PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Health and economic benefits of reducing sugar intake in the United States, including effects via non-alcoholic fatty liver disease: A microsimulation model
AUTHORS	Vreman, Rick; Goodell, Alex; Rodriguez, Luis; Porco, Travis; Lustig, Robert; Kahn, James

VERSION 1 - REVIEW

REVIEWER	Amedeo Lonardo, M.D. Azienda USL - Internal Medicine -NOCSAE - Baggiovara, Modena, Italy
REVIEW RETURNED	30-Aug-2016

GENERAL COMMENTS	GENERAL COMMENT An interesting proof-of-concept study evaluating the benefit of a single, specific and theretically feasible dietary intervention. Referencing should be improved and so are a couple of misconceptions regarding the relationship of NAFLD with the MetS. The submission should be made more consistent by highlighting the pathogenic impact of simple sugars on epidemiology and pathogenesis of NAFLD. Finally, a list of those obstacles preventing the limitation of added simple sugars should be added. SPECIFIC COMMENT Introduction This article specifically focuses on the economical benefits of limiting the consumption of added simple sugars. However, relevant literature regarding NAFLD-related costs is not cited and it should (Gastroenterology. 2008;134:85-94; Hepatology. 2016 Aug 20. doi: 10.1002/hep.28785. [Epub ahead of print] PubMed PMID: 27543837). Moreover, I found that the definition of NASH as a condition "with or without scarring" (Introduction, lines 13 and 14) should best adhere to the standard nomenclature (i.e. "fibrosis"). (Nat Rev Dis Primers. 2015 Dec 17;1:15080. doi: 10.1038/nrdp.2015.80; Int J Mol Sci. 2016 Jan 13;17(1). pii: E97. doi: 10.3390/ijms17010097). "Furthermore, NAFLD has been shown to regularly precede the metabolic syndrome, and scientists now argue that NAFLD is the hepatic manifestation of metabolic syndrome, and should be included in its definition.". This sentence includes an internal conflict (if " NAFLD regularly precedes the metabolic syndrome" then it is a precursor and not "the hepatic manifestation of metabolic syndrome"). Furthermore, it is not particularly updated in as much as it fails to

	render the complex and bi-directional relationship linking NAFLD with the metabolic syndrome. Accordingly, this statement should undergo full reworking based on recent views (Refs 10 and 24 + Ballestri S, Hepatol Res. 2016 Jan 19. doi: 10.1111/hepr.12656. [Epub ahead of print] PubMed PMID: 26785389. Ballestri S, J Gastroenterol Hepatol. 2016;31:936-44. doi: 10.1111/jgh.13264. PubMed PMID: 26667191.Dig Liver Dis. 2015;47:181-90) . This submission may be made more consistent by highlighting how the consumption of simple sugars impacts on epidemiology and pathogenesis of clinical and experimental NAFLD (Dig Dis Sci. 2016;61:1282-93. Gastroenterology. 2016;150:956-67. Hepatology. 2016;63:2032-43. Am J Clin Nutr. 2014;100:833-49. Hepatology. 2014 Nov;60:1581-92. Am J Pathol. 2014;184:1550-61. Eur J Clin Nutr. 2014;68:416-23.) Discussion Authors may be willing to discuss what obstacles prevent the limitation of added simple sugars.

REVIEWER	Luc Tappy University of Lausanne Switzerland
REVIEW RETURNED	27-Oct-2016

GENERAL COMMENTS	This paper uses a modelled cohort study to assess the impact of a reduced sugar consumption on health outcomes. Its originality is alledgedly to include non-alcoholic fatty liver disease in the model. I must admit that I am not familiar with modelling, and even less in modelled epidemiology. I nonetheless feel that this approach is not adequate for the aims stated by the authors. 1. Like for any model, one major critical step is to assign parameters to the variables to be studied (here, sugar intake, nafld, bmi,....). I would think that these parameters should be obtained from experimental data. This step is not presented here, and the reader cannot determine how parameters were determined or ehether they are likly to be valid. To the best of my knowledge, no strong data exist relating sugar and nafld.... 2. The initial evaluation of the model should be that it fits the real world; ie: do the incidence of health outcomes related to sugar intake from this model fit those of other real cohort studies? 3 The outcome presented look to me as little informative. If you build up a model predicting that sugar will favor nafld, and that both sugar and nafld favor cardiovascular diseases, then this model will always predict that sugar reduction improves health outcomes and reduces health costs Again, I am no specialist in prediction midels, and may have competely missed the aims of this article. If I did, it is likely that many other MDs reading BMJ will do the same, so a presentation of "models for the nerds" may be useful to include...

REVIEWER	Scott M. Grundy UT Southwestern Medical Center, U.S.A.
REVIEW RETURNED	23-Nov-2016

GENERAL COMMENTS	1. This article proposes that nonalcoholic fatty liver disease (NAFLD) is a mediator of the metabolic syndrome, and it asks whether reducing sugar intake will decrease fatty liver and its consequences. 2. In the view of this reviewer, it is uncertain whether the metabolic syndrome is mediated by fatty liver, or whether it is but one manifestation of nutrient overload but not directly in the causal link with metabolic syndrome. The authors might want to address this question. 3. The authors constructed a model in which they estimated that a 20% reduction in intake of added sugars will reduce fatty liver, cirrhosis, metabolic syndrome, and coronary heart disease. This appears to be an ambitious model which includes many factors. The question is whether such a model can make accurate predictions as the authors claim. 4. They go a step further and attempt to estimate the number of people who would benefit from removing 20% of the added sugars that are normally present in the diet. 5. One question is whether removal of excess calories of any type, such as starch or fat, would produce comparable benefit in reduction of fatty liver or coronary heart disease. In other words, is there something unique about added sugars compared to other micronutrients? 6. Is idea that if we want to reduce total caloric intake, added sugars would be the easiest target start with? 7. Are added sugars unique respect to fatty liver? Are you proposing that sugar is the preferred substrate hepatic de novo lipogenesis? 8. The cost of fatty liver must be trivial compared to that of coronary heart disease. 9. A direct link between fatty liver and coronary heart disease, or diabetes for that matter, is not so clear as suggested in this analysis. 10. It is interesting to speculate the magnitude of risk reduction for each morbid condition related to a given reduction in caloric intake. Certainly, every little bit helps. But to make a precise calculation of the relation between caloric intake and medical complications does not seem simple. This is because there's so much individual variation in response to a given change in caloric intake. 11. The assumption is made that if one reduces added sugar they will not be replaced other calories. Certainly, sugars are one nutrient that contribute to the obesity epidemic. But can we be sure that taking out sugar will not lead to the replacement other nutrients, e,g., fat? 12, If excess calories are considered to form of fat, would this not also contribute to fatty liver due to increased flux of free fatty acids into the liver? 13. This reviewer is impressed by the volume of data generated by

	the model employed. One can assume that if you put in certain assumptions the model will generate a set of data as shown. In this reviewer's opinion, the problem lies in the reliability of the assumptions, and that there are no compensatory changes secondary to dietary changes. Can you enlighten the reviewer on this point? 14. One question about this paper is whether it is too ambitious. It is difficult to review because of the complexity of the assumptions made. With this said, the reviewer must admit that this is an interesting exercise. However, I have the impression that you "have it in for sugar" and you do not adequately account for excesses in other nutrients leading to the obesity epidemic. Could you address this general impression? 15. An alternate view, which has been expressed by others, is that nutrients are equivalent and are not metabolically distinct with regards to the obesity epidemic. Several studies show that changing the percentage of fat in the diet, or the percentage carbohydrate, produces little change in body weight or metabolic responses. Regardless, I am in favor of reducing total caloric intake in overweight people, and if this can be done by curtailing civil sugars, that would be fine. I think this paper implicitly holds that sugars are uniquely pathogenic, compared to other nutrients; but I find little evidence from the literature to support this contention.

REVIEWER	Mosca, Antonella University Of Rome- Sapienza
REVIEW RETURNED	29-Nov-2016

GENERAL COMMENTS	in this work, the authors demonstrate that the costs of public spending were higher if the analysis was added to the obesity and T2D NAFLD and CHD, while the decrease of the incidence and prevalence of the disease is similar to the results of other models. All this to emphasize that we must reduce consumption of sugars to improve public health and the economy: 1. It should be explained better to the pathophysiological mechanism of NAFLD due to sugar intake, as well as in obesity and T2D. 2. In the introduction, they should illustrate the pathophysiology of NAFLD 3. They need to explain better the figure 1, changing the title 4. In the paragraph "added sugars", they should explain the role of sugar, especially fructose in the pathogenesis of NASH and metabolic syndrome. 5. They must explain the sugar limits not only the AHA but also the EFSA, and the difference between fructose and glucose in the account of the calories and the damage of organs. 6. Good the forecast model exhibited, considering the age, sex and ethnicity. Why in the discussion still has to be explained the difference between ethnic groups for T2D and NAFLD in the adult and children population.

	7. In the discussion goes exposed the role of the decrease in the consumption of sugars known in the literature on liver disease. 8. the authors have questioned instead a possible provision in the adolescent population?

REVIEWER	C. Ronald Kahn (with Samir Softic) Joslin Diabetes Center Boston, MA 02215
REVIEW RETURNED	30-Nov-2016

GENERAL COMMENTS	The manuscript by Vreman et al., reports on microsimulation model constructed to assess the health and economic benefits of reducing added sugar in diet by 20 and 50 percent. This model appears to be an improvement to previous models, since it includes morbidity and mortality associated with NAFLD, which is emerging as an important part of metabolic syndrome. Their results are in line with previous models of reduced sugar intake on health outcomes, but obviated costs and DALYs were higher, due to inclusion of NAFLD. Major Concerns: To someone who is not an expert in modeling, there appear to be two or three limitations of the study that need to be considered and discussed more fully. (It would also be important to have a review from a modeling expert). 1. First, the major mortality associated with progressive NAFLD is from Coronary Heart Disease (CHD) and not from liver cirrhosis. The authors need to provide more detailed description of how these two conditions relate and whether patients with NAFLD that died of CHD were included in CHD morbidity or non-disease related death. Also were patients with CHD that died from concomitant liver death due to progressive NAFLD counted as CHD deaths or non-disease related death. 2. A second limitation of the study is that the authors did not make predictions or discuss whether 20 or 50% reduction in any other source of calories would lead to larger or lesser improvements in health and economic benefits. In their introduction referring to the effects of fructose on hepatic de novo lipogenesis they point out that “This effect appears to be specific for sugar and independent of calories consumed or BMI.” However, these are highly linked, and how definitively they can be independently assessed in unclear. This needs more consideration and the authors should analyze/discuss whether improvements would be found if patients restricted their fat or protein intake by the same percent. 3. Along the same line, it is not clear if this model incorporates substitutions of the reduced sugar intake by increases in other food categories. The authors did acknowledge this in their discussion, but this is a potentially important limitation of the current study which needs consideration. Minor Concerns: 1. The authors need to more clearly acknowledge that while

	canonical thinking is that NAFLD progresses to NASH to cirrhosis, this is not necessary true in all cases, and some individuals may progress from NAFLD directly to cirrhosis. In addition, while cirrhosis is thought to be irreversible process, some forms of liver fibrosis, especially in children, may be reversible. 2. The authors predict that by 2035 obesity could decrease by 1 and 6 percent if there were 20 and 50% decreases in added sugar intake. Over the same period of time, the prevalence of steatosis is projected to decrease by 0.5 and 2 percent, respectively. This is a rather modest reduction in steatosis. Also the relationship between steatosis, i.e. triglyceride deposited in liver, and weight loss may be complex and not progressive, but have certain points of inflection or thresholds. There may also be hysteresis in these relationships, i.e., the effects of increasing carbohydrate may have different magnitude, kinetics and physiology than decreasing carbohydrate by a similar amount. For example, in one study, short-term carbohydrate overfeeding for 3 weeks increased liver fat by 27 %, while total body weight increased by only 2 %. Conversely, following 6 months of a hypocaloric diet, the same subjects lost 25 % of liver fat and 4 % of body weight (Sevastianova, et al. Effect of short term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. Am J Clin Nutr. 2012;96: 727–734.) The authors need to consider these possibilities in their projections.

REVIEWER	Wenrui Hao Penn State University, USA
REVIEW RETURNED	05-Feb-2017

GENERAL COMMENTS	I would like to recommend to accept this paper for publication.

REVIEWER	Gregory Nuel LPMA, UMR CNRS 7599, Université Pierre et Marie Curie, Sorbonne Universités, Paris, France
REVIEW RETURNED	08-Mar-2017

GENERAL COMMENTS	The purpose of the paper is to assess the public health and economic benefits of reducing the consumption of added sugar in the American population. The study considers a total of four correlated diseases: BMI (obesity), NAFLD (fatty liver), T2D (type 2 diabetes), CHD (coronary heart) and four covariates (age, sex, ethnicity and sugar consumption). Outcomes of interest include disease prevalence, direct costs of the disease (in 2015 USD) and patient impact (in disability-adjusted life-year). Two intervention scenarios are considered: one with 20% added sugar reduction, one with 50% added sugar (which roughly corresponds to the American Heart Association recommendation). In order to evaluate these two scenarios, the authors perform a simulated cohort of a total of n=22,400 invididuals or age 20+ at inclusion in 2015, and perform a micro simulation model over 20 year until 2035. The microsimulation model is a multi-state Markov chain which covariate dependent transition matrices are calibrated from an extensive literature study. The authors have carefully built

	and validated their model using sensitivity experiments for the parameters. The results of the study are presented/discussed in detail and basically show that reducing the sugar consumption could improve dramatically the public health and decrease economic costs. The objective of the paper are clearly written, as well as the results and discussion. The principle of the micro-simulation model is also rather well explained. However has two major issues that should be discussed/corrected by the authors prior to publication: M1) The model parameters are insufficiently described. M2) The competing risks in the multi-state model might not be taken in account. Here follow the detailed comments and suggestions for these two major issues. M1) The model parameters are insufficiently described. The model covariates (fixed over time) and states (evolving over time) should be distinguished described in detail as soon as possible. These informations are indeed present in the manuscript and its supplementary material but they should be presented along with the method. Covariates: age: 20, 21, 22, … , 84, 85+ sex: male, female ethnicity: hispanic, non-hispanic white, non-hispanic black sugar consumption: low consumption (<50g added sugar a day), high consumption (>=50g) States: BMI: healthy weight, over-weight, obese NAFLD: non-NAFLD, Hepatic steasis, NASH, Cirrhosis, HCC T2D: non-T2D, T2D CHD: non-CHD, CHD death: non disease-related death, T2D death, CHD death, Liver death Then covariates and tables used for each initial and transition distribution must be specified. Example: Covariates distribution: age (Supp Table 2), Sex (Supp Table 3), Ethnicity (Supp Table 4), Added Sugar consumption (Supp Table 9). Initial distributions: BMI: depends on sex, ethnicity and age [3 classes] => 18 free parameters (Supp Table 8) NAFLD: depends on ethnicity => 12 free parameters (Supp Table 5) T2D: depends on sex, ethnicity and age [7 classes] => 42 free parameters (Supp Table 7) CHD: depends on sex, ethnicity and age [7 classes] => 42 free parameters (Supp Table 6) Transitions: non-CHD -> CHD: baseline age-period incidence in Supp Table 12 + the following risk factors: overweight, obesity, T2D (unclear, see Figure 1 ? See Table 2 « risk factors »)

	non-T2D -> T2D: baseline age incidence in Supp Table 14 + the following risk factors: overweight as a factor (healthy weight as a reference) (unclear again, see Figure 1 and Table 2) and this for all transitions Moreover, the model used for the altering risk factors should be detailed. In survival, we would expect - hazard_[non-CHD -> CHD](t) = baseline x exp(alpha x 1(BMI=overweight) + beta x 1(BMI=obese) + gamma x 1(T2D=TD2)) which corresponds to a a proportional hazard model with BMI and T2D as factors, BMI=healthy weight and TD2=non-T2D taken as reference. Is it your model, and if not, what are you using exactly ? And why not using the ultra-standard proportional hazard model ? M2) The competing risks in the multi-state model might not be taken in account. The Markov model used in this paper is obviously the discretized version of a multi-state survival model (see putter2007tutorial for an introduction to multi-state survival models and willekens2014software for a review of software for micro-simulation). Although it would have been possible to perform this microsimulation using a proper continuous multi-state survival model, a year-discretized Markov version is indeed acceptable as long as annual incidence remain low (ex: ~1% max), but only if the incidence transition are correct. The problem of multi-state survival models is the fact that transitions events are mutually censored by the competing risks, and this has to be taken into account rigorously during the estimation. For example, it means that transition Non-CHD -> Non-disease-related death should be estimated using CHD events as a censoring. For relatively rare disease like cancer, it is common to neglect this point by simply assuming that the disease event is rare enough, but for common disease like CHD this censoring has to be taken into account. I suggest the authors to explain how they take into account the competing risks in their model. If, as I suspect, the literature and available data do not allow to take properly into account these competing risks, the discussion should at try to evaluate the qualitative impact on the results and mention it as a known limitation of the study. @article{putter2007tutorial, title={Tutorial in biostatistics: competing risks and multi-state models}, author={Putter, Hein and Fiocco, M and Geskus, RB}, journal={Statistics in medicine}, volume={26},

	number={11}, pages={2389--2430}, year={2007}, publisher={Wiley Online Library} } @article{willekens2014software, title={Software for multistate analysis}, author={Willekens, Frans and Putter, Hein}, journal={Demographic Research}, volume={31}, pages={381}, year={2014}, publisher={Max Planck Institut f{\"u}r Demografische Forschung} }

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Amedeo Lonardo, M.D.

Institution and Country
Azienda USL - Internal Medicine -NOCSAE - Baggiovara, Modena, Italy

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
GENERAL COMMENT
An interesting proof-of-concept study evaluating the benefit of a single, specific and theretically feasible dietary intervention.

1. Referencing should be improved and so are a couple of misconceptions regarding the relationship of NAFLD with the MetS.
-> We have revised the Introduction to make it clear that NAFLD travels with metabolic syndrome. Yki-Jarvinen (2014) has argued that NAFLD may be either a cause or a consequence of metabolic syndrome. However, as we demonstrate in our pediatric isocaloric fructose restriction study (Lustig 2016; Gugliucci 2016, new manuscript), we show that changes in DNL and liver fat predict changes in insulin sensitivity; therefore we believe that at least for a portion of the population that are heavy sugar consumers, NAFLD may be an intermediate between sugar consumption and the other diseases of metabolic syndrome.

2. The submission should be made more consistent by highlighting the pathogenic impact of simple sugars on epidemiology and pathogenesis of NAFLD.
-> We have expanded our Introduction to explain the role of added sugars in the various diseases of metabolic syndrome apart from its caloric value or its effects on adiposity. We have also expanded on the specific mechanism of fructose driving de novo lipogenesis (DNL) in NAFLD. Finally, we have expanded the discussion on our study of isocaloric fructose restriction in adolescents with NAFLD and metabolic syndrome, demonstrating that by reducing DNL, liver fat is also reduced, and metabolic parameter improve commenusurately with the reduction in liver fat. We include as supplementary material the manuscript that is currently under review at another journal so that our rationale for

focusing on NAFLD as a primary driver of chronic metabolic disease can be more fully appreciated.

3. Finally, a list of those obstacles preventing the limitation of added simple sugars should be added.
-> We have amended our Discussion to include various societal obstacles that will likely impede progress on removing added sugars from the diet. Some are societal, some are business-driven, and some are political.
SPECIFIC COMMENT

Introduction
4. This article specifically focuses on the economical benefits of limiting the consumption of added simple sugars. However, relevant literature regarding NAFLD-related costs is not cited and it should (Gastroenterology. 2008;134:85-94; Hepatology. 2016 Aug 20.
doi: 10.1002/hep.28785. [Epub ahead of print] PubMed PMID: 27543837).
-> We thank the reviewer for his insight. We have included the relevant points of the Younossi article in our Discussion. The Baumeister article is cited as a cost input.

5. Moreover, I found that the definition of NASH as a condition "with or without scarring" (Introduction, lines 13 and 14) should best adhere to the standard nomenclature (i.e. "fibrosis"). (Nat Rev Dis Primers. 2015 Dec 17;1:15080. doi: 10.1038/nrdp.2015.80; Int J Mol Sci. 2016 Jan 13;17(1). pii: E97. doi: 10.3390/ijms17010097).
-> We have amended our introduction to utilize standard nomenclature for the complications of NAFLD.

6. "Furthermore, NAFLD has been shown to regularly precede the metabolic syndrome, and scientists now argue that NAFLD is the hepatic manifestation of metabolic syndrome, and should be included in its definition.". This sentence includes an internal conflict (if " NAFLD regularly precedes the metabolic syndrome" then it is a precursor and not "the hepatic manifestation of metabolic syndrome"). Furthermore, it is not particularly updated in as much as it fails to render the complex and bi-directional relationship linking NAFLD with the metabolic syndrome. Accordingly, this statement should undergo full reworking based on recent views (Refs 10 and 24 + Ballestri S, Hepatol Res. 2016 Jan 19. doi:
10.1111/hepr.12656. [Epub ahead of print] PubMed PMID: 26785389. Ballestri S, J Gastroenterol Hepatol. 2016;31:936-44. doi: 10.1111/jgh.13264. PubMed PMID: 26667191.Dig Liver Dis. 2015;47:181-90) .
-> We have amended our Introduction to more fully explain the intertwined relationship between NAFLD and metabolic syndrome. In some, NAFLD may be consequence; while in others, it may be a cause. Because metabolic syndrome is likely not one disease process, NAFLD may be specifically causative in those with high sugar consumption, whereas in others it may represent collateral damage to the liver from hepatic uptake from visceral and/or peripheral fat. We have included the suggested literature.

7. This submission may be made more consistent by highlighting how the consumption of simple sugars impacts on epidemiology and pathogenesis of clinical and experimental NAFLD (Dig Dis Sci. 2016;61:1282-93. Gastroenterology. 2016;150:956-67. Hepatology. 2016;63:2032-43. Am J Clin Nutr. 2014;100:833-49. Hepatology. 2014 Nov;60:1581-92. Am J Pathol. 2014;184:1550-61. Eur J Clin Nutr. 2014;68:416-23.)

-> We have added a section to the discussion on how fructose (through DNL) can promote NAFLD, but that genetics and other nutritional factors likely play a role.

Discussion
8. Authors may be willing to discuss what obstacles prevent the limitation of added simple sugars.

-> We have elaborated on potential obstacles to reducing added sugars in the diet in the Discussion.

Reviewer: 2

Reviewer Name
Luc Tappy

Institution and Country
University of Lausanne
Switzerland

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
This paper uses a modelled cohort study to assess the impact of a reduced sugar consumption on health outcomes. Its originality is alledgedly to include non-alcoholic fatty liver disease in the model. I must admit that I am not familiar with modelling, and even less in modelled epidemiology. I nonetheless feel that this approach is not adequate for the aims stated by the authors.

1. Like for any model, one major critical step is to assign parameters to the variables to be studied (here, sugar intake, nafld, bmi,....). I would think that these parameters should be obtained from experimental data. This step is not presented here, and the reader cannot determine how parameters were determined or ehether they are likly to be valid. To the best of my knowledge, no strong data exist relating sugar and nafld....
-> It is a common modelling practice to use input data derived from published demographic or experimental data as available. We state our sources in Tables 1 and 2. The majority of our demographic assumptions come from two major US surveys, the National Health and Nutrition Survey (NHANES) and the National Health Interview Survey (NHIS). Other data concerning the transition probabilities, effect of interventions, etc were obtained from a variety of sources as listed in our Tables 1 and 2. We have more extensively discussed the link between sugar and NAFLD in the introduction.

2. The initial evaluation of the model should be that it fits the real world; ie: do the incidence of health outcomes related to sugar intake from this model fit those of other real cohort studies?
-> To our knowledge, the studies assessing taxing sugar on a population level (e.g. Mexico) have only yielded information on consumption; they have not yet assessed health benefits. However, there is abundant evidence linking sugar to health outcomes (see point 1). We now address this issue in the Discussion. Additionally, we do point out that the outcomes of this study fit other modelling studies.

3 The outcome presented look to me as little informative. If you build up a model predicting that sugar will favor nafld, and that both sugar and nafld favor cardiovascular diseases, then this model will always predict that sugar reduction improves health outcomes and reduces health costs.

Again, I am no specialist in prediction midels, and may have competely missed the aims of this article. If I did, it is likely that many other MDs reading BMJ will do the same, so a presentation of "models for the nerds" may be useful to include...
-> This is an interesting point. In part, the value of modeling exercises lies in connecting individual-level processes to population-level outcomes. We agree that when we input an effect on health into a model, we can expect to see this reflected in our results—but the model reveals the quantitative effect. The population model allows us to calculate how the effect of individual level risk and progression factors depend on overall prevalence, age structure, and competing risks, for example.

Thus, the goal of this study is not to show that there is an effect (as is already established through experimental studies) but the size of the effect. We have tried to make this more clear in our objective statement in the introduction.

Reviewer: 3

Reviewer Name
Scott M. Grundy

Institution and Country
UT Southwestern Medical Center, U.S.A.

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
1. This article proposes that nonalcoholic fatty liver disease (NAFLD) is a mediator of the metabolic syndrome, and it asks whether reducing sugar intake will decrease fatty liver and its consequences.
-> Yes. We have stressed this point in both the Introduction and Discussion.

2. In the view of this reviewer, it is uncertain whether the metabolic syndrome is mediated by fatty liver, or whether it is but one manifestation of nutrient overload but not directly in the causal link with metabolic syndrome. The authors might want to address this question.
-> As per Reviewers 1 and 2, we have elaborated this issue in the Introduction.

3. The authors constructed a model in which they estimated that a 20% reduction in intake of added sugars will reduce fatty liver, cirrhosis, metabolic syndrome, and coronary heart disease. This appears to be an ambitious model which includes many factors. The question is whether such a model can make accurate predictions as the authors claim.
-> We performed several validation steps (internal and external validation) and performed sensitivity analysis. We are confident that we can make predictions (with certain statistical limits).

4. They go a step further and attempt to estimate the number of people who would benefit from removing 20% of the added sugars that are normally present in the diet.
-> Correct.

5. One question is whether removal of excess calories of any type, such as starch or fat, would produce comparable benefit in reduction of fatty liver or coronary heart disease. In other words, is there something unique about added sugars compared to other micronutrients?
-> In the introduction and the discussion we have more extensively elaborated on this issue.

6. Is idea that if we want to reduce total caloric intake, added sugars would be the easiest target start with?
-> There is no question that, aside from added salt, added sugars would be the easiest component of the diet to manipulate on a population basis. However, this is not the point of the article. Our goal was to assess cost savings if added sugars were to be reduced.

7. Are added sugars unique respect to fatty liver? Are you proposing that sugar is the preferred substrate hepatic de novo lipogenesis?

-> There are four components of the diet that specifically drive the development of NAFLD (Lustig et al., Pediatrics 2012). 1) Trans-fats. The trans double bond prevents oxidation, and they precipitate in the liver. But trans-fats are now off the GRAS list, and so they are coming down. 2) Branched chain amino acids (leucine, isoleucine, valine). These are deamidated in the liver, get turned into alpha-ketoglutarate, which then enter the TCA cycle, overwhelming it, and so the liver has no choice but to turn the excess into liver fat. 3) Alcohol. But children don't drink alcohol and still get NAFLD & obesity. 4) Fructose. And that is the component that has increased 25-fold in the last century, and the component that children are exposed to.

8. The cost of fatty liver must be trivial compared to that of coronary heart disease.
-> Yes. This can be seen in table 1 and also in the results table 4.

9. A direct link between fatty liver and coronary heart disease, or diabetes for that matter, is not so clear as suggested in this analysis.
-> There are several studies in the literature that demonstrate the association between NAFLD, diabetes, and heart disease. We have highlighted those studies in the Introduction.

10. It is interesting to speculate the magnitude of risk reduction for each morbid condition related to a given reduction in caloric intake. Certainly, every little bit helps. But to make a precise calculation of the relation between caloric intake and medical complications does not seem simple. This is because there's so much individual variation in response to a given change in caloric intake.
-> True, and it is likely that specific subgroups might preferentially benefit, but with a microsimulation representing the complete US population, we hope to divert such individual variation.

11. The assumption is made that if one reduces added sugar they will not be replaced other calories. Certainly, sugars are one nutrient that contribute to the obesity epidemic. But can we be sure that taking out sugar will not lead to the replacement other nutrients, e,g., fat?
-> Yes, but the relation stated is one that is irrespective from calories, as sugar has direct detrimental effects due to its unique metabolism in the liver, driving NAFLD. Furthermore, while the issue of caloric compensation has not been settled, there are studies that do not demonstrate replacement by other nutrients after sugar reduction. We have added this to the Discussion.

12, If excess calories are considered to form of fat, would this not also contribute to fatty liver due to increased flux of free fatty acids into the liver?

-> Dietary fat is handled differently. It is made up of all different types of fatty acids (saturated, monounsaturated, polyunsaturated), it is absorbed from the gut, packaged into chylomicrons, and enter the liver, where they are unbundled and packaged with ApoB to be secreted into the circulation as LDL. Rather, sugar is converted to palmitate and packed with ApoB100 to form VLDL. While at any moment intrahepatic lipid is a composite of both pathways, isotope studies show that only 15% of intrahepatic fat comes from dietary sources (Donnelly et al. J Clin Invest 115:1343-1351, 2005). Furthermore, it appears that newly formed fat will more likely precipitate as an intrahepatic lipid droplet. Otherwise people on low-carb high-fat diets would get NAFLD; yet such a diet is one way to improve NAFLD (Kirk et al. Gastroenterology 136:1552-1560, 2009; Perito et al. Curr Opin Gastroenterol 29:170-176, 2013). Explaining this effect is beyond the scope of this paper, and so we have not included this point in the Discussion.

13. This reviewer is impressed by the volume of data generated by the model employed. One can assume that if you put in certain assumptions the model will generate a set of data as shown. In this reviewer's opinion, the problem lies in the reliability of the assumptions, and that there are no compensatory changes secondary to dietary changes. Can you enlighten the reviewer on this point?

-> Unfortunately, research investigating the compensation of dietary changes was not sufficient to include it in our analysis. However, the stated relation between sugar and health outcomes is also irrespective of calories consumed. Though we do agree with the reviewer that the exclusion of other dietary element is a limitation, we have argued in the discussion that this would likely have a minor impact on the results of the mode, because the excess consumption of sugars overshadows effects of other dietary elements in such individuals.

14. One question about this paper is whether it is too ambitious. It is difficult to review because of the complexity of the assumptions made. With this said, the reviewer must admit that this is an interesting exercise. However, I have the impression that you "have it in for sugar" and you do not adequately account for excesses in other nutrients leading to the obesity epidemic. Could you address this general impression?

-> We do acknowledge that sugar is of major concern in this paper, and other nutrients are considered less relevant. However, we do believe this is justified because the excess consumption of added sugar in the US is not observed on a similar scale (anymore; e.g. trans fat) for other nutrients and recent research has highlighted that sugar is a main driver for the metabolic syndrome epidemic. We discuss why added sugar is of greater concern more thoroughly in the Introduction.

15. An alternate view, which has been expressed by others, is that nutrients are equivalent and are not metabolically distinct with regards to the obesity epidemic. Several studies show that changing the percentage of fat in the diet, or the percentage carbohydrate, produces little change in body weight or metabolic responses. Regardless, I am in favor of reducing total caloric intake in overweight people, and if this can be done by curtailing civil sugars, that would be fine. I think this paper implicitly holds that sugars are uniquely pathogenic, compared to other nutrients; but I find little evidence from the literature to support this contention.

-> We don’t completely agree, as is explained in the manuscript. Where those calories come from determines where they go in the body, and which diseases they generate. Indeed many investigators have made similar arguments (e.g. David Ludwig, Sonia Caprio, Frank Hu, Walt Willett). As to the reviewers comment that “changing the percentage of fat in the diet, or the percentage carbohydrate”, one of the problems with these studies is that they equate sugar with other carbohydrate, which is a mistake based on its unique metabolism. While we acknowledge that many investigators are heavily invested in the “calorie hypothesis” and that this is not settled science, based on our previous work we feel justified to examine added dietary sugar as a cause of disease, and its reduction as a mode of therapy.

Reviewer: 4

Reviewer Name

Antonella Mosca

Institution and Country

University Of Rome- Sapienza

Please state any competing interests or state ‘None declared’:
none declared

Please leave your comments for the authors below
in this work, the authors demonstrate that the costs of public spending were higher if the analysis was added to the obesity and T2D NAFLD and CHD, while the decrease of the incidence and prevalence of the disease is similar to the results of other models. All this to emphasize that we must reduce consumption of sugars to improve public health and the economy:

1. It should be explained better to the pathophysiological mechanism of NAFLD due to sugar intake, as well as in obesity and T2D.
-> Agreed. This has been raised by several of the reviewers. We have altered our Introduction accordingly.

2. In the introduction, they should illustrate the pathophysiology of NAFLD
-> As per Reviewer 1, we have revised our Introduction to discuss NAFLD, and the role added sugars play in its pathogenesis.

3. They need to explain better the figure 1, changing the title
-> This figure has been changed. The title is more explanatory and we have elaborated on its function.

4. In the paragraph "added sugars", they should explain the role of sugar, especially fructose in the pathogenesis of NASH and metabolic syndrome.

-> Again, we have more fully elucidated the role of fructose in the pathogenesis of metabolic syndrome and NAFLD.

5. They must explain the sugar limits not only the AHA but also the EFSA, and the difference between fructose and glucose in the account of the calories and the damage of organs.

-> This has been included in the introduction.

6. Good the forecast model exhibited, considering the age, sex and ethnicity. Why in the discussion still has to be explained the difference between ethnic groups for T2D and NAFLD in the adult and children population.

-> Children are not included in the model (age 20+). Differences in costs and health outcomes between ethnic groups is part of additional analyses in follow-up research and therefore not included in this paper. We have included the mention of children in the Discussion.

7. In the discussion goes exposed the role of the decrease in the consumption of sugars known in the literature on liver disease.

-> We have elaborated on the role of added sugars in both NAFLD and the other diseases of metabolic syndrome in the Introduction.

8. the authors have questioned instead a possible provision in the adolescent population?

-> The adolescent population is excluded in this model, we have more explicitly made this clear in the Discussion.

Reviewer: 5

Reviewer Name
C. Ronald Kahn (with Samir Softic)

Institution and Country
Joslin Diabetes Center
Boston, MA 02215

Please state any competing interests or state ‘None declared’:
None

Please leave your comments for the authors below
The manuscript by Vreman et al., reports on microsimulation model constructed to assess the health and economic benefits of reducing added sugar in diet by 20 and 50 percent. This model appears to be an improvement to previous models, since it includes morbidity and mortality associated with NAFLD, which is emerging as an important part of metabolic syndrome. Their results are in line with previous models of reduced sugar intake on health outcomes, but obviated costs and DALYs were higher, due to inclusion of NAFLD.

Major Concerns:

To someone who is not an expert in modeling, there appear to be two or three limitations of the study that need to be considered and discussed more fully. (It would also be important to have a review from a modeling expert).

1. First, the major mortality associated with progressive NAFLD is from Coronary Heart Disease (CHD) and not from liver cirrhosis. The authors need to provide more detailed description of how these two conditions relate and whether patients with NAFLD that died of CHD were included in CHD morbidity or non-disease related death. Also were patients with CHD that died from concomitant liver death due to progressive NAFLD counted as CHD deaths or non-disease related death.

-> This is a good point. The way it worked is that disease chains were updated consecutively. So death is assigned to the chain which was updated that instance (non-disease related death is also a chain). The order of chain updates was randomized to ensure the fair distribution of disease related deaths. We have explained this more thoroughly.

2. A second limitation of the study is that the authors did not make predictions or discuss whether 20 or 50% reduction in any other source of calories would lead to larger or lesser improvements in health and economic benefits. In their introduction referring to the effects of fructose on hepatic de novo lipogenesis they point out that “This effect appears to be specific for sugar and independent of calories consumed or BMI.” However, these are highly linked, and how definitively they can be independently assessed in unclear. This needs more consideration and the authors should analyze/discuss whether improvements would be found if patients restricted their fat or protein intake by the same percent.

-> We have more extensively elaborated on the effects of added sugars in the introduction. The effects of uptake of other nutrients is more thoroughly discussed in the introduction and the discussion

3. Along the same line, it is not clear if this model incorporates substitutions of the reduced sugar intake by increases in other food categories. The authors did acknowledge this in their discussion, but this is a potentially important limitation of the current study which needs consideration.

-> Similar to Reviewer 3's concern, we have mentioned the issue of caloric compensation. Clinically, we see unopposed weight loss in children after improvement of insulin sensitivity, when we remove the added sugar from their diets in the UCSF Pediatric Obesity Clinic.

Minor Concerns:

1. The authors need to more clearly acknowledge that while canonical thinking is that NAFLD progresses to NASH to cirrhosis, this is not necessary true in all cases, and some individuals may progress from NAFLD directly to cirrhosis. In addition, while cirrhosis is thought to be an irreversible process, some forms of liver fibrosis, especially in children, may be reversible.

-> Agreed. The reversibility is now acknowledged in the discussion. However, it should be noted that children are not incorporated in the model. Also, progression directly from healthy to NASH is possible, and from steatosis directly to cirrhosis as well (see table 2).

2. The authors predict that by 2035 obesity could decrease by 1 and 6 percent if there were 20 and 50% decreases in added sugar intake. Over the same period of time, the prevalence of steatosis is projected to decrease by 0.5 and 2 percent, respectively. This is a rather modest reduction in steatosis. Also the relationship between steatosis, i.e. triglyceride deposited in liver, and weight loss may be complex and not progressive, but have certain points of inflection or thresholds. There may also be hysteresis in these relationships, i.e., the effects of increasing carbohydrate may have different magnitude, kinetics and physiology than decreasing carbohydrate by a similar amount. For example, in one study, short-term carbohydrate overfeeding for 3 weeks increased liver fat by 27 %, while total body weight increased by only 2 %. Conversely, following 6 months of a hypocaloric diet, the same subjects lost 25 % of liver fat and 4 % of body weight (Sevastianova, et al. Effect of short term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. Am J Clin Nutr. 2012;96: 727–734.) The authors need to consider these possibilities in their projections.

-> We agree. This is a nice study to elaborate that carbohydrates can directly impact liver fat without significantly changing body weight. We have included it the suggested article.

BTW, our colleague Jean-Marc Schwarz showed that isocaloric fructose-for-glucose in adults with no change in weight resulted in 38% increase in liver fat in just 2 weeks (Schwarz, J.M., Noworolski, S.M., Wen, M.J., Dyachenko, A., Prior, J.L., Weinberg, M.E., Herraiz, L.A., Tai, V.W., Bergeron, N., Bersot, T.P., et al. (2015). Effect of a high-fructose weight-maintaining diet on lipogenesis and liver fat. J Clin Endocrinol Metab 100, 2434-2442.).

Reviewer: 6

Reviewer Name
Wenrui Hao

Institution and Country
Penn State University, USA

Please state any competing interests or state 'None declared':
None

Please leave your comments for the authors below
I would like to recommend to accept this paper for publication.

-> Thank you.

Reviewer: 7

Reviewer Name
Gregory Nuel

Institution and Country
LPMA, UMR CNRS 7599,
Université Pierre et Marie Curie,
Sorbonne Universités,
Paris, France

Please state any competing interests or state ‘None declared’:
none declared

Please leave your comments for the authors below
The purpose of the paper is to assess the public health and economic benefits of reducing the consumption of added sugar in the American population. The study considers a total of four correlated diseases: BMI (obesity), NAFLD (fatty liver), T2D (type 2 diabetes), CHD (coronary heart) and four covariates (age, sex, ethnicity and sugar consumption). Outcomes of interest include disease prevalence, direct costs of the disease (in 2015 USD) and patient impact (in disability-adjusted life-year). Two intervention scenarios are considered: one with 20% added sugar reduction, one with 50% added sugar (which roughly corresponds to the American Heart Association recommendation).

In order to evaluate these two scenarios, the authors perform a simulated cohort of a total of n=22,400 invididuals or age 20+ at inclusion in 2015, and perform a micro simulation model over 20 year until 2035. The microsimulation model is a multi-state Markov chain which covariate dependent transition matrices are calibrated from an extensive literature study. The authors have carefully built and validated their model using sensitivity experiments for the parameters. The results of the study are presented/discussed in detail and basically show that reducing the sugar consumption could improve dramatically the public health and decrease economic costs.

The objective of the paper are clearly written, as well as the results and discussion. The principle of the micro-simulation model is also rather well explained. However has two major issues that should be discussed/corrected by the authors prior to publication:

M1) The model parameters are insufficiently described.
M2) The competing risks in the multi-state model might not be taken in account.

->We have elaborated on these issues below.

Here follow the detailed comments and suggestions for these two major issues.

M1) The model parameters are insufficiently described.

The model covariates (fixed over time) and states (evolving over time) should be distinguished described in detail as soon as possible. These informations are indeed present in the manuscript and its supplementary material but they should be presented along with the method.

Covariates:
age: 20, 21, 22, … , 84, 85+
sex: male, female
ethnicity: hispanic, non-hispanic white, non-hispanic black
sugar consumption: low consumption (<50g added sugar a day), high consumption (>=50g)

States:
BMI: healthy weight, over-weight, obese
NAFLD: non-NAFLD, Hepatic steasis, NASH, Cirrhosis, HCC
T2D: non-T2D, T2D
CHD: non-CHD, CHD
death: non disease-related death, T2D death, CHD death, Liver death

Then covariates and tables used for each initial and transition distribution must be specified. Example:

Covariates distribution: age (Supp Table 2), Sex (Supp Table 3), Ethnicity (Supp Table 4), Added Sugar consumption (Supp Table 9).

Initial distributions:
BMI: depends on sex, ethnicity and age [3 classes] => 18 free parameters (Supp Table 8)
NAFLD: depends on ethnicity => 12 free parameters (Supp Table 5)
T2D: depends on sex, ethnicity and age [7 classes] => 42 free parameters (Supp Table 7)
CHD: depends on sex, ethnicity and age [7 classes] => 42 free parameters (Supp Table 6)

Transitions:
non-CHD -> CHD: baseline age-period incidence in Supp Table 12 + the following risk factors: overweight, obesity, T2D (unclear, see Figure 1 ? See Table 2 « risk factors »)
non-T2D -> T2D: baseline age incidence in Supp Table 14 + the following risk factors: overweight as a factor (healthy weight as a reference) (unclear again, see Figure 1 and Table 2)
and this for all transitions

-> It is a fair point that we did not include this in the paper. As is stated by the reviewer, we did include it in the supplementary materials so all the information is available. Our consideration to not extensively discuss it in the article was that we thought BMJ Open readers would not be particularly interested in all the specifics considering the model parameters, besides the overview provided in figure 1. However, considering this reviewers comment, we have included it as was suggested.

Moreover, the model used for the altering risk factors should be detailed.

In survival, we would expect
- hazard_[non-CHD -> CHD](t) = baseline x exp(alpha x 1(BMI=overweight) + beta x 1(BMI=obese) + gamma x 1(T2D=TD2))
which corresponds to a a proportional hazard model with BMI and T2D as factors, BMI=healthy weight and TD2=non-T2D taken as reference.

Is it your model, and if not, what are you using exactly ? And why not using the ultra-standard proportional hazard model ?

-> For our discrete time Markov chains, the fundamental computations are based on the transition probability matrix (conceptually); with 3x6x3x3=162 states, the matrix has 162x162=26244 elements and was not explicitly written (but is implicit in the computational algorithm—the goal was to efficiently simulate without writing such a matrix). Each individual has a specific probability, given their

obesity/liver/diabetes/CHD status, of undergoing a transition to another state in the model. In some cases, we converted probabilities to odds before multiplying by odds ratios (and then converted back to the probability scale) to fill out the appropriate transition probabilities from one state to another. Similar formulas were used when relative hazards were available.

M2) The competing risks in the multi-state model might not be taken in account.

The Markov model used in this paper is obviously the discretized version of a multi-state survival model (see putter2007tutorial for an introduction to multi-state survival models and willekens2014software for a review of software for micro-simulation).

Although it would have been possible to perform this microsimulation using a proper continuous multi-state survival model, a year-discretized Markov version is indeed acceptable as long as annual incidence remain low (ex: ~1% max), but only if the incidence transition are correct.

The problem of multi-state survival models is the fact that transitions events are mutually censored by the competing risks, and this has to be taken into account rigorously during the estimation.

For example, it means that transition Non-CHD -> Non-disease-related death should be estimated using CHD events as a censoring. For relatively rare disease like cancer, it is common to neglect this point by simply assuming that the disease event is rare enough, but for common disease like CHD this censoring has to be taken into account.

I suggest the authors to explain how they take into account the competing risks in their model. If, as I suspect, the literature and available data do not allow to take properly into account these competing risks, the discussion should at try to evaluate the qualitative impact on the results and mention it as a known limitation of the study.

-> We thank the reviewer for this comment, and apologize for any unclarity.
Our model is framed directly as a discrete time model. For simulation given a fixed set of parameters, the discrete time chain can simply be simulated for any transition probability matrix, the only requirement being that the matrices be stochastic matrices (in the usual sense of the column sums being 1). However, we agree with the reviewer that when looking at competing risks, the low incidence rate is desirable.
We in fact chose the multistate (event history) framework in part because it permits a proper modeling of competing risks. Each individual has a state-dependent risk of mortality due to causes in the model, as well as a competing risk of mortality due to other causes (e.g. stroke, traffic accidents, and so on). These competing risks may be age and risk-factor dependent, and are explicitly included. Because the risks of mortality due to modelled causes and the risks of mortality due to other causes are correlated to some extent, the benefits of prevention of mortality due to liver disease, diabetes, and CHD are attenuated to the extent that individuals who would have died of modelled causes are likely to die of other causes. Our model was explicitly designed to reflect this in a prospective way. Additionally, updates of chains is randomised to ensure fair chances of progression to death states.

VERSION 2 – REVIEW

REVIEWER	Amedeo Lonardo, M.D. AOU Modena, Italy
REVIEW RETURNED	19-Apr-2017

GENERAL COMMENTS	Authors have satisfactorily addressed the points raised by this Referee.

REVIEWER	Mosca Antonella Hospital Bambino Gesù, Rome, Italy
REVIEW RETURNED	07-May-2017

GENERAL COMMENTS	In the manuscript Vreman et al. Have tried to demonstrate how reducing sugar consumption helps prevent diseases such as NAFLD and decreases public spending. 1. In the introduction cited the limits of added sugars for adults, teenagers should also be referred, as it is referred to an average consumption of 90 grams per day. 2. The methods are difficult to understand, should be simplified. Work is drawn on a very large population stratified by age, sex, and ethnicity. All chains for NAFLD, T2D, BMI and CHD were considered. Maybe for the BMI would it be useful to do the opposite, starting from obesity? Or simplifying, inserting the BMI with obesity and overweight as a NAFLD chain, T2De CHD. 3. Explain the limit of 50 for the consumption of sugars. Enter explanation or reference. 4. The number of tables is too high and difficult to evaluate, while the figures are well done, but it would be useful to delete some tables by trying to explain them better in the text. 5. Because differences have been considered by gender and ethnicity, the NAFLD is more frequent in Hispanics, while the same differences should be explained for T2D and CHD. 6. It is also unclear how they calculated the consumption of sugars, should be explained in the results. 7. The discussion should better explain the results obtained in order to simplify the reading of results to clinicians. It seems that reducing sugar consumption helps reduce spending on T2D, CHD and obesity, but is minimal in NAFLD. Explain why. Same results for mortality and morbidity by looking at individual illnesses, explain.

REVIEWER	Gregory Nuel LPMA, CNRS 7599, UPMC, Paris, France
REVIEW RETURNED	17-May-2017

GENERAL COMMENTS	In my previous review, I was pointing out two main issues that have been partially taken into account in the present revised version: M1) The model parameters are insufficiently described. M2) The competing risks in the multi-state model might not be taken in account. Despite the clear progress in the new version, I think that both these

	issues still need some additional (however minor) clarifications. M1) The model parameters are insufficiently described. The presentation is now much cleared and detailed. The only problem that remains is the fact that the model used for transition are still not clearly explained. Of course, as stated by the authors in their answer, no one is really interested by their virtual « 162x162=26244 elements » transition matrix. It is, however, critical to elaborate a little more on the model used. In particular, how exactly the OR of Table 2 are used to alter the baseline transitions. An explicit explanation and a couple of examples would obviously be a useful addition. M2) The competing risks in the multi-state model might not be taken in account. You basically explain that you choose the discrete framework from Day 1 which is clearly acceptable. Since you calibrated/validated, at least partially, your model using real data, we can reasonably expect your model to take into account competing risk at the global level. However, as stated in the manuscript, most of your baseline transition probabilities (see Table 2) come from literature sources. It is highly unlikely that these sources estimated incidences in the competing context of your model. This issue could be a limitation of your study and as such should be pointed out and discussed.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 4

Reviewer Name
Mosca Antonella

Institution and Country
Hospital Bambino Gesù, Rome, Italy

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below

In the manuscript Vreman et al. Have tried to demonstrate how reducing sugar consumption helps prevent diseases such as NAFLD and decreases public spending.
1. In the introduction cited the limits of added sugars for adults, teenagers should also be referred, as it is referred to an average consumption of 90 grams per day.
-> This is a good point. We have added this in the introduction under ‘added sugars’.

2. The methods are difficult to understand, should be simplified. Work is drawn on a very large population stratified by age, sex, and ethnicity. All chains for NAFLD, T2D, BMI and CHD were considered.
Maybe for the BMI would it be useful to do the opposite, starting from obesity? Or simplifying, inserting the BMI with obesity and overweight as a NAFLD chain, T2D, or, CHD.

-> This comment partly interferes with other reviewers' previous comments about the description of our methodology. We have rewritten the 'Model Structure' section completely according to those previous comments. Are there specific paragraphs that need further clarification?
Considering the suggested simplification, it seems proposed that we incorporate the BMI chain with other (eg NAFLD) chains to create mutually exclusive states representing multiple independent pathophysiologic processes, i.e. a version of classic Markov structure. Because we include several pathophysiologic processes, this would result in over 300 states, which makes the model even harder to understand (and to handle computationally). We have therefore chosen to remain with the microsimulation model. Integrating some chains (e.g. BMI and NAFLD) while leaving others separated is impractical and confusing.

3. Explain the limit of 50 for the consumption of sugars. Enter explanation or reference.
-> We have added this in the introduction under 'added sugars' with references.

4. The number of tables is too high and difficult to evaluate, while the figures are well done, but it would be useful to delete some tables by trying to explain them better in the text.
-> Thank you for your comment on the figures. Considering the tables, do you have specific suggestions on which ones should be deleted? We presume you are referring to results table 3, 4 or 5? Or would you argue that the tables on input parameters (1 and 2) belong in the supplementary material? Of course we could describe either one of these tables as text, but this would result in an additional increase in word count. We are unsure whether converting tables to text would actually lead to these data being interpreted more easily. We propose no change.

5. Because differences have been considered by gender and ethnicity, the NAFLD is more frequent in Hispanics, while the same differences should be explained for T2D and CHD.
-> We completely agree with this comment. However, elucidating differences in gender and ethnicity is the subject of further research, and therefore not included in this manuscript We have therefore chosen not to report on the differences in NAFLD amongst different ethnic groups in this manuscript (though the reviewer rightly notes that they will likely be present).

6. It is also unclear how they calculated the consumption of sugars, should be explained in the results.
-> We have now included an explanation in the Methods section under 'Model Structure', including the reference to the analytic guidelines of NHANES so readers can easily find the full methodology.

7. The discussion should better explain the results obtained in order to simplify the reading of results to clinicians. It seems that reducing sugar consumption helps reduce spending on T2D, CHD and obesity, but is minimal in NAFLD. Explain why. Same results for mortality and morbidity by looking at individual illnesses, explain.
-> We have now included an elaboration of the cost dichotomies between diseases in the Discussion.

Reviewer: 7

Reviewer Name
Gregory Nuel

Institution and Country
LPMA, CNRS 7599, UPMC, Paris, France

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
In my previous review, I was pointing out two main issues that have been partially taken into account in the present revised version:

M1) The model parameters are insufficiently described.
M2) The competing risks in the multi-state model might not be taken in account.

Despite the clear progress in the new version, I think that both these issues still need some additional (however minor) clarifications.

M1) The model parameters are insufficiently described.

The presentation is now much cleared and detailed. The only problem that remains is the fact that the model used for transition are still not clearly explained.

Of course, as stated by the authors in their answer, no one is really interested by their virtual « 162x162=26244 elements » transition matrix. It is, however, critical to elaborate a little more on the model used. In particular, how exactly the OR of Table 2 are used to alter the baseline transitions. An explicit explanation and a couple of examples would obviously be a useful addition.
-> We have now included an example in the ‘Model Structure’ section.

M2) The competing risks in the multi-state model might not be taken in account.

You basically explain that you choose the discrete framework from Day 1 which is clearly acceptable. Since you calibrated/validated, at least partially, your model using real data, we can reasonably expect your model to take into account competing risk at the global level.

However, as stated in the manuscript, most of your baseline transition probabilities (see Table 2) come from literature sources. It is highly unlikely that these sources estimated incidences in the competing context of your model. This issue could be a limitation of your study and as such should be pointed out and discussed.
-> We agree with this point and have included this in the Discussion.

VERSION 3 – REVIEW

REVIEWER	Grégory Nuel CNRS 7599, LPMA, UPMC, Paris, France
REVIEW RETURNED	01-Jun-2017

GENERAL COMMENTS	I am basically satisfied by the last version of the manuscript.

VERSION 3 – AUTHOR RESPONSE

Reviewer Name
Grégory Nuel

Institution and Country
CNRS 7599, LPMA, UPMC, Paris, France

Please state any competing interests or state ‘None declared’:
None declared.

Please leave your comments for the authors below
I am basically satisfied by the last version of the manuscript.
-> Thank you.