Author's response to reviews

Title: Prevalence and determinants of a normotensive blood pressure in a German population based cohort of hypertensive study participants

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Version: 3 Date: 28 October 2012

Author's response to reviews: see over
Dear Mr. Silvestre,

Thank you very much for giving us the opportunity to revise the manuscript on the basis of the remarks of the reviewers. We think, the manuscript improved significantly and I hope we could meet all demands of the reviewers. Below you’ll find the particular comments of the reviewers together with our detailed answers (in red).

We are looking forward to responding to any criticism and comments.

Yours sincerely,

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Reviewer: Fangjian Guo
- Major Compulsory Revisions
1. Though the authors used sample-design-weights to adjust for different selection probabilities when calculating hypertension prevalence in SHIP-0, they did not include sample weights for calculating the classification of blood pressure values of hypertensive patients in Table 2. Table 3-7 also did not include sample weights when calculating treatment rates and rates of achieving target blood pressure. My suggestion is to include sample weights in the weight statement in the SAS programs for all the Tables. Or, the authors should provide justifications for not using sample weights.

This is an important comment. In the previous version of the manuscript we did most of the calculations without using sample weights because the weighted point estimators were usually within the confidence intervals of the unweighted point estimators. You are right, that a constant method of calculation throughout the paper is better for understanding. Therefore we calculated all tables using sample weights.

We modified the part of the methods section of the manuscript referring to the sample weights (page 11):

“All calculations were conducted using sample-design-weights to adjust for different selection probabilities within the sample [11] by using the SURVEY procedures by SAS 9.2, SAS Institute Inc., Cary, NC, USA.”

2. One of the major limitations of this study is the absence of data for medication adherence in hypertensive patients. However, the author arbitrarily concluded in paragraph 6 of the discussion part that non-adherence to antihypertensive medication is likely to be one major reason for not reaching the target blood pressure values. Then the author discussed adherence issue in the following several paragraphs. The discussion of adherence issue took up about half of the space in the discussion part, but provided little information related to the study. My suggestion is that the authors should not focus their attention on non-adherence issue. Comparing blood pressure control rates and the factors related to blood pressure control in hypertensive patients in different countries may provide more interesting information for the readers.
Thank you for this important advice. We shortened the non-adherence part of the discussion significantly. The modified text is as follows (page 17-18):

“Nevertheless, non-adherence to antihypertensive medication may be a reason for not reaching the target blood pressure values. The results of a study on elderly patients of Turner et al. show that non-adherence leads to poorer blood pressure control in this patient group [15]. At the same time, non-adherence is a modifiable, patient-related factor [16] which belongs to a variety of drug related problems which affect treatment effectiveness [17].”

- Minor Essential Revisions "Minor issues not for publication"
1. In the method part, the authors may want to describe the statistical method with more details. It would be preferable to put the statistical method in a single paragraph.

We added the statistical methods to the methods section. See also remark 12 of the Reviewer: Idris Guessous

2. There are numerous spelling mistakes, and grammatical errors.

We revised the manuscript thoroughly, I hope this is better now.

Reviewer: Renata Cifkova
1. The major problem is an incorrect definition of hypertension (page 7). The authors mix up the definition of hypertension (BP # 140/90 mmHg or taking antihypertensive drugs) and goal BP values, which may be dependent on comorbidities. Generally, lower goal BP values for hypertensive patients with comorbidities were recommended by the 2007 ESH-ESC guidelines; however, this issue was extensively addressed in the Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document published in 2009 (J Hypertens), which is completely disregarded in the manuscript by van den Berg et al.

Thank you for this important comment. We implemented the issue, addressed in the reappraisal and changed the text in the background part of the paper (page 6) (see also remark 3 of the reviewer Idris Guessous):

“Most important goal of the treatment of hypertension patients is to reach normotensive blood pressure values to decrease the risk for secondary disorders. Reaching normotensive blood pressure values can therefore be considered as an indicator of the effectiveness of antihypertensive therapy. According to major guidelines targeted values are below 140/90 mmHg [6,7]. Although targeted values below 130/80 mmHg in the current guidelines are recommended for patients with risk-comorbidity (diabetes, stroke, coronary heart disease, and renal insufficiency), assessment of recent studies has shown that the evidence for this is unclear. Nevertheless, actual reappraisals of the guidelines recommend treatment goals below 130/80 mmHg for hypertension patients with risk-comorbidity for the time being [8,9].”

We also completed the first research question:
“1. The proportion of study participants with a controlled hypertension in the population-representative German SHIP-cohort taking account of risk comorbidities. Controlled is operationalized here as: blood pressure values <140/90 mmHg, for patients with risk comorbidities < 130/80 mmHg.”
2. In the Methods section, on page 9, there is missing information about BP measurement, particularly the device used should be specified as the results are further discussed in the Discussion section on page 17 and compared with Canadian data using either a mercury sphygmomanometer or an oscillometric automated device.

We added a more detailed description of the blood pressure measurement to the methods section of the manuscript (page 9):

“Blood pressure measurements in SHIP-0 and SHIP-1 were carried out with an automated oscillometric device (HEM-750CP, Omron Corporation, Tokyo, Japan). The measurements were conducted after a rest period of five minutes in a sitting position on the right arm. Blood pressure was measured three times at an interval of three minutes by trained and certified personnel. The mean value of the second and third measurement was used in the analysis.”

References should be updated.

We completed the reference list with the actual reappraisal of the guidelines and an amendment of the German guidelines:


Reviewer: Idris Guessous

Reviewer’s report:
The objectives are of interest, but the methods used and the way results are presented and discussed have to be reconsidered before publication might be considered. Throughout the manuscript, there is a major lack of statistical inferences using standard procedures (statistical tests, measure of dispersion, etc).

A. Major Compulsory Revisions:
0. Throughout the manuscript (including the abstract), rates are sometime inappropriately used to describe prevalences.

BACKGROUND
1. Reference 1 is in german. I would suggest providing (key) references written in English for the international readers of the journal.

We moved the first reference to the 3rd place and used already listed references (now references 1 and 2) to describe hypertension prevalences in Germany.

2. Suggest to stress that the prevalence is highly dependent on age and gender.

We changed 2 parts of the background section (both page 5):
“...In Germany, about half of all adults have high blood pressure values (≥140/90 mmHg), with increasing prevalence in the higher age groups and higher rates in the male population [1,2].”
3. Third and Fourth paragraphs are slightly redundant.

We changed these paragraphs, included also changes asked by reviewer Renata Cifkova and removed redundancies:

“Most important goal of the treatment of hypertension patients is to reach normotensive blood pressure values to decrease the risk for secondary disorders. Reaching normotensive blood pressure values can therefore be considered as an indicator of the effectiveness of antihypertensive therapy. According to major guidelines targeted values are below 140/90mmHg [6,7]. Although targeted values below 130/80mmHg in the current guidelines are recommended for patients with risk-comorbidity (diabetes, stroke, coronary heart disease, and renal insufficiency), assessment of recent studies has shown that the evidence for this is unclear. Nevertheless, actual reappraisals of the guidelines recommend treatment goals below 130/80mmHg for hypertension patients with risk-comorbidity for the time being [8,9].

Pharmacotherapy of hypertension adopts a stepwise approach. Medical treatment can start with a single antihypertensive drug (monotherapy), usually an inhibitor of the angiotensin converting enzyme (ACE). If the target blood pressure values are not reached, the dosage should be increased, if this doesn’t show effect, an alternative drug should be prescribed. If the target blood pressure values cannot be reached under monotherapy, a combination of drugs can be prescribed (combination therapy, defined as treatment with two or more antihypertensive drugs from different substance classes). In many cases, a combination therapy is needed for patients with more severe hypertension [6,7,10].”

4. How does the prevalence of 23.1% reported in the last paragraph fit with the previous information that “compared to other countries, the prevalence in Germany is high:...28%...38%...42%”. It seems contradictory.

23.1% refers to the prevalence of known hypertension. The other prevalences also include the unaware proportion of patients.

5. Last paragraph belongs to the methods section.

We moved this paragraph to the methods section.

6. In the methods section, information on participation rates, means of recruitment and recall (letters, phone, language restriction) is missing.

We added following text to the methods section (page 8):

“6267 persons (age 20-79 years) with German citizenship were drawn from population registries in the region of Western Pomerania, selected persons received up to three written invitations, followed by a telephone call or home visit in the case of non-response. At the end, the response was 68.7% (N=4308) [11.12].”

7. Parts of the third paragraph of the methods section belongs to the results.

METHODS
8. Which devices were used to measure blood pressure? Did the devices change between SHIP-0 and SHIP-1?

We added a more detailed description of the blood pressure measurement to the methods section of the manuscript (page 9):

“Blood pressure measurements in SHIP-0 and SHIP-1 were carried out with an automated oscillometric device (HEM-750CP, Omron Corporation, Tokyo, Japan). The measurements were conducted after a rest period of five minutes in a sitting position on the right arm. Blood pressure was measured three times at an interval of three minutes by trained and certified personnel. The mean value of the second and third measurement was used in the analysis.”

9. How were diabetes and the other risk-comorbidity defined?

Patients were asked for confirmed diagnoses by physicians and medication. We added the following text to the last part of the methods section (page 9):

“Study participants with risk-comorbidity (diabetes, stroke, angina pectoris, and/or myocardial infarction) and blood pressure values ≥130/80mmHg. Risk-comorbidities were assessed by asking the patients for physician-confirmed diagnoses and the assessment of medication [11].”

10. Age range should be defined. It seems that participants younger the 24 years were also included in the study.

The age range (20-79 years) is mentioned in the methods section now (page 8).

11. All (including association analyses) statistical analyses must take into account the sample-design-weights, not only the prevalence of hypertension.

See reply to remark 1 of the reviewer Fangjian Guo.

12. Description of the logistical regression models are totally missing in the Methods section.

We added the following text to the last part of the methods section (page 10-11):

“Descriptive statistics were applied to calculate prevalences and treatment rates. To identify possible determinants for normotensive blood pressure values, two multivariate logistic regression models were applied. Subjects with missing values on any of the analytical variables (n=12) were excluded. Independent variables were sex, age, risk-comorbidity, obesity, smoking status, household size, and antihypertensive drug therapy. The first model comprises active substances with the indication hypertension. The second model comprises the kind of therapy (no therapy against mono or combination therapy)”

RESULTS:

13. Throughout the manuscript, measures of dispersion must be provided, moreover because several stratified analyses rely on really small sample sizes.

We added the confidence intervals to the tables 1 – 3.

14. Statistical differences need to be tested and p values for significance must be reported throughout the analyses. These tests must also take into account the complex design.

To improve the interpretation of the results, we added the p-values to the logistic regression models (table 4).
Because treatment is the main focus of the manuscript, we added the p-value to the difference between males and females with regard to antihypertensive treatment.

The section “Antihypertensive treatment” in the results section was modified (page 12-13):

“The proportion of study participants in need of treatment to the time of SHIP-0 who actually received antihypertensive medication to the time of SHIP-1 is shown in table 3. 58.7% of all hypertensive patients (N=1761) were on some antihypertensive drug treatment. Gender differences are apparent: 67.5% of the female patients were treated, however only 51.8% of the males (p<0.001)."

15. Suggest providing in Table 1 the N from which estimated are derived for each cells and to reconsider the number of cells compared; sample sizes of some cells are probably very small (see Table 5). This will of course be translated by very large confidence intervals.

Table 1 was removed from the manuscript.

16. From the text, information on chronic disease seems to be available on only N=1754. It is not clear how Table 6 provides information on yet N=1761 stratified by risk-comorbidity?

This wording was not quite correct. We know the defined risk-comorbidities (diabetes, stroke, angina pectoris, and/or myocardial infarction) for all 1761 participants. Beside of this, we know about further comorbidities from 1754 participants.

We implemented a flowchart (fig. 1) to improve the description.

17. Differences reported in Table 3, 4, 5, etc (and mentioned in the text) must be tested.

See aremark 14. The former tables 1, 3, and 5 were removed from the manuscript.

18. The precision of the proportion derived from the cohort of N=10 must be provided.

See remark 13.

19. Description of the logistic models does not belong to the Results section.

We added the following text to the last part of the methods section (page 10-11):

“Descriptive statistics were applied to calculate prevalences and treatment rates. To identify possible determinants for normotensive blood pressure values, two multivariate logistic regression models were applied. Subjects with missing values on any of the analytical variables (n=12) were excluded. Independent variables were sex, age, risk-comorbidity, obesity, smoking status, household size, and antihypertensive drug therapy. The first model comprises active substances with the indication hypertension. The second model comprises the kind of therapy (no therapy against mono or combination therapy)"

We removed the description of the models fro the results section.

20. The major limitation of the interpretation of table 7 and of the corresponding section of the manuscriptis the lack of adjustment for blood pressure at baseline. In addition, the models do not take into account whether participants at baseline were treated or not and the type of treatment. Most of the determinants reported in Table 7 might be confounded by the disease severity; i.e. the level of high blood pressure (expressed as mmHg or combination therapy) at baseline.
Thank you for this important remark. We analysed the treatment rates and determinants of participants with hypertension and blood pressure values in need of treatment at the time of SHIP-1 without adjusting for the disease severity at the time of SHIP-0. It is difficult or even impossible to assess the real severity of the disease in patients with treatment. Therefore, we concentrated in this analysis on the influence of different treatment options on normotensive blood pressure values.

DISCUSSION:
Although the information on adherence is clearly missing in the study, yet the major part of the discussion focuses on it. I would suggest spending more time discussing the results for which the authors have some data on. Moreover, the content of the discussion should be reconsidered once the differences between groups tested statistically.

See remark 2 of the reviewer: Fangjian Guo.

B. Minor Essential Revisions:
Suggest using proportions "of" throughout the manuscript.
Thank you, we corrected this.

Methods: “The” main goal; population-based data
Thank you, we corrected this.

Suggest not reporting % and N of male if this same information regarding female is given in the same sentence (third paragraph of the methods section).
We changed this wording in the manuscript and removed the % and N of the male.

Sociodemographic data as well as the presence of diagnoses and risk factors WERE assessed
Thank you, we corrected this.

Suggest defining the WHO/ISH classification.

We modified this section (page 10):
“The participants were allocated to the different categories of the WHO/ISH-classification. This classification has seven categories:
optimal blood pressure (syst: <120 mmHg/diast:<80 mmHg), normal (syst: 120–129 mmHg/diast:80–84 mmHg), high-normal (syst: 130–139 mmHg/diast: 85–89 mmHg), mild hypertension (syst: 140–159 mmHg/diast: 90–99 mmHg), moderate hypertension (syst:160–179 mmHg/diast:100–109 mmHg), severe hypertension (syst: ≥180 mmHg/diast: ≥110 mmHg), and isolated systolic hypertension (syst: ≥140 mmHg/diast: <90 mmHg)[14].”

Reconsider the first sentence of the paragraph after Table 1 insertion.
Because 3 tables were removed, the wording of the results section changed significantly.

Reference message error in the paragraph following Table 5 insertion.
Thank you, we corrected this

Suggest using “determinants” instead of “correlates”.
We changed this wording in the manuscript.

Suggest using “Hypertensive” patients instead of hypertension patients.
We changed this wording in the manuscript.
Reviewer: Ulf Lindblad

MAJOR COMPULSORY REVISIONS

1. The paper would improve much if the text were focused excluding many details in the Background. Avoiding duplicate presentation in tables and Results as well as repeated results in the Discussion would improve flow and keep the readers interest. Professional review of the English language is also recommended.

Thank you for this important remark. The background and results sections were shortened, redundant parts of the text were removed.

2. I am not clear over the design of this study. In Table 1 the total number of patients in the SHIP-0 cohort is 3278, while the number of the same cohort in Table 2 is 1761. Further, in Table 5 the total is 1074. A flow-chart would be needed to guide the reader to understand what is going on.

Thank you for this very useful suggestion. We made a flowchart of the numbers of patients included in the analyses (fig. 1). The flowchart is included in the results section (page 11).

3. The difference in total number between Table 1 and Table 2 is presumably due to different target populations; presentation of a baseline survey in Table 1 while only those participation in both surveys are kept in Table 2? This has to be sorted out.

Table 1 in the previous version of the manuscript (we sorted this table out in the new version) showed prevalences (total number of hypertensive patients: 1761 of the total cohort 3278). Table 2 in the previous version (table 1 in the actual version of the manuscript) shows the number of hypertensive patients (total N=1761) in the different blood pressure categories.

4. If the assumption in item 3 is correct about 1500 patients were lost to follow-up and the reasons for that should be presented and discussed.

We hope, due to the implementation of the flowchart the course of the cohort is clearer now. The difference between SHIP-0 and SHIP-1 is 1008. This number consists of participants that died between SHIP-0 and SHIP-1 and participants that did not want to participate anymore.

5. Typically studies on the prevalence, treatment and control are based on cross-sectional surveys. Its not clear to me what the SHIP-1 adds to this study. It says that the information on treatment is observed over the 5 years to SHIP-1, however, what kind of longitudinal observations were actually analysed? If the 2 surveys are to be optimally utilised some change in status should be presented, but I cannot find any.

We defined the patients with hypertension and blood pressure values in need of treatment from the data of SHIP-0. One criterion for being included in the study was having blood pressure values ≥140/90mmHg (or ≥130/80mmHg with risk comorbidities). These patients would have no possibility to reach normotensive values using SHIP-0 data for analysing possible determinants for normotensive blood pressure values. For this reason we decided to use SHIP-1 values for the analyses.
6. I think blood pressure #130/#80 mm Hg in association with risk-comorbidity confers an overestimation of the prevalence of hypertension in an epidemiological study. In a clinical setting it would be more reasonable. Thus, a major part of the patients in this study were recruited that way and I do not rely on that.

Thank you for this remark. We changed the results section on page 11:

“Applying the criteria described in the methods section, in SHIP-0, 1761 of 3278 included study participants had hypertension or blood pressure values in need of treatment (raw rate: 50.9%).”

See also remark 1 of the reviewer Renata Cifkova

7. There are 7 tables and that is at least 3 too many. That is consistent with a need of condensed text (30%) and a reduction in details and repeated information.

We removed 3 tables (tables 1,3, and 5 in the previous version of the manuscript) and condensed the text in the results section.

8. The conclusions are in general not based on findings in the current study, but rather speculations based on assumption, or in the best of findings in other studies. These speculations have to be taken out or corrected.

See remark 2 of the reviewer Fangjian Guo

MINOR ESSENTIAL REVISIONS
Beta-blockers were the most common medication for treatment of hypertension in this study. This is in contrast to current recommendations and the outcome from several meta-analyses. This observation calls for a comment.

The reason may be changes in prescription since the data collection of SHIP-1 (2002-2006).