Author's response to reviews

Title: High blood pressure prevalence and associated factors in a North African adolescent population. A national cross-sectional study in Tunisia

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Author's response to reviews: see over
Authors’ responses

MS: 1880314576581162
High blood pressure prevalence and associated factors in a North African adolescent population. A national cross-sectional study in Tunisia

Authors’ response to editor’s comments

"I do not appreciate the meaning of pre-hypertension primarily for children and adolescents studies. An evaluation by percentile is much more real, concrete than an apparent artificial categorization.

Authors’ response:

We agree that there is a continuous distribution of values and that any categorization is rather artificial for BP measures. We also acknowledge that there are discussions still about the concept of prehypertension when dealing with children and adolescents. In clinical situations, clearly it should be confirmed by further observations. But in populations studies, where the aim is to look at possible risk factors and understand which percentage may eventually benefit from adapted preventive measures (physical activity and/or diet counseling), categorization remains useful. As a matter of fact, as we adopted a pragmatic view in this article we thought that a presentation according to standard definitions was required and we followed the JNC7 committee for definition of prehypertension and hypertension. We however do agree that one should keep a rather conservative view either in analysis or interpretation of results.

Considering the comments from our reviewers, I strongly recommend to rerun the statistical analysis applying a post-hoc test for ANOVA, the most conservative possible. (see note #5)

Authors’ response:

We agree with the editor and also one of the reviewers (c.f. his comment #5) that the first type error rate must be dealt with at a global level (study wise / experiment wise error rate). Indeed repeated tests with a given alpha level (here 0.05) can result in a much higher overall error rate if the number of tests increases. A number of multiple testing corrections have been devised to deal with that problem; the Bonferroni correction (dividing the alpha error rate by the number of tests performed) is historically one the first ones, but is very conservative and is thus known for resulting in a highly augmented second type error rate and thus low power to detect associations. To our opinion, among all the corrections available to deal with that problem of multiple testing at the level of a whole study, there is no straightforward best choice. So that a prudent heuristic approach is often used: i.e. without technically correcting the alpha error rate, a honest researcher must indeed be cautious not to over-interpret P-values and/or difference which are marginally “significant” especially when the number of tests increases, as we have tried to do in the new version of the manuscript.

After that, please answer all questions from our reviewers.
Please, avoid some generic conclusions as stated at the abstract

Authors’ response:
The conclusion in the text and in the abstract was modified accordingly so as to be less generic and more specific to the study and the data themselves.

Additional editorial requirement
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Please make the following formatting changes during the revision of your manuscript. Ensuring that the manuscript meets the journal’s manuscript structure will help to speed the production process if your manuscript is accepted for publication:

“We note that your study was approved by the Tunisia Ministry of Health. However, please clarify in your manuscript on whether this was ethically approved by the Ministry of Health.”

Authors’ response:
All applicable institutional and governmental regulations concerning the ethical use of human volunteers were respected during this study. We added more precision in the new version of the manuscript:
“The protocol of the survey was reviewed and approved by the Ethics Committee on Human Research of the National Institute of Nutrition and the Tunisian National Council of Statistics (visa n°5/2005).” (Page 5 lines 26-27 - page 6, line 1).

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Authors’ response to reviewer Decio Mion

We thank the reviewer for his positive comments

Authors’ response to reviewer Pascal Bovet

Reviewer’s report
Title: High blood pressure prevalence and associated factors in a North African adolescent population. A national cross-sectional study in Tunisia
Version: 1 Date: 17 September 2011
Reviewer’s report:
Major revisions
1) The definition of categories of elevated blood pressure should be properly referenced. Reference 15 is not presenting the age-sex-height specific reference values but only using them. A reference should be given on the original paper presenting the reference (likely 2004 National High Blood Pressure Education Program Working Group guidelines). There is a need to mention in the text whether BP categories were based on sex, age and height specific cut offs?
Authors’ response:

We thank the reviewer for the relevant remark; we replaced the reference [15] by the following one in the new version of the manuscript.


Also, as recommended, we added in the text the following precision:

“For 15-17 y, pre-hypertension (pre-HT) was defined as average systolic BP (SBP) and/or diastolic BP (DBP) ≥ 90th age, sex and height specific percentile …” (page 5, lines 18-20)

2) The categories of elevated BP should be referred exactly as they appear in the original reference. It is misleading to refer to “high BP” for values including the category “pre-hypertension”. At best a category including prehypertension and hypertension could be labeled as “elevated BP”, but it would be best to refer to prevalence of “pre-hypertension” and to prevalence of “hypertension” separately.

Authors’ response:

We have replaced the “high BP” labelling by “elevated BP” throughout the text when relevant. Also in accordance with what the reviewer suggests, for descriptive purposes we have kept the 3 category variable “normal BP / preHT / HT”, but indeed for analysis purposes (although we could have analyzed a 3 category response variable normal BP /preHT /HT) we have analyzed in parallel the elevated BP and HT binary variables (as analyzing preHT itself vs. the rest would not be meaningful).

3) This reference 15 underlies an important issue that the authors should discuss in their paper, which is that the actual status of elevated BP categories should be based on BP based on BP readings on several occasions. Reference 15 well shows that prevalence of elevated BP largely decreases when BP is measured several times. Another similar study is “Chiolero A et al. Prevalence of hypertension in schoolchildren based on repeated measurements and association with overweight. J Hypertension 2007;25:2209-17”. The authors of the Tunisia paper likely don’t have readings on several occasions, but they should at least acknowledge this important caveat (which tends to largely overestimate the actual prevalence of hypertension in their study. This should be explicitly recognized in the text and in the abstract as the actual prevalence of elevated hypertension is likely much lower than that presented based on only 2 readings in only 1 visit).

Authors’ response:

We agree with the reviewer that there is an issue for descriptive purposes (prevalences) but likely less so for analytic purposes under the reasonable (?) hypothesis of no differential bias between the groups which are compared. Firstly, independently of the BP measurement issue itself, as for all indicators derived from a cutpoint at the left or right tail of a distribution, a regression to the mean type of phenomenon can indeed never be ruled out (which indeed could result in our study in a higher prevalence of HT or elevated BP).

Secondly, as for the BP measurement itself, indeed we did not perform it on several occasions as the two measurements where performed during the same visit; nevertheless we have added in the methodology section the precision that the
second measure of BP was done at the end of the interview i.e. on average 30 minutes after the first one.

As for the measurement itself, it was based on the auscultatory method. But in the reference 15, they used the oscillometric method, and according to them “However, oscillometric BP readings, particularly initial readings, tend to be higher than auscultatory readings and thus may overestimate the presence of hypertension” (ref 15: page 643, column 2, lines 13-16).

So, in order to give more precision for the used method, we modified the following sentence in “Methods”

“Blood pressure: The BP was measured twice by the auscultatory method using a stethoscope and calibrated sphygmomanometers ...” (page 5, lines 15-16)

Besides, we added the precisions recommended by the reviewer:

**In the abstract:**

“BP status was measured twice during the same visit” (page 2, lines 11-12)

“Within the limits of BP measurement on one visit only, the results suggest that Tunisian adolescents of both genders are likely not spared from early elevated BP. Further research is needed to confirm the extent of the problem. ...” (page 2, lines 28-30)

**In the discussion chapter:**

The definition of the BP status was based on two measures of the BP during the same visit and not on different set of measurements on repeated visits as advised in the literature [30]. This may lead to some overestimation of the prevalence of elevated BP and/or hypertension [McNiece KL, Poffenbarger TS, Turner JL, Franco KD, Sorof JM, Portman RJ. Prevalence of hypertension and pre-hypertension among adolescents. J Pediatr 2007, 150(6): 640-4, 644 e1] (page 11, lines 8-10)

4) The choice of the covariates (for the analysis of BP with various characteristics) should be based on current knowledge, or if some new variable is presented, on some hypothesis. I don’t see any rationale from the literature (or stated hypothesis in the paper) to select “eating daily meals” or “regular snacking” with regards to BP. These variables are very un-specific, prone to recall bias and other biases (SES; etc), likely very imprecise, and not closely related to variables of real interest (sodium, potassium, fibers, chocolate, nuts, etc) that are known to relate with BP). I would advise to drop these variables for the analyses as they do not add meaningful information to the complex issue of nutrition and BP.

**Authors’ response:**

We agree with the reviewer that these variables are quite imprecise and not really relevant for the study of relationships between nutrition and BP so the analyses have been rerun without taking them into account.

5) Emphasis on results should be based on sex specific multivariate analysis. Univariate results have little interest as they are prone to biases by other covariates. Tables on univariate results could be maintained (or dropped) but there is no need to have a detailed description of these univariate results (as is the case now). Multivariate results (which are indeed a main result in the paper) largely show no substantial association with BP except for BMI. The few other associations are very
close to statistical non significance, and would become statistically not significant (except for BMI) if adjustment was made for multi testing (Bonferoni). Furthermore the few barely statistically significant results are not consistent (systolic/diastolic, BP continuous/hypertension category, boys/girls) which further limits their interest. Also it seems that these associations were not pre-specified and results then seem to relate more to some “fishing” than clearly stated hypotheses. Hence the emphasis in the association results should be on BMI and make little case of the other associations, with emphasis on this association (BMI) in discussion and not much focus on the other weak or non coherent findings with other variables. More comments could be made on the role of BMI (a risk factor of BP but also a discrepancy in many countries between decreasing BP (in adults and in children) and increasing BMI, e.g. your reference 53, but several other similar papers.

Authors’ response:

We agree with the reviewer that indeed repeated tests with a given alpha level (here 0.05) can result in a much higher overall / study wise error rate if the number of tests increases. So that without technically correcting the alpha error rate (Bonferronni or other type of corrections), a prudent researcher must indeed be cautious not to over-interpret P-values and/or difference which are marginally “significant” especially when the number of tests increases.

As for the case of univariate vs. multivariate results, our opinion is that both have their specific meaning and interest, though of course for analytic purposes, adjusted effects derived from multivariate analyses are likely more relevant to assess unconfounded associations. As suggested by the reviewer, in the new version of the manuscript the paragraph on univariate analysis has been rewritten/shortened (page 7, lines 11-22) but not removed entirely, partly due to comment from the second reviewer “The authors separated the results of univariate and multivariate analysis, making clear understanding by the reader.”

We removed the results concerning systolic and diastolic BP in the univariate and multivariate analysis. We rewrote the paragraph of multivariate analysis according to the new results after re-running the analyses.

We modified the discussion according to the recommendation of the reviewer:

- We developed the paragraph related to the association between BMI/WC and BP.
- We removed the paragraph concerning meals frequency and economic level.
- Also in the new version of the manuscript the initial set of socio-economic variables has been shortened as we have tried to keep the same list of covariates from the descriptive to the more analytic part (and this also with a positive impact on the experiment wise alpha error risk as this decreases the number of tests performed)

6) More details should be given to methods: how the students were selected, what was the number of eligible participants, what is the proportion of refusal/non participation (it seems that there were only 2873 participants 6580 households?).

Authors’ response:

We thank the reviewer for this relevant remark. We added the following precisions in the methods section.
With reference to the 0.48 ratio of 15-19 year old per household (2004 Tunisian census), about 3,138 subjects were thus expected to be included. (page 4, lines 7-9)

The following sentence was added in the results section.

Taking into account refusals, absences and missing BP data, 2870 subjects out of the expected 3138 subjects were used in the analyses i.e. an overall response rate of 91.5%. (page 6, lines 20-21)

7) I don’t understand what is “correspondence analysis” used for SES scale. Could the authors be more explicit on how they derived their SES score (which variable brought how many points for which response?). Could they use some straightforward score having points added (explicitly) in relation to some wealth attributes in household (non cable TV, cable TV, video, running water, etc) and make clear how many points are attributed to these various items, range of SES score, etc?

Authors’ response:

As we have already used in several published papers pertaining to the Tunisian (cf the following references: 1. [Aounallah-Skhiri H, Romdhanne HB, Traissac P, Eymard-Duvernay S, Delpeuch F, Achour N, et al. Nutritional status of Tunisian adolescents: associated gender, environmental and socio-economic factors. Public Health Nutr 2008;11(12):1306-17.]; 2. [Aounallah-Skhiri H, Traissac P, El Ati J, Eymard-Duvernay S, Landais E, Achour N, et al. Nutrition transition among adolescents of a south-Mediterranean country: dietary patterns, association with socioeconomic factors, overweight and blood pressure. A cross-sectional study in Tunisia. Nutr J 2011;10(1):38.]) and/or other contexts (Delpeuch F, Cornu A, Massamba JP, Traissac P, Maire B. Is body mass index sensitively related to socio-economic status and to economic adjustment? A case study from the Congo. Eur J Clin Nutr 1994;48 Suppl 3:S141-7.), the household economic proxy is based not on a priori and/or explicit scoring of the different items: it is a weighted average (maximum variance linear combination of the context specific items), which weights take into account the inter-relationships between the different items and their specific “between household” variability. This type of so called “asset-based” proxy, which is often used in epidemiologic studies as proxy for household economic level is usually derived as the first principal axis of a Principal Component Analysis of Factor Analysis. Without getting into too many details, multivariate correspondence analysis is a data analysis technique closely related to principal component analysis but specifically designed for analysis of categorical variables so that we preferred to use it instead of PCA. Whatever the technical aspects, with a relevant choice of context specific items, careful interpretation/validation of the first principal component often results in that it can be interpreted as a “wealth index” and be used for analysis as a proxy for income level. For each household, the value of the index is a weighted average of the binary variables coding for the different items, thus has no “absolute” meaning (so that the range has no direct interpretation); but it indeed can be used either as such for individually ranking the households according to their index values and/or as a categorical variable after recoding e.g. in quintiles or terciles (as we did in the present study).

8) For education and job, how was categories estimated? Which category if mother is low education and father high education (or reverse)?
Authors’ response:

Job categories (of the mother & the father separately) were obtained by interview and coded using a 12 category classification derived from that of the Tunisian National Institute of Statistics. They were then recoded during the data management process: - for men in 1. upper (upper and intermediate professions), 2. intermediate (employee/worker), 3. not working (retired, unemployed), - for mothers, because of the low proportion of women working outside the home in the Tunisian context, we opted for a classification in two items: ‘working’ (outside the home) vs. ‘not working’.

Detailed information on the last class attended (for the mother and the father separately) was also obtained during the interview. We then recoded the information into two categories for “Education”: 1. primary level or less (illiterate), 2. secondary or university level.

In the new version of the manuscript these variables have been removed from the analysis as we have tried to keep the same list of covariates from the descriptive to the more analytic part (and this also with a positive impact on the experimentwise alpha error risk as this decreases the number of tests performed)

9) How were categories of overweight / obesity calculated from the WHO reference data? (one by one? using some “do file” etc. Same question for BP categories.

Authors’ response:

We are not sure what the reviewer means by “one by one”? All the data management and analysis process were handled in order to maximize traceability and reproducibility of the results (e.g. as defined Peng RD, Dominici F, Zeger SL. Reproducible epidemiologic research. Am J Epidemiol 2006 May 1;163(9):783-91.; so that all computations, i.e. statistical analysis but also generation of all the derived variables (including categories of “overweight / obesity” and those of “blood pressure” according to the specific references) were done in programming mode (using .do files in Stata V11).

10) It is stated (line 7, background page) that there are few studies on prevalence of elevated BP in developing countries. There are several dozens of them, and it would useful to provide here references for a few (e.g. your referecne 53 but many others as well).

Authors’ response:

We thank the reviewer for the relevant comment. In the new version of the manuscript, we modified the sentence and in order to be coherent two references were replaced by two others. Also, we added another sentence in the background.

“Several studies have shown a rising frequency of this disease in children and adolescents in many countries [14-17].” (page 3, lines 6-8)

“…; however, no study has attempted yet to assess the extent of elevated BP at large scale among Tunisian adolescents.” (page 3, lines 12-13).

11) There is a need of a major revision of the text in relation to English (“tensional”, “corpulence”, etc are not words commonly used in English in this field, and there are many orthographic mistakes).
Authors’ response:
We replaced the term “corpulence” by overweight and/or obesity when relevant and “tensional” by “BP”. We also tried to enhance as much as possible the overall quality of the English.

12) For tables and graphs, as stated above, make sure to use proper words for “pre-hypertension” and “hypertension”, and refer in text to the fact that these estimates are based BP measured on only one visit (hence overestimation of "hypertension" as compared to estimates based on several visits, as usually recommended)

Authors’ response:
We have paid as much as possible attention to those vocabulary issues as detailed in response to question #3.
We have underlined the limits of measuring BP only on one visit both in the abstract (page 2, line 28), in the discussion section of the paper (page 11 lines 8-9) and in the conclusion (page 11, line 17).

Level of interest: An article of importance in its field
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