Author's response to reviews

Title: Validation of self reported diagnosis of hypertension in a cohort of university graduates in Spain

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Author’s response to reviews: see over
We appreciate very much the comments raised by the reviewers and answer them point by point. In **bold text** we point out the reviewers’ comment, and in plain text we include our responses.

**Reviewer 1 (Dr. Takayoshi Ohkubo)**

1. Abstract, main results, line 2, and Introduction, 3rd Para, line3
   Although the authors used the term “direct measurement of blood pressure”, this term generally means “invasive intra-arterial measurement of blood pressure”. Please change it to” conventional measurement of blood pressure”.
   We have modified both sentences as suggested.

2. Methods, Questionnaires, lines 4-5 “…and their most recent BP measurement…”
   Did the BP measurement include ambulatory blood pressures or blood pressures measured at home? Please clarify if it included only conventional casual (clinic, office, screening) blood pressures or not.
   The questionnaire did not specify the type of BP measurement, so it is assumed that included both causal BP determinations and more formal BP measurements performed with diagnostic purposes. We have included a brief sentence in the methods section explaining this issue.

3. Methods, Validation study, line 3, “Based in results from the literature, ……”
   Please insert appropriate reference(s).
   We have included the references used to estimate the expected positive predictive value.
4. Methods, Validation study, 4th Para
Please describe the methods of blood pressure measurements in detail. Did doctors, or nurses measure the blood pressures? For those who took antihypertensive medication, were their blood pressures measured after administration of the antihypertensive drug(s)? Has the device used (Omron M4-I) been enough validated? Refer the validation paper(s) or website http://www.dableducational.org/
We have included more detailed information about the BP measurements. The BP determinations were performed by medical doctors (AA, JJB). We did not ask participants to stop taking any medication. Nonetheless, the interview gathered information about use of antihypertensive drugs, because current use of antihypertensive medication was confirmatory of true hypertension. For our validation purposes, it did not matter if the final hypertension diagnosis was made based on the use of antihypertensive medication or BP figures. Finally, as suggested, we have included the reference for the validation study of the measurement device.

5. Results, 3rd Para and Table1
Indicate p-values for the differences between (or “among” for the age) subgroups. We have included the p-values for the comparisons between groups.

6. Discussion, 2nd Para
Please insert appropriate reference(s) for the EPIC-Murcia cohort.
As commented, we have included the reference.

7. Discussion, 6th line from the end “…………. a possible white-coat effect”.
Please insert appropriate reference(s).
We have included a reference to support this statement.

Discretionary Revisions (which the author can choose to ignore)
It would be of interest if there were substantial differences in the results according to the faculties /departments the participants graduated, for example, medicine, nursing, health science versus others, etc.

We have included in table 1 the separate results for those with and without a biomedical degree. Validity was better for graduates from biomedical/health sciences schools, but the number of biomedical graduates was low to observe statistically significant differences.

Reviewer 2 (Dr. George Stergiou)

General

1. The study sample is too small to address this issue and, therefore, this work can only be accepted as a pilot study.

We concur with the reviewer in his comments about the small sample size of our study. Nonetheless, we believe that this study offer enough information to answer our research question: is the self-reported diagnosis of hypertension provided by the participants in the SUN cohort valid enough as to be used as an outcome or as a confounding variable?

In the future, we will try to conduct a larger validation study that allows us to determine those factors associated to misclassification and to correct in some degree this type of error.

2. Important findings based on subgroup analysis regarding the effect of age or sex on validation of self-reported hypertension cannot be investigated.

We agree. The limited sample size precludes any meaningful conclusion about differences in subgroups. We include this information mainly for descriptive purposes. In fact, the table 2 (table 1 in the initial version of the manuscript) now includes p-values for comparison between groups. Those comparisons show that there are no differences in validity among different subgroups (with the exception of those with a family history of hypertension).

3. Why did the investigators select an even smaller control group?
Our sample size calculations were based on an 80% positive predictive value and a 90% negative predictive value. Accepting the same precision for both measures, the number of individuals required is lower when the expected proportion moves further away from 50%. That is the reason for a lower number in the ‘control’ group (Elashof JD, Lemeshow S. Sample size determination in epidemiologic studies. In: Ahrens W, Pigeot I. Handbook of epidemiology. Berlin: Springer-Verlag, 2005;562-4.).

4. Table 2: The confidence intervals suggest low precision of the study and need for larger study sample.
We agree. As we have commented in point 1, in the future we will try to perform a new and more powerful validation study. However, we consider that the reported results help to decide whether self-reported hypertension is valid enough as to be used in future analysis in this cohort.

5. There is a potential for a selection bias because study subjects were participants of cohort study. These suspects are being regularly asked about their hypertension status and blood pressure levels. As a result it might be more likely that these subjects have their blood pressure measured. Therefore, the information they provided regarding hypertension diagnosis might be more reliable than non-study participants.
Our stated aim was not to extrapolate our results to the Spanish general population, but to apply these results precisely to the educated and health-conscious participants of this cohort. Most probably the participants in the cohort are more health conscious than non-participants. But, actually, this is one of the main advantages of the cohort: the health information provided by these individuals will be more accurate increasing the internal validity of findings. This is the reason also to include university graduates. They have a higher educational level and, then, they will provide more precise information. A similar approach was followed for the Nurses’ Health Study or the Health Professionals Follow-up Study, conducted at Harvard School of Public Health. Both cohorts selected a population with high educational level, particularly in health-related issues, and probably very motivated to participate in a follow-up study. Both facts are not obstacles for the
internal validity of their results. However a cautionary advice is appropriate regarding external validity and generalizability of the results.

Our participation proportion in this validation study was relatively high, 80%, and it allays threats of an important selection bias. That is, we feel confident in the internal validity of our results, i.e. the observed results can be directly applied to the whole cohort.

Our objective was not to assess whether the self-reported diagnosis of hypertension is valid in the general population but whether that self-reported diagnosis is valid in our cohort. Once we have shown that that information is valid in our population (internal validity), we could think about the generalizability of our results (external validity). But that is not our main objective and we leave that decision to the paper’s reader.

**Major Compulsory Revisions**

1. **How many subjects in each group were treated for hypertension?** In treated subjects the validation of self-reported hypertension is not a big issue. The challenging question is the validation of self-reported diagnosis in untreated subjects. These diagnoses are questionable and therefore require separate analysis and report.

There were no antihypertensive drug users among those not reporting a diagnosis of hypertension, and 46% of those reporting a diagnosis of hypertension (36 out of 79) were under antihypertensive drug treatment at the moment of the interview. Among the remaining 43, only 14 (33%) had BP measurements under 140/90 and were not receiving drug treatment for hypertension. To comply with your suggestion, we now include this information in the results.

However, although it is very likely that individuals taking antihypertensive medication will report a diagnosis of hypertension, we had to check this assumption. In fact, if the gold standard had been only "being currently under antihypertensive medication", the sensitivity and the negative predictive value would have been 100% (because there would be no false negatives).
2. A table providing comparative information of the two study groups regarding the available parameters (age, sex, BMI, confirmed hypertension, confirmed normotension and over- and underdiagnosed hypertension) should be added.

According to your suggestion, we have included a new table (table 1) with this information. Information about confirmed normal blood pressure and about over- and under-diagnosed hypertension is already provided in table 2 (table 1 in the first version of the manuscript).

3. 95% confidence intervals for sensitivity, specificity and kappa should be provided.

Our study design does not allow the direct computation of confidence intervals for sensitivity, specificity and kappa indexes because the sampling method was based in the proportions for self-reported classification and not in actual diagnoses of hypertension (a similar method was used by Colditz et al. Am J Epidemiol 1986;123:894-900 and Ascherio et al. Circulation 1992;86:1475-84, refs. 5 and 19 in the revised version of the manuscript). Based on those sampling fractions we re-built the 2-by-2 table needed to estimate sensitivity, specificity and kappa values. However, that table is not the actual data from our validation study and, then, estimation of confidence intervals directly from that table would give a false sense of precision because we would be using 2929 individuals instead of the 127 participants in the validation study. We have made a reference to this limitation in the discussion.

4. Table 1: p values for comparisons between age groups and BMI groups are needed together with 95% confidence intervals.

Table 1 (table 2 in the new version of the manuscript) now includes p values for comparisons among groups, and confidence intervals for the different estimations.

5. The proportion of invited subjects that was included in the final analysis (about 76%) should be provided in the abstract.

According to your indication, the abstract now includes the proportion of invited subjects included in the final analysis.
6. A reference with validation data confirming the accuracy of the automatic device used for blood pressure measurement should be provided.

According to your indication, now we have included a reference for the validity of the automatic device used in this study.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Table 1: Omit “CI: confidence interval”

In the new version, table 2 (table 1 in the first version) includes confidence intervals. Then, we believe that it can be useful for readers to maintain those words.