay et al. 2008, Dong et al 2011, Sluijs et al 2010, Livesey et al. 2013b). There is convincing evidence from clinical trials that diets low in glycemic index improve glycemic control in people with type 2 and type 1 diabetes (Giacco et al. 2000, Brand-Miller et al. 2003, Rizkalla et al. 2004, Livesey et al. 2008a, Jenkins et al. 2008 and 2012) at levels that are considered therapeutically meaningful for type 2 diabetes (HbA1c: 0.3%-0.5%, Jenkins et al. 2008 and 2012) by the US Food and Drug Administration (US Food and Drug Administration. Guidance for industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation

/Guidances/ucm071624.pdf). Potential mechanisms for reduction of type 2 diabetes include evidence that low glycemic index diets improve insulin sensitivity and beta-cell function in people with type 2 diabetes and those at risk for type 2 diabetes (Rizkalla et al. 2004, Solomon et al. 2011). Potential mechanisms for reduction of coronary heart disease include evidence that low glycemic index diets improve blood lipids and inflammatory markers including C-reactive protein (Frost et al. 1999, Liu et al. 2001, Liu et al. 2002, Wolever et al. 2008, Shikany et al. 2010, Goff et al. 2013). Finally there is convincing evidence from a large body of prospective cohort studies that low glycemic index diets reduce the risk of CVD (Liu et al. 2000, Mirrahimi et al. 2012, Ma et al. 2012, Fan et al. 2012) one of the major causes of death in people with diabetes. The proof of principle for the low glycemic index effects is the use of alpha-glucosidase inhibitors (e.g. acarbose) to reduce progression to type 2 diabetes and coronary heart disease (Chiasson et al. 2002 and. 2003).

Other weaknesses of the SACN report

The exclusion of people from Oriental, African and Asian racial backgrounds because considered not relevant for the UK population, making this study report not generalizable even if properly executed.

Regarding weight loss trials the authors were unduly critical. Reduction in glycemic load can induce weight loss. Potentially this is a part of the mechanism, not a real confounder. In the DioGenes trial we clearly showed under ad lib conditions that both lowered glycemic index and lowered glycemic load improved weight control and many risk factors, but its effect on energy balance was clearly working through food intake. The glycemic index section overall seems to lack expertise.

How to read the following sections of our commentary

Details of references omitted from the draft Report are not necessarily provided here as it is not intended to perform the task allocated to SACN to undertake the literature searches necessary to bring both data and contemporary thinking up to date. In summary, the subject matter in the report is important to address, is impressive in breadth, though it is neither comprehensive (in breadth or depth or update) nor duly accurate.

Comments below are listed by paragraph numbers as used in the draft Report, and often are headed by quotations from the paragraph cited. Each paragraph may be addressed more than once.

One additional set of comments is made at the end (headed **Last words on GI and GL**) which has great importance for aligning perspective with science.

Conflict of interest statements appears towards the end of this document, and recent publications authored by the ICQC that are relevant to the SACN draft Report and the comments made herein are listed.

Methodology

1.3 "Due to the wealth of data available and because of the concerns around their limitations, case-control, cross-sectional and ecological studies were not considered. Only prospective cohort studies and randomised controlled trials were considered for this report. ".

- The statement admits to not examining the totality of evidence. Scientific reasons for not doing so are not presented; administrative reasoning alone is of questionable acceptability.
- The opening statement appears in stark contrast with the conclusions, which often indicate there is limited evidence or insufficient data.
- A more appropriate rationale would simply be one that seeks the highest levels of evidence according to study design, a rationale that is widely accepted.
- Where limited evidence is found after systematic search (not older than 6 months), it is inaccurate to draw any conclusion yet there are several instances where such inaccuracy arises. The category of insufficient evidence as proposed would be appropriate but is too seldom used.

1.3 "Evidence on adverse effects of very high intakes of specific carbohydrates, e.g. gastrointestinal symptoms, was not part of the remit of this report. "

- Consideration of "adverse effects" is an essential part of any assessment of benefits since at a national and individual level the risk of adverse effect can be persuasive of no overall benefit.
- The statement leaves open whether or not adverse effects other than gastrointestinal ones sometimes mentioned arise. If it is intended to not mention adverse effects, a rationale should be provided; the administrative "remit" is of questionable acceptability.
- If adverse effects are to be considered elsewhere, such as a committee on toxicology, this ought to be the rationale given for the non-considerations'.

1.4 "These [reviews] were based on literature published through December 2009, November 2010 and January 2012, respectively." "

- This range of years is too out of date to be representative or even systematic. January 2012 is 2.5 years ago. It is well recognized that such reviews should include at least the last 6th months of publications and aim to include later ones wherever possible.
- A cumulative meta-analysis is essential to assess the stability of effects/associations, but there is no evidence of any having been performed.

1.5 "[Last search dates of] January 2010…December 2010…February 2011…June 2012"

- Again, these are the last search dates and are insufficiently up to date to demonstrate the results are current or representative of the available literature.

1.5 "the update search was not a systematic review"

- What does this mean? Either the Report accepts systematic reviews or it doesn't.
- Systematic reviews should be described either as meta-analytical systematic reviews when meta-analyses are conducted or narrative systematic reviews when there is insufficient data for meta-analysis.

1.5 "After this cut-off date additional studies were considered only if they were thought potentially to impact on or inform the conclusions drawn in this report."

- All data and all studies should be included before drawing a conclusion.
- The Report includes the nonsense statement quoted here. One is obliged to consider the data to be able to think whether the additional study could potentially impact on the conclusion drawn and so reconsider the conclusion. Moreover, without the attendant search critical publications might be missed. The procedure as has been adopted allows reporting bias into the Report's conclusions. In a systematic meta-analytical review one can only disregard the recent studies if a cumulative meta-analysis has found prior stability for the conclusion reached.

1.5 "This was particularly the case where there was limited evidence or when it was difficult to interpret how evidence from the update search affected the conclusion."

- The first part of the statement is ambiguous. Please be clear about what was limited, the data already considered, the data in total with the most recent study/ies, or the data in the most recent study/ies?
- The second part of statement seems outrageous. If it is not known how a new study affects the conclusion, then no conclusion can be reached.

18.1 Interpretation of cohort studies.

- The Report does not provide an unbiased statement. Comments in the Report describe the weaknesses of cohort studies, yet few strengths are reported; one has to get to the subsequent paragraph to find a strength, then it seems only one is given.

18.1 Interpretation of interventional studies.

- The opening statement leaves it unclear about what to do when the disease is defined by metabolic or physiological states, e.g. blood glucose and diabetes, hypertension and high blood pressure.
- The examples as given in this section of the Report are particularly poor. Variation in nutrient compositions which differ among studies might simply enable meta-regression to adjust for potential confounding. In this section of the Report there are no strengths considered attributable to RCTs. A key weakness of long-term RCTs is the convergence of regular and treatment diet interventions, which may arise when participants in the regular arm learn via the grape-vine that a treatment diet might have some benefits. It is never clear how soon that convergence might arise making a no-effect conclusion open to doubt.
- The last sentence in the paragraph is hard to understand. Does "total carbohydrate" mean the total of available carbohydrate or does total carbohydrate include unavailable carbohydrates. Or is the author of the sentence trying to say that the definitions of carbohydrate are often unclear, and can sometimes be Available carbohydrate and sometimes Total carbohydrate (including dietary fibre) or other definition, or is there some implied reference to variation in carbohydrate intakes often being accompanied by variation in fat intake?

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A2.8 The criterion (I^2>75%): "It was agreed that if the result produced an I_2 of more than 75%, the pooled estimate would not be presented because it indicates that there is excessive heterogeneity and the result would have little meaning."

- This criterion would exclude outcomes with a large heterogeneity even if all results were in the same direction and have a large effect. In other words, could exclude important information about health with a size of effect/association that is conditional to subgroups and covariate domains (which could be hidden by the procedures in A2.8). The criterion would also include studies perceived originally as large (adequately powered) but in practice were imprecise due to error attributable to large-study inefficiency.
- It is always better to present the result, and speak to the caveat. The alternative risks assertions of lack of transparency (such as made here) and prevents retrospective re-consideration of the result when/if appropriate. Being transparent also treats outcomes with I^2 of 75% and 76% as the same, to suggest a difference between the two would be entirely arbitrary and unwarranted.

A2.10 Conversion of NSP to AOAC fibre and vice versa

- It is good that this discrepancy is highlighted. Nevertheless, sensitivity analysis ought to have been undertaken—here there is no mention of one in the draft Report. The sensitivity analysis would explain the potential relative bias of three different modes of expressing the results (NSP, AOAC, and MIXED in a combined result if used). Perhaps better still would have been a dummy covariate centred on AOAC (AOAC=0, NSP=1), which would have informed about the size of difference between the two fibre analysis approaches and whether the results were significantly different; this could be achieved without having to implicate a conversion factor, which might be inaccurate for the populations instant.

A2.16 and A2.17

- The difference between the two paragraphs is not adequately drawn to the eye.

A2.21 “relative risk above 1.2 for greater risk or below 0.8 for decreased risk”

- Unclear, take RR=1.2? Does this mean say RR=1.2 over 5 quantiles, 1.2 over one quantile or 1.2 over 1SD or 1.2 over a targetable range of intakes irrespective of habitual range of intake?

A2.22 “No conclusion- insufficient evidence. & No conclusion- inconsistent evidence.”

- The first of these categories is not applied sufficiently often (problem suspected is in the definitions developed for attribution).
- What is meant by inconsistency here, does this mean probable heterogeneity or something else?

A2.23 “normal diet”

- What is a normal diet?
- There is no specification here, but something possibly like it does appear in the main article.

A21 to A2.23 ……..

- All is written in the past tense. Likely, all would have been written in the future tense if agreed beforehand. This brings some concern that the protocol was stitched together after the results became known.
- It is unclear whether data from prospective cohort studies were appropriately transformed before meta-analysis.
- There was no identification of the cause of curvature in dose-response studies as reported. Such can arise because of inequality of the dose range among studies. In such case, further evidence of non-linearity is essential; otherwise there is a real possibility that the meta-analysis will have underestimated heterogeneity (as it is then hidden in the curvature).
- There is no evidence that individual studies were assessed for significant or even visual nonlinearity. If linearity is indicated at the level of individual studies, then two-step meta-analysis would be appropriate (i.e. dose-response with linear trend within study, followed by meta-analysis with or without covariates to the combined trends.)

*****Literature selection and Data analysis in the evidence base.

- The body of the Report is unclear about methodology used, as often noted in the forgoing.
- Examination of data analysis details in the evidence-base reveals a number of issues that are surprising. It is essential that meta-analysis results are corrected to avoid finding an effect due to bias towards low combined errors.
- Studies are excluded when “less than one year in duration” or “have not prescribed ad libitum dietary regimen”. However:

- there are several weight loss trials referred to in the main body of the text / appendix that are from 6 weeks to 6 months duration.
- The same criteria might well apply to food intake /energy intake and satiety trials when these are used to make inferences about obesity, but this has not been adhered to.

- Excluded are interventions that use a dietary portfolio (combination diet) or mixed component regimen, e.g. the prescribed diet included plant sterols, soy protein, viscous fibres, and nuts etc. or studies that do not permit the effect of carbohydrate/carbohydrate type to be evaluated
  - This is not always adhered to with respect to sugars, some of which are accompanied by modified fat intake.
- Concern about inclusion of low quality prospective cohort studies has been expressed previously in this response.
- Scoring for study quality is not defined.
- Body weight can be in the causal pathway but is always considered in the Report as a confounder, it might not be.
- "I^2 >50%" is purely arbitrary, this whatever 'experts' have done this beforehand. They too need to consider what they have done. Nutritional studies cannot be considered like drug studies, and drug studies are known to have biases.
- "I^2 …more useful proportion of total variation" Sometimes tau^2 is more useful, I2 is more useful for tests because it is more precise than tau^2.
- "lack of information" allowing individual studies to be excluded. It is customary to write to authors of original studies to acquire the missing data. To not do so is to not maintain necessary standards

******Chapter 4 Diabetes.pdf Figure 4.8, Funnel plot:

"There was no evidence of any small-study effect such as publication bias, as is shown by the contour-enhanced funnel plot below:
Figure 4.8 Contour-enhanced funnel plot for publications presenting incident diabetes mellitus type 2 and dietary fibre"

- The plot is confusing—it doesn't appear to have been constructed correctly because the plot indicates (contrary to the Report's statement quoted) that there is massive publication bias but this is due to the pseudo-confidence bounds being plotted about zero association; this rather than correctly about the combined mean.
- Trim-and-fill analysis is preferable to Eggers plot, the hypothetical 'missing' or 'filled data' and 'filled mean' can be shown, too, together with the adjusted combined mean and test of significance of bias when residuals are analysed.
- It is seldom done, but the pseudo-confidence bounds ought also to be presented for the random effect analysis, too, whenever $I^2>0$ whether or not I^2 is significant.

*****Chapter 4 Diabetes.pdf Figure 4.10, Funnel plot:

- The plot has the same problem as mentioned above for Figure 4.7 in the same pdf.
- All funnel plots released need to be checked for correct construction and drawn to be correct and informative without confusing the reader.

*****Chapter 4 Diabetes.pdf "Please interpret observational data with caution: With observational studies there is substantial potential for biases."

- The Report's statement in itself is biased because nutritional intervention studies also have considerable potential for biases.
- The more general and well accepted caution is sufficient, that observational studies are not sufficient to prove causality.
- Observational studies provide what one hopes is the best estimate of risk. This is the best one can do also with RCTs when measurements are risk factors, but even then risk is often not estimated but is unquantified and only inferred as important. Quite possible the Observational studies are the more transparent of the two.
- RCTs to test diets for incident diabetes or incident colorectal cancer may well be impractical and unethical if diabetes type 2 and colorectal cancer take the generally accepted 10 or 20 years for development. All this leaves RCTs being ideal theoretically but doubtful practically when starting with heathy participants. Starting with diseased participants one can at least begin to monitor progress, such is the advantage when examining drugs.
- A less biased perspective towards favouring RCTS over Observational studies would be appropriate for the measures made among studies in this draft report.

*****Chapter 4 Diabetes.pdf Figure 4.10, Forest plot for glycaemic index and Diabetes type 2.

- The plot and conclusions are inaccurate—see next.

*****Chapter 4 Diabetes.pdf Figure 4.10, Funnel plot: "There was a little evidence of possible small-study effect from the contour-enhanced funnel plot, though half the studies did not suggest any evidence of a protective association."

- The statement strongly indicates the authors lack an appropriate ability to present and interpret funnel plots (see above comments).
- In addition, the claim made is contrary to the observations in Figure 4.19.
- There is also a failure to account for adequacy of the FFQs for carbohydrate among these studies. Meyer et al 2000, Stevens et al, 2002, Mosdol et al 2007 and Sahyoun et al 2008 all had inadequate FFQs (Barclay et al 2008, Livesey et al. 2013b). If an FFQ has poor correlation for the amount of carbohydrate in food, its use will cause a heavy bias towards the null. Interestingly these are the studies that found no significant effect.
- The last study reported is 2008, why are there no studies of later date? Remember too that there are problems in the EPIC studies, with FFQ needing to be validated within each region, and difficulty of small numbers in each region, which limits the number of adjustments that can be made.

*****Chapter 4 Diabetes.pdf Incident Diabetes Mellitus type 2 and glycaemic load.

- The section and analyses are out of date.
- The conclusions reached are inaccurate.
- A comprehensive meta-analysis of the relation between diabetes type 2 and glycaemic load is available (Livesey 2013a and 2013b).

*****Chapter 4 Diabetes.pdf

- In view of the forgoing it is known that:

- Some of the combined outcome results for observational studies are inaccurate beyond the draft Report's meta-analyst expectations.
- None of the combined outcome results of observational studies take account of the adequacy of the FFQ for optimal reporting quantitatively and could have done so. Thus none of combined outcome results are likely to be accurate. This includes also the subgroup analyses.
- Consequently, extreme caution should be taken when applying results from this Report, whether for intervention studies or for prospective cohort studies.
- These problems affect all chapters
- The only solution is to update and redo the analyses.

Chapter 10 Glycaemic index and load

*10.3 "measures of the glycaemic characteristics of the diet"

- Strictly, they are measures of the glycaemic characteristics of foods used to estimate the glycaemic characteristics of diets.

*10.3 "The GI is a relative measure of the plasma glucose response induced"

- Strictly, 'since standardisation, GI is a relative measure of the capillary blood glucose response induced …'

*10.3 "quality and quantity of carbohydrate"

- This one may seem pedantic; however, it is the 'quality of the carbohydrate food/meal/ingredient and the quantity of carbohydrate in the food/meal/ingredient'. This recognises that GI is a measure for the food/meal/ingredient, not the carbohydrate, as the GI is affected by non-carbohydrate in the food/meal/ingredient as well as the structures and composition of the carbohydrate in the food as eaten.

*10.4 GI and GL units

- Neither GI nor GL are unitless. Moreover, both are linked to a particular standard but the Report doesn't state which applies here (e.g. % of glucose or % white bread, and g/d or g/2000kcal etc).

*10.4 two GI unit increment….and…20 GL unit increase.

- Why 2 and 20? The SD's are reported in this paragraph to be 5 for GI and 26 for GL. Isn't 1 SD the SACN standard for reporting for the project?
- Also, it ought to be recognised that adoption of SD values for the UK can give a false impression of the importance of GI and GL among and across other world regions because the SD value is greater worldwide and can be greater, too, in regions other than the UK.

*10.5 "The difference between these two types of trials is that the glycaemic index trials do not vary carbohydrate quantity, but change the quality to modify the GI. The GL trials reduce carbohydrate intake, resulting in a higher proportion of fat, often including saturated fatty acids, and/or protein intake, as well as changing the carbohydrate quality to modify the GI"

- Although the paragraph may appear clear, in the context of the Report's mention of effects on macronutrient intakes, weight loss and confounding of GI and GL trials by weight loss, the paragraph and immediate following sections give a false impression of GI and GL and how trials can modify these quantities, macronutrient intakes and body weight.
- GL trials can aim to modify GI, protein, fat, fibre, etc. etc. GI trials modify GL only by exchanges of foods of different GI and carbohydrate content. Such GI trials also aim to balance changes in protein, fat, fibre, etc., with the specific objective to balance differences in composition between foods of lower GI used in place of foods of higher GI. As a side issue; this balancing act might not take place among free-living persons when choosing lower GI in place of higher GI. Even in studies aiming to achieve such balances they can fail. Thus outcomes depend on the circumstances (Livesey et al 2008a and 2008b). Thus lower GI trials of ad libitum food intakes have been associated with lower energy intake (from available carbohydrate, protein, and fat) but not lower dietary fibre intake. Trials of lower GI under conditions of controlled energy intakes have shown only minor changes in macronutrient intakes. Trials of intermediate levels of control of food intake show intermediate effects [2].
- The Report's comment that trials on GI and GL induced some weight loss may be used in the Report unduly critically. Reduction in GL can induce weight loss as shown in randomised controlled trials [1]. Potentially this is a part of the mechanism (not a real confounder). Nearly all dietary trials result in weight loss – likely more so among persons in an overweight environment and especially as they regain 'food consciousness', but also because where food selection is concerned, aiming for a new goal limits food choices - at least until the new approach to eating is learned.

10.6 to 10.7 "No association" and total cardiovascular disease events"

- Total cardiovascular disease events need defining here, even if defined elsewhere the are not found in the draft Report.
- What events were included? What events were excluded? Were FFQ adequately validated in each included study? Was exclusion of studies undertaken when the correlation for the FFQ was 60 or less? Were studies included that did not demonstrate their own validation of FFQ (for example most EPIC study centres do not report independent validations)? Were studies of low validity for carbohydrate also excluded?
- Men and women may differ. Women being more susceptible than men for a GI-CHD relation, and perhaps men more susceptible than women for a stroke event, these perhaps tending to cancel out each other in a total cardiovascular disease all sexes combined analysis (or causing apparent non-significance even when there is a real association). Mixing near to no association with an association would be a sure way to get borderline significance/non-significance as reported in the Report.
- Given the above it is questionable whether the borderline non-significance reported is interpretable.

- The conclusion of “No association” is wrong for the data available in the literature, this SACN activity definitely needs to be updated and executed correctly.
- Why were meta-analyses by Mirrahimi et al. 2012 and Ma et al. 2012 not included?

10.8 to 10.9 “Coronary events” and “No association”

- This collection of conditions needs to be defined even if defined elsewhere.
- The conclusion here differs from those in published meta-analyses.
- It is certain that the present meta-analysis has not been conducted adequately (cf above for total coronary events).

10.10-10.11 Stroke and GI.

- It is unclear whether the meta-analysis result includes the 2 studies in the update search and others since, if published.
- It is unclear whether the literature is up to date (to within six months of the reports intended publication data).

10.12-10.13 Blood pressure and GI.

- It is unclear whether the meta-analysis results include the 2 studies in the update search.
- It is unclear whether the literature is up to date (to within six months of the reports intended publication data).

10.12-10.16 Fasting total-, LDL-, & HDL-cholesterol & triacylglycerol and GI.

- The discussion in 10.16 and in the boxed conclusions is somewhat lazy, it implies rejection of effects of GI on these blood lipids if secondary to effects of GI on bodyweight—without evidence. An unbiased approach would be to state that ‘the effects may be primary to reduction in GI whether directly or indirectly via effects on body weight. Effects on body weight may also be confounded by factors other than GI.’ Etc.

10.21-10.22 “(C-reactive protein)”.

- No meta-analysis is mentioned. It is unclear whether a meta-analysis if conducted would reveal a significant effect, which is one objective of meta-analysis, to improve power of observation to a greater level than in small studies with non-significant results.
- The RCT Diogenes and the CCD clearly demonstrated an effect of GI [ref 8 and 9]

10.23-10.24 “Eating motivation” , “No effect” and “moderate evidence”.

- So many factors affect eating motivation. To date all such studies (whether or not about GI or GL) appear to lack sufficient power to yield stable and clinically relevant effects.
- A claim to no effect needs to be qualified.

- A claim of moderate evidence fails to recognise that study protocols have not yet reached a suitable stage of development to address low but potentially meaningful differences in eating motivation.

****10.25-10.26 “Type-2 diabetes” and GI

- The analysis includes results from some studies rejected by other meta-analysts for inadequate FFQs.
- Inadequacy of FFQs relates to their validity (poor correlation between FFQ used and a better measure for the food component/factor under study).
- If there is a poor correlation during validation, there is a greater likelihood of poorer correlation, and higher risk of confounding when attempting a correlation with incident disease, such studies are generally biased to the null.
- One or more studies also have FFQs that were not validated within the population studied, so has a doubtful FFQ.
- Most studies did not validate their FFQ for GI, though did validate the FFQ for carbohydrate, which is important in that diet GI is weighted by carbohydrate intake so requires FFQs to be adequately validated for carbohydrate at least.
- It is unclear whether GI values used in the meta-analysis are adjusted for energy intake according to the method of Stampfer and Willett. If not they will be biased towards null.
- For each one of the above reasons a meta-analysis result can be rejected.
- The Report result will be biased towards marked underestimation of the role of GI in prevention of type-2 diabetes.

****10.27-10.28 “Fasting blood glucose” and GI, and “No effect”

- It has been established (independently of regression to the mean) that lower GI and GL can elevate fasting blood glucose in those persons with rested and fasted morning plasma glucose <5mmol/L, but lower it in those with fasting blood glucose > 5mmol/L (online supplement to Livesey et al. 2008a) – thus it appears that low GI is normalising of blood glucose.
- It is not surprising, therefore, that combing results from all such studies reveals little effect, as indicated in the ‘meta-analysis’ conducted for the draft Report.
- The conclusion of no effect is therefore premature, and for the present can be rejected.

****10.31-10.32 “Insulin sensitivity” and GI, and “No effect”

- There is no mention of attempts to create a common metric for these studies.
- There is no mention of any temporal effects, since earlier studies of shorter duration generally indicate improvement.
- It is unclear whether duration of intervention is a significant factor in these studies.
- It is possible that increasing duration of study associates with lowering of power of these studies (errors become larger over time).
- These considerations are significant because small effects in the right direction may mount-up over time.

*10.33-10.34 “Colorectal cancer” and “No-association”

- It remains to be established whether a no-association is due to inadequate FFQs in some of the included studies (cf comments immediately above).
- The issue of adequacy of FFQs may also apply to studies of ‘total or available carbohydrate’ intake, and possibly other nutrients [3-5]).

*10.35-10.36 “Total cardiovascular events”

- Total cardiovascular events is undefined.
- It is unclear which variables are confounding.
- No attempt is described to eliminate potential co-variables.
- It is unclear whether the comment that “it is not possible to exclude confounding variables” has specific information supporting it or whether the comment is just a repeatedly stated bias against prospective cohort studies in favour of intervention studies or whether it is stated whenever there is a feeling of bias against the effectiveness of an intended nutrient or dietary factor. Because nutritional intervention studies are difficult to fully control, the issue of confounding arises there too, but is often overlooked or suggested is negligible, but upon detailed analysis can be found statistically significant and of importance (Livesey et al. 2008a).

*10.39-10.40 “Fasting total-, LDL-, HDL-cholesterol and triacylglycerol” and GL

- The results according to study designs are most pertinent to those persons striving for weight reduction. The majority of the population is ‘walking’ into weight gain.
- Thus the Report’s results are not relevant for the majority of the population.

*10.41-10.42 “(C-reactive protein)” and GL

- Too few studies were analysed to establish stability of this result.
- “No- significant effect” is meaningless if studies were underpowered or not representative, so more detail needs to be presented to be convincing.
- No meta-analysis appears to have been conducted.
- At least one epidemiological study has indicated an association.

****10.43-10.44 “(Body weight)” and GL

- Too little information is presented to claim no-effect.
- Studies of short to long (12 mo) duration have previously shown effect when meta-analysed with time as a non-linear covariate, and when GL reduction breaches an apparent threshold (Livesey et al. 2005, 2008a).
- It appears probable that collection of insufficiently data and performance of inadequate analysis could be the problem underlying the claimed no-effect.

*****10.45-10.46 “Type-2 diabetes” and GL

- GL has units, a statements of unit/day is somewhat lazy reporting (unit is not expressed).
- Moreover, original studies mostly report GLs that were adjusted to a mean or median energy intake for the study, a mean or median energy intake that varies among studies. This expression (g GL reported/amount of study mean energy reported) does not have the errors implicit in g/day for data collected from food frequency questionnaires.
- A comprehensive meta-analysis of more studies than in the SACN draft Report has already been published (Livesey et al. 2013a and 2013b, and online supplement) but is not referred to in the draft Report, finding:
    - Association, RR =1.08 per 20 g GL/2000kcal – average for men and women and higher when accounting for higher actual intakes according to the SACN energy requirement report for people in the UK
    - Significant in both men and women.
    - Heterogeneity reduced to 3% by three out of four pre-published hypothesized factors:
        1. Significantly higher RR in women than in men.
        2. Significantly dependence on the FFQ correlation for carbohydrate, implying the studies markedly underestimate the importance of GL.
        3. Ethnicity, significantly higher values in studies of European-Americans versus all other ethnicities combined.
    - No significant effect (for the present) of duration of follow-up due to instability about this factor (inadequate number of very long term studies, >15y).
    - Significance of effect at all doses >95g GL/2000kcal.
    - Stability of outcomes over increasing number of studies (except for duration of follow-up >15y).
    - Stability against a wide range of potential confounders that were explored.
    - Discussion that reduced GI could achieve sufficient GL reductions except at very high intakes of GL when carbohydrate reduction would also be required to meet an optimum target GL of 100g/2000kcal—chosen as a rounded value closely above a lowest point of significant effect on the dose-response curve.

****10.47-10.48 “Fasting blood glucose [and] No effect” and GL

- Really needs to consider <5mmol/L and >5mmol/L separately and in a meta-analysis with treatment average fasting blood glucose, fibre intake and GL dose modelled in.
- “No effect” is doubtful. Studies including shorter duration show significant effects of severity of abnormality of fasting glucose concentration (including <5 mmol/L), fibre intake and GL (or GI) as determinants in an appropriately structured meta-analytical model (Livesey et al 2008a)
- Combing all studies together (<5 mmol/L and >5mmol/L) can be suspected to average out as no effect among healthy persons.
- For some purposes, an analysis excluding pre-diabetes and diabetes from the analytical model has some limitation, for example, when fasting blood glucose can be considered as a continuum throughout the range. The exclusions are artificial cut points relevant to clinical issues rather than scientifically defined. Cut points should be defined scientifically.

- It can be considered that the no-effect could be due to insufficient detail and range of results in the analytical model.
- In addition, studies of too long duration (beyond achievement of steady state) may lose power compared with studies of moderate duration.
- The reported “no-effect” risks being misleading.

****10.51-10.52 “Insulin sensitivity/resistance [and] No effect” and GL

- Information is too limited to be convinced of a no effect.
- No effort is mentioned to find a common metric.
- Modification of carbohydrate intake is expected to modify GL and in short term probably influences insulin sensitivity/resistance.

10.55 Outcomes with insufficient evidence (tables 10.1, 10.2, 10.3

- The criteria for deducing this is unclear, as sometimes no-effects are concluded when there is insufficient evidence, especially as presently presented in the Report.
- Being able to undertake a meta-analysis with sufficiently low I^2, and being able to establish stability of effect, each seem not to be among any criteria.
- The veracity of the lists is unclear. At least the searches performed are not up-to-date.
- The accuracy of Table 10.3 is doubtful. It may be more a matter of need for more evidence to apply appropriate analyses to rid the collection of studies of heterogeneities. Inconsistency may imply inaccuracy of studies, but it may be inaccuracy of the models used for analysis of the studies and/or having sufficient numbers of studies to reveal factors hypothesized as explanatory.
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Chapter 12 Overall Summary and Conclusions [concerning GI and GL]

*****12.2 “In accord with the SACN Framework for Evaluation of Evidence, strict inclusion and exclusion criteria were applied in the systematic reviews to ensure the evidence considered was of sufficient quality to be able to draw sound conclusions (SACN, 2012).

- It is clearly evident that the criteria are neither strict nor adequate in regard the prospective cohort studies as is particularly evident for “carbohydrate”. Since drawing up the guidelines there is now significant additional confirmatory evidence on the adequacy of food frequency questionnaires (FFQs) and hence prospective cohort studies using them. It is evident that the use of FFQs with low correlations between carbohydrate content of food intake assessed by FFQ compared with more accurate methods yield results strongly biased towards the null. This was identified by (Brunner et al. 2001), shown to matter for carbohydrates by Barclay et al. 2008 and confirmed and established as highly significant cause of strong bias to the null during a comprehensive dose-response meta-analysis (Livesey et al. 2013b). The Report includes meta-analysis of prospective cohort studies without examining the sensitivity of combined outcomes to the size of the FFQ correlation.

- Through not taking this issue into account, we can no longer consider the assurance given within the quoted statement extracted (above) that the draft Report has excluded studies low in quality

12.4***"carbohydrate, glycaemic index, and glycaemic load"

- It is unclear why there is negative focus in the draft Report particularly on carbohydrate, glycaemic index, and glycaemic load. The same negatives apply to dietary fibre intake, whole grain intake and added sugars intake, all of which are imprecise 'measures' and reveal considerable conditionality in their associations with incident disease which can be accompanied by varied intakes of other micro- and macronutrients and phytochemicals. There is no review of this issue in the draft Report to justify the negative focus identified, so that reporting bias and speculation are not excluded. It is fine to have statements about the nature of problems, it is wrong to target individual examples without proper analysis of the issue. Among the Report's presented meta-analyses, none were encountered to have addressed this issue analytically.
- Not mentioned is that a major downfall of intervention studies is that long-term studies tend towards convergence of treatments and controls.
- Not mentioned another major problem with the consideration of intervention studies and their meta-analyses, is that it is often not stipulated whether the analysis is for a rate of change over a defined period or for a new steady state.
- Overall the draft Report reports negatively rather than on balance. There are few statements of advantages. For example, population based studies concern relevant doses, while intervention studies may not do so. By contrast, intakes of particular nutrients or nutritional aspects may be uniform across the population, making the range of intakes too small to see a significant association even when one actually exists.

12.21 "There is no evidence from prospective cohort studies to suggest an association between glycaemic index and cardiovascular disease or coronary heart disease."

- Wrong, totally wrong.
- The conclusion would be stunning if it were not for knowing the review is well out of date.
- Published meta-analysis of prospective cohort studies show a strong association for CHD and glycaemic index and load in women, with no significant association in men. The lack of effect in men might be attributed to several things, possible higher levels of alcohol consumption; possibly poorer reporting on FFQs when conducted on large numbers of participants compared with smaller numbers in FFQ validation studies. Combined studies for the mixed-sex population with dummies centred on 0 for gender has potential to retain a very significant relation between CHD and both GI and GL for the population as a whole.
- One might in addition note that since there is a well-established association with type 2 diabetes, there is a high risk expected for CHD and GI and GL owing to CHD risk being more sensitive to perturbations in HbA1c than is the risk of type 2 diabetes.

12.21 "Glycaemic load is associated with a greater risk of cardiovascular disease"

- Even though there were a small number of studies captured in the search performed, there are more now. Consideration should be given to exclusion criteria; studies with inadequate FFQs should be excluded or built into an appropriate model rather than ignored as was done in the SACN commissioned meta-analyses.

*****12.21 "The available evidence does not suggest an association between glycaemic index or load and colo-rectal cancer incidence."

- The review is out of date. New meta-analyses are required.
- The review took no account of adequacy of FFQs, a new meta-analysis should do so.
- The review for GI and GL should , where possible, ensure data entered is energy adjusted according to Willett's / Stampfer and Willett's method in the original studies, and importantly, too, across the studies towards a common energy intake, e.g. 2000kcal.

*****12.23 "……."

- What is stated might well be perceived as reporting bias.
- For diets, GI and GL inform about a domain that is associated with risk/benefits that are not accessed by the other carbohydrate components reviewed in the draft Report. It is not intended that GI or GL be used alone as the indicator of a healthful diet (as often seems to be wrongly implied elsewhere), rather GI and GL are applied within the context of what is deemed healthy food-based advice. It should be further recognised that healthy food-based advice is not optimal for identifying higher versus low GI or GL foods, despite the occasional opinion claiming that it does so (analysis shows the contrary).
- The bias expressed in the Report would limit a consumer's ability to identify an optimum diet, prevent appropriate dietary choice (as well as blocking free choice), and unduly worry many type 2 diabetes patients and others world-wide who apply GI and GL to their own benefit.

*****Last words on GI and GL

- All too frequently, GI and GL attract negative comment because commentators think the scientific community present these concepts as primary health measures. They are wrong. GI and GL are one of several attributes of foods (and diets) that impact on health. In general, food-based advice has primary position, only within food groups is a GI or GL measure selected. No food-based advice (and no compositional based advice) has been devised to select an optimal diet since all food-based advice and compositional-based advice can result in food selections of only high or only low GI as well as only moderate GI overall and so also optimal and suboptimal GL. For the forseeable future, only when GI or GL is used with an appropriately healthy food-based selection process can optimal diets be obtained.
- Omitting GI and GL from choices of healthy nutritional advice is further suboptimal. Individuals choose their preferred approach to organising their diets. Unduly ignoring an important option limits the potential success of health measures in total.
- It is uncomfortable to consider that the UK continues not to recognise that the quality of fatty foods and quality of carbohydrate foods matter more than is evident among the UK's

health messages, food labels and food tables, most especially that the quantities of fat and carbohydrate together have proved difficult to control in the UK and other world regions

Conflict of interest statements.

Arne Astrup, is consultant/member of advisory boards for Dutch Beer Knowledge Institute, NL; Global Dairy Platform, USA; McCain Foods Limited, USA and McDonald's, USA. He is currently principal investigator of research projects supported by grants from Arla Foods AMBA, DK; The Danish Dairy Research Foundation, DK; Global Dairy Platform, USA and the Danish Agriculture and Food Foundation, DK.

Livia S Augustin, has received a honorarium from one of the organizers of the Glycemic Index, Glycemic Load and Glycemic Response Summit (Nutrition Foundation of Italy).

Sara Baer-Sinnott is the president of Oldways is a nonprofit food and nutrition organization. We receive support from a wide variety of organizations -- foundations, government entities and companies. We were also the co-organizer of the Glycemic Index, Glycemic Load and Glycemic Response Summit.

Alan Barclay, is Vice President of the Glycemic Index Foundation, an international not-for-profit organisation which endorses healthy low GI food products by means of a certified GI symbol. He is a co-author of lay books about the glycemic index of foods.

Jennie Brand-Miller, is President of the Glycemic Index Foundation, an international not-for-profit organisation which endorses healthy low GI food products by means of a certified GI symbol. She manages a glycaemic index testing service at the University of Sydney and is the co-author of lay books about the glycemic index of foods.

Furio Brighenti, is affiliated to a department of the University of Parma that does Glycemic index analysis as a service to third parties.

David JA Jenkins, reported serving on the Scientific Advisory Board of Unilever, Sanitarium Company, California Strawberry Commission, Loblaw Supermarket, Herbal Life International, Nutritional Fundamental for Health, Pacific Health Laboratories, Metagenics, Bayer Consumer Care, Orafti, Dean Foods, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Pulse Canada, Saskatchewan Pulse Growers, and Canola Council of Canada; receiving honoraria for scientific advice from the Almond Board of California, International Tree Nut Council Nutrition Research and Education Foundation, Barilla, Unilever Canada, Solae, Oldways, Kellogg's, Quaker Oats, Procter & Gamble, Coca-Cola, NuVal Griffin Hospital, Abbott, Canola Council of Canada, Dean Foods, California Strawberry Commission, Haine Celestial, and Alpro Foundation; being on the speakers panel for the Almond Board of California; receiving research grants from Loblaw Brands Ltd, Unilever, Barilla, Almond Board of California, Solae, Haine Celestial, Sanitarium Company, Orafti, International Tree Nut Council, and Peanut Institute; and receiving travel support to meetings from the Almond Board of California, Unilever, Alpro Foundation, and International Tree Nut Council, Canadian Institutes for Health Reseach, Canada Foundation for Innovation, Ontarion Research Fund. Dr. Jenkins receives salary support as a Canada Research Chair from the federal government of Canada. Dr Jenkins' wife is a director of Glycemic Index Laboratories, Toronto, Ontario, Canada.

Cyril WC Kendall, has received research grants, travel funding, consultant fees, honoraria, or has served on the scientific advisory board for Abbott Laboratories, Advanced Food Materials Network, Agrifoods and Agriculture Canada (AAFC), Almond Board of California, American Peanut Council, American Pistachio Growers, Barilla, California Strawberry Commission, Calorie Control Council, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, The Coca Cola Company (investigator initiated, unrestricted), Danone, General Mills,

Hain Celestial, International Tree Nut Council, Kellogg, Kraft, Loblaw Brands Ltd, Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, Peanut Institute, Pepsi-Co, Pulse Canada, Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate & Lyle and Unilever.

Geoff Livesey, none here other than to seek for necessary higher standards of meta-analyses and to see the science and appropriate application of GIycaemic Index and Glycaemic Load. Geoff. Livesey holds shares in Independent Nutrition Logic Ltd, Wymondham, Norfolk

Simin Liu, received consulting fees from Stanford University, Fred Hutchinson Cancer Research Center, honoraria from General Mills Co, and royalty payment from UpToDate, Inc.

Andrea Poli, is the scientific director of the Nutrition Foundation of Italy (NFI) which was a co-organizer of the Glycemic Index, Glycemic Load and Glycemic Response Summit.

Gabriele Riccardi, is a member of the scientific advisory board of Barilla Center for Food and Nutrition.

John L Sievenpiper, has received research support from the Canadian Institutes of health Research (CIHR), Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted grant), Pulse Canada, and The International Tree Nut Council Nutrition Research & Education Foundation. He has received travel funding, speaker fees, and/or honoraria from the American Heart Association (AHA), American College of Physicians (ACP), American Society for Nutrition (ASN), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), Canadian Diabetes Association (CDA), Canadian Nutrition Society (CNS), University of South Carolina, Calorie Control Council, Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), International Life Sciences Institute (ILSI) North America, International Life Sciences Institute (ILSI) Brazil, Abbott Laboratories, Pulse Canada, Canadian Sugar Institute, Dr. Pepper Snapple Group, and The Coca-Cola Company. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of both the Canadian Diabetes Association (CDA) and European Association for the study of Diabetes (EASD), as well as being on the American Society for Nutrition (ASN) writing panel for a scientific statement on the metabolic and nutritional effects of fructose, sucrose and high fructose corn syrup. He is an unpaid scientific advisor for the International Life Science Institute (ILSI) North America, Food, Nutrition, and Safety Program (FNSP). His wife is an employee of Unilever Canada.

Thomas MS Wolever, receives payment as President, Medical Director and scientific consultant for Glycemic Index Laboratories Inc. (GI Labs), a contract research organization, and as President and part owner of Glycaemic Index Testing Inc., which provides services to GI Labs; Dr. Wolever's wife receives payment as Financial Officer and part owner of these 2 corporations. Dr. Wolever has received royalties as co-author of a number of popular books on GI under the general title of The Glucose Revolution, and consulting fees from Tamasek Polytechnic, Singapore for advice related to GI research. In the last 3 years, Dr. Wolever has received payment as a consultant from McCain Foods Inc., Bunge and Procter and Gamble. Except for the preceding, Dr. Wolever has no stocks or shares in any company that may gain or lose financially through publication (with the possible exception of companies included in mutual funds) and has no financial interest in any patents or patent applications whatsoever.

Inger Bjorck, is managing director of a centre of excellence in research and innovation, the " Antidiabetic Food Centre" at Lund University, Sweden. Partners of the centre are Lund University, the regional health care system and food industries.

Anette Buyken, Antonio Ceriello, Carlo La Vecchia, Salwa Rizkalla, Antonia Trichopoulous and Walter Willett, do not declare any conflicts of interest.

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International Carbohydrate Quality Consortium (ICQC) Members:

David J.A. Jenkins (ICQC chair), MD, PhD, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada
Walter C. Willett (ICQC chair), MD, PhD, Department of Nutrition, Harvard School of Public Health, Boston, USA
Arne Astrup, MD, DMSc, Department of Nutrition, Exercise and Sports (NEXS) Faculty of Science, University of Copenhagen, Copenhagen, Denmark
Livia S.A. Augustin, PhD, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada
Sara Baer-Sinnott, Oldways, Boston, USA
Alan W. Barclay, PhD, Australian Diabetes Council, Glycemic Index Foundation, Sydney, Australia
Inger Björck, PhD, Functional Food Science Centre, Lund University, Lund, Sweden
Jennie C. Brand-Miller, Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Sydney, Australia
Furio Brighenti, PhD, Department of Food Science University of Parma, Parma, Italy
Anette E. Buyken, PhD, Department of Nutritional Epidemiology, University of Bonn, Bonn, Germany
Antonio Ceriello, MD, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
Cyril W.C. Kendall, PhD, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Canada College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada
Carlo La Vecchia, MD, Department of Epidemiology, Mario Negri Institute, and Professor of Epidemiology, University of Milan, Milan, Italy
Geoffrey Livesey, PhD, Independent Nutrition Logic, Wymondham, UK
Simin Liu, Department of Epidemiology and Medicine, Brown University, Providence, USA
Andrea Poli, MD, Nutrition Foundation of Italy, Milan, Italy
Gabriele Riccardi, MD, Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy
Salwa W. Rizkalla, MD, PhD, National Institute of Health and Medical Research (INSERM), ICAN Institute of Cardiometabolism & Nutrition, University Pierre et Marie Curie-Paris 6, Centre of Research in Human Nutrition, Pitié Salpêtrière Hospital, Paris, France.
John L. Sievenpiper, MD, PHD, Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada, Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Canada
Antonia Trichopoulou, PhD, World Health Organization Collaborating Centre for Food & Nutrition, Department of Hygiene and Epidemiology, University of Athens Medical School, Hellenic Health Foundation, Athens, Greece
Thomas M.S. Wolever, MD, PhD, Department of Nutritional Sciences, University of Toronto, Toronto, Canada

The views expressed herein this document are without prejudice and are approved by ICQC.

Corresponding author:
Arne Astrup