



RESEARCH ARTICLE

REVISED Blood pressure and 10-year all-cause mortality: Findings from the PERU MIGRANT Study [version 2; peer review: 1 approved with reservations]Aida Hidalgo-Benites¹, Valeria Senosain-Leon¹, Rodrigo M. Carrillo-Larco^{2,3}, Andrea Ruiz-Alejos², Robert H. Gilman^{2,4}, Liam Smeeth⁵, J. Jaime Miranda ^{2,6}, Antonio Bernabé-Ortiz ^{2,7}¹Universidad Peruana de Ciencias Aplicadas, Lima, Peru²CRONICAS Center of Excellence in Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru³Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK⁴Department of International Health, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland, USA⁵Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK⁶Department of Medicine, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru⁷Universidad Científica del Sur, Lima, Peru**V2** First published: 09 Nov 2021, **10**:1134
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<https://doi.org/10.12688/f1000research.73900.3>**Abstract****Background**

The long-term impact of elevated blood pressure on mortality outcomes has been recently revisited due to proposed changes in cut-offs for hypertension. This study aimed at assessing the association between high blood pressure levels and 10-year mortality using the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) and the American College of Cardiology and the American Heart Association (ACC/AHA) 2017 blood pressure guidelines.

Methods

Data of the PERU MIGRANT Study, a prospective ongoing cohort, was used. The outcome of interest was 10-year all-cause mortality, and exposures were blood pressure categories according to the JNC-7 and ACC/AHA 2017 guidelines. Log-rank test, Kaplan-Meier and Cox regression models were used to assess the associations of interest controlling for confounders. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated.

Results

A total of 976 records, mean age of 60.4 (SD: 11.4), 513 (52.6%) women, were analyzed. Hypertension prevalence at baseline almost doubled from 16.0% (95% CI 13.7%–18.4%) to 31.3% (95% CI

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28.4%–34.3%), using the JNC-7 and ACC/AHA 2017 definitions, respectively. Sixty-three (6.4%) participants died during the 10-year follow-up, equating to a mortality rate of 3.6 (95% CI 2.4–4.7) per 1000 person-years. Using JNC-7, and compared to those with normal blood pressure, those with pre-hypertension and hypertension had 2-fold and 3.5-fold increased risk of death, respectively. Similar mortality effect sizes were estimated using ACC/AHA 2017 for stage 1 and stage 2 hypertension.

Conclusions

Blood pressure levels under two different definitions increased the risk of 10-year all-cause mortality. Hypertension prevalence doubled using ACC/AHA 2017 compared to JNC-7. The choice of blood pressure cut-offs to classify hypertension categories need to be balanced against the patients benefit and the capacities of the health system to adequately handle a large proportion of new patients.

Keywords

Hypertension, pre-hypertension, blood pressure, mortality

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REVISED Amendments from Version 1

This new version of the manuscript contains extra information in the introduction as requested by the reviewer. Changes have been done especially in the Methods and Results sections to clarify the settings and participants and statistical analysis plan. We have improved our analysis and new results have been added as age was categorized in 4 groups (instead of 2 as originally showed) to improve control in our Cox regression models. In the discussion section, we have strengthened the public health relevance of our findings as suggested by the reviewer as well as given more details about studies that are compared with our results. Finally, typos and grammatical spelling mistakes have been corrected.

Any further responses from the reviewers can be found at the end of the article

Introduction

Ischemic heart disease and cerebrovascular disease are the first and second cause of death globally.^{1,2} Hypertension, as a cardiovascular risk factor, was the cause of 9.4 million deaths and is closely related to ischemic heart and cerebrovascular disease.³ Worldwide, the number of adults living with hypertension has increased from 563 million in 1975 to 1.13 billion in 2015, and the prevalence of hypertension in 2015 was estimated to be 24.1% and 20.1% in men and women, respectively.⁴

Levels of blood pressure before the development of hypertension are known as pre-hypertension according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (known as JNC-7),⁵ and those with pre-hypertension are more likely to develop hypertension and its consequences. In 2017, as part of the ongoing review process of full guidelines commissioned in about 6-year cycles, the American College of Cardiology and the American Heart Association (ACC/AHA 2017) changed the proposed cut-off points used for defining hypertension, and for instance, included part of the pre-hypertension cases as hypertension (known as stage 1 hypertension).⁶ The adoption of the ACC/AHA 2017 guidelines may produce changes in the proportion of cases with hypertension as reported for the US general population by the Systolic Blood Pressure Intervention Trial (SPRINT) Study, where the prevalence of hypertension almost doubled from 49.7% using JNC-7 to 80.1% by ACC/AHA 2017.⁷ Similar changes in hypertension prevalence have been described in different countries.^{8–13}

Different reports associate arterial mean and blood pressure levels with all-cause mortality and cardiovascular mortality.^{14–16} Whilst the association between blood pressure levels, defined by JNC-7, and mortality has been well described,¹⁷ the evidence of the impact of the new definitions of hypertension on all-cause mortality in resource-constrained settings remains limited.^{15,18} Therefore, long-term studies involving populations from low- and middle-income countries (LMICs) are needed given that raised blood pressure is a major contributor to the global burden of disease.¹⁹

This study aimed at assessing whether the levels of blood pressure, using two different guidelines, JNC-7 and ACC/AHA 2017, are associated with 10-year mortality using an ongoing Peruvian cohort study.

Methods**Study design**

Data analysis of the PERU MIGRANT Study, a prospective ongoing cohort conducted enrolling three different population groups: rural, rural-to-urban migrants, and urban dwellers was carried out.²⁰ The baseline of the study was conducted in 2007–2008 and follow-ups were carried out in 2012–2013, 2015–2016, and 2018.²¹ For this analysis, data from the baseline assessment and 2018 follow-up were used.

Settings and participants

Las Pampas de San Juan de Miraflores, a highly urbanized area in the city of Lima, was selected as the urban environment, whereas San Jose de Secce, a district of Ayacucho in the highlands, was selected as the rural site. Individuals who were ≥30 years of age and habitual residents in the selected study sites were invited to participate at baseline. Rural dwellers were enrolled in San Jose de Secce, while urban residents and rural-to-urban migrants were recruited from Las Pampas de San Juan de Miraflores in Lima.²⁰ Pregnant women or potential participants unable to understand procedures and consent were excluded.

Participants were randomly selected using an age- (30–39, 40–49, 50–59, and 60+) and sex- stratified sampling approach, utilizing the most up-to-date census in the study area. San Jose de Secce (Ayacucho) was the area chosen for the selection of rural dwellers. Migrants were those born in Ayacucho but living in Las Pampas de San Juan de Miraflores (Lima) at the time of the study enrolment. Finally, urban dwellers were those permanently living in the same area.²⁰

Power estimations were based on major risk factors in Huaraz (highlands) and Lima. The baseline study aimed at recruiting 1000 participants (200 in rural and urban groups, and 600 in the migrant group). Comparing Lima and highlands groups, the study had 84% power to detect a difference in the prevalence of hypertension (33% vs. 19.5%) enrolling 200 subjects in each group. Such power was 81% in the case of type 2 diabetes (7.6% versus 1.3%).²⁰

Definition of variables

Outcome The outcome of interest was the time until an event, defined as the time, in years, lapsed from the baseline assessment (2007–2008) to death or censorship during follow-up. Information about vital status and date of death (or censoring) was obtained via assessment of the National Record of Identification and Civil Status (RENIEC (Spanish acronym)) conducted in 2018.

Exposure The exposure variable was hypertension-related categories using measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) under two different definitions, JNC-7 and ACC/AHA 2017. Under the JNC-7 definition,⁵ individuals were split into three categories: normal (SBP < 120 mm Hg and DBP < 80 mm Hg without using specific medication), pre-hypertension (SBP 120–139 mm Hg and DBP 80–89 mm Hg without anti-hypertensive therapy), and hypertension (SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, or those reporting previous diagnosis done by a physician or current anti-hypertensive treatment). On the other hand, under the ACC/AHA 2017 definition,⁶ participants were split into four categories: normal (same as those in JNC-7), elevated blood pressure (SBP 120–129 mm Hg and DBP < 80 mm Hg, without medication), stage 1 hypertension (SBP 130–139 mm Hg and DBP 80–89 mm Hg without treatment), and stage 2 hypertension (same as those with hypertension in the JNC-7).

Covariates Other variables included as potential confounders in the analysis were: age (30–39, 40–49, 50–59, and 60+ years), sex (men vs. women), education level (less than seven vs. more than seven years), socioeconomic status, defined by using an assets index and then split in tertiles (low, middle, high), and population group (rural, rural-to-urban migrant, and urban). In addition, behavioural variables were also included: daily smoking, self-reported, based on the consumption of at least one cigarette per day; alcohol use, defined according to the self-reported consumption of six or more beers (or equivalent) on the same occasion at least once a month (low vs. high); and physical activity level, based on the short version of the International Physical Activity Questionnaire (IPAQ) and split into low and moderate/high (www.ipaq.ki.se). Finally, total cholesterol (< 200 mg/dL and ≥ 200 mg/dL) and type 2 diabetes, defined as fasting glucose ≥ 126 mg/dL or previous diagnosis made by a physician, were also included.

Procedures

Recruitment of participants was conducted by community health workers utilizing standardized tools. Questionnaires were based on the World Health Organization (WHO) STEPwise approach to surveillance (STEPs), validated in a pilot study and previously published.²⁰ Fieldworker's training included application of informed consent and questionnaires, and the attainment of clinical measurements using appropriate and calibrated methods. Blood pressure was measured in seated position after a resting period of five minutes. Measures were done by triplicate using an automated device (OMRON HEM-780) and the average of the second and third measurements was used to define hypertension. Laboratory assessments were performed on venous samples taken in the morning after a minimum of eight hours (maximum 12 hours) of fasting. Total cholesterol was measured in serum, and fasting glucose was measured in plasma using a Cobas® 6000 Modular Platform automated analyser and reagents supplied by Roche Diagnostics.

Statistical analysis

STATA 16 for Windows (Stata Corp, College Station TX, US; RRID:SCR_012763) was used for statistical analysis. An open-access alternative that can provide an equivalent function is the **R stats** package (R Project for Statistical Computing, RRID:SCR_001905). Sociodemographic, lifestyle behavioural and anthropometric variables were described according to each definition of blood pressure levels (JNC-7 and ACC/AHA 2017) using the Chi-squared test. Variables were also described according to vital status using the Log-rank test. A plot of the Kaplan-Meier estimator was used to evaluate the assumption of proportional hazards graphically, whereas such assessment was done in post-hoc analysis using the Schoenfeld residuals. Crude and adjusted Cox regression models were used to estimate the strength of the association between variables of interest (i.e., blood pressure and all-cause mortality), reporting hazard ratios (HR) and 95% confidence intervals (95% CI). Using full-adjusted models, Akaike and Bayesian information criteria (AIC and BIC) as well as the Nelson-Aalen graphs were utilized to compare both blood pressure level definitions and their impact on mortality.

Ethics

The original PERU MIGRANT Study was approved by Institutional Review Boards (IRB) at Universidad Peruana Cayetano Heredia (approval codes: 51103, 60014 and 64094) in Peru and London School of Hygiene and Tropical

Medicine (approval code: 5115) in the UK. Follow-up was approved by the IRB at the UPCH only. Written informed consent was given by study participants prior to starting research activities. Permission was obtained to use personal identifiers to link participant's information with vital status records; and only deidentified and anonymized data was used for publication.²² The protocol for this secondary data analysis was approved by the ethics committee at Universidad Peruana de Ciencias Aplicadas (approval code: PI178-17) in Lima, Peru.

Results

Characteristics of the study population at baseline

A total of 989 participants were enrolled at baseline, but 13 (1.3%) were excluded as no mortality information was available at the end of the study. Thus, only 976 were included in further analyses. Of them, 196 (20.1%) were rural, 582 (59.6%) migrants, and 198 (20.3%) were urban dwellers, have a mean age of 60.4 (SD: 11.4), and 513 (52.6%) were women.

Hypertension prevalence at baseline almost doubled from 16.0% (95% CI 13.7%–18.4%) to 31.3% (95% CI 28.4%–34.3%) using the JNC-7 and ACC/AHA 2017 guidelines, respectively. In both definitions, high blood pressure levels were more frequent among males, older subjects, migrant and urban dwellers, as well as those with obesity and those with type 2 diabetes mellitus (Table 1 and Table 2).

Table 1. Characteristics of the study population by blood pressure levels according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7).

	Blood pressure level			p-value*
	Normal (n = 508)	Pre-hypertension (n = 312)	Hypertension (n = 156)	
Sex				
Men	181 (35.6%)	206 (66.0%)	76 (48.7%)	<0.001
Age				
30–39 years	194 (38.2%)	74 (23.7%)	13 (8.3%)	<0.001
40–49 years	158 (31.1%)	90 (28.9%)	30 (19.2%)	
50–59 years	119 (23.4%)	99 (31.7%)	52 (33.4%)	
60+ years	37 (7.3%)	49 (15.7%)	61 (39.1%)	
Education level				
<7 years	237 (46.7%)	148 (47.6%)	86 (55.1%)	0.18
7+ years	270 (53.3%)	163 (52.4%)	70 (44.9%)	
Socioeconomic status				
Low	226 (44.5%)	134 (43.0%)	64 (41.0%)	0.54
Middle	113 (22.2%)	79 (25.3%)	45 (28.9%)	
High	169 (33.3%)	99 (31.7%)	47 (30.1%)	
Population group				
Rural	105 (20.7%)	68 (21.8%)	23 (14.7%)	<0.001
Rural-to-urban migrant	316 (62.2%)	192 (61.5%)	74 (47.4%)	
Urban	87 (17.1%)	52 (16.7%)	59 (37.8%)	
Daily smoking				
Yes	14 (2.8%)	9 (2.9%)	10 (6.4%)	0.08
Alcohol use				
High consumption	38 (7.5%)	33 (10.6%)	15 (9.6%)	0.29
Physical activity				
Low levels	132 (26.2%)	72 (23.2%)	48 (31.2%)	0.18
Obesity				
BMI \geq 30 kg/m ²	90 (17.7%)	57 (18.3%)	49 (31.4%)	0.001

Table 1. *Continued*

	Blood pressure level			p-value*
	Normal	Pre-hypertension	Hypertension	
	(n = 508)	(n = 312)	(n = 156)	
Total cholesterol				
≥200 mg/dL	124 (24.4%)	117 (37.6%)	63 (40.4%)	<0.001
Type 2 diabetes				
Yes	11 (2.2%)	15 (4.8%)	13 (8.4%)	0.002

*Chi-squared test was used for comparisons.

Table 2. Characteristics of the study population by blood pressure levels according to the American College of Cardiology and the American Heart Association (ACC/AHA) 2017.

	Blood pressure level				p-value*
	Normal	Elevated	Stage 1 hypertension	Stage 2 hypertension	
	(n = 508)	(n = 163)	(n = 149)	(n = 156)	
Sex					
Men	181 (35.6%)	104 (63.8%)	102 (68.4%)	76 (48.7%)	<0.001
Age					
30–39 years	194 (38.2%)	41 (25.1%)	33 (22.1%)	13 (8.3%)	<0.001
40–49 years	158 (31.1%)	39 (23.9%)	51 (34.2%)	30 (19.2%)	
50–59 years	119 (23.4%)	56 (34.4%)	43 (28.9%)	52 (33.4%)	
60+ years	37 (7.3%)	27 (16.6%)	22 (14.8%)	61 (39.1%)	
Education level					
<7 years	237 (46.7%)	80 (49.4%)	68 (45.6%)	86 (55.1%)	0.27
7+ years	270 (53.3%)	82 (50.6%)	81 (54.4%)	70 (44.9%)	
Socioeconomic status					
Low	226 (44.5%)	73 (44.8%)	61 (41.0%)	64 (41.0%)	0.44
Middle	113 (22.2%)	35 (21.5%)	44 (29.5%)	45 (28.9%)	
High	169 (33.3%)	55 (33.7%)	44 (29.5%)	47 (30.1%)	
Population group					
Rural	105 (20.7%)	37 (22.7%)	31 (20.8%)	23 (14.7%)	<0.001
Rural-to-urban migrant	316 (62.2%)	104 (63.8%)	88 (59.1%)	74 (47.4%)	
Urban	87 (17.1%)	22 (13.5%)	30 (20.1%)	59 (37.8%)	
Daily smoking					
Yes	14 (2.8%)	3 (1.8%)	6 (4.1%)	10 (6.4%)	0.10
Alcohol use					
High consumption	38 (7.5%)	18 (11.0%)	15 (10.1%)	15 (9.6%)	0.47
Physical activity					
Low levels	132 (26.2%)	39 (24.2%)	33 (22.2%)	48 (31.2%)	0.31
Obesity					
BMI ≥ 30 kg/m ²	90 (17.7%)	31 (19.0%)	26 (17.5%)	49 (31.4%)	0.001
Total cholesterol					
≥200 mg/dL	124 (24.4%)	61 (37.7%)	56 (37.6%)	63 (40.4%)	<0.001
Type 2 diabetes					
Yes	11 (2.2%)	5 (3.1%)	10 (6.7%)	13 (8.4%)	0.002

*Chi-squared test was used for comparisons.

Mortality and associated factors

A total of 63 (6.4%) participants died during the 10-year follow-up with 9992.6 person-years of follow-up and a mortality rate of 3.6 (95% CI 2.4–4.7) per 1000 person-years. In bivariable model, men, older individuals, those with lower education, those with lower socioeconomic status, and having type 2 diabetes mellitus had an increased risk of 10-year mortality (Table 3).

Table 3. Characteristics of the study population by vital status.

	Vital status		p-value*
	Alive (n = 913)	Dead (n = 63)	
Sex			
Women	491 (95.7%)	22 (4.3%)	0.004
Men	422 (91.1%)	41 (8.9%)	
Age			
30–39 years	279 (99.3%)	2 (0.7%)	<0.001
40–49 years	272 (97.8%)	6 (2.2%)	
50–59 years	254 (94.1%)	16 (5.9%)	
60+ years	108 (74.5%)	39 (26.5%)	
Education level			
<7 years	428 (90.9%)	43 (9.1%)	0.001
7+ years	483 (96.0%)	20 (4.0%)	
Socioeconomic status			
Low	386 (91.0%)	38 (9.0%)	0.01
Middle	229 (96.6%)	8 (3.4%)	
High	298 (94.6%)	17 (5.4%)	
Population group			
Rural	178 (90.8%)	18 (9.2%)	0.19
Rural-to-urban migrant	550 (94.5%)	32 (5.5%)	
Urban	185 (93.4%)	13 (6.6%)	
Daily smoking			
No	880 (93.5%)	61 (6.5%)	0.95
Yes	31 (93.9%)	2 (6.1%)	
Alcohol use			
Low consumption	834 (93.7%)	56 (6.3%)	0.52
High consumption	79 (91.9%)	7 (8.1%)	
Physical activity			
High/moderate levels	667 (93.2%)	49 (6.8%)	0.35
Low levels	239 (94.8%)	13 (5.2%)	
Obesity			
BMI < 30 kg/m ²	727 (93.2%)	53 (6.8%)	0.39
BMI ≥ 30 kg/m ²	186 (94.9%)	10 (5.1%)	
Total cholesterol			
<200 mg/dL	623 (92.9%)	48 (7.1%)	0.13
≥200 mg/dL	290 (95.4%)	14 (4.6%)	
Type 2 diabetes			
No	879 (93.9%)	57 (6.1%)	0.02
Yes	33 (84.6%)	6 (15.4%)	

*P-value estimated using Log-rank test.

Table 4. Association between blood pressure levels by Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) and American College of Cardiology and the American Heart Association (ACC/AHA) 2017 definition and 10-year mortality: crude and adjusted Cox models.

Blood pressure definition	Vital status		Crude model HR (95% CI)	Adjusted model 1* HR (95% CI)	Adjusted model 2** HR (95% CI)
	Alive (n = 913)	Dead (n = 63)			
JNC-7					
Normal	497 (97.8%)	11 (2.2%)	1 (Reference)	1 (Reference)	1 (Reference)
Pre-hypertension	289 (92.6%)	23 (7.4%)	3.50 (1.71-7.19)	2.04 (1.02-4.25)	2.00 (1.01-4.18)
Hypertension	127 (81.4%)	29 (18.6%)	9.4 (4.71-18.89)	3.52 (1.68-7.36)	3.45 (1.62-7.33)
ACC/AHA 2017					
Normal	497 (97.8%)	11 (2.2%)	1 (Reference)	1 (Reference)	1 (Reference)
Elevated blood pressure	153 (93.9%)	10 (6.1%)	2.87 (1.21-6.75)	1.64 (0.69-3.91)	1.55 (0.63-3.81)
Stage 1 hypertension	136 (91.3%)	13 (8.7%)	4.22 (1.89-9.42)	2.54 (1.11-5.84)	2.47 (1.07-5.74)
Stage 2 hypertension	127 (81.4%)	29 (18.6%)	9.44 (4.71-18.89)	3.55 (1.69-7.42)	3.48 (1.64-7.39)

Bold estimates are significant at p < 0.05 level.* Adjusted model 1 was controlled by age, sex, population group, education level, and socioeconomic status.
 ** Adjusted model 2 was controlled by age, sex, population group, education level, socioeconomic status, daily smoking, alcohol use, physical activity, obesity status, total cholesterol, and type 2 diabetes mellitus.

Blood pressure levels and 10-year mortality

There was evidence of an association between hypertension-related categories and all-cause mortality (Table 4). Using the JNC-7 guideline and compared to those with normal blood pressure, those with pre-hypertension and hypertension had 2-fold and 3.4-fold increased hazard of death, respectively. On the other hand, using the ACC/AHA 2017 definition and compared to those with normal blood pressure, stage 1 and stage 2 hypertension were associated with a 2.5- and 3.5-fold increase in the hazard of mortality. There was no evidence of an association between the ACC/AHA 2017's elevated blood pressure category and mortality.

When comparing adjusted models, AIC and BIC were very similar (AIC was 741.3 for JNC-7 vs. 742.2 for ACC/AHA 2017, whereas BIC was 824.1 for JNC-7 vs. 829.9 for ACC/AHA 2017), highlighting no difference between models.

Discussion

Main findings

According to our findings, high blood pressure levels increased the risk of 10-year all-cause mortality, and our estimates showed similar long-term effect sizes across blood pressure categories using two different guidelines. As countries move into better universal health coverage, primary prevention and access to medications should be secured to reduce the health burden of raised blood pressure. However, how countries prepare and secure resources to successfully meet the challenges of hypertension will depend on how this is defined. There was a remarkable difference on hypertension prevalence depending on whether the JNC-7 or the ACC/AHA 2017 definition was followed, but the latter definition would avoid approximately 20% more deaths than the JNC-7 guideline. This carries relevant implications and repercussions for patients and health systems. Should the ACC/AHA 2017 definition be adopted because this will require securing treatment for a substantial larger population with the costs and challenges it entails.

Comparison with previous studies

In the US, the SPRINT Study, conducted in 2010, reported that the ACC/AHA 2017 definition significantly increased the prevalence of patients with hypertension and identified more patients who will experience adverse cardiovascular events.⁷ However, it can be argued that information came from a clinical trial, which may have included more high-risk patients than in the general population; also, participants in the SPRINT Study were followed-up for 3.3 years. Conversely, we conducted a population-based 10-year follow-up study, advancing the evidence for the general population.

Because of data availability, we could not assess cardiovascular mortality; nonetheless, it is likely that we would have seen a similar – or even larger – effect as the one herein reported for all-cause mortality. In a pooled analysis of prospective cohorts conducted in China, starting from 1996 to 2010,¹⁵ the ACC/AHA 2017 stage I hypertension was associated with an increased risk of cardiovascular disease mortality; notably, another cohort study with participants recruited from 1997 to 1999, and with 20 years of follow-up, did not find such association in rural dwellers in the same country.¹⁸ The difference could be explained by different risk factor profiles in rural areas, or presumably lower levels of risk factors over twenty years ago. Using the National Health and Nutrition Examination Surveys between 2003 and 2014, a study found that the ACC/AHA 2017 guidelines would increase the proportion of stroke survivors in the US compared to the JNC-7 definition.²³ Thus, there is a potential benefit of applying the ACC/AHA 2017 guidelines, although this needs to be verified in different population groups.

Public health relevance

The ACC/AHA 2017 guidelines radically proposed to change definitions of blood pressure levels, with pre-hypertension split into two categories: elevated blood pressure and stage I hypertension. Multiple authors have questioned this change, and pinpointed that hypertension prevalence would increase, pharmacotherapy of hypertension will start at a lower blood pressure level, and the threshold for hypertension control will decrease.^{10,24} Thus, cases of stage I hypertension, previously classified as pre-hypertension in JNC-7, will start treatment with an initial anti-hypertensive drug if estimated 10-year cardiovascular risk is $\geq 10\%$,⁶ but CV risk scores have showed poor concordance in Latin America populations²⁵; whereas those in stage II hypertension would start with two anti-hypertensive drugs.^{26–28} In support of these concerns, a study showed that hypertension prevalence would increase by 40% in the US.¹⁰ Similarly in Peru, using information from a population-based survey, the prevalence of hypertension would increase from 14% to 32%.¹² Peru is a middle-income country with a fragile and fragmented healthcare system, with poor response to the challenges of chronic conditions. Increasing the number of people with hypertension may benefit those with blood pressure levels in the range 130–139/80–89 mm Hg, but would represent a major investment so that these patients can receive adequate treatment. A thoroughly planned and balanced policy would be needed to provide care to those who most needed it. A combination of population-wide interventions,²⁹ along with high-risk stratification may be considered.

As the risk of coronary artery disease and stroke rise progressively increases as blood pressure increases above 115/75 mm Hg,³⁰ the beginning of antihypertensive therapy will certainly have advantages, especially the reduction of patient's complications and mortality.³¹ However, there will be an increase of primary care costs, which can be more deleterious in resource-constrained settings. A recent study conducted in the US has estimated that reaching the goals of the ACC/AHA 2017 guidelines will reduce 610,000 cardiovascular events and avoid 334,000 total deaths per year among adults 40 years and older.³² Nevertheless, the potential increase of adverse events related to the use of anti-hypertensive drugs should be also considered³³ as well as a substantial number of hypertension cases giving up or taking medication irregularly. Thus, although the adoption of ACC/AHA 2017 guidelines may seem pertinent in term of complications and mortality reduction, Peru as well as other low- and middle-income countries, may not be prepared for this scenario.

Strengths and limitations

This study takes advantage of an ongoing population-based cohort study conducted in a resource-constrained setting with three different population groups to evaluate the impact of two definitions of high blood pressure levels and 10-year mortality. However, this study has some limitations that should be highlighted. First, due to data availability, this study analysed all-cause mortality as outcome instead of assessing cardiovascular mortality. Since blood pressure increases the risk of cardiovascular events and mortality, we can speculate that the association of interest will be stronger and probably did not vary between hypertension definitions as in our analysis. Second, diet patterns and salt consumption, two potential confounders, were not included in our models as they were not available. Third, although left truncation can be present as subjects <30 years were excluded, the potential effect of such limitation may be negligible as the prevalence of hypertension is low in that age group. Finally, we did not assess the potential effect of anti-hypertensive drugs on mortality due to limited sample size.

Conclusions

Blood pressures levels under two different definitions increased the risk of 10-year all-cause mortality. Hypertension prevalence doubled using the ACC/AHA 2017 compared to the JNC-7 definition. The choice of blood pressure cut-offs to classify hypertension categories need to be balanced against the patient's benefit and the capacities of the health system to adequately handle a large proportion of new patients. Cardiovascular disease prevention, and, in particular, the prevention of blood pressure-related mortality, will benefit from the estimates reported in this study to adequately inform local decision making, which in addition to disease burden should recognize balance benefits and risks within existing capacities to secure and guarantee adequate and effective treatment for all the new patients with raised blood pressure.

Data availability

Underlying data

Figshare: Underlying data for 'Blood pressure and 10-year all-cause mortality: Findings from the PERU MIGRANT Study', 'PERU MIGRANT Study', <https://doi.org/10.6084/m9.figshare.16811350.v3>.²²

This project includes the following underlying data:

- PERU MIGRANT Dataset (mortality).csv
- Dictionary.txt

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

Author contributions

Aida Hidalgo-Benites: conceptualization, data curation, formal analysis, investigation, methodology, writing original draft, and writing review and editing.

Valeria Senosain-Leon: conceptualization, data curation, formal analysis, investigation, methodology, writing original draft, and writing review and editing.

Rodrigo M. Carrillo-Larco: data curation, formal analysis, investigation, methodology, validation, and writing review and editing.

Andrea Ruiz-Alejos: data curation, formal analysis, funding acquisition, investigation, methodology, and writing review and editing.

Robert H. Gilman: funding acquisition, investigation, methodology, supervision, validation, and writing review and editing.

Liam Smeeth: funding acquisition, investigation, methodology, supervision, validation, and writing review and editing.

J. Jaime Miranda: conceptualization, funding acquisition, investigation, methodology, supervision, validation, and writing review and editing.

Antonio Bernabe-Ortiz: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, supervision, and writing review and editing.

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? **Annika Hoyer** 

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The authors have responded and acted well to the points and comments raised to the previous version of the manuscript. However, we still have some open questions and remarks.

1. We do now understand the age cut-off at year 30 and thank the authors for clarification. Nonetheless, we are wondering how the new categorization is justified. With regards to blood pressure and mortality, we would think that particularly the age group 60+ might be at high risk and thus, more detailed analysis (i.e. splitting into further age group 60-69, 70-79, etc.) might be of interest. We kindly ask the authors for more details on the stratification choice. Overall though, we still recommend including age as a covariate measured on a continuous scale to improve the power of the analysis.
2. Current guidelines used to report the results of observational studies such as STROBE clearly state that inferential measures should not be used for description of the study population. In line with that, we strongly suggest to delete all p-values from tables 1-3 and to simply describe the characteristics of the study participants. Further, and also as advanced by current guidelines, the use of p-values is not an appropriate criterion for selecting which confounders to adjust for in the analysis. Consequently, we advocate that any statement about potential associations based on single p-values should be avoided.
3. We thank the authors for rewriting the Statistical analysis section where they refer to the Kaplan-Meier estimator. In the text it now reads that the evaluation of the proportional hazards assumption is based on visual inspection of a graph. For higher transparency and better understanding, we would suggest to include the graph in the article or as supporting material.
4. We are pleased to see that the authors followed our recommendation and changed the term "bivariate model". Though, the term "bivariable model" is still somewhat misleading and rather uncommon to use. We would suggest to simply refer to an "association".
5. As suggested by the authors, we have reviewed the Public health relevance section for more

information on how their study provides input e.g. for local decision making or public health implications. From our point of view, the article still lacks precise guidance in which way the estimates/results from the study presented in the article can be used for decision making with respect to benefits and risks for patients with newly diagnosed hypertension. Consequently, we highly recommend that the authors explain the implications of their study in more detail and that they provide concrete ideas of possible future activities.

6. In our first review we noted that the authors were not consistent in their writing and with the vocabulary used in the tables, e.g. "stage 1" vs. "stage-1" vs. "stage I" (same applies for "stage 2"). In the reviewed article we still find inconsistencies, particularly comparing the Public health relevance section with the rest of the text.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics, Epidemiology, Diabetes, Chronic Diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Apr 2023

Antonio Bernabe-Ortiz

1. We do now understand the age cut-off at year 30 and thank the authors for clarification. Nonetheless, we are wondering how the new categorization is justified. With regards to blood pressure and mortality, we would think that particularly the age group 60+ might be at high risk and thus, more detailed analysis (i.e., splitting into further age group 60-69, 70-79, etc.) might be of interest. We kindly ask the authors for more details on the stratification choice. Overall, though, we still recommend including age as a covariate measured on a continuous scale to improve the power of the analysis.

Response: The categorization of the age variable is due to the fact that the sampling approach was stratified by age in that way (i.e., 30-39, 40-49, 50-59, and 60+). For instance, even we can adjust for that variable in different forms (i.e., using different cut-offs or in a continuous fashion), the best way would be to adjust for the form the variable was stratified. This was explained in the "Settings and participants" subheading in the Methods section. In addition, this was added in the Statistical analysis subheading:

"Potential confounders were selected under epidemiological criteria. Since the selection of the participant's sample was stratified by age (i.e., 30-39, 40-49, 50-59, 60+), such variable was included in that form in adjusted models."

2. Current guidelines used to report the results of observational studies such as STROBE clearly state that inferential measures should not be used for description of the study population. In line with that, we strongly suggest to delete all p-values from tables 1-3 and to simply describe the characteristics of the study participants. Further,

and also as advanced by current guidelines, the use of p-values is not an appropriate criterion for selecting which confounders to adjust for in the analysis. Consequently, we advocate that any statement about potential associations based on single p-values should be avoided.

Response: We have deleted p-values from tables 1 to 3 as suggested. We have not selected confounders based on p-values, but in an epidemiological approach (pre-specified model).

3. We thank the authors for rewriting the Statistical analysis section where they refer to the Kaplan-Meier estimator. In the text it now reads that the evaluation of the proportional hazard assumption is based on visual inspection of a graph. For higher transparency and better understanding, we would suggest to include the graph in the article or as supporting material.

Response: We have included the figure in the manuscript as requested. We believe the figure does not add more information. Thus, we think the figure should be included in online material but F1000Research does not accept supplemental material. We leave the final decision to include the figure to the reviewer and the editor.

4. We are pleased to see that the authors followed our recommendation and changed the term "bivariate model". Though, the term "bivariable model" is still somewhat misleading and rather uncommon to use. We would suggest to simply refer to an "association".

Response: We have deleted the word bivariable from the text of the manuscript.

5. As suggested by the authors, we have reviewed the Public health relevance section for more information on how their study provides input e.g. for local decision making or public health implications. From our point of view, the article still lacks precise guidance in which way the estimates/results from the study presented in the article can be used for decision making with respect to benefits and risks for patients with newly diagnosed hypertension. Consequently, we highly recommend that the authors explain the implications of their study in more detail and that they provide concrete ideas of possible future activities.

Response: This is an observational study looking at the association between two different guidelines for hypertension definition and all-cause mortality, and not a clinical trial to do decision making. However, according to our results, we have added some lines:

"Treatment must be guaranteed for hypertension (using JNC-7) and stage 2 hypertension (ACC/AHA 2017) to reduce mortality risk. If this effect can be seen in pre-hypertension (JNC-7) and stage 1 hypertension (ACC/AHA 2017) should be further assessed."

6. In our first review we noted that the authors were not consistent in their writing and with the vocabulary used in the tables, e.g. "stage 1" vs. "stage-1" vs. "stage I" (same applies for "stage 2"). In the reviewed article we still find inconsistencies, particularly comparing the Public health relevance section with the rest of the text.

Response: We have reviewed through manuscript, tables and figures to keep consistency.

Competing Interests: No competing interest to report.

Version 1

Reviewer Report 22 July 2022

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Annika Hoyer 

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In the manuscript at hand, the authors report results from a study evaluating the association between blood pressure and all-cause mortality. They aim to investigate whether there are differences in the association using two different definitions of hypertension: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) and the more recent guideline of the American College of Cardiology and the American Heart Association (ACC/AHA). The main difference between them is that the JNC-7 guideline consists of three categories whereas the ACC/AHA guideline comprises four stages, leading to a change in the cut-off points for defining hypertension and the corresponding disease prevalence. Based on data from the PERU MIGRANT study, the authors found that there is evidence for an association between the different definitions of hypertension and mortality while accounting for potential confounders. This finding is in line with the results from previous studies, but has the advantage that it is based on a large population-based cohort study. As a main conclusion the authors recommend that the choice of cut-off values for defining hypertension should be balanced with respect to the patient's benefit and the capacities of the health system because of a rising number of people with hypertension using the ACC/AHA guideline.

The article is well written and spreads light on the association between blood pressure and mortality depending on the cut-off for defining high blood pressure in the Peruvian population. However, we have some comments and suggestions that may improve the article:

1. In the introduction, it was written that "prevalence of hypertension was estimated to be 24.1% and 20.1% in men and women, respectively". It would be helpful to add the year that corresponds to these prevalence's.
2. In the introduction, we would suggest to briefly discuss the reasons that initially led to a reformulation of the definition of hypertension, i.e. what were the motives of the ACC/AHA

to change the cut-off levels, and why did they introduce four instead of three categories?

3. In the "Settings and participants" section, it remains unclear what is meant by an "age and stratified sampling approach" which is used to select participants of the PERU MIGRANT study. This should be clarified.
4. What is the reason for splitting age into two categories (< 50 vs. >= 50)? With respect to the power of the analysis, it would be far better to include age as a covariate measured on a continuous scale.
We were also wondering about the reason for the age cut-off at year 30? Is there a reason why no children, adolescents and any other people below 30 years are excluded?
5. We would strongly recommend to delete all p-values from tables 1-3 and to purely report on the characteristics of the population. This would be in line with current guidelines used to report the results of observational studies (e.g. STROBE).
6. We are a bit confused about the term "Kaplan-Meier test" and would suggest that the authors explain in more detail what specific kind of statistical test they used. If they are interested in the association between the exposure and outcome, it would be also possible to assess the estimated hazard ratios (HR) and their confidence intervals based on the proportional hazard regression approach.
7. Drawing conclusions about potential associations between variables based on univariate p-values (tables 1-3) alone should be viewed critically because the PERU MIGRANT study is a cohort study. That means that there are indeed confounding variables that are not adjusted for in tables 1-3. Again, we would recommend to delete all p-values from tables 1-3, to simply describe the characteristics of the study participants and to avoid statements about potential associations based on single p-values.
8. The term "bivariate model" should be avoided when only the association between two variables is meant because in a bivariate analysis, the outcome consists of two variables.
9. With respect to the Cox model, we would suggest to interpret the HR in terms of hazards and not risks. That means, a HR of 5.1 indicates a 5.1-fold increased hazard (and not a risk). It should also be added compared to which group the hazard is increased (or decreased).
10. We were wondering if the authors took account for possible left truncation which maybe occurred because the minimum age of entry is 30 years.
11. When discussing the AIC and BIC for the models, the authors should be more precise and state which models were compared and which result refers to which comparison.
12. In the section where the authors compare their findings with other studies, the dates of the studies mentioned should be added.
13. In the introduction and conclusion, the authors highlight that three different population groups were separately considered. Though, in the result section this is not further taken up. We would recommend that the authors explain why the distinction is yet so important

and if the findings of their study differ with regards to the different groups.

14. From our point of view, the conclusion that 46% of deaths could be avoided using the JNC-7 definition, and 66.7% using the ACC/AHA 2017 guideline if hypertension is treated, seem a bit speculative. Could deaths be really prevented if people are classified as being hypertensive? We think such a conclusion cannot be drawn from a cohort study and the analysis done by the authors because it is not known if hypertension was the reason for all reported deaths. Only associations are seen. This should be discussed in more detail. We would also suggest to weaken this conclusion.
15. We would suggest that the authors explain the implications of their study in more detail. As a concluding remark, they have written that their estimates can be used to inform local decision making. We were wondering how this can be achieved based on the estimated HRs because they do not differ that much between the two definitions of hypertension. It would be helpful to describe in which way these estimates can be used for decision making with respect to benefits and risks for patients with newly diagnosed hypertension.

Minor comments:

1. The authors may want to add a decimal separator (e.g. 1,000 person years).
2. With regards to abbreviations: They should be introduced when first used (e.g. page 9 "CV risk scores"), and only introduced when needed (e.g. STEPs is never referred to again). First, the full name should be spelled and then the abbreviation should be added in brackets (e.g. Systolic Blood Pressure Intervention Trial Study (SPRINT)). Abbreviations in the abstract should be avoided (e.g. HR).
3. The authors should be consistent in their writing and with the vocabulary used in the tables. E.g. "stage 1" vs. "stage-1" vs. "stage I" (same applies for "stage 2") and "Las Pampas de San Juan de Miraflores" vs. "San Juan de Miraflores".
4. Abstract: The data of the PERU MIGRANT Study was used, not the analysis, we think.
5. Page 3, Settings and Participants: The sentence "In Lima, a highly urbanized city, Las Pampas de San Juan de Miraflores was selected as the urban environment," should be rephrased as follows "Las Pampas de San Juan de Miraflores, a highly urbanized city in Lima, Peru, was selected as the urban environment....".
6. Page 4: There is a typo in the Procedures section. It should be read "measured" instead of "measure" in the following sentence: "Blood pressure was measured in seated position after a resting period of five minutes."
7. Page 4: Another typo is found in the Ethics section. Instead of "in UK" the authors should write "in the UK" at the end of the first sentence of the mentioned paragraph.
8. Page 7: When discussing the main findings, we would suggest reformulating the following sentence on page 7 to "High blood pressure levels have been found to increase the risk of 10-year all-cause mortality (*please add a reference*) ...".

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Biostatistics, Epidemiology, Diabetes, Chronic Diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Jan 2023

Antonio Bernabe-Ortiz

REVIEWER 1 - ANNIKA HOYER

The article is well written and spreads light on the association between blood pressure and mortality depending on the cut-off for defining high blood pressure in the Peruvian population. However, we have some comments and suggestions that may improve the article:

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What is the reason for splitting age into two categories (< 50 vs. ≥ 50)? With respect to the power of the analysis, it would be far better to include age as a covariate measured on a continuous scale.

Response: Age is considered as confounder in our models. However, we have changed the categorization of age in four categories based on the stratification of the sample (30-39, 40-49, 50-69, and 60+ years). We have accordingly modified paper results. Overall, HR reduced after controlling for age in 4 categories, but are yet consistent.

We were also wondering about the reason for the age cut-off at year 30? Is there a reason why no children, adolescents and any other people below 30 years are excluded?

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Response: Although left truncation can be present as minimum age at study entry was 30 years, we believe the effect can be negligible as the prevalence of hypertension in Peruvian population aged <30 years is very low (<3%). However, we have added that in the limitations section: *"Third, although left truncation can be present as subjects <30 years were excluded, the potential effect of such limitation may be negligible as the prevalence of hypertension is low in*

that age group."

When discussing the AIC and BIC for the models, the authors should be more precise and state which models were compared and which result refers to which comparison.

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From our point of view, the conclusion that 46% of deaths could be avoided using the JNC-7 definition, and 66.7% using the ACC/AHA 2017 guideline if hypertension is treated, seem a bit speculative. Could deaths be really prevented if people are classified as being hypertensive? We think such a conclusion cannot be drawn from a cohort study and the analysis done by the authors because it is not known if hypertension was the reason for all reported deaths. Only associations are seen. This should be discussed in more detail. We would also suggest to weaken this conclusion.

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