PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Potential benefits of Healthy Food and Lifestyle Policies for Reducing Coronary Heart Disease Mortality in Turkish Adults by 2025: A Modelling Study
AUTHORS	Sahan, Ceyda; Sozmen, Kaan; Unal, Belgin; O'Flaherty, Martin; Critchley, Julia

VERSION 1 - REVIEW

REVIEWER	Takeki Suzuki, MD, PhD University of Mississippi Medical Center
REVIEW RETURNED	20-Mar-2016

GENERAL COMMENTS	Sahan and colleagues investigated potential benefits of healthy food and lifestyles policies for reducing coronary heart disease mortality in Turkish adults in 2025. The study used a modelling approach. The authors estimated that only modest risk factor changes in salt saturated fat/unsaturated fats and F&V intake could prevent 16,000 CHD deaths in 2025. The largest contribution came from salt intake (15,265 fewer deaths), energy from saturated fat (7690 fewer death), and increase in F&V consumption (9095 fewer deaths). They concluded that implementation of population based, multisectoral interventions to reduce salt and saturated fat consumption and increase F&V consumption should be scaled up in Turkey. Major comments: 1. These risk/protective factors included in the study (physical activity, dietary salt, saturated fat intakes, mean BMI levels, diabetes prevalence, and fruit-vegetable consumptions) are highly interrelated. For example, physical activity and fat intakes would be associated with BMI and diabetes prevalence. How did the authors evaluate these factors? Did they evaluate for interactions among these factors? Minor comments: 1. In Page 2, the first bullet point: a cumulative adjustment …. was maden. Is 'maden' typo? 2. Fruit-vegetable consumptions are not risk factors for CHD. Would suggest adding some words to explain that F&V consumptions are protective factors, not risk factors. 3. Curious to know if results would be different if stroke is added as one of the cardiovascular diseases in addition to CHD.

REVIEWER	Pamela Coxson, PhD, Mathematics Specialist University of California San Francisco USA
REVIEW RETURNED	21-Mar-2016

GENERAL COMMENTS	This manuscript describes an application of the IMPACT model, a well-established approach for explaining the effect of observed or projected changes in risk factors for coronary heart disease (CHD) on mortality from CHD based on national data in a wide range of countries, using it to look at the potential benefits of dietary and lifestyle changes that are proposed as feasible public policy objectives in Turkey. The use of modeled projections of population-wide benefits of national public policy goals is a valuable contribution that can inform the discourse among policy-makers, legislators, and the general public. The model parameters for this study are based on contemporary Turkish national and regional sources and the projected policy objectives are appropriate to the Turkish situation, which includes very high salt intake (15g/day) as well as BMI and diabetes increases in line with worldwide trends. Specific issues that should be addressed: 1. Estimating future CHD mortality to 2025 (p. 4). Mortality benefits are reported based on two alternative assumptions about background CHD mortality: a) no change in CHD mortality 2008-2025 except as modeled for the projected changes in diet and lifestyle; and b) a background trend of declining CHD mortality based on historical trends. The results from these two scenarios are presented in parallel in the manuscript, but only the larger effects from the no change scenario are listed in the abstract. If there is a strong rationale for assuming one of these scenarios is more likely, then the other scenario should be presented as a secondary result or as a sensitivity analysis. Otherwise, it would be better to present the more conservative outcome or the range of the two (which is substantially greater than the multivariate sensitivity “95% credible” ranges currently presented). 2. Effect of risk factor changes on CHD mortality (pp. 5 and 33-35). Based on the Table 5-10 footnotes, risk factor effects were not fully adjusted for the multivariate relationships among them. For example, BMI effects were not adjusted for diabetes, the diabetes effect was not adjusted for lipids, blood pressure, and BMI and physical activity effects were not adjusted for blood pressure and cholesterol. Without these multivariate adjustments, the combined effects are likely somewhat overstated. If this cannot be corrected, it should be mentioned as a limitation. 3. Cumulative adjustment for risk factor changes done simultaneously (p. 6). It is not clear how the mortality effect sizes were adjusted to account for the simultaneous implementation of risk factor changes. The formula shown on page 6, Cumulative effect = 1-((1-a)*(1-b)*(1-c)*…(1-n)) is incorrect (n = 6, so the last factor is -5). Presumably, the factors are intended to be risk factor specific relative risks so that the formula would represent the cumulative effect of the other 6 risk factors (or should it be all 7?). This process should be explained clearly in the text and in full detail with an example in the supplementary material. 4. Scenario design BMI (p.7). BMI increases of 1.4 (ref. 21) or 0.68 (ref 38) are cited as trends expected by 2025, and the modest (decrease of 0.7) and ideal (decrease of 1.4) are chosen presumably to counter those trends. Are the expected increases due primarily to a change in the age-distribution? If not, are these trends taken into

	account in calculating the expected CHD mortality for 2025 (before the calculation of the policy benefits?). Could this trend (along with increases in diabetes) result in a 3rd CHD mortality scenario with increasing rather than steady CHD mortality? This needs clarification and requires a nuanced discussion (urgency of addressing a trend that threatens to worsen health outcomes, as well as working to accelerate positive trends in salt, smoking, etc). 5. Results (p.9). The list (a. through g.) of CHD mortality benefits attributed to individual risk reduction goals gives the numbers of deaths prevented or postponed, but states “fewer” deaths (“fewer” should be deleted in each item).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Takeki Suzuki, MD, PhD
Institution and Country: University of Mississippi Medical Center, USA

Major comments:
C3- These risk/protective factors included in the study (physical activity, dietary salt, saturated fat intakes, mean BMI levels, diabetes prevalence, and fruit-vegetable consumptions) are highly interrelated. For example, physical activity and fat intakes would be associated with BMI and diabetes prevalence. How did the authors evaluate these factors? Did they evaluate for interactions among these factors?
A3- Thank you for your comment. We added some explanation in strengths and limitations section of the paper as below:
"The risk/protective factors which included in the study (physical inactivity, dietary salt, saturated fat intakes, mean BMI levels, diabetes prevalence, smoking prevalence and fruit-vegetable consumptions) are highly interrelated. Some of the relative risks or beta coefficients were not adjusted for each factors due to the feature of the studies . This might cause a relatively small overestimation while calculating DPPs, after all cumulative adjustments. Multivariate probabilistic sensitivity analyses were done to deal with this limitation."

Minor comments:
C4- In Page 2, the first bullet point: a cumulative adjustment …. was maden. Is ‘maden’ typo?
A4-Yes, it is a typo. We checked and corrected the typos/ grammatical errors.

C5- Fruit-vegetable consumptions are not risk factors for CHD. Would suggest adding some words to explain that F&V consumptions are protective factors, not risk factors.
A5-We explained that F&V consumptions are protective factors as below in the methods section:
"There is enough evidence that F&V consumption plays a role in the prevention of cardiovascular diseases."

C6- Curious to know if results would be different if stroke is added as one of the cardiovascular diseases in addition to CHD.
A6- This model evaluates only CHD mortality. But also, we know that the impact of risk factors on stroke mortality is not very different. Islek at al. stated that "Approximately 32%, 29%, 11% and 6% of total stroke and IHD deaths prevented could be attributed to a decreased consumption of transfat, dietary salt, saturated fats and fall in smoking prevalence and 22% could be attributed to increased fruit and vegetable consumption. "(1).

Reviewer: 2

Reviewer Name: Pamela Coxson, PhD, Mathematics Specialist
Institution and Country: University of California San Francisco, USA

C7- Estimating future CHD mortality to 2025 (p. 4). Mortality benefits are reported based on two alternative assumptions about background CHD mortality: a) no change in CHD mortality 2008-2025 except as modeled for the projected changes in diet and lifestyle; and b) a background trend of declining CHD mortality based on historical trends. The results from these two scenarios are presented in parallel in the manuscript, but only the larger effects from the no change scenario are listed in the abstract. If there is a strong rationale for assuming one of these scenarios is more likely, then the other scenario should be presented as a secondary result or as a sensitivity analysis. Otherwise, it would be better to present the more conservative outcome or the range of the two (which is substantially greater than the multivariate sensitivity “95% credible” ranges currently presented).
A7-We present the more conservative outcomes. So, we changed the results section in the abstract as below:
''Assuming lower mortality, modest policy changes in risk factors would result in approximately 25,635 (range:20,290-31,125) fewer CHD deaths in the year 2025; 35.6% attributed to reductions in salt consumption, 20.9% to falls in diabetes, 14.6% to declines in saturated fat intakes; 13.6% to increase in F&V intake. In the ideal scenario, 45,950 (range: 36,780-55,450) CHD deaths could be prevented in 2025. Again, 33.2% of this would be attributed to reductions in salt reduction; 19.8% to increases in F&V intake, 16.7% to reductions in saturated fat intakes, 14.0% to the fall in diabetes prevalence.''

C8- Effect of risk factor changes on CHD mortality (pp. 5 and 33-35). Based on the Table 5-10 footnotes, risk factor effects were not fully adjusted for the multivariate relationships among them. For example, BMI effects were not adjusted for diabetes, the diabetes effect was not adjusted for lipids, blood pressure, and BMI and physical activity effects were not adjusted for blood pressure and cholesterol. Without these multivariate adjustments, the combined effects are likely somewhat overstated. If this cannot be corrected, it should be mentioned as a limitation.
A8- Thank you for your comment. We added explanations on this limitation in strengths and limitations as below:
''The risk/protective factors which included in the study (physical inactivity, dietary salt, saturated fat intakes, mean BMI levels, diabetes prevalence, smoking prevalence and fruit-vegetable consumptions) are highly interrelated. Some of the relative risks or beta coefficients were not adjusted for each factors' due to the feature of the studies . This might cause overestimation while calculating DPPs, after all cumulative adjustments. Multivariate probabilistic sensitivity analyses were done to deal with this limitation.''
C9- Cumulative adjustment for risk factor changes done simultaneously (p. 6). It is not clear how the mortality effect sizes were adjusted to account for the simultaneous implementation of risk factor changes. The formula shown on page 6,
Cumulative effect = 1-((1-a)*(1-b)*(1-c)*…(1-n))
is incorrect (n = 6, so the last factor is -5). Presumably, the factors are intended to be risk factor specific relative risks so that the formula would represent the cumulative effect of the other 6 risk factors (or should it be all 7?). This process should be explained clearly in the text and in full detail with an example in the supplementary material.
A9-We changed the formula as below:
''Where n is the total number of additional risk factors (in this case 6 as in total we modelled 7) ''. This approach was explained with an example in the supplementary appendix.
We also added a new example to explain this process in supplementary appendix as below:
Cumulative adjustment for risk factor changes
There is a paucity of data on the efficacy of treatment combinations. Simply assuming that the efficacy of multiple treatments was additive would over-estimate the treatment effect; we therefore we used the Mant and Hicks method to estimate case-fatality reduction by polypharmacy for all treatments evaluated(2). This approach was subsequently endorsed by Yusuf(3) and Law and

Wald(4). We used this approach to estimate the efficacy of a cumulative relative benefit with reductions in risk factors as follows:
Relative Benefit = 1 - ((1-relative reduction in mortality for risk factor A) X (1- relative reduction in in mortality for risk factor B) X ...X (1- relative reduction in mortality for risk factor N).
EXAMPLE:
EXAMPLE: Estimation of reduced benefit if people having multiple risk reductions (Mant and Hicks approach)
For the men between 25 and 35 years old, applying relative risk reductions (RRR) for smoking, diabetes, physical inactivity, sistolic blood pressure, F&V consumption, BMI and total cholesterol then gives:
Relative Benefit = 1 - [(1 – smoking RRR) X (1 - diabetes RRR) X (1 - physical inactivity RRR) X (1-systolic blood pressure RRR) X (1- F&V consumption RRR) X (1- BMI RRR) X (1- total cholesterol RRR)]
= 1 - [(1- 0.12) X (1-0.06) X (1-0.04) X (1- 0.34) X (1- 0.11) X (1-0.02) X (1- 0.08)]
= 1 - [(0.88) X (0.94) X (0.96) X (0.66) X (0.89) X (0.98) X (0.92)]
= 1 - [0.58]
= 0.42 i.e. a 42 % lower mortality.
C10- Scenario design BMI (p.7). BMI increases of 1.4 (ref. 21) or 0.68 (ref 38) are cited as trends expected by 2025, and the modest (decrease of 0.7) and ideal (decrease of 1.4) are chosen presumably to counter those trends. Are the expected increases due primarily to a change in the age-distribution? If not, are these trends taken into account in calculating the expected CHD mortality for 2025 (before the calculation of the policy benefits?). Could this trend (along with increases in diabetes) result in a 3rd CHD mortality scenario with increasing rather than steady CHD mortality? This needs clarification and requires a nuanced discussion (urgency of addressing a trend that threatens to worsen health outcomes, as well as working to accelerate positive trends in salt, smoking, etc).
A10-The changes in BMI levels are due to both aging population, urbanization and changes in nutrition and lifestyle pattern(5). The effect of changes in risk factors on CHD mortality rates by 2025 was not taken into account. The CHD mortality rates have been declining since year 1995(6) and many countries experienced the same decreasing trend as a part of demographical and epidemiological transition and also advances in health care system (Even the number of people with CHD or other long term conditions is increasing the mortality rates from these conditions have been decreasing as a result of improvements in management of CVD events). Unal et al used IMPACT model for Turkey and they reported that the adverse trends in obesity and diabetes together contributed over 9000 additional deaths in 2008 which cancelled out much of the benefits attained by the decreases in blood pressure and smoking prevalence during the same period (1995-2008)(6). Hence 3rd scenario is unlikely, according to Turkish data because there are other risk factors which decreased the mortality rates and the improvements in treatments have a major role in this decline (47% of the decrease in CHD mortality rate was explained by treatments), where we still expect more improvements in CHD management in Turkey (6). We added the following interpretation to the discussion section;
"Some risk factors such as prevalence of DM and mean BMI values were increasing rapidly in Turkey (7); where these factors caused 9000 additional deaths in 2008(6). In our case we might have underestimated the 2025 death rates as we did not take into account the impact of increasing trends in DM and BMI on CHD mortality. It is also likely that the contrasting trend of these factors might cancel out much of the benefits that would be attained from improvements in other risk factors. Hence, it calls for a better application of public health policies on reducing burden of DM and high BMI, as well as working to accelerate positive trends in salt, smoking and physical inactivity."

C11- Results (p.9). The list (a. through g.) of CHD mortality benefits attributed to individual risk reduction goals gives the numbers of deaths prevented or postponed, but states "fewer" deaths ("fewer" should be deleted in each item).

A11-Thank you. We deleted 'fewer' in each item (in Page 9).

References
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6. Unal B, Sozmen K, Arik H, Gercekliogl u G, Altun DU, Simsek H, et al. Explaining the decline in coronary heart disease mortality in Turkey between 1995 and 2008. BMC public health. 2013;13:1135.
7. Sozmen K, Unal B, Capewell S, Critchley J, O'Flaherty M. Estimating diabetes prevalence in Turkey in 2025 with and without possible interventions to reduce obesity and smoking prevalence, using a modelling approach. International journal of public health. 2015.

VERSION 2 – REVIEW

REVIEWER	Takeki Suzuki, MD, PhD University of Mississippi Medical Center, Jackson, Mississippi, USA
REVIEW RETURNED	16-May-2016

GENERAL COMMENTS	The authors responded to my comments (Reviewer #1) appropriately.

REVIEWER	Pamela G. Coxson University of California San Francisco USA
REVIEW RETURNED	23-May-2016

GENERAL COMMENTS	Most points were addressed appropriately, but the cumulative effect formula in the Methods is still incorrectly presented. This needs to be corrected. Either use the long form presented in the Appendix (instead of "a", write out "relative reduction in mortality for risk factor A", etc; OR, for a more concise presentation, use subscripted variables r1, r2, ... rn instead of a, b, ..., n, with an explanation that ri is the relative reduction in mortality for the ith risk factor). As it is currently presented, the final factor in the product is (1-n) which is not what you intend.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Takeki Suzuki, MD, PhD
Institution and Country: University of Mississippi Medical Center, Jackson, Mississippi, USA

Competing Interests: None declared

C1: The authors responded to my comments (Reviewer #1) appropriately.
A1: Thank you for your constructive comments which improved our manuscript

Reviewer: 2
Reviewer Name: Pamela G. Coxson
Institution and Country: University of California San Francisco, USA Competing Interests: None declared

C2: Most points were addressed appropriately, but the cumulative effect formula in the Methods is still incorrectly presented. This needs to be corrected. Either use the long form presented in the Appendix (instead of "a", write out "relative reduction in mortality for risk factor A", etc; OR, for a more concise presentation, use subscripted variables r1, r2, ... rn instead of a, b, ..., n, with an explanation that ri is the relative reduction in mortality for the ith risk factor). As it is currently presented, the final factor in the product is (1-n) which is not what you intend.
A2: Thank you for your comment. We used the long form presented in the Appendix to explain cumulative effect formula as below:
"Instead, the effects of risk factor changes were jointly estimated using the cumulative relative benefit approach. This can be stated in the equation:
Cumulative Relative Benefit = 1 - ((1-relative reduction in mortality for risk factor A) X (1- relative reduction in in mortality for risk factor B) X ...X (1- relative reduction in mortality for risk factor N)."