

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Factors associated with hypertension among adults in Nepal as per the Joint National Committee 7 and 2017 American College of Cardiology/American Heart Association hypertension guidelines: a cross-sectional analysis of the demographic and health survey 2016
AUTHORS	Das Gupta, Rajat; Bin Zaman, Sojib; Wagle, Kusum; Crispen, Reese; Hasan, Mohammad Rashidul; Al Kibria, Gulam Muhammed

VERSION 1 – REVIEW

REVIEWER	Zahra Mohtasham-Amiri Guilan University of Medical Sciences, Rasht, Iran
REVIEW RETURNED	13-May-2019

GENERAL COMMENTS	<p>In Title: It is not necessary to mention the guidelines that were used in study.</p> <p>In Abstract: It is better to delete guidelines from objectives section. There are not any description about statistical tests that were used for analysis. Residence in province 4 or 5 is not clear for reader before completing reading of manuscript. In STRENGTHS AND LIMITATIONS OF THIS STUDY, There is not any information about background diseases such as DM, also one of the most risk factor for HTN, eating behaviors and salt daily consumption.</p> <p>In introduction: This sentence is not correct. " Uncontrolled hypertension due to high blood pressure is the leading risk factor of CVD".</p> <p>In materials and methods: There is not any information about selection of participants from households. How the sample was selected? There are not any data about levels of variable, it is not clear for reader about type of multilevel regression (such as fixed effect , random effect ,..).</p> <p>In results: It is expected to see some information about multilevel regression in outputs.</p> <p>In discussion: This sentence " To the best of our knowledge, this is the first study that investigated the determinants of hypertension according to the 2017 ACC/AHA guideline " is not correct. Cut of AHA is the same as JNC7 pre-HTN categories. There are many studies that focus on determinants of pre- HTN. This claim is not correct unless for study in Nepal.</p>
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REVIEWER	Eyitayo Omolara Owolabi University of Fort Hare, South Africa
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REVIEW RETURNED	13-May-2019
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GENERAL COMMENTS	<p>REVIEW REPORT</p> <p>Thank you for the opportunity to review this manuscript titled “Determinants of hypertension among adults in Nepal as per the Joint National Committee 7 and 2017 American College of Cardiology/American Heart Association hypertension guidelines”. The study presents data on hypertension, a disease of significant public health concern. The study reported the various determinants of hypertension in Nepal, using two different criteria. The obvious strength of the study is the use of a nationally representative data.</p> <p>Generally, the article is well written, methods clearly presented as well as the results. The extra information the study adds is the variation in the determinants of hypertension when classified using the mostly used cut-off and the new cut-off values. However, there is a need for the authors to provide more background information on hypertension and the determinants in that setting. Also, the discussion section appears scanty. More detailed information should be provided on the various associations reported and the possible reasons.</p> <p>Few other specific comments include:</p> <ul style="list-style-type: none"> - Line 10, Pg 6, in the sentence, uncontrolled hypertension due to high blood pressure.....appears like a tautology, the authors may consider removing “due to high blood pressure”. - Line 40, Pg 7, create a space between recent and 2016 NDHS data - Create a space between Province 4 and the presented AOR results in 47, pg 13. - It would be good enough if the authors provide information about the provinces to better understand their peculiarities. - Line 18, pg 16, the sentence “males have higher likelihood hypertension than females” should be corrected. Likewise, the authors should provide possible reason or explanation for the higher odds of hypertension among men. - Further explanation could also be provided on the possible association between weight and hypertension. <p>GENERAL COMMENT: The article can be accepted after minor revisions. The article could also benefit better from the service of a professional language editor.</p>
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REVIEWER	Dr Muhammad Fadhli Mohd Yusoff Institute for Public Health Ministry of Health Malaysia
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REVIEW RETURNED	14-May-2019
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GENERAL COMMENTS	<p>The objective of the study to compare the determinants of hypertension when 2 different definitions were used is indeed a good intention. However, there are important variables that are associated with hypertension from other studies such as diabetes, smoking, physical inactivity, family history were not included in the study. Without some of important variables, the associated factors could not determined correctly. Therefore, I would not recommend this paper for publication</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. In Title: It is not necessary to mention the guidelines that were used in study.

Response: Thank you honorable reviewer for this suggestion. However, the main objective of this study was to the determinants of hypertension in Nepal according to both the Joint National Committee 7 (JNC7) and The American College of Cardiology/American Heart Association (2017 ACC/AHA) guidelines. We respectfully disagree with the reviewer about suggestion. Unfortunately, many other studies have already investigated determinants, but none of them actually looked by both guidelines. The editor has also advised us to include the research question, study design and setting in the title. As a result, we have retained the guidelines that were used in study in the title.

2. In Abstract: It is better to delete guidelines from objectives section.

Response: Thanks! As we already explained, the main objective of this study was to the determinants of hypertension in Nepal according to both the Joint National Committee 7 (JNC7) and The American College of Cardiology/American Heart Association (2017 ACC/AHA) guidelines. So we will keep the guidelines' name in the objectives section. Unfortunately, we respectfully disagree with the reviewer about suggestion.

3. There are not any description about statistical tests that were used for analysis.

Response: Thank you honorable reviewer for bringing this issue to our attention. We have now added the following sentence "After descriptive analysis, multilevel logistic regression was applied to obtain odds ratios."

Residence in province 4 or 5 is not clear for reader before completing reading of manuscript.

Response: Thank you for the suggestion! We have included the description of the provinces in the methods section: "As a part of the reformation in 2015, Nepal was divided into seven provinces.¹³ The provinces were given name as Province 1 to 7. Provinces 2 and 5 are mainly located in the Terai region of Nepal (plain land) and rest of the provinces contain all three ecological regions: the Terai, hills and the mountains (snow-covered Himalayan region). Each of the provinces has different ethnic groups.²⁴"

4. In STRENGTHS AND LIMITATIONS OF THIS STUDY, There is not any information about background diseases such as DM, also one of the most risk factor for HTN, eating behaviors and salt daily consumption.

Response: Thank you for your suggestion! We have revised the strength and limitation section as following: "Except BMI, the association of hypertension with other metabolic determinants including diabetes mellitus or dyslipidemia and life-style factors (smoking, physical activity, dietary habit, daily salt consumption), family history was not evaluated, as those data were not collected."

5. In introduction: This sentence is not correct." Uncontrolled hypertension due to high blood pressure is the leading risk factor of CVD".

Response: Thanks for pointing out this mistake. We have revised the line as "Uncontrolled hypertension is the leading risk factor of CVD."

6. In materials and methods: There is not any information about selection of participants from households.

Response: Thanks! We have added this information under the sampling and data collection subsection: "NDHS utilized a standard, pretested, and validated biomarker questionnaire (in the local context of Nepal) for to collect data on blood pressure measurements and anthropometry measurements (height and weight). All the men and women aged 15 years and above who were residents in half of the selected households were considered eligible for blood pressure measurements. The questionnaire was finalized in English and then translated and pretested in Nepali, Maithili, and Bhojपुरi language.¹³ The data collection took place from June 19, 2016 to January 31, 2017. Trained enumerators carried out the data collection. The data was collected by sixteen teams. Each team comprised of a supervisor, three female interviewers, and one male

interviewer. Two female members and the male member of the team were trained to measure the height and body weight. The male team member also received training on blood pressure measurement. Rigorous monitoring was done by ICF staff, quality control team, and technical team from the Ministry of Health and the Nepal Health Research Council.¹³

7. How the sample was selected?

Response: The biomarker questionnaire was used to collect data blood pressure measurements, anthropometry measurements (height and weight) and hemoglobin testing from respondents in a subsample of the households. In this subsample, blood pressure was measured for all the men and women aged 15 years and above. We have added this information under the study design subsection.

8. There are not any data about levels of variable, it is not clear for reader about type of multilevel regression (such as fixed effect , random effect ,...).

Response: Thank you for highlighting this issue. We have used multilevel mixed-effects logistic regression model. We have revised this in the statistical analysis sub section: "After that, multilevel mixed-effects logistic regression analyses were performed to identify the determinants of hypertension according to both guidelines."

9. In results: It is expected to see some information about multilevel regression in outputs.

Response: Thank you honorable reviewer for this suggestion. We have included AIC of the model in Table 2.

10. In discussion: This sentence " To the best of our knowledge, this is the first study that investigated the determinants of hypertension according to the 2017 ACC/AHA guideline " is not correct Cut of AHA is the same as JNC7 pre-HTN categories. There are many studies that focus on determinants of pre- HTN. This claim is not correct unless for study in Nepal.

Response: Thanks! We have revised the statement as following: "To the best of our knowledge, this is the first study that investigated the determinants of hypertension according to the 2017 ACC/AHA guideline and then compared it with the determinants identified according to the JNC7 guideline in the context of Nepal."

Reviewer: 2

1. Thank you for the opportunity to review this manuscript titled "Determinants of hypertension among adults in Nepal as per the Joint National Committee 7 and 2017 American College of Cardiology/American Heart Association hypertension guidelines". The study presents data on hypertension, a disease of significant public health concern. The study reported the various determinants of hypertension in Nepal, using two different criteria. The obvious strength of the study is the use of a nationally representative data. Generally, the article is well written, methods clearly presented as well as the results. The extra information the study adds is the variation in the determinants of hypertension when classified using the mostly used cut-off and the new cut-off values. However, there is a need for the authors to provide more background information on hypertension and the determinants in that setting. Also, the discussion section appears scanty. More detailed information should be provided on the various associations reported and the possible reasons.

Response: Thanks for this important suggestion. We added following background information on hypertension in the manuscript: "Different studies estimated the prevalence of hypertension in Nepal from 21% to 34%.⁷⁻¹² Two wave of the STEPS survey conducted by the World Health Organization (WHO) estimated that the prevalence of hypertension increased from 21.5% in 2008 to 26.0% in 2013 among Nepalese aged 15-69 years.^{8 12} The information on previously known determinants of hypertension in Nepal was mentioned in the last paragraph of the introduction section: "This study investigated and compared the determinants of hypertension among Nepalese adults using both the JNC7 and 2017 ACC/AHA guidelines. Previous studies found that multiple factors such as age, sex,

body weight, socioeconomic status, and regions of residence are associated with hypertension in Nepal.^{14 22 23}

Few other specific comments include:

2. Line 10, Pg 6, in the sentence, uncontrolled hypertension due to high blood pressure.....appears like a tautology, the authors may consider removing “due to high blood pressure”.

Response: Thanks! We have removed “due to high blood pressure” as per advice.

3. Line 40, Pg 7, create a space between recent and 2016 NDHS data

Response: Thanks! We have created a space between recent and 2016 NDHS data.

4. Create a space between Province 4 and the presented AOR results in 47, pg 13.

Response: Thanks! We have created a space between Province 4 and the presented AOR results.

5. It would be good enough if the authors provide information about the provinces to better understand their peculiarities.

Response: Thanks! We added the following information: “As a part of the reformation in 2015, Nepal was divided into seven provinces.¹³ The provinces were given name as Province 1 to 7. Provinces 2 and 5 are mainly located in the Terai region of Nepal (plain land) and rest of the provinces contain all three ecological regions: the Terai, hills and the mountains (snow-covered Himalayan region). Each of the provinces has different ethnic groups.²⁴”

6. Line 18, pg 16, the sentence “males have higher likelihood hypertension than females” should be corrected. Likewise, the authors should provide possible reason or explanation for the higher odds of hypertension among men.

Response: Thanks for this important suggestion. We have added the following explanation “Sex is a non-modifiable risk factor of hypertension.³⁷ It is hypothesized that endogenous estradiol in premenopausal females has a protective role against hypertension. Animal models suggest that sex differences in T-cells and activation of the Renin Angiotensin System (RAS) may also contribute to higher blood pressure level among males.^{38 39} For prevention and control purposes, public health programs in Nepal should aim to increase awareness among males.”

7. Further explanation could also be provided on the possible association between weight and hypertension.

Response: Thanks for this important suggestion. We have added the following explanation in the revised manuscript: “Overweight/obese individuals were three times more likely to be hypertensive than those with a normal BMI in this study. Excessive weight predisposes a person to hypertension, which could increase the risk of CVD.⁴⁰ Overweight/obesity causes raised blood pressure by increasing sympathetic nervous system activity and increased renal sodium retention due to impaired pressure natriuresis.⁴¹ Obesity is also associated with impaired endothelial function which in turn increases the blood pressure.⁴² Also overweight/obesity is associated with type 2 diabetes mellitus and chronic kidney diseases which in turn predispose a person to hypertension.⁴³ As Nepal is currently going through nutritional transition and the burden of overweight and obesity is increasing in both urban and rural areas, the burden of hypertension is more likely to increase in the upcoming days unless this problem is addressed with a multifaceted approach.⁴⁴”

8. GENERAL COMMENT: The article can be accepted after minor revisions. The article could also benefit better from the service of a professional language editor.

Response: The article has been further revised by an in house language editor who is a native English speaker. Thank you for this suggestion.

Reviewer: 3

1. Please leave your comments for the authors below

The objective of the study to compare the determinants of hypertension when 2 different definitions were used is indeed a good intention. However, there are important variables that are associated with hypertension from other studies such as diabetes, smoking, physical inactivity, family history were not included in the study. Without some of important variables, the associated

factors could not be determined correctly. Therefore, I would not recommend this paper for publication

Response: Thank you honorable reviewer for your feedback. We have included your raised point in the limitation section: "Except BMI, the association of hypertension with other metabolic determinants including diabetes mellitus or dyslipidemia and life-style factors (smoking, physical activity, dietary habit), family history was not evaluated, as those data were not collected."

Reviewer: 4

Thank you for the opportunity of reviewing the manuscript entitled "Determinants of Hypertension among adults in Nepal as per the Joint National Committee 7 and 2017 American College of Cardiology/American Heart Association Hypertension Guidelines". Overall it is well written and covers an important aspect of the evolving increase of Non-Communicable Diseases - however, I have some brief comments:

Comment 1: Under introduction - the authors give relevant and sufficient information about the previous study results for readers to follow the significance, purpose and objectives for the present study. They acknowledge that the prevalence and factors associated with hypertension may change as a result of the introduction of the new guideline which defines hypertension as SBP/DBP $\geq 130/80$ from previous SBP/DBP $\geq 140/90$. They claim that the new prevalence was associated with an increase of 23%¹¹ from JNC7 but there is no information relating to the determinants of hypertension according to the new guideline. They also claim that according to the JNC7 age, sex, BMI, socioeconomic status and region of residence were associated with hypertension in Nepal.^{8,16,17} Therefore, their study used the 2016 NDHS data aimed to compare the determinants of hypertension among Nepalese adults obtained using the JNC7 guideline with 2017 ACC/AHA guideline.

Response: Thanks!

Comment 2: Under methodology, the issue of language and who did the data collection was not described. This requires some further brief description.

Response: Thanks for this important suggestion! We have added the information under the methodology section: "NDHS utilized a standard, pretested, and validated biomarker questionnaire (in the local context of Nepal) for to collect data on blood pressure measurements and anthropometry measurements (height and weight). All the men and women aged 15 years and above who were residents in half of the selected households were considered eligible for blood pressure measurements. The questionnaire was finalized in English and then translated and pretested in Nepali, Maithili, and Bhojpuri language.¹³ The data collection took place from June 19, 2016 to January 31, 2017. Trained enumerators carried out the data collection. The data was collected by sixteen teams. Each team comprised of a supervisor, three female interviewers, and one male interviewer. Two female members and the male member of the team were trained to measure the height and body weight. The male team member also received training on blood pressure measurement. Rigorous monitoring was done by ICF staff, quality control team, and technical team from the Ministry of Health and the Nepal Health Research Council.¹³"

Comment 3: The process of identifying the respondents within the cluster has not fully described (i.e. in terms of the inclusion/exclusion criteria, were bed-ridden and disabled individuals included? Also were individuals that were visiting the area included? How did they account for individuals that were working during the day? A discussion on such issues would be useful as part of limitations.

Response: Thanks! We have mentioned how the respondents were selected from the cluster: "NDHS utilized a standard, pretested, and validated biomarker questionnaire (in the local context of Nepal) for to collect data on blood pressure measurements and anthropometry measurements (height and weight). All the men and women aged 15 years and above who were residents in half of the selected households were considered eligible for blood pressure measurements. The questionnaire was finalized in English and then translated and pretested in Nepali, Maithili, and Bhojpuri language.¹³ The data collection took place from June 19, 2016 to January 31, 2017. Trained enumerators carried out the data collection. The data was collected by sixteen teams. Each team comprised of a supervisor,

three female interviewers, and one male interviewer. Two female members and the male member of the team were trained to measure the height and body weight. The male team member also received training on blood pressure measurement. Rigorous monitoring was done by ICF staff, quality control team, and technical team from the Ministry of Health and the Nepal Health Research Council.¹³

The NDHS report did not mention about inclusion of the bed-ridden and disabled individuals. The women and men who spent night in the selected households were included in the main survey but it was not mentioned whether they were included for the biomarker survey. Nothing was mentioned in the NDHS 2016 report whether they accounted for individuals that were working during the day.

Comment 4: In terms of the interpretation of the data, it would be useful to describe the demographics of the participants first, followed by the prevalence and factors associated with hypertension according to the two guidelines as shown below.

A. Background Characteristics of the respondents

A total of 13 393 individuals participated in this study of which 69.8% were less than 50 years of age, (58.0%) were females, (21.5%) were overweight/obese etc.

B. Prevalence and factors associated with hypertension according to guidelines

With regard to the prevalence of hypertension, according to the JNC 7 and ACC/AHA guidelines, around 21.0% (n=2827) and 44.0% (5918) of the respondents were classified as hypertensive, respectively. Both guidelines show that the prevalence of hypertension significantly increase with age (p<0.05) and males are more likely to be hypertensive than females (JNC7: 25% vs 18%, p<0.05; ACC/AHA:51% vs 39%, p<0.05).

NB: For comparison, it better to use row per cent and include the p-values for association (see example below). Again the authors must make sure that the absolute numbers are correct on the table.

	N=13393	Participants with Hypertension Under Guidelines					
		JNC 7			2017 ACC/AHA		
		Yes	No	p-value	Yes	No	p-value
Age(year)							
18-29	4337	266(6)	4071(94)	<0.001	1079(25)	3257(75)	<0.001
30-49	5002	1083(22)	3919(78)		2463(49)	2539(51)	
50-69	3188	1101(35)	2087(65)		1851(58)	1337(42)	
≥70	866	377(44)	489(56)		525(61)	341(39)	
Gender							
Male	5620	1429(25)	4191(75)	<0.001	2863(51)	2757(49)	<0.001
Female	7773	1398(18)	6375(82)		3055(39)	4717(61)	
Obese/overweight							
No	10513	1802(17)	8711(83)	<0.001	4073(39)	6440(61)	<0.001
Yes	2880	1025(36)	1855(64)		1845(64)	1034(36)	
Level of education							
None	5573	1365(25)	4208(75)	<0.001	2649(48)	2922(52)	<0.001
Primary	2171	473(22)	1698(78)		975(45)	1197(55)	
Secondary	3696	680(18)	3016(82)		1549(42)	2150(58)	
Tertiary	309	309(16)	1641(84)		745(38)	1205(62)	
Household wealth index							

Poorest	2396	449(19)	1947(81)	<0.001	1043(44)	1353(56)	<0.001
Poorer	2594	548(21)	2046(79)		1163(45)	1432(55)	
Middle	2666	475(17)	2191(82)		1075(40)	1590(60)	
Richer	2917	554(19)	2363(81)		1201(41)	1715(59)	
richest	2820	801(28)	2019(72)		1436(51)	1384(49)	
Place of residence							
Urban	8191	1831(22)	6360(78)	<0.001	3708(45)	4482(55)	0.002
Rural	5202	996(19)	4206(81)		2210(43)	2992(57)	

Response: Thank you honorable reviewer for the suggestion! We have restructured the findings/results section according to your suggestion. We have included row percentage instead of column percentage to show the prevalence of hypertension according to two guidelines. We have also added the p-values in Table 1.

Comment 5:

Under discussion, line 36-37 stated age, sex, overweight/obesity and province of residence were significantly associated with hypertension according to both guidelines. On the other hand, household weight status and ecological zone of residence were only significant per the JNC7 guideline. The authors should elaborate on the implication of these findings.

Response: Thank you for your suggestion! We have mentioned the implications in the discussion section of the manuscript: "To prevent complications of hypertension, including reducing the burdens of NCDs in Nepal, prevention and control programs should prioritize these known determinants irrespective of socio-economic status or place of residence."

Other statements such as "Around 60% of the individuals age ≥ 70 years were hypertensive according to ACC/AHA guidelines. "Males had higher likelihood hypertension than females". These statements can only be supported by using row per cent instead of column per cent as shown in Table 1 above.

Response: Thank you honorable reviewer for the suggestion! We have included row percentage instead of column percentage to show the prevalence of hypertension according to two guidelines. We have also added the p-values in Table 1.

VERSION 2 – REVIEW

REVIEWER	Sam T Ntuli University of Limpopo, South Africa
REVIEW RETURNED	18-Jun-2019
GENERAL COMMENTS	I've review this article previously and the authors made some corrections as suggested