Reviewer's report

Title: HYPEST study: Epidemiology of hypertensive patients of Estonia

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Reviewer: Harold Snieder

Reviewer's report:

This paper provides a description of the Hypertension in Estonia (HYPEST) study, which is the country’s first hypertension-targeted sample collection aiming to examine the epidemiological and genetic determinants of hypertension and related cardiovascular diseases in the Estonian population. Estonia has a particularly high prevalence of hypertension with over one third of the population affected. This may be one important explanation of the fact that mortality from CVD of Estonian men before age 65 is three times higher than the average of the EU member states. The authors therefore need to be commended for setting up this study aiming to investigate these major health problems in their country. However, I have a number of concerns and suggestions that may benefit the comprehensiveness and clarity of the paper if incorporated.

1) HYPEST consists of 1007 patients with HTN and 910 controls. To provide a complete and comprehensive description of the study it would have my strong preference to include description of the population controls in the current paper. Please check the numbers throughout the paper, 1007 and 910 do not add up to 1823. The authors mention their study is a case-cohort study, this would imply that the HTN patients are followed prospectively? Or is the data retrospective only? In short, the design of the study is not entirely clear. Perhaps a case-control cohort study, if both cases and cohorts are followed prospectively?

2) Abstract: “The participation rate among men and women was 39 and 61% respectively.” I believe this is simply the distribution of men and women in the case sample as stated later in the results section. Please make a clear distinction between the distribution and the response rate. The latter seems indeed rather different between the sexes but is not explicitly calculated and reported. What was the % of men and women actually participating that were invited to do so?

3) A large part of the paper presents and discusses sex differences. However, the fact that the male/female distribution is not representative of the existing patient population may seriously bias these comparisons. What is the direction of this selection bias? Is there any information on the differences between those males (& females) that participate versus those that do not? Perhaps only the more severe male patients participate? At the very least the selection bias needs to be acknowledged and discussed how it might have affected results.

4) P6: The HYPEST sample was recruited to study genetic epidemiological aspects. However, there is no further mention of this genetic component. Is DNA extracted and stored? Please describe all aspects of data collection as
comprehensively as possible, such that future papers can refer to this one describing the cohort.

5) Abstract: “The age of hypertension onset was significantly correlated with the reduction of smoking (P=0.00007), stress (P=0.0003), overweight (P=0.0003) and alcohol consumption (P=0.004).” The word “reduction” implies a decrease over time, which is probably not what the authors mean here? Also the direction of the association is unclear. How about: “An earlier age of onset of hypertension was significantly associated with smoking (P=0.00007), more stress (P=0.0003), obesity (P=0.0003) and more alcohol consumption (P=0.004).” Another issue here is the definition of the lifestyle factors. Is smoking defined as smoking at the time of diagnosis rather than current smoking? This is what Fig 2 seems to indicate and what I would regard as logical, although the figure legend states it concerns smoking at recruitment, which seems wrong. A cut-off of BMI=30 is used, which is the cut-off for obesity, not overweight. Also, I wonder whether obesity, alcohol use and stress were exposures at the time of diagnosis rather than at the time of recruitment? If not, please explain how current BMI/alcohol use/stress is expected to affect age of onset of HTN. I do believe this is one of the more interesting analyses reported in the paper. However, it is well known that lifestyle factors are often interrelated. My suggestion, therefore, is to include them as predictors in a multivariate model to see which affect age of HTN onset independently. Other lifestyle factors such as physical activity need to be included as well.

6) Availability of current and retrospective BP measures (both pre- and post antihypertensive treatment) is highly relevant in this cohort of hypertensive patients and could be reported in greater detail. For example the distribution of number of measurements collected over how many years in the different categories could be presented in a Table.

7) P 11: “the observed differences among sexes may reflect older age of female compared to male patients (Table 2).” These analyses can and should be adjusted for age to control its influence. Please report age-adjusted p-values only.

8) The distribution of number and kind of prescribed medications is highly relevant and should be presented in greater detail. They can perhaps be incorporated in the Table mentioned under point 6.

9) P12: “This may be related to earlier onset of hypertension in men in general (Table 4).” My suggestion would be to actually test this in the data available. That is, whether an earlier onset of HTN is associated with higher prevalence of MI.

10) P15: “The most common self-reported cardiovascular problem for both sexes was heart arrhythmia, followed by myocardial infarction among men and ischemic heart disease in case of women.” Please note that IHD comes 2nd for men as well (not MI).

11) P16: “increased total and LDL cholesterol”; compared to which reference group? How much is it increased?

12) P16: “Current study clearly demonstrates that reducing the conventional life-style risk factors could decrease the age of hypertension onset.” Do the
authors mean delay the age of onset? But see my comments above regarding these analyses.

13) P17: Limitations of the study and their potential implications for the reported results need to be discussed in much greater detail and not just in one sentence in the concluding paragraph.

14) Table 3: How were birth wt and ht and wt at age 18 measured? I assume by self report via questionnaire. Or were birth records available? Please describe in methods section.

15) Table 4: Please report numbers of individuals (m/f) on which the results are based. How was BP without treatment determined? Is this BP prior to HTN onset?

Minor points:
1) P5: complex hypertension: I assume the authors mean essential hypertension?
2) P6: Tallinn needs to be mentioned as one of the sites.
3) P7: conges = congestive
4) P7: Self-administrated = self-administered
5) P8: self-prescribed drugs; is this drug use for which no prescription is needed (over the counter)?
6) P8: 757 individuals = 756 as in Table 1?
7) Measurement uncertainty; do the authors mean intra- and inter-assay reliability?
8) P11: exhibited higher BP = higher SBP
9) P13: p=0.0091 is not bolded in the Table.
10) P13: “The proportion of never-smokers was substantially higher in women (75.5% vs. 24.9%)”. I couldn’t find this information in the Table.
11) P16: daily smokers = current smokers?
12) Tables: please report p-values as p<0.0001 rather than p<1x10-4, also to be consistent with the p-values in the text.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

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'