PEER REVIEW HISTORY

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Estimating the risk of cardiovascular disease using an obese-years metric
AUTHORS	Abdullah, Asnawi; Amin, Fauzi; Stoelwinder, Johannes; Tanamas, Stephanie; Wolf, Rory; Barendregt, Jan; Peeters, Anna

VERSION 1 - REVIEW

REVIEWER	Andrew Hinde University of Southampton United Kingdom
REVIEW RETURNED	03-Jul-2014

GENERAL COMMENTS	1. The computation of the obese-years variable is not described clearly enough on p. 8, ll. 12-17. I should like an example to be added to make the computation clear. For example, consider a person who at seven consecutive observations and had a BMI of 27, 29, 31, 34, 35, 29 and 29 respectively. My understanding is that this person's obese units at the seven observations are 0, 0, 2, 5, 6, 0 and 0. This person would therefore contribute (2 + 5 + 6) x 2 = 26 obese-years (assuming each observation was two years apart). Is this correct? If so, I think an example like this would make the computation clearer. 2. The authors do not say anything about whether the assumption of proportional hazards is valid. This should be rectified. They are using a model with time-dependent covariates, although so far as I can make out they are not using duration itself as a covariate. This means that they still need to test whether the impact of obese-years on the hazard is the same at all durations. See the excellent review of this issue and some suggestions for testing by Bellera et al. (2010) 'Variables with time-varying effects and the Cox model', BMC Medical Research Methodology. http://www.biomedcentral.com/1471-2288/10/20 3. The English will need careful editing in places before publication. It is intelligible for the most part but there are one or two places where it becomes hard to follow (e.g. p. 10, ll. 13-15 and p. 12, l. 14) I have checked 'major revision' as tackling the assumption of proportional hazards will involve some additional analysis, and not

	just re-writing sections of text. However I think the authors should be able to produce a convincing test of the proportionality assumption without too much extra work. One issue which the authors do not address is how often we are likely to have the data required to compute a time-varying obese years variable. The fact that they have resorted to the Framingham study to test the idea out may be revealing. There are not too many data sets as comprehensive as the Framingham study out there! So although the obese-years idea is great in theory (and would be great in practice if the data to apply it were available) it is only rarely that we are likely to possess the data to use it. Moreover, I do not think from the authors' own results in Table 5, that the use of obese-years provides such a great additional precision in predicting the risk of cardiovascular disease compared with Level of BMI to justify the additional cost of collecting these data specifically for this analysis.

REVIEWER	Andre P Kengne South African medical Research Council
REVIEW RETURNED	07-Jul-2014

GENERAL COMMENTS	This manuscript is essentially inspired by a paper published by the same authors about two years ago (their reference 7), but for a different outcome (incidence diabetes); as such there are overalaps between the two manuscript Estimating the risk of cardiovascular disease using an obese-year metric In the current manuscript, Dr Abdullah and co-workers have reproduced for the outcome of 'incident cardiovascular diseases', analyses they published about two years ago for the outcome of 'Incident type 2 diabetes' (their reference 7 or Am J Epidemiol. 2012;176(2):99–107). The current paper essentially extend to CVD their previous findings for diabetes, by showing that combining both the level of obesity and the duration of obesity likely better capture the predictive information for the exposure to obesity in relation with the occurrence of major obesity related outcomes. Major comments This work has value by providing concrete data to support the contribution of cumulative exposure to obesity to disease risk. However, unlike the authors' conclusion, the integration of this information in routine quantification of population's risk from obesity is not straightforward, and should probably not form a recommendation. The analogy to cumulative exposure to smoking is not all correct: 1) The zero level exposure to active smoking truly exist, while the zero level exposure to obesity (in this study) is rather an artificial construct considering the continuous association between level of adiposity and disease risk. The use of BMI 30 kg/m2 as a threshold for instance in this study suppose BMI below 30 does not cover disease risk, which is not true. 2) Measurement of the cumulative exposure to active smoking can be more accurately done using a retrospective approach, meaning that such a measurement can be readily available at the population level. Measurement of cumulative exposure to obesity is more likely to be captured rather prospectively considering the requirement to measure BMI at several time-points; and as shown in this study, even in good cohort like the Framingham, such a measurement is not always complete for all participants. As such, the complexity of

	the measurement of the cumulative exposure to obesity makes it a less appealing marker of obesity in the assessment of population risk. For such a purpose, simplicity is the rule. 3) Even in the current study, what the authors' perceive as a discriminatory advantage of cumulative exposure of obesity (differences in AIC) is very small and would be clinically trivial to justify the adoption of obesity-years over simple measures like BMI alone. The authors should probably tone down on this claim of superiority and discuss the clinical significance/relevance. Other comments - Table 1 in this paper is not that different from Table 1 in Am J Epidemiol. 2012;176(2):99–107. The authors should consider presenting it differently. Since they use stratified analyses by gender throughout the manuscript, perhaps in addition to the total, they should also show data for men and women separately in Table 1 and provide the p-values for comparison. - Both the cumulative obesity duration and obese-years are likely skewed variables. Should median not be a better measure of central tendency for those parameters?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1: Dr Andrew Hinde

Comment No. 1

1. The computation of the obese-years variable is not described clearly enough on p. 8, ll. 12-17. I should like an example to be added to make the computation clear. For example, consider a person who at seven consecutive observations and had a BMI of 27, 29, 31, 34, 35, 29 and 29 respectively. My understanding is that this person's obese units at the seven observations are 0, 0, 2, 5, 6, 0 and 0. This person would therefore contribute (2 + 5 + 6) x 2 = 26 obese-years (assuming each observation was two years apart). Is this correct? If so, I think an example like this would make the computation clearer.

Our response

In the revised version, the computation of obese-years variable has been described in detail, including illustration of the Calculation of an Obese-Years Construct for a Single Hypothetical Individual.
The following paragraphs have been added in the methodology section, page 10 and 11.

Table 1 illustrates the calculation of obese-years for a single individual. This participant first had a measurement of obesity at examination 2 and was assigned obesity duration of zero at this examination. At examination 3, this participant was assumed to have lived with obesity for 2 years (the interval between examination 2 and examination 3) with a degree of obesity of 1 kg/m2. This approach assumes that an individual's BMI is carried forward from a given examination (i.e., examination 2) and does not change until a different BMI value at a subsequent examination (i.e., examination 3). The number of obese-years at examination 3 was therefore 2 obese-years (1 BMI unit X 2 years in the preceding interval). From examination 3 to examination 4 (a 3 year interval), the participant was still obese with a degree of obesity of 3 kg/m2 (BMI 32 kg/m2). At examination 4, the number of obese-years was 9 (3BMI unit X 3 years) and the cumulative obese-years at this examination was 11 obese-years (2 plus 9).

This method implies that individuals accumulating 50 obese-years, for example, could have reached this quantity either by having been obese with BMI of 30 kg/m2 for approximately 50 years or by having been obese with BMI of 34 kg/m2 for approximately 10 years or, indeed, many other combinations.

Comment No. 2

2. The authors do not say anything about whether the assumption of proportional hazards is valid. This should be rectified. They are using a model with time-dependent covariates, although so far as I can make out they are not using duration itself as a covariate. This means that they still need to test whether the impact of obese-years on the hazard is the same at all durations. See the excellent review of this issue and some suggestions for testing by Bellera et al. (2010) 'Variables with time-varying effects and the Cox model', BMC Medical Research Methodology. http://www.biomedcentral.com/1471-2288/10/20

Our response

In our study obese-years and other time-dependent variables were included in the model as time-varying covariates and not as variables with time-varying effects as discussed by Bellera et al. (Bellera et al., 2010) although we recognize the close similarities of the two (Dekker et al., 2008) and in particular note that they define non-proportional hazards models (the time-dependent effect version being a common solution to invalid proportional hazards assumptions). The extended time-dependent Cox regression model implies non-proportional hazards although recognition of this does complicate the interpretation of the resulting “hazard ratios” (Fisher and Lin, 1999, Kleinbaum and Klein, 2005, Dekker et al., 2008, Cleophas and Zwinderman, 2013). Hence we have provided additional detail on the model structure on this issue and emphasized reference to Chapter 6 of the textbook by Kleinbaum & Klein.

Comments No. 3

3. The English will need careful editing in places before publication. It is intelligible for the most part but there are one or two places where it becomes hard to follow (e.g. p. 10, ll. 13-15 and p. 12, l. 14)

Our response
The text has been edited extensively throughout the article. The changes have been highlighted.

Additional comment (No 4)

One issue which the authors do not address is how often we are likely to have the data required to compute a time-varying obese years variable. The fact that they have resorted to the Framingham study to test the idea out may be revealing. There are not too many data sets as comprehensive as the Framingham study out there! So although the obese-years idea is great in theory (and would be great in practice if the data to apply it were available) it is only rarely that we are likely to possess the data to use it. Moreover, I do not think from the authors' own results in Table 5, that the use of obese-years provides such a great additional precision in predicting the risk of cardiovascular disease compared with Level of BMI to justify the additional cost of collecting these data specifically for this analysis.

Our response

We acknowledge that a major challenge in examining the obese-years metric is to have information on both the degree of obesity and the duration of obesity. It is true that not many cohort studies measure obesity and health outcomes regularly like FHS. However, we believe that it is important to explore whether there would be value in more detailed assessment of height and weight on multiple repeated occasions in future cohort studies.
We believe our results inform both future epidemiological analyses, suggesting that the risk of obesity on some health outcomes is being underestimated if duration is not being taken into account. In addition, the results inform public health policy, demonstrating further rationale for preventing weight gain and delaying onset of obesity.

Reviewer 2: Dr Andrea P Kengne

Comment No 1:

This work has value by providing concrete data to support the contribution of cumulative exposure to obesity to disease risk. However, unlike the authors' conclusion, the integration of this information in routine quantification of population's risk from obesity is not straightforward, and should probably not form a recommendation.
The analogy to cumulative exposure to smoking is not all correct: 1) The zero level exposure to active smoking truly exist, while the zero level exposure to obesity (in this study) is rather an artificial construct considering the continuous association between level of adiposity and disease risk. The use of BMI 30 kg/m2 as a threshold for instance in this study suppose BMI below 30 does not cover disease risk, which is not true. 2) Measurement of the cumulative exposure to active smoking can be more accurately done using a retrospective approach, meaning that such a measurement can be readily available at the population level. Measurement of cumulative exposure to obesity is more likely to be captured rather prospectively considering the requirement to measure BMI at several time-points; and as shown in this study, even in good cohort like the Framingham, such a measurement is not always complete for all participants. As such, the complexity of the measurement of the cumulative exposure to obesity makes it a less appealing marker of obesity in the assessment of population risk. For such a purpose, simplicity is the rule. 3) Even in the current study, what the authors' perceive as a discriminatory advantage of cumulative exposure of obesity (differences in AIC) is very small and would be clinically trivial to justify the adoption of obesity-years over simple measures like BMI alone.
The authors should probably tone down on this claim of superiority and discuss the clinical significance/relevance.

Our response

• It is true that this analysis builds upon the previous work that we published in American Journal of Epidemiology but the outcome is different. In the previous analysis, it was found that the obese-years metrics provides more precision in estimating the risk of type-2 diabetes. Using the same approach, the analysis in this paper aimed to test whether the obese-years metric also provides more precision in estimating the risk of CVD. The overlap, in terms of the population used and the methodological approach taken is unavoidable.

• It is true that the analogy between obese-years and pack-years is limited. We have deleted this from the introduction and we have increased the clarity on this point in the discussion section. We feel it is still a useful analogy to improve the reader's understanding of the concept.

• Although AIC suggested that the obese-years metric provided more precision than the level of obesity or the duration alone, we agree that the results do not warrant a strong claim that obese-years model is superior compared to other two models because the differences in AIC are relatively small. Therefore, the conclusion has been revised as below:

In the previous version:

Conclusions: This study confirms that the obese-years construct is an independent risk factor for CVD. Obese-years metric is a better predictor the risk of CVD although it shows similar risk estimation to other two models.

Now in the revised version.

Conclusions: This study demonstrates that the risk of CVD associated with obesity is derived both from the level of obesity attained and also the length of time lived with obesity. The obese-years metric conceptually captures the cumulative damage of obesity on body systems, and is found to provide slightly more precise estimation of the risk of CVD than level or the duration of obesity alone.

• In addition, the clinical implication of this study has been discussed in the revised version of the manuscript as below
It is important that these results inform future epidemiological analyses, as they suggest that the risk of obesity on some health outcomes is being underestimated if duration is not being taken into account. This has consequent implications for underestimation of obesity-related burden of disease modelling and cost-effectiveness analyses. In addition, the results inform public health policy, demonstrating further rationale for preventing weight gain and delaying the onset of obesity.

Additional Comment:
-Table 1 in this paper is not that different from Table 1 in Am J Epidemiol. 2012;176(2):99–107. The authors should consider presenting it differently. Since they use stratified analyses by gender throughout the manuscript, perhaps in addition to the total, they should also show data for men and women separately in Table 1 and provide the p-values for comparison.
-Both the cumulative obesity duration and obese-years are likely skewed variables. Should median not be a better measure of central tendency for those parameters?

Our Response:

In the revised version, table 1 (table 2 in revised version) has been presented differently, stratified by gender (including P value for difference proportion/median between males and females) as suggested.
The cumulative obese-years also is now summarized using median instead of mean.

Thank-you once again for the opportunity to respond to the reviewer's comments and we look forward to hearing from you.

Best regards

Dr Asnawi Abdullah
On behalf of the authors

REFERENCE
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concepts illustrated with a prognostic factor study in breast cancer. BMC Med Res Methodol, 10, 20.
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VERSION 2 – REVIEW

REVIEWER	Andre P Kengne South African medical Research Council
REVIEW RETURNED	28-Aug-2014

GENERAL COMMENTS	The authors should consider turning the p-values showing 0.000 into p<0.001