Author's response to reviews

Title: The impact of a healthy lifestyle on Disability-Adjusted Life Years: a prospective cohort study

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Version: 2 Date: 29 January 2015

Author's response to reviews: see over
Dear Dr. Barnard,

We thank you for this opportunity to respond to the questions and comments of the reviewers to our manuscript entitled “The impact of a healthy lifestyle on Disability-Adjusted Life Years: a prospective cohort study”.

We have revised our manuscript and indicated revised fragments with highlights. We have provided detailed responses to each and every point mentioned by the reviewer, which we have enclosed with this letter.

We trust we have responded adequately to the points raised. However, in case any further information is required please do not hesitate to let us know.

We look forward to your response

Sincerely on behalf of all authors,

Anne May
Rebuttal:

Reviewer’s report

Title: The impact of a healthy lifestyle on Disability-Adjusted Life Years: a prospective cohort study

Version: 1 Date: 30 December 2014

Reviewer: frank hu

Reviewer’s report:

Minor Essential Revisions

This study examined the combined effects of several lifestyle factors including non-smoking, low BMI, being physically active and adherence to a Mediterranean diet on DALYs. The authors found that people adhering to all four healthy lifestyle characteristics lived a minimum of two years longer in good health (DALYs: -2.13; 95%-CI: -2.65; -1.62) than persons with none. Overall the paper is well written. The statistical analysis appears to be sound. The findings have important public health implications. I have only a few minor comments.

1. The authors stated that "Continuous analysis showed an on average 7 more months in good health per additional healthy behaviour (DALYs: -0.57; 95%-CI: -0.67; -0.47)." Because the four lifestyle factors have different effects on chronic disease risk and DALYs, it is questionable to conduct continuous analysis, which assumes the same effect for each factor.
   • The continuous analysis shows the average effect of the lifestyle factors on DALYs and indeed assumes the same effect for each factor, which may be incorrect. We therefore have now excluded the continuous analysis from the paper.

2. The authors stated "Due to our non-extinct cohort, true health benefits of a healthy lifestyle will be even larger." This statement is unclear and needs to be explained.
   • We have now extended this statement in the abstract ‘Due to our non-extinct cohort, the total number of DALYs and consequently the estimates are underestimated. Therefore, true lifetime health benefits of a healthy lifestyle will be even larger.’ (Line 19-21).

3. It would be interesting to look at the impact of "other lifestyle factors" on DALYs among individuals with one risk factor (e.g. overweight/obesity).
   • Restricting our analysis to participants who are overweight (BMI >= 25) yields comparable results: Overweight persons who are not inactive, do not smoke and adhere to a healthy diet live on average 1.57 years longer in good health compared to those who do not adhere to these healthy behaviours. The results in table 1 of this rebuttal shows that persons with an unhealthy diet benefit most from adhering to the other three lifestyle behaviours. This is in line with the
results from the individual lifestyle analysis that showed that high adherence to the mMDS had the lowest impact on DALYs compared to the other lifestyle factors.

- We have added these results to the paper. ‘... restricting to several high-risk subgroups, persons with one of the four risk factors, hypertension or high cholesterol (Total cholesterol/HDL ratio above 5).’ (Methods: Line 187-188). ‘Restricting the analysis to individuals with one of the four risk factors yields comparable results’ (Results: Line 221-222).

<table>
<thead>
<tr>
<th>Health behaviour score</th>
<th>BMI &gt;=25 kg/m²</th>
<th>Physically inactive</th>
<th>Current smoking</th>
<th>Low adherence to mMDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>2</td>
<td>-0.94 (-1.43; -0.44)</td>
<td>-0.63 (-1.26; -0.05)</td>
<td>-0.86 (-1.32; -1.72)</td>
<td>-0.92 (-1.43; -0.40)</td>
</tr>
<tr>
<td>3</td>
<td>-1.42 (-1.91; -0.90)</td>
<td>-1.61 (-2.34; -0.93)</td>
<td>-1.25 (-1.72; -0.78)</td>
<td>-1.45 (-1.96; -0.95)</td>
</tr>
<tr>
<td>4</td>
<td>-1.57 (-2.07; -0.05)</td>
<td>-1.73 (-2.95; -0.54)</td>
<td>-1.56 (-2.04; -1.06)</td>
<td>-2.11 (-2.63; -1.57)</td>
</tr>
</tbody>
</table>

Table 1 Regression coefficient and 95% CI of the association between health behaviour score and DALYs in specific subgroups

4. It would be also interesting to look at the impact of these factors among individual with high blood pressure or high cholesterol.

- We have conducted the suggested analysis which showed that persons with hypertension or high cholesterol seem to benefit more from a healthy lifestyle compared to the total study population. Restricting our analysis to participants who had hypertension at baseline gave slightly stronger associations (table 2: 2.51 years vs 2.31 in the total study population). In persons with high cholesterol it shows that persons with all four health behaviours live on average 3.72 years longer in good health compared to those without the four health behaviours (table 2).

- We have added the following sentence to the paper. ‘The associations between the health behaviour score and DALYs when restricting the analyses to persons with hypertension are slightly stronger (4 vs. 0 health behaviours, Mean DALY: -2.51; 95% CI: -3.31; -1.75). Analysis among persons with a high cholesterol shows that participants with all four health behaviours live on average 3.72 (95% CI: -4.75; -2.77) years longer in good health compared to those without the four health behaviours.’ (Line 222-226).
Table 2 Regression coefficient and 95% CI of the association between health behaviour score and DALYs in specific subgroups

<table>
<thead>
<tr>
<th>Health behaviour score</th>
<th>Hypertension (N=11 900)</th>
<th>High cholesterol ratio (Ratio total cholesterol/HDL = &gt;5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1 -1.01 (-0.75; -0.30)</td>
<td>-1.79 (-2.71; -0.90)</td>
<td></td>
</tr>
<tr>
<td>2 -1.61 (-2.31; -0.91)</td>
<td>-2.38 (-3.26; -1.48)</td>
<td></td>
</tr>
<tr>
<td>3 -2.77 (-2.27; -1.37)</td>
<td>-2.72 (-3.65; -1.85)</td>
<td></td>
</tr>
<tr>
<td>4 -2.51 (-3.31; -1.75)</td>
<td>-3.72 (-4.75; -2.77)</td>
<td></td>
</tr>
</tbody>
</table>

Multivariable model: adjusted for gender, age at recruitment, education level, energy intake.

5. Is there any gender difference in the estimates?

- The analysis between the health behavior score and DALYs were stratified by gender showing comparable results. Estimates are given in the results section ‘The associations for persons with all four health behaviours compared to those without any were similar for men and women (mean DALYs men: -2.02; 95%-CI: -2.97; -1.15; mean DALYs women -2.14; 95%-CI: -2.73; -1.46).’ (Line 217-219).
- Testing for interaction by including the interaction term into the logistic and linear models did not show interaction between the health behavior score and gender. P-value for interaction was 0.24 in the logistic model and 0.77 in the linear model. This has now been added to the manuscript. ‘We investigated interaction with age and sex by including an interaction term in the logistic and linear model.’ (Methods: Line 184-185), ‘Interaction terms between the health behaviour score or lifestyle factors and age or sex were not statistically significant (p>0.05).’ (Results: Line 216-217).

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests: none
Reviewer's report

Title: The impact of a healthy lifestyle on Disability-Adjusted Life Years: a prospective cohort study

Version: 1 Date: 29 December 2014

Reviewer: Fernando Rodríguez-Artalejo

Reviewer's report:

Among 33,066 apparently healthy men and women followed during 12 years within the EPIC-NL study, the authors found that non-smoking, having a BM < 25 kg/m², being physically active and the adherence to a Mediterranean-style diet are associated with longer life in a good health. This manuscript is well written, the methods are correct, and their results make a useful addition to the literature on the health effects of lifestyle scores, because they show, for the first time, that the accumulation of certain health behaviors translates into a progressively lower disease burden, assessed with individual-level DALYs.

DISCRETIONARY REVISIONS

1. In my view, it is a pity that the authors opted not to include moderate alcohol consumption within the studied behaviors, because some of the previous publications on lifestyle scores did include it and it is a relevant issue for public health. Authors argue that “We did not include alcohol intake in our health behaviour score... because... a moderate alcohol intake is associated to lower CVD risk but on the other hand related to a higher risk of breast cancer”. The use of a summary measure of health, such as DALYs, allows for estimating the net effect resulting from the benefits and harms associated with moderate alcohol intake, particularly when the results are disaggregated by sex. Thus, I suggest to include results on moderate alcohol intake (versus no or excessive intake) and to create a score with 5 health behaviors. It would also be interesting to check whether the dose-response between the lifestyle score and lower disease burden also holds after including moderate alcohol intake.

- We thank the reviewer for this suggestion. For this paper we use our previously pragmatic defined health behavior score that did not include alcohol [1, 2]. The aim of this study was to investigate this health behavior score in association with total disease burden using DALYs. The score is based on a priori knowledge and exists of dichotomous lifestyle characteristics; a score of one is assigned for a healthy behavior (e.g. a normal BMI) and a score of 0 to an unhealthy behavior (e.g. a high BMI). For alcohol this dichotomization is not self-evident. In most observational studies moderate alcohol intake is associated with decreased risks of cardiovascular disease and diabetes, but any consumption of alcohol is a risk factor for some cancers [3]. Because the health behavior score is meant to promote healthy behaviors we have chosen not to take up alcohol in our score. Any alcohol use may increase the risk of binge drinking and alcohol abuse causes health-related harms and higher disease burden [4, 5].
A moderate alcohol intake is originally part of the Mediterranean diet score. Also in response to comment 3, we have conducted sensitivity analysis using the original Mediterranean diet score including moderate alcohol intake. This result shows slightly stronger estimates between the health behavior score and DALYs shown in table 3 of this rebuttal. We have added the following lines to the paper: ‘Furthermore, we run analysis … including a moderate alcohol intake (10-50g of alcohol a day for men and 5-25g of alcohol a day for women) in the mMDS score and without adjusting the analysis for alcohol intake.’ (Methods: Line 190-192), ‘Adding the alcohol component to the mMDS did not materially change the findings (mean DALYs 4 vs. 0 health behaviours: -2.25; 95%-CI: -2.80; -1.73) (data not shown in table).’ (Results: Line 229-231).

Table 3 Regression coefficient and 95% CI of the association between health behaviour score and DALYs including the alcohol component of the modified Mediterranean Diet Score (mMDS)

<table>
<thead>
<tr>
<th>Health behaviour score</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>1</td>
<td>-0.88 (-1.45; -0.35)</td>
</tr>
<tr>
<td>2</td>
<td>-1.40 (-1.89; -0.87)</td>
</tr>
<tr>
<td>3</td>
<td>-1.77 (-2.27; -1.25)</td>
</tr>
<tr>
<td>4</td>
<td>-2.25 (-2.80; -1.73)</td>
</tr>
</tbody>
</table>

Multivariable model: adjusted for gender, age at recruitment, education level, energy intake.

References
2. Authors might comment on possible reasons why, compared to being inactive, the relative effect on disease burden of being moderately inactive is similar to that of being active (table 2).

- The reviewer is right that these estimates are very similar. This result suggests that not being inactive is important and that the level of activity is less important. This may be the case, but misclassification might play a role here too. Therefore, we have added the following to the discussion section of the paper. ‘The results for the individual lifestyle factor physical activity showed that compared to being inactive, the estimate for being moderately inactive is similar to that of being active. This indicates that it is mainly important not to be inactive and that level of activity is less important. However, it may also reflect misclassification between the moderately active and moderately inactive categories.’ (Line 255-259).

3. It would be worthwhile to comment on reasons why the association with disease burden was stronger for smoking and BMI than for physical activity and Mediterranean diet. Is it because of the dichotomous categorization used for the studied health behaviors? (If other categorization were used, would the results have been similar?) Is it because once BMI is taken into account, the role of physical activity is only minor? As for the small association seen for the Mediterranean diet, could it be due to the exclusion of alcohol from the Mediterranean diet score? In fact, in a previous paper (BMJ 2009;338:b2337) Trichopoulou showed that the main contributor to the reduced mortality associated with the Mediterranean diet was alcohol intake

- The results were indeed stronger for smoking and BMI than for physical activity and the mMDS. It is possible that the categorization/choice of cut-off point plays a role here, as suggested by the reviewer. We have now given attention to these issues by adding the following section to the discussion section of the paper. ‘The individual lifestyle variables are not independent. The analyses of physical activity in association with disease burden are adjusted for BMI which decreases the size of the estimate. The results for the individual lifestyle factor physical activity showed that compared to being inactive, the estimate for being moderately inactive is similar to that of being active. This indicates that it is mainly important not to be inactive and that level of activity is less important. However, it may also reflect misclassification between the moderately active and moderately inactive categories. Furthermore, it has to be taken into account that differences in results of the individual lifestyle factors may partly be caused by the categorization used.’ (Line 254-261).

- As described above we have now conducted sensitivity analyses including the alcohol component of the mMDS. This results in a stronger estimate for the association between the mMDS and DALYs. Higher adherence to the mMDS including an alcohol component was associated with a 0.39 year longer life in good health (table 4 of this rebuttal) compared to 0.24 years when excluding the alcohol component (mean DALYs: -0.24; 95%-CI: -0.44; -0.02). However, this does not change the final conclusion of our paper. The estimates of the association between the other lifestyle factors and DALYs remain stronger; 0.54 for a high physical activity, 1.04 for a low BMI and 1.15 for never smoking. We have now indicated in the paper that inclusion of the alcohol component to the mMDS does not change the conclusion.
‘Adding the alcohol component to the mMDS did not materially change the findings ...’ (Line 229-231).

**Table 4** Regression coefficient and 95% CI of the association between the modified Mediterranean Diet Score (mMDS) and DALYs including the alcohol component of the mMDS

<table>
<thead>
<tr>
<th>mMDS category</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-2)</td>
<td>Reference</td>
</tr>
<tr>
<td>Moderate (3-5)</td>
<td>-0.19 (-0.39; -0.00)</td>
</tr>
<tr>
<td>High (6-9)</td>
<td>-0.39 (-0.62; -0.16)</td>
</tr>
</tbody>
</table>

Multivariable model: adjusted for gender, age at recruitment, education level, energy intake, smoke duration and intensity, BMI (continuous) and CPAI (4 cat).

4. Readers may benefit from a brief comment on how the weights to calculate YLD were estimated for the different diseases. It may have had certain influence on study results.

- We have now included more information about how disability weights were defined. ‘The disability weights were derived from the Dutch Disability Weight study by 3 panels of medical experts that evaluated a large number of disease stages using techniques such as person trade-off.’ (Line 156-158).

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests
A) Major compulsory Revisions

1) Is the effect of each of these behaviors the same regardless of the age of the participant? I would expect that age may be an effect modifier for some of them, for example for BMI

- Testing for interaction by including an interaction term into the logistic and linear models did not show interaction between the four lifestyle factors and age. P-values for interaction are shown in table 5 of this rebuttal. Results for the health behavior score stratified for 2 age groups are shown in table 6. The manuscript was adapted accordingly: ‘We investigated interaction with age and sex by including an interaction term in the logistic and linear model.’ (Methods: line 184-185), ‘Interaction terms between the health behaviour score or lifestyle factors and age or sex were not statistically significant (p>0.05).’ (Results: Line 216-217). ‘The associations for persons with all four health behaviours compared to those without any were comparable for men and women; as well as for younger and older participants (<=50 years mean DALYs: -2.11; 95%-CI: -3.33; -0.75; >50 years mean DALYs -2.07; 95%-CI: -2.68; -1.50) (Results: Lines 217-221).

<table>
<thead>
<tr>
<th>Table 5</th>
<th>P-values for interaction with age (&gt;50/&lt;=50 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle factor</td>
<td>Logistic model</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.80</td>
</tr>
<tr>
<td>BMI</td>
<td>0.95</td>
</tr>
<tr>
<td>CPAI</td>
<td>0.86</td>
</tr>
<tr>
<td>mMDS</td>
<td>0.62</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Regression coefficient and 95% CI of the association between health behaviour score and DALYs stratified for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health behaviour score</td>
<td>Age &lt;=50 years</td>
</tr>
<tr>
<td>0</td>
<td>Reference</td>
</tr>
<tr>
<td>1</td>
<td>-0.96 (-2.12; -0.30)</td>
</tr>
<tr>
<td>2</td>
<td>-1.49 (-2.64; -0.26)</td>
</tr>
<tr>
<td>3</td>
<td>-1.62 (-2.81; -0.31)</td>
</tr>
<tr>
<td>4</td>
<td>-2.11 (-3.33; -0.75)</td>
</tr>
</tbody>
</table>

Multivariable model: adjusted for gender, age at recruitment, education level, energy intake.
2) There are 2 dimensions of active/sedentary lifestyles that can operate independently: hours of sedentary activity and practice of physical activity or exercise. You can explore whether the addition of hours devoted to television or, in general screen use, provides additional information to your healthy behavior score.

- We thank the reviewer for his suggestions. Unfortunately we do not have information about screen use of our participants. We have included this limitation in the discussion. ‘Unfortunately no information was available to expand the health behavior score with additional health behaviours such as sleep, weak social support and screen use.’ (Lines 308-309).

3) Other healthy behaviors have been also found to be associated with poorer survival or poorer quality of life, such as living alone, sleeping <7 to >8 h/d, and weak social support or not seeing friends frequently. Please check BMC Med. 2013 Feb 22;11:47. If you have information on any of these behaviors you can add them to the score, at least as a sensitivity analysis in order to assess to what extent they can further account for a greater burden of DALYs lost.

- Again we thank the reviewer for these interesting suggestions. Unfortunately we also do not have information about the number of hours of sleep or the social support structure around our participants for the whole study population. We have included this limitation in the discussion as described above.

4) You excluded alcohol from the Mediterranean diet score. However, you should have assessed the effect of alcohol and alcohol drinking pattern on DALYs. Please check PMID: 24480368

- We agree that the association between alcohol consumption and DALYs is interesting. In the current manuscript we focus on a previously defined pragmatic health behavior score as indicated under point 1 of reviewer 2. Due to the fact that it is difficult to dichotomize alcohol intake into an optimal healthy intake and an unhealthy intake we have decided not to include alcohol as a separate component but included it into the mMDS in sensitivity analysis. We agree that alcohol is an important lifestyle factor associated with chronic diseases. However, before including it in a health behaviour score we believe more information is needed on what the net effect is of alcohol on disease burden and what might be an optimal intake. Therefore, the association between alcohol and disease burden first needs to be investigated further.

5) Pages 8-9: "Information on disease occurrence (Cancer, Coronary Heart Disease (CHD), Cerebrovascular Accident (CVA), Diabetes Mellitus, Chronic Obstructive Pulmonary Disease (COPD), Asthma, Parkinson’s disease, Rheumatoid Arthritis, Osteoarthritis, and Inflammatory Bowel Disease (IBD)) was obtained from the National Cancer Registry and the national hospital discharge diagnosis database from the Dutch National Medical Registry". Please provide objective assessment of the comprehensiveness of these sources. In other words, you completely relied in a single source of information for the ascertainment of your outcome, can you be sure that you captured all relevant outcomes using only this source? Can you give some quantitative estimate of the information bias derived from only using this source of information to ascertain the outcome.
Information on disease occurrence was obtained from several different registries. The success rate of linking our cohort to these registries is over 95% [1] and thus rather complete. The accuracy of the different registries differs and is described in more detail below. Causes of death were obtained by linkage with the causes of death registry of ‘Statistics Netherlands’. The information for this source is almost complete and validity is high. Occurrence of cancer is obtained by linkage to the Dutch Cancer Registry and is based on hospitalization records and pathology records. The information from the Dutch Cancer Registry is 95% complete since 1989. Linkage to these two registries is based on identifying information. Therefore these linkages are assumed to be approximately 100% accurate. Cases of diabetes are mainly based on self-reports and linkage to the hospital discharge diagnosis registry. The self-reported potential cases of diabetes have been verified against medical and pharmacy records [2]. Only verified cases of diabetes have been included in this analysis and this diagnosis is therefore 100% correct. However, we may have missed yet undiagnosed cases of diabetes, since the disease may remain undetected for several years. All other diseases have been obtained from the Hospital Discharge Diagnosis Registry. Since 1990, admission files have been stored continuously from almost all general and university hospitals in The Netherlands. Data on sex, date of birth, dates of admission and discharge are recorded whenever a patient is discharged from hospital. One mandatory principal diagnosis and up to nine optional additional diagnoses are reported. All diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9). Coding of the diagnoses is performed by qualified medical administrative personnel in the hospitals. The National Medical Registry (NMR) collects these data in the Hospital Discharge Diagnosis Database. These data are checked by the NMR, mistakes are corrected by the hospitals, and unlikely diagnoses are discussed with the hospital. The database is linked to the cohort based on information of birth date, gender, postal code and general practitioner with a validated probabilistic method. Validity of the Hospital Discharge Diagnosis Registry has been investigated for cardiovascular outcomes and was good for coronary heart disease, but lower for other cardiovascular outcomes such as angina pectoris and heart failure. However, positive predictive values were still around 80% [3]. However, it is probable that the less severe cases are not reported in the database as hospitalized cases are most likely to be more severe. Therefore, for diseases obtained from this registry, we will have missed non-hospitalised cases. This leads to underestimation of the DALYs and may therefore lead to underestimation of the associations observed in our study. This limitation is now more clearly described in the discussion (Line 303-307), as indicated under point 2 of ‘Discretionary Reviews’.

References
6) The relative risks (95% CI) of mortality for each of the behaviors included in the score should be presented. They should be estimated with hazard ratios (HRs) using multivariable-adjusted Cox proportional hazards models. The fact is that you are assuming the same weight for each of these 4 behaviors in building your 0- to 4-point score, but this should be better supported by a similarity of their HRs.

- We understand the problem, however basing the weight of the individual healthy behaviours on mortality HRs is undermining the aim of our study. We want to address morbidity and mortality, and include also disability as a consequence of morbidity. So, using weights based on mortality only seems not appropriate. In addition, we did not want to derive a data driven health behavior score, but to assess relations between a previous proposed pragmatic score, easily accessible also in other populations, and subsequent disease burden expressed as losses in disability-adjusted life years.

- We have now clarified in the paper that we use a previously defined pragmatic health behavior score (Line 103-104).

B) Minor Essential Revisions

1-Abstract, results: "low BMI", please define the cutoff point here
- We have now included the cutoff point for BMI in the abstract `(BMI < 25)` (Line 16).

2-Page 6: "a general questionnaire and a food-frequency questionnaire (FFQ) were administered and a physical" Please provide the number of items of each questionnaire.
- The food-frequency questionnaire contains questions on the frequency of consumption of 79 main food items. Information about the food-frequency questionnaire has been described in the measurement section of the methods. `Daily dietary intakes were obtained from a self-administered validated FFQ containing questions on the usual frequency of consumption of 79 main food items during the year preceding enrolment.` (Line 90-92). We have extended the information with the following line `This questionnaire allowed the estimation of the average daily consumption of 178 foods.` (Line 92-93). The EPIC-NL cohort consists of Prospect-EPIC and MORGEN-EPIC which have slightly different general questionnaires and the number of items can differ per person dependent on a participant’s characteristics therefore we do not give the exact number of items for the general questionnaire.

3-Page 6: "men and women who suffered from any of the studied diseases at baseline". Please provide the list of these diseases.
- The list of diseases has now been added to the sentence `men and women who suffered from any of the studied diseases at baseline (Cancer, Coronary Heart Disease (CHD), Cerebrovascular..."
Accident (CVA), Diabetes Mellitus, Chronic Obstructive Pulmonary Disease (COPD), Asthma, Parkinson’s disease, Rheumatoid Arthritis, Osteoarthritis, and Inflammatory Bowel Disease (IBD)." (Line 76-78).

4-Page 7: "missing data was imputed using single linear regression modelling" Did you use multiple imputation? How many sets of imputations did you perform? The sentence about SPSS is not consistent with your last sentence in page 10 that "All statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, US)."

• We have imputed missing data using single imputation. One of the main reasons for this is that we used a two-part model, which combines logistic regression with linear regression to investigate the association of the mMDS with DALYs. For this model, we have used bootstrapping to create confidence intervals with the point estimates. Using multiple imputations to account for missing values in such an analysis will be very complex. Moreover, many studies compared multiple imputation and single imputation, which showed that these methods provided similar results in terms of bias, i.e. similar regression coefficients, even in the presence of high percentages of missing values [1]. Nevertheless, indeed multiple imputation produces more correct standard errors, as compared to single imputation, which usually produces too small standard errors. We had a very large sample size of over 35,000 participants, where still 28,437 participants were available for the imputation of the 14% missing data on physical activity. Therefore we think the underestimation of the standard errors of the performance by using SI is very limited.

• The sentence about the statistical programs used has been changed. ‘Statistical analyses were conducted using SAS 9.2 (SAS Institute, Cary, US), except imputation which has been conducted using SPSS 14.0 (Chicago, IL, USA).’ (Line 193-194).

Reference

5-Page 8: "lifestyle indices beside physical activity, smoking and dietary intake (kan je hier refs geven)." Please be careful. There is a sentence in Dutch, apparently as a provisional communication between co-authors that was not erased before submission.

• This sentence has now been deleted.

6-Page 8: "the Mediterranean diet that has previously shown a beneficial impact on disease burden [25]." Please consider to provide stronger references such as the following ones: PMID: 25055810, PMID: 23432189 or PMID: 24370845

• The references have now been added to the paper (Line 113).

7-In the mMDS, did you include nuts in the group of fruit, i.e. fruit+nuts?
• Yes nuts are included in the fruit group. This has now been clarified ‘... fruit and nuts, vegetables,’ (Line 114).

8-Page 9 "diabetes (disability weight 0.20)” You should provide a complete table with the weights given to each disease.
• We have now given all the weights in a supplemental table. ‘The disability weights can range between zero (no burden) and one (death) (Supplemental table 1)’ (Line 159; Supplemental table 1).

C) Discretionary Reviews

1-Perhaps you can show months instead of years in your Tables 2-3 to better show the details of the coefficients. In any case, please indicate the units of measurements and the real life interpretation of these coefficients.
• We have chosen to provide the estimates in years because of the term Disability-Adjusted Life Years. In the result section we describe what the impact is in months. ‘Physically active persons lived approximately 6 months longer in good health than physically inactive persons (mean DALYs: -0.54; 95%-CI: -0.80; -0.27). The association was weakest for diet but still significant with approximately 3 months longer life in good health for persons with a high adherence to a Mediterranean diet compared to those with a low adherence (mean DALYs: -0.24; 95%-CI: -0.44; -0.02).’ (Line 206-210).

2-Perhaps you should further discuss your information bias and further insist in the underestimation that you are providing here.
• We have now further discussed possible information bias and reasons for underestimation of the DALYs. ‘Not all relevant diseases could be incorporated in our analysis and for other major diseases only severe cases resulting in hospitalization were included. In addition, the registered date of onset of disease (date of hospital discharge) is likely to be later than the true date of onset when the disease started to contribute to disease burden. However, we did include those diseases that are most strongly associated with lifestyle.’ (Line 303-307). ‘Another limitation is that we cannot rule out the possibility of residual confounding due to misclassification of any of the lifestyle behaviours.’ (Line 309-311).

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I declare that I have no competing interests