Author's response to reviews

Title: The association of education with body mass index and waist circumference in the EPIC-PANACEA study

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Author’s response to reviews: see over
Replies to the reviewers’ comments

Reviewer: Marjaana Lahti-Koski
Reviewer’s report:

Major compulsory revisions

The associations of BMI and waist circumference with education were examined for the total EPIC cohort and by country. Given that both education level (as shown in Table 1) and the levels of obesity/abdominal obesity (my personal assumption) vary across the countries, analyses concerning the total cohort need to be adjusted for country (results presented in tables 3-4). As far as I understand it correctly, this geographical variation was taken into account in analyses using multilevel mixed linear models as stated in statistical methods.

Reply: The reviewer is correct. This has been described in the Methods section, page 7, lines 18-23.

I think, however, that this information needs to be given in tables 3-4, too.

Reply: We added a footnote to Tables 3 and 4.

My further comments on statistical analyses include concerns on adjusted models used. As both education and obesity are strongly age-dependent, it would be important to investigate the associations using age and country adjusted models. I think the main results to be based on these analyses. After that the effects on energy intake, physical activity and other lifestyle factors might be investigated using full models to see if the associations between SES and obesity are explained by differences in these factors. In sum, I suggest three models to be used and results to be presented in tables 3-4: crude, age-adjusted, age+lifestyle adjusted (incl. adjustment for region).

Reply: We agree with the reviewer that both obesity and education are age-depending. We have therefore shown crude and adjusted results in Tables 3 and 4 for all participants. However, we believe that showing crude information also for sub-analyses does not add much information and we prefer not to show crude results for sub-analyses.

In tables 3-4 also results on secondary analyses were presented. It remains unclear, however, for which variables these analyses were adjusted.

Reply: All models shown in Tables 3 and 4 were adjusted for the same set of variables as indicated in the footnote of the tables. We added the footnote to Table 4.

In the abstract, it was stated that in all three higher education categories BMI and WC were lower than in the lowest educational group, consistently across all countries. The presented results support this statement for the total cohort but not for all countries since data by country (supplementary figures 1-4) were presented only by comparing the lowest education level with the highest, not with intermediate levels.

Reply: We agree with the reviewer that our statement in the Abstract is not evident from the results shown in the Results section. We changed the Results section on page 8 as follows: “For all countries, but men of the Greek and Danish cohorts there was a clear trend between level of education and BMI; however, in all countries, BMI was significantly lower for all three higher education categories compared with the lowest education level (data not shown).”

Minor revisions

In the abstract, there is no need to present results with two decimals (e.g 2.12) but one decimal will do.

Reply: Changed.

In tables 3-4, instead of abbreviation “smk” I would prefer smoking.

Reply: Changed.

In the figures, an explanation for dotted vertical lines should be given.

Reply: We added the following to fig. 1-4: “The dotted vertical line indicates the overall mean difference between highest and lowest educational level.”

Results by country are mean differences with confidence intervals, I assume.

Reply: Yes. We added this to the legend of the figures.

Discretionary revisions
In the methods it was said that total energy intake was computed from the dietary assessment instruments. More information on dietary assessment methods should be given (base on FFQ, 24h RC or what).

Reply: We added the following to the Methods section on page 6: “Seven countries adopted an extensive self-administered dietary questionnaire. In Greece, Spain and Ragusa a dietary questionnaire was administered by direct interview. A food frequency questionnaire and a seven-day record were adopted in the UK. In Malmö, Sweden, a quantitative questionnaire combined with a 7-day menu book and an interview was used.”

Referring to table 2 it was said that subjects with a low educational level were shortest. This information, however, was not given in the table.

Reply: The reviewer is correct. We deleted this statement from the text.

I understand that data for this study were comprised from an ongoing prospective cohort study, and in EPIC reports it is important to state at which stage the information was collected. As a whole, however, the data used in this particular study were collected at baseline, and thus the design here is cross-sectional. Therefore, I find it a bit confusing to talk about baseline data randomly in different places. For example, referring to table 2 in the results it was said that women had the lowest alcohol consumption at baseline whereas the baseline data were not referred to regarding physical activity. Similarly, in the title for table 2, it might be no need to talk about baseline characteristics but only about characteristics.

Reply: The reviewer is correct that it might be confusing when we refer to “baseline characteristics” in some parts of the text, but not in others. In Table 1, we prefer to keep the term “baseline characteristics” as these characteristics were indeed assessed at recruitment of the participants. We now start this paragraph on page 8 with “Baseline characteristics of the study participants are shown in Table 2.” We deleted the word “baseline” when describing alcohol consumption by different educational categories in Table 2.

BMI information was available for all subjects whereas only 73% of the subjects had information on waist circumference. I wonder whether these missing values (27%) were equally distributed across the subsamples, and if this had any effect on results. I suggest this issue to be considered to be included in discussion.

Reply: Waist circumference has not been measured in Norway, Umea, and in the majority of the French cohort. In all other centers, waist circumference is available for more than 90% of the study participants. We, therefore, think that this does not introduce bias into our results as the missing of information on waist circumference does not depend on educational status. We added this information to the Methods section.

Reviewer: Benoit Salanave
Reviewer's report:

- Major Compulsory Revisions
  1) It is not possible to write that anthropometric measurements were “highly standardized” when:
  - information on weight and height were self-reported in 3 countries and measured in 7 others,
  - body measures have been predicted using linear regression in the Oxford centre (but not in the other centres in which self-reported data have been collected),
  - a “method for correcting for different measurement protocol among centers” has been used “to reduce heterogeneity due to protocol differences in clothing worn during measurement”,
  - WC were measured “either at the narrowest torso circumference or midway between the lower ribs and the iliac crest” (the narrowest torso circumference is usually not recommended due to a lack of accuracy),
  - information “were assessed using questionnaires and/or interviews” according to each country.

I agree with the authors that underreporting has probably caused a weaker association between BMI and SES, but the other discrepancies between protocols need to be analysed and discussed in a specific paragraph of the discussion.

Reply: We deleted the words “highly standardized” from the text. We rewrote parts of the Discussion (page 12, line 1-5). However, we would like to stress here that the majority of data have been measured in a standardized manner in the core countries of the EPIC cohort (i.e., France, Spain, most Italian centers, Great Britain, Germany, Netherlands). Results from countries, which have measured data are very comparables.
2) Differences between country cohorts need to be clarified and discussed. This major point is tackled in one sentence (the last one) at the end of the discussion. The fact that “comparisons between cohorts should be interpreted with caution” because “the cohorts are in the majority not representative of a country” should be discussed in a specific paragraph, earlier in the discussion, and examined in more details. Which are the consequences to pool such different populations together (teachers, blood donors, participants in breast cancer programs, vegetarians) for both, the comparison between cohorts and, the assessment of the association between BMI/WC and education?

Reply: We discussed differences between the cohorts in the third paragraph of the Discussion (starting at the end of page 10). We moved part of the last paragraph of the Discussion (“In our analysis, it has to be taken into account, that although most cohorts were recruited from the general population, the cohorts are in the majority not representative of a country. Furthermore, as some cohorts have been recruited from specific subgroups of the population such as blood donors comparisons between the cohorts should be interpreted with caution.”) to the end of this paragraph to better connect these two parts.

More details on the recruitment in the different countries are needed: date of recruitment varies from 1992 to 2000, age ranges are not described (were they different between countries? “in majority 35 to 70 years of age” is not informative).

Reply: We agree with the reviewer that it would be very interesting to give more information on recruitment details of the EPIC participants in the cohorts. However, due to space constraints we do not want to extend this section of the manuscript. Instead, we refer to a publication by Riboli et al. (2002; European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection), in which the recruitment procedures and details on the participants have been described in detail. There, it is also listed that most of the cohort members were in the age of 35-65 years.

Further more, I think it is important to give details on inclusion procedures: individuals were not randomly selected but were volunteers.

Reply: Of course, all participants are volunteers. However, in most study centers, participants were recruited from the population of this city, region, or country. Others were recruited from specific groups of the population, such as blood donors, participants in cancer screening programs etc. This is described in the Methods section. However, due to lack of space, we do not want to go too much into detail but rather refer to the paper by Riboli et al. (2002).

It is also important to explain that, although EPIC is a prospective cohort study, analyses for this paper have been realized on cross-sectional data collected at recruitment.

Reply: We agree with the reviewer that this analysis is a cross-sectional analysis as all information has been assessed at baseline. However, our “exposure” variable is highest educational degree, which has been obtained in the past.

3) An other important point is not discussed, the fact that more than a quarter of the study population (27%) has missing data for WC. What is the effect on the association between WC and SES? This point must be mentioned at least in the discussion. In addition, it should be necessary to compare excluded subjects and subjects for which WC data were available.

Reply: Please see our reply to the last comment by reviewer 1.

4) Another point concerning missing data needs to be clarified. In “Materials and Methods / Covariates”, the authors explain that missing data has been defined as a specific category for smoking status, physical activity and marital status. Then, in table 2, these three variables are differently presented: smoking status has a footnote explaining that percentages don’t "add up 100% due to missing information" , physical activity has percentages that add up 100% (missing data would have been excluded in fact, contrary to what is written in the Methods?) and missing data for marital status are notified in a specific line?

Reply: According to the suggestion of the reviewer, we added lines with % missing information for smoking status and physical activity to Table 2.
5) In “Materials and Methods / Anthropometric measurements”, the definition of overweight according to the WHO is not correct. As mentioned in http://apps.who.int/bmi/index.jsp?introPage=intro_3.html, overweight for WHO is BMI ≥25 without upper limit. 

Reply: We agree with the reviewer that WHO does not refer to the category of BMI 25-29.9 kg/m² as overweight but rather as pre-obese. However, according to usual use of the term overweight, we prefer to use the term overweight for participants with a BMI 25-29.9 kg/m². We will delete the WHO reference (as suggested by this reviewer in comment 12).

6) In the "discussion, 5th paragraph", the authors discuss about the choice of education as an indicator of SES but they don’t argue that education is considered to influence obesity-related health behaviour (Ball K, Soc Sci Med 2005,60:1987-2010). Compared to occupation and income, education is assumed to be stable throughout life and to reflect childhood conditions. In the GLOBE longitudinal study (Giskes K, Obesity 2008,16:1377-1381) both childhood and adulthood socioeconomic deprivation increase the risk of overweight in adult women, whereas only adult SES influences overweight in adult men. Since the publication of the review of Sobal and Stunkard in 1989 (Sobal J, Psychol Bull 1989,105:260-75), several cross-sectional and longitudinal studies have shown a more consistent relationship between SES and overweight in women than in men (Wardle J, Am J Public Health 2002,92:1299-1304 / Wardle J, J Epidemiol Community Health 2001,55:185-190 / Novak M, Int J Obes 2006,30:191-200). Although occupation, income and education are not completely independent, it would be of interest to discuss more in depth the influence of these three SES dimensions on the relation between SES and overweight or obesity (Turrell G, Public Health Nutr 2003,6:191-200).

Reply: We agree with the comment of the reviewer that occupation, income, and education are used to define SES, and each of these variables reflects specific aspects. We re-worded the last paragraph of the Discussion by adding the suggestions of the reviewer. However, we believe that it is beyond the scope of this manuscript to discuss the advantages and disadvantages of education, income, and occupation as indicators of SES in detail, since we do not have this information in EPIC for the majority of centers. The view of our work is exclusively focusing on education, as already reflected in the title.

- Minor Essential Revisions

7) Introduction / last sentence: delete “highly standardized”.

Reply: Done.

8) Materials and Methods / Population and study design: “(in majority 35 to 70 years of age)” give detailed age-range by country.

Reply: As we explain in our reply to comment 2, this will be too much information and we, therefore, refer to the publication by Riboli et al. 2002.

9) Materials and Methods / Population and study design / 2nd paragraph: “we excluded subjects with missing information on dietary and non-dietary variables” ie all variables? But smoking status, physical activity and marital status have a specific missing category and are not concerned?

Reply: Participants are excluded from the dataset if they did not fill in the dietary questionnaire and/or the core lifestyle questionnaire. For dietary data, checks on completeness were run and participants were asked to complete missing information if at least parts of the questionnaire have been completed. Therefore, for example, alcohol consumption is not missing for any participant included in our analyses. Other variables that have not been assessed in all centers, such as marital status and physical activity do not lead to automatic exclusion because this would result in the exclusion of complete centers. For these variables, we created a missing category in our analysis. Moreover, it should be of interest to know if the subjects with missing data on alcohol consumption, for example, have been excluded or not? This point needs clarifications.

Reply: Please see our previous reply.

10) Materials and Methods / Anthropometric measurements / 1st paragraph: “For part of the Oxford (UK) cohort [add: for which measured data were not available], linear regression models were used …”.

Reply: Done (page 6).
11) Materials and Methods / Anthropometric measurements / 1st paragraph: “The measured anthropometric data were adjusted to reduce heterogeneity …” Although reference is mentioned, a few words are needed to explain how data were adjusted.

Reply: We changed the sentence as follows “To reduce heterogeneity due to protocol differences in clothing worn during measurement, correction factors of – 1.5 kg for weight and – 2.0 cm for WC were adopted for subjects who were normally dressed and without shoes, while an adjustment for weight of – 1.0 kg was applied for subjects in light clothing.” (page 6, line 28-32).

12) Materials and Methods / Anthropometric measurements / 2nd paragraph: delete “according to the World Health Organization guidelines”.

Reply: Done.

13) Materials and Methods / Covariates: it is important to mention that all variables were recorded at recruitment at baseline (not only age).

Reply: See our reply to a similar comment by reviewer 1.

14) Materials and Methods / Statistical methods / 1st paragraph: UK is mentioned neither in the list of countries with one centre nor in the list of countries with more than one centre?

Reply: We added the UK to the countries with more than one center (page 7).

15) Results / 2nd paragraph: the comments on table 2 have to be revised. The authors write that “subjects with a low educational level were … shortest” but height is not mentioned in the table, “they were more frequently current smokers” but it is not the case for women.

Reply: We deleted the comment that subjects with low educational level were shortest (see our reply to a similar comment by reviewer 1) and modified our sentence on smoking habits by educational level (page 8, line 22).

16) Results / 4th paragraph: Figures have been inverted between men and women.

Reply: We reordered the figures.

17) Results / last paragraph: idem for Figures numbers. I have not understood the last sentence: What “also” refers to? What is concerned by the “respectively”? Is non-significant difference compared to low education or is it between secondary and professional schools?

Reply: We rewrote the last paragraph and think that our wording is clearer now.

18) Discussion / 2nd paragraph: replace “(see Table 1)” by Table 2

Reply: Done.

19) Discussion / 5th paragraph: delete “highly standardized measured anthropometric data for most participants”.

Reply: Done.

- Discretionary Revisions

20) I’m surprised by the fact that no French women have attained the “vocational secondary education” category. Does it mean that definitions of education levels could be so different between countries? Or is there a particular reason?

Reply: The difference between France and other countries in our studies is due to the fact that only members of a health insurance plan for school employees were included in the cohort. This includes mainly teachers but also other school workers. The latter includes women with either only primary school or women with another secondary education than a vocational training.

21) I’m also surprised by the important rate of missing data for the marital status. This rate varied strongly by education level. Did it vary by country, too? It is probably one of the main reasons to explain that “adjusting for marital status did not change the results”.

Reply: Marital status was not assessed in the Spanish and Danish centers. Rather than excluding participants with missing information (which excludes complete centers), we introduce a missing category into our models.

Reviewer: Pedro Marques-Vidal
Reviewer's report:
Major compulsory revisions
In the methodology, the authors state that educational level was classified into four (4) groups (primary school or less; vocational secondary education; other secondary education and university). Still, in table 1, the educational level is presented in five (5) categories. For clarity, all data should be presented using the initially defined four categories.

Reply: We changed Table 1 according to the suggestion of the reviewer and now show “no formal degree” and “primary school completed” combined

Also in the methodology, the authors state that a “missing” category for physical activity was created. Still, in table 1, the “non-missing” categories add to 100, while for smoking (which also includes a “missing” category) it is indicated that the percentages do not add to 100 due to missing data. Again, for clarity, it would be better to state in table 1 the percentages corresponding to the missing data for smoking and physical activity, as it was made for marital status.

Reply: Please see our reply to the same comment by reviewer 2.

It is somewhat strange that relatively “neutral” data such as physical activity is missing, while other data such as drinking has no missing data. This should be clarified.

Reply: Please see our reply to the same question by reviewer 2.

In the methodology, alcohol consumption was divided in six categories for women and seven for men, but in table 2 only two categories (0-6 and ≥6 g/day) are presented. Also, in table 3, were the data adjusted for the 6/7 categories or the two categories of alcohol consumption?

Reply: Due to space constraints, we collapsed categories of higher alcohol consumption in Table 2. In Tables 3 and 4, the analyses were adjusted as described in the Methods section (i.e., for 6 or 7 categories).

In the results (line 2), it would be better to state “men having completed primary school ONLY ranged…” as all subjects with an University level (for example) have also completed primary school. Similar comment for women.

Reply: We changed the text according to this suggestion.

In table 1, the authors should explain the 0 (zero) percent of women with educational level 2 in France.

Reply: Please see our reply to the same comment by Reviewer 1.

Minor essential revisions

In table 1, some percentages add to 100.1 instead of 100 (Italy, the Netherlands, German women) or to 99.9 (Greek men). Also, some percentages are presented with two decimal figures (Germany and Sweden men); one decimal would be enough.

Reply: Inconsistencies are due to rounding errors. However, rather than artificially deciding not to round a figure to achieve 100%, we prefer to keep the number as they are (and were computed).

In table 2, is alcohol consumption for all subjects (including nondrinkers) or drinkers only?

Reply: Mean alcohol consumption was computed from all subjects including non-drinkers.

Figures 1-4: it would be good to draw a line at the zero (0) level, so the reader can see if the difference is significant or not (which is the case of waist in France).

Reply: Done. Figures have been replaced.

Also, indicate in the figure legends that the results shown are (I think) adjusted differences and 95% confidence intervals.

Reply: See our reply to reviewer 1.

In the references, please include accents in the names of the authors (ref. 13: Mäkinen, Prätällä; ref. 15: Pérez-Rodrigo, etc.)

Reply: We checked the spelling of the authors’ names in the reference list.

Reviewer: Jean Dallongeville

Reviewer's report:

Minor comments.
Although SES and education tend to correlate there is no perfect overlap between the two indicators. In the introduction of the manuscript the authors seem not to distinguish SES and education in their report of NHANES 1999/2000 data.

Reply: The authors of the referenced publication state that they used the variable “education” as an indicator of SES in their analysis. To be more neutral, we changed the wording of the sentence in the Introduction as follows: “Data from NHANES 1999/2000 survey have shown a higher prevalence of obesity in low educated men and women compared with high educated subjects, although the difference between these groups decreased between the survey in the early 1970s and the 1999/2000 survey [4].”

Similarly, in the discussion the authors mention that they "used education as an indicator of SES". I am not sure whether education is an appropriate surrogate of SES. There are (I don't recall exactly the reference) indications that education and other indicators of SES, such as occupation or income, are independently associated with obesity and gender. I recommend to suppress this part of the discussion (starting "Education was used…..to dissatisfaction in wome as well as in men") that is misleading.

Reply: According to the reviewer’s suggestion we deleted the paragraph (marked using “strikethrough”).

Would you please check the legend (or the numbering) of the figures. I believe there is an inversion of gender.

Reply: Please see our reply to the comments made by previous reviewers.