PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Self-rated Health and Type 2 Diabetes Risk in the EPIC-InterAct Study: a case-cohort study
AUTHORS	Wennberg, Patrik; Rolandsson, Olov; van der A, Daphne; Spijkerman, Annemieke; Kaaks, Rudolf; Boeing, Heiner; Feller, Silke; Bergmann, Manuela; Langenberg, Claudia; Sharp, Stephen; Forouhi, Nita; Riboli, Elio; Wareham, Nicholas

VERSION 1 - REVIEW

REVIEWER	Christina Halford, MD PhD Department of Public Health and Caring Sciences Uppsala University BMC Box 564 SE-751 22 Uppsala Sweden I hereby declare that there are no known conflicts of interest associated with the review of this paper and that there has been no significant financial support for this work that could have influenced its outcome
REVIEW RETURNED	03-Jan-2013

THE STUDY	Details are supplied in the attached file
GENERAL COMMENTS	**Introduction** Comment 1 (page 5). The two research questions which are addressed in the article need to be (more) clearly defined in the introduction. Comment 2 (page 5): The rational behind the study needs to be clarified, so that readers, potentially less familiar with SRH as a concept, understand why you are investigating the association between SRH and risk of T2DM! Comment 3 (page 5, line 20-21) …the passage “bodily sensations and symptoms that can reflect disease in clinical or pre-clinical stages” could be could be indicated as a quote [Benyamini 2011, reference nr 4, page 1408, opening sentence of the third paragraph] Comment 4 (page 5, line 33): Would it be more correct to phrase the

	association in terms of "poorer" SRH was associated with – instead of "reduced"? **Methods** ***Are the participants adequately described, their conditions defined and inclusion/exclusion criteria described?*** Comment 5 (page 6): Exclusion criteria and attrition for the EPIC-Interact study as a whole are briefly described in the reference provided (no.15. Langenberg C et al 2011). However, the present study refers to a subset of participants, and, since heterogeneity between centres is investigated, the reader needs to be provided with descriptive data concerning the different centres, for example in a descriptive table; how large were the study-populations of the five centres from which cases and the sub-cohorts were identified? Are inclusion criteria and study population characteristics similar or do they differ significantly between the different centres? Comment 6 (page 6): Attrition needs to be described, both in terms of numbers and in terms of reasons for attrition, for example using a flow-chart. ***Are the patients representative of actual patients the evidence may affect?*** Comment 7: The question concerning whether or not the study populations of the different centres are representative of the general population needs to be addressed. ***Are the methods adequately described?*** Comment 8 (page 6, line 52 - p7, line 5): The last two sentences are not clear to me – they need to be clarified. Was, for example, an individual medical-record review performed for all T2DM-cases? Comment 9 (page 7, line 15): The rationale behind the authors choice on how to standardize the SRH-responses needs to be clarified. See for example [Jűrges H, Avendano M, Mackenbach J. Are different measures of self-rated health comparable? An assessment in five European countries. Eur J Epidemiol. 2008;23:773-781]. Comment 10 (page 7, line 19-21)**:** The expressions "poor" and

	"better" or "good" SRH would be clearer than using the terms low and high. This, since the way SRH is scored differs between studies; excellent SRH is for example sometimes scored = 1. Comment 11 (page 7, line 21): Since dichotomising SRH responses leads to loss of power, and SRH can be entered as an ordinal variable into the Cox regression, why was SRH dichotomised into high and low SRH? This issue needs to be clarified. It is not enough to state that SRH was dichotomised in conformity with previous research. Comment 12 (page 8, line 40-43): Concerning the sentence "To investigate the implact of missing data, a third sensitivity analysis ….": It is unclear to me what this means. The sentence needs to be clarified **Results** Comment 13 (page 9, line 12-14, line 28-29): "Participants with low SRH ….had lower alcohol consumption and estimated reported energy intake", and "The strength of the association between SRH and T2DM was mainly unaffected by smoking, alcohol consumption and energy intake": Were these expected findings? If not, they need to be addressed in the discussion. Comment 14 (page 10, line 5-6): I suggest that the sentence "Because of missing data on covariates, 323 T2DM cases and 405 members of the subcohort were excluded from analyses" is moved to the methods section (see comment 6) **Discussion** Comment 15 (page 9, line 42-44, and page 10 line 25-26): The statement "we found no indication of heterogeneity" needs to be elaborated in the discussion. Could the result for example be due to lack of power? (see comment nr 11). Comment 16 (page 11, third paragraph, final sentences): There are differences not only in time frame, but also in that SRH in four of the centres was measured in terms of perceptions of health, and in two of the centres in terms of satisfaction with health. Could this affect results – or the interpretation of results? Furthermore there were differences in response alternatives between the centres which were handled through standardisation (see comment 8). These issues

	need to be addressed as part of the limitations of the study. Comment 17 (page 12 line 25-27): ”It is likely that the differences in SRH across centres to some extent can be explained by differences in sampling strategies and age distributions” **:** see comment 5 – these differences need to be described earlier on in the manuscript (in the methods or in the results section) ***Are the abstract/summary/key messages/limitations accurate?*** Comment 18. Abstract: No. Two conclusions are stated – but only one objective. Comment 19. Summary/Limitations (p4, line 50): The assessment of self-rated health differed not only with regards to time frame … (see comment 16) ***Is the standard of English acceptable for publication*** No. The manuscript needs proof reading. ***Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?*** Yes. see comments above

REVIEWER	Kenzie Latham, PhD NIA Postdoctoral Research Fellow Population Studies Center Institute for Social Research University of Michigan
REVIEW RETURNED	14-Jan-2013

THE STUDY	The authors may want to compare their findings to a recently published article in the Journals of Gerontology, Series B: Social Sciences: Latham, K. and C. W. Peek. 2013. “Self-Rated Health and Morbidity Onset among Late Midlife Adults.” The Journals of Gerontology, Series B: Social Sciences, 68, 1, 107-116. Latham and Peek also explored diabetes incidence using self-reported physician diagnoses among a late midlife US cohort.

	Similarly to the current study, SRH predicted diabetes incidence, net of socio-demographic characteristics and health risk factors.
GENERAL COMMENTS	It is the opinion of this reviewer that this manuscript is well written and that the methodology of the study is sound. Limitations of this research were adequately addressed, and this research uniquely contributes to the extant literature.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Christina Halford, MD PhD
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I hereby declare that there are no known conflicts of interest associated with the review of this paper and that there has been no significant financial support for this work that could have influenced its outcome

Introduction
Comment 1 (page 5). The two research questions which are addressed in the article need to be (more) clearly defined in the introduction.
Answer: We have clarified this by describing explicitly the two research questions.

Comment 2 (page 5): The rational behind the study needs to be clarified, so that readers, potentially less familiar with SRH as a concept, understand why you are investigating the association between SRH and risk of T2DM!

Answer: We have added a rationale in the Introduction section.

Comment 3 (page 5, line 20-21) …the passage "bodily sensations and symptoms that can reflect disease in clinical or pre-clinical stages" could be could be indicated as a quote [Benyamini 2011, reference nr 4, page 1408, opening sentence of the third paragraph]
Answer: We thank for the suggestion. This has been changed in the revision according to the reviewer's suggestion.

Comment 4 (page 5, line 33): Would it be more correct to phrase the association in terms of "poorer" SRH was associated with – instead of "reduced"?
Answer: We agree with the reviewer that "poorer" is a more correct phrase and have changed the phrase accordingly.

Methods
Are the participants adequately described, their conditions defined and inclusion/exclusion criteria described?
Comment 5 (page 6): Exclusion criteria and attrition for the EPIC-Interact study as a whole are briefly described in the reference provided (no.15. Langenberg C et al 2011). However, the present study refers to a subset of participants, and, since heterogeneity between centres is investigated, the reader needs to be provided with descriptive data concerning the different centres, for example in a descriptive table; how large were the study-populations of the five centres from which cases and the sub-cohorts were identified? Are inclusion criteria and study population characteristics similar or do they differ significantly between the different centres?

Answer: We thanks for the suggestion and have included a descriptive table (table 1). The recruitment procedures were rather similar but the age-groups differed somewhat between the included centres in this study.

Comment 6 (page 6): Attrition needs to be described, both in terms of numbers and in terms of reasons for attrition, for example using a flow-chart.
Answer: We have added a flow chart to describe the attrition (figure 1).

Are the patients representative of actual patients the evidence may affect?
Comment 7: The question concerning whether or not the study populations of the different centres are representative of the general population needs to be addressed.
Answer: EPIC-InterAct is based on the EPIC study, which was a cancer study and at some centres (not included in the current study) only women were invited. EPIC-InterAct utilize the variation in exposure between the centres to increase the generalizability to general population in the included European countries. The centres are now described in table 1.

Are the methods adequately described?
Comment 8 (page 6, line 52 - p7, line 5): The last two sentences are not clear to me – they need to be clarified. Was, for example, an individual medical-record review performed for all T2DM-cases?
Answer: Individual medical-record review was conducted at some centres. We have added this information and changed the disposition of the paragraph to make it more clear that T2DM cases were included in the study only if confirmation of the diagnosis was secured from no less than two independent sources.

Comment 9 (page 7, line 15): The rationale behind the authors choice on how to standardize the SRH-responses needs to be clarified. See for example [Jűrges H, Avendano M, Mackenbach J. Are different measures of self-rated health comparable? An assessment in five European countries. Eur J Epidemiol. 2008;23:773-781].
Answer: The standardization of SRH-responses was part of an earlier general standardization process in EPIC (involving a large number of variables) and was not conducted by the authors of this manuscript. To avoid the use of several differently standardized SRH-responses within EPIC we chose not to "re-standardize" this variable. Moreover, as suggested by Jűrges H et al. 2008, differences are minimised by collapsing the two top/bottom categories. However, we have added the differences in the construct of the SRH question as a limitation in the Discussion section.

Comment 10 (page 7, line 19-21): The expressions "poor" and "better" or "good" SRH would be clearer than using the terms low and high. This, since the way SRH is scored differs between studies; excellent SRH is for example sometimes scored = 1.
Answers: We think that using "poor" and "good" could lead to mix-up with the original SRH categories (excellent, good, moderate, and poor), especially among readers who are not that familiar with the SRH concept. Therefore we would prefer to keep the terms low and high SRH.However, if the reviewer still thinks another terminology would be more appropriate, we are willing to change this.

Comment 11 (page 7, line 21): Since dichotomising SRH responses leads to loss of power, and SRH can be entered as an ordinal variable into the Cox regression, why was SRH dichotomised into high and low SRH? This issue needs to be clarified. It is not enough to state that SRH was dichotomised in conformity with previous research.

Answer: The dichotomising of SRH responses was conducted to increase the statistical power by increasing the number of participants in each category; "Given the low frequency of responses in the extreme categories (n=305 in the lowest category) we dichotomized the SRH variable in the analysis by combining the two highest categories (high SRH) and the two lowest categories (low SRH)...". To

further clarify this we have added "...to increase statistical power". When we calculated the main analysis using SRH as an ordinal variable this did not alter the conclusion, but the confidence intervals for hazard ratios in the extreme categories were substantially wider.

Comment 12 (page 8, line 40-43): Concerning the sentence "To investigate the implact of missing data, a third sensitivity analysis ….": It is unclear to me what this means. The sentence needs to be clarified
Answer: We have added that the sensitivity analysis was conducted "to investigate the impact of excluding 323 T2DM cases and 405 members of the subcohort with missing data on covariates".

Results
Comment 13 (page 9, line 12-14, line 28-29): "Participants with low SRH ….had lower alcohol consumption and estimated reported energy intake", and "The strength of the association between SRH and T2DM was mainly unaffected by smoking, alcohol consumption and energy intake": Were these expected findings? If not, they need to be addressed in the discussion.

Answer: We agree that these findings were somewhat unexpected and have added this to the Discussion section.

Comment 14 (page 10, line 5-6): I suggest that the sentence "Because of missing data on covariates, 323 T2DM cases and 405 members of the subcohort were excluded from analyses" is moved to the methods section (see comment 6)

Answer: To increase the clarity we have added this to the Methods section (see answer to comment 12), but kept the sentence in the Results as well.

Discussion
Comment 15 (page 9, line 42-44, and page 10 line 25-26): The statement "we found no indication of heterogeneity" needs to be elaborated in the discussion. Could the result for example be due to lack of power? (see comment nr 11).

Answer: We have added an elaboration of this finding/statement in the Discussion.

Comment 16 (page 11, third paragraph, final sentences): There are differences not only in time frame, but also in that SRH in four of the centres was measured in terms of perceptions of health, and in two of the centres in terms of satisfaction with health. Could this affect results – or the interpretation of results? Furthermore there were differences in response alternatives between the centres which were handled through standardisation (see comment 8). These issues need to be addressed as part of the limitations of the study.

Answer: We agree with the reviewer and have made additions to the limitations of the study regarding the construct of the SRH question.

Comment 17 (page 12 line 25-27): "It is likely that the differences in SRH across centres to some extent can be explained by differences in sampling strategies and age distributions" : see comment 5 – these differences need to be described earlier on in the manuscript (in the methods or in the results section)
Answer: We have added a descriptive table (table 1).

Are the abstract/summary/key messages/limitations accurate?
Comment 18. Abstract: No. Two conclusions are stated – but only one objective.

Answer: We have clarified this by adding the secondary objective.

Comment 19. Summary/Limitations (p4, line 50): The assessment of self-rated health differed not only with regards to time frame … (see comment 16)

Answer: We thank for pointing this out. We have added this to the limitations.

Is the standard of English acceptable for publication
No. The manuscript needs proof reading.
Answer: The manuscript has been proof read by a professional proof reader before submission.

Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?
Yes. see comments above

Reviewer: Kenzie Latham, PhD
NIA Postdoctoral Research Fellow
Population Studies Center
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University of Michigan

The authors may want to compare their findings to a recently published article in the Journals of Gerontology, Series B: Social Sciences:

Latham, K. and C. W. Peek. 2013. “Self-Rated Health and Morbidity Onset among Late Midlife Adults.” The Journals of Gerontology, Series B: Social Sciences, 68, 1, 107-116.

Latham and Peek also explored diabetes incidence using self-reported physician diagnoses among a late midlife US cohort. Similarly to the current study, SRH predicted diabetes incidence, net of socio-demographic characteristics and health risk factors.
It is the opinion of this reviewer that this manuscript is well written and that the methodology of the study is sound. Limitations of this research were adequately addressed, and this research uniquely contributes to the extant literature.

Answer: We thank the reviewer for the reference to this recent report which has been cited and commented in the revised version of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Christina Halford, MD PhD Department of Public Health and Caring Sciences Uppsala university Sweden I hereby declare that there are no competing interests involved
REVIEW RETURNED	15-Feb-2013

- The reviewer completed the checklist but made no further comments.