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Jeffrey Hodis Date

Association of hypertension according to new ACC/AHA blood pressure guidelines with incident dementia in the Atherosclerosis Risk in Communities cohort

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Master of Public Health

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2019

Abstract

Association of hypertension according to new ACC/AHA blood pressure guidelines with incident dementia in the Atherosclerosis Risk in Communities cohort
By Jeffrey Hodis

Background
Associations between midlife hypertension and the development of dementia have been established. However, the impact of the new 2017 ACC/AHA hypertension guidelines on dementia risk at the population level has not been evaluated.

Objectives
To assess the association of hypertension categories with the risk of incident dementia and to calculate the population attributable fraction (PAF) for dementia from hypertension categories defined by ACC/AHA guidelines, compared to the associations with hypertension defined by JNC7.

Methods
We studied dementia-free participants recruited to the Atherosclerosis Risk in Communities (ARIC) cohort in 1987-89. Hypertension was defined by 2003 JNC7 and 2017 ACC/AHA guidelines using blood pressure (BP) measured at baseline. Dementia was defined using adjudicated consensus diagnoses at visit 5 (2011-13), informant telephone interviews, and ICD-9 codes from hospitalizations and death certificates through 2013. Cox proportional hazards regression models estimated hazard ratios (HR) and 95% confidence intervals (CI) by hypertension categories, adjusting for potential confounders. PAF of dementia by hypertension category was calculated using rate ratios from Poisson regression and the prevalence of the risk factor in the population.

Results
Among 13,971 participants followed for a median of 23.0 years, 1381 cases of dementia were identified. HRs (95%CI) compared to normal BP according to ACC/AHA categories were 1.35 (1.12, 1.61) for elevated BP, 1.28 (1.07, 1.52) for hypertension stage 1 and 1.36 (1.18, 1.57) for hypertension stage 2. PAF (95%CI) of dementia from BP categories were 3% (1%, 5%), 3% (1%, 5%) and 9% (4%, 14%), respectively. PAF using JNC7 categories were similar to ACC/AHA: 6% (3%, 9%) for prehypertension, 0% (-2%, 2%) for hypertension stage 1, and 9% (5%, 13%) for hypertension stage 2.

Conclusions
Risk of dementia was increased across categories defined by ACC/AHA guidelines. However, the population impact on dementia incidence using ACC/AHA was similar to the impact of JNC7. This suggests that new criteria for hypertension will not increase the number of persons in whom hypertension could be labeled as a risk for dementia.

Association of hypertension according to new ACC/AHA blood pressure guidelines with incident dementia in the Atherosclerosis Risk in Communities cohort

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Table of Contents

Association of hypertension according to new ACC/AHA blood pressure guidelines with incident dementia in the Atherosclerosis Risk in Communities cohort

Background/Objectives

Hypertension, more commonly known as high blood pressure, has long been hypothesized to have a negative impact on cognitive function. The first widely cited study of the association between hypertension and cognitive function was a case-control study published in 1964 that indicated commercial air traffic controllers and aircraft pilots with hypertension exhibited decreased levels of psychomotor speed.[1] Since this publication, numerous other studies have suggested that hypertension is a key risk factor for impaired cognitive function and various dementias. Midlife (defined as 44-54 years old) hypertension may have a stronger impact on late-life cognitive decline and incident dementia than late-life hypertension.[2] The Honolulu-Asia Aging Study, a community-based study of Japanese American men, reported that midlife blood pressure (systolic blood pressure being a stronger predictor than diastolic blood pressure) was associated with incident dementia[3,4] and late-life cognitive decline.[5] A prospective population-based study on a Finnish cohort similarly reported that midlife hypertension led to an increase in the risk of late-life Alzheimer's disease[6] and mild cognitive impairment.[7]

Numerous analyses from the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) have established associations between cardiovascular risk factors, primarily midlife hypertension and diabetes, and the development of incident dementia and cognitive decline.[2,8,9] However, in 2017, the American College of Cardiology (ACC) and the American Heart Association (AHA) changed the definition of high blood pressure, lowering the cutoff to define hypertension. This announcement marks the first comprehensive change to the categorization of hypertension since 2003 and is now estimated to include about 46% of the United States adult population as having hypertension.[10,11] According to the guideline authors, it is expected that the prevalence of high blood pressure will triple among men under

the age of 45.[10] The most significant change to the categorization of BP is the removal of the prehypertension classification, instead classifying people as having normal blood pressure (BP), elevated BP, stage 1 hypertension, or stage 2 hypertension. The rationale behind changing the categorization of hypertension was a result of recent controlled studies and expert consensus that concluded more intensive prevention of cardiovascular risk factors are needed to reduce the risk of various cardiovascular diseases and all-cause mortality.[12] One such study, the SPRINT-MIND randomized clinical trial, found that the risk of hypertension complications is elevated at prehypertension/elevated BP levels and that reducing BP below these levels is beneficial in reducing the risk of cognitive impairment.[13] Previous studies examining the association of hypertension with dementia risk conducted on ARIC-NCS were based on the previously used Seventh Report of the Joint National Committee (JNC7) guidelines, leaving unanswered questions as to how the new categorization of hypertension relates to the development of incident dementia.

The first objective of this analysis was to assess the association of hypertension and of BP categories defined according to the new ACC/AHA guidelines with the risk of incident dementia, and compare these associations with those using the previous JNC7 categorization. We hypothesized that midlife hypertension, as defined by the new guidelines, is related to an increased risk of incident dementia, especially among the black population as several studies suggest this racial group is more likely to experience higher rates of dementia compared to whites.[9,14,15] The association of stage 2 hypertension with dementia would be stronger than the association for stage 1 hypertension, compared to normal BP. The second objective was to calculate the population attributable fraction (PAF) of hypertension and of BP categories defined according to both the ACC/AHA guidelines and the JNC7 definition with the risk of incident dementia. We hypothesized that hypertension would be responsible for a large proportion of dementia cases in the ARIC cohort, although the PAF with the new definition will be only modestly larger that with the old hypertension definition.

Methods

Participants

The ARIC study was a prospective cohort that recruited 15,792 participants aged 44 to 66 years old from 1987-1989 from fields centers in 4 United States communities: Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi; and Minneapolis suburbs, Minnesota.[9,16] The goals of the ARIC study were to investigate the etiology of atherosclerosis and the variation in cardiovascular risk factors by race, sex, location, and time.[9,16] After the initial baseline visit, participants were followed up and seen at 4 visits, including visit 5 (2011-2013) which was part of the ARIC Neurocognitive Study (ARIC-NCS).[16]

13,971 of the initial 15,792 participants who were recruited to the ARIC-NCS were included in the analysis. These participants were dementia-free and had information on BP and other covariates at the baseline visit. For the purposes of this analysis, those who were not identified as black or white were excluded, in addition to the small black population from the Maryland and Minnesota field centers due to issues with adjusting for race and center that would arise when the two populations in questions are too small. The ARIC study was approved by each field center's institutional review board (Johns Hopkins University, Wake Forest University, University of Mississippi, University of Minnesota) and all participants provided written informed consent (along with proxies, when required).[2,9]

Blood Pressure

Hypertension was defined by the 2003 JNC7 and 2017 ACC/AHA guidelines using BP measured at baseline. For both sets of guidelines, participants using antihypertensive medication were included in stage 2 hypertension.

Hypertension defined according to the new ACC/AHA guidelines is systolic blood pressure (SBP) ≥130 mm Hg or diastolic blood pressure (DBP) ≥80 mm Hg. Individuals were also categorized according to BP categories as follows: normal (SBP <120 mm Hg and DBP <80 mm Hg), elevated (SBP 120-129 mm

Hg and DPB <80 mm Hg), stage 1 hypertension (SBP 130-139 mm Hg or DBP 80-89 mm Hg), and stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg) (**Table 1**).[11]

Hypertension defined according to the old JNC7 guidelines is SBP ≥140 mm Hg or DBP ≥90 mm Hg. Individuals were also categorized according to BP categories as follows: normal (SBP <120 mm Hg and DBP <80 mm Hg); prehypertension (SBP 120-139 mm Hg or DBP 80-89 mm Hg); stage 1 hypertension (SBP 140-159 mm Hg or DBP 90-99 mm Hg); and stage 2 hypertension (SBP ≥160 or ≥100) (**Table 1**).[17]

Covariates

Covariates that were considered as potential confounders include age, sex, race, field center, and education level (grade school or 0 years; high school, no degree; high school graduate; vocation school; college; graduate or professional school) of which sex, race, and education level were self-reported. APOEε4 carriers were identified by genotyping and were defined by the number of ε4 alleles (0, 1, or 2) they carried. History of smoking (current, former, or never), and alcohol use (g/week) were self-reported. Physical activity (a calculated score based on the intensity, hours a week, and months a year spent for sport or exercise during leisure time) was assessed using the ARIC/Baecke questionnaire which recorded information on physical activity in sports, during leisure time, and at work.[18,19] Total cholesterol (mmol/L) and HDL cholesterol (mmol/L), and BMI (kg/m^2) were measured and included as potential confounders. Presence of diabetes was defined as fasting blood glucose level of at least 126 mg/dL, non-fasting blood glucose level of at least 200 mg/dL, use of diabetes medications or insulin, or self-report of a physician's diagnosis. Prevalent coronary heart disease, prevalent heart failure, and prevalent stroke (all measured yes or no) were defined based on self-reported information.[2,9]

Dementia

Dementia was defined using adjudicated dementia diagnoses at visit 5 (2011-2013) which included data from longitudinal cognitive evaluations, a complete neuropsychological battery at visit 5, and informant telephone interview.[20] Dementia was also identified by ICD-9 codes from hospitalizations

and death certificates through 2013 along with classification of cognitive status based on standardized definitions of dementia.[16,20]

Statistical Analysis

Statistical software SAS Version 9.4 was used for this analysis. Primary analyses used Cox proportional hazards regression models to estimate hazard ratios (HR) and 95% confidence intervals (CI) of incident dementia by hypertension categories, adjusting for potential confounders listed above in the Covariates subsection. The primary endpoint was time between visit 1 and diagnosis of dementia, loss to follow-up, or administrative censoring (at the latest date for visit 5 assessment or the date of last participant contact up to September 1st, 2013), whichever occurred first.[9] Several models were run, the first of which included all variables that were considered potential confounders: age, sex, race, field center, education level, APOEε4 genotype, smoking status, alcohol use, physical activity, total cholesterol, HDL cholesterol, BMI, presence of diabetes, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke. Subsequent models were stratified by sex and race separately. We also tested for an interaction between BP categories and the stratifying variable. These models were run for both the new ACC/AHA and the old JNC7 guidelines, and each model was run using the full BP categories (all 4 categories) in addition to binary categories (normal and prehypertension/elevated were grouped as not having hypertension, stage 1 and stage 2 hypertension were group as having hypertension).

PAF of dementia by categories of hypertension were calculated using standard approaches to determine the possible impact, if any, of preventing hypertension on the incidence of dementia. Rate ratios were calculated using Poisson regression and the prevalence of hypertension in the population was calculated for each BP category. The equation pd [(RR – 1)/RR], where pd is equal to the proportion of cases exposed to hypertension, was used to calculate the PAF.[21,22] The PAF was calculated for the 2

sets of hypertension guidelines and for the full BP categories and binary categories as described above for the Cox proportional hazards models.

Results

Cohort Characteristics

A total of 13,971 participants contributed to the analysis and were followed for a median of 23.0 years. The mean age of this sample at baseline was 54.1 (SD = 5.7) years, and 55.2% (n = 7711) identified as female and 73.3% (n = 10,238) identified as white. In total, 1381 cases of dementia were identified among the 13,971 participants, which represents 9.9% of the sample. The overall incidence rate of dementia among the cohort was 4.9 per 1000 person-years.

According to the old JNC7 guidelines, 41.5% (n = 5793) of participants were categorized as normal, 24.1% (n = 3369) as prehypertensive, 7.2% (n = 1000) as stage 1 hypertension, and 27.3% (n = 3809) as stage 2 hypertension. Overall, the prevalence of hypertension was higher among females compared to males and among whites compared to blacks. The prevalence of hypertension (stage 1 and 2 hypertension) in the cohort according to the old guidelines was 34.5% (**Table 2**).

According to the new ACC/AHA guidelines, 41.5% (n = 5793) of participants were categorized as normal, 10.3% (n = 1433) as elevated, 13.9% (1936) as stage 1 hypertension, and 34.4% (n = 4809) as stage 2 hypertension. The prevalence of hypertension was also higher among females compared to males and among whites compared to blacks. The prevalence of hypertension in the cohort according to the new guidelines was 48.3% (**Table 3**).

Cox Proportional Hazards Regression Models on Non-Binary Categorizations

Cox proportional hazards regression models were run using the normal BP category as a reference for the other categories. The hazard ratios (HR) and 95% confidence intervals (CI) for the JNC7 guidelines were as follows: prehypertension (HR: 1.31; 95% CI: 1.13, 1.51); stage 1 hypertension (HR: 1.12; 95% CI: 0.89, 1.41); and stage 2 hypertension (HR: 1.44; 95% CI: 1.24, 1.66). The number of

incident dementia cases per category were 396, 376, 96, and 513 for normal, prehypertension, stage 1 hypertension, and stage 2 hypertension, respectively. The number of person-years contributed to each category was 123,571, 68,882, 19,501, and 71,369 which resulted in incidence rates of dementia (per 1000 person-years) of 3.2, 5.5, 4.9, and 7.2, respectively (**Table 4**).

The HRs and 95% CIs for the ACC/AHA guidelines were as follows: elevated (HR: 1.35; 95% CI: 1.12, 1.61); stage 1 hypertension (HR: 1.28; 95% CI: 1.07, 1.52); and stage 2 hypertension (HR: 1.36; 95% CI: 1.18, 1.57). The number of incident dementia cases per category were 396, 176, 200, and 609 for normal, elevated, stage 1 hypertension, and stage 2 hypertension, respectively. The number of person-years contributed to each category was 123,571, 29,052, 39,829, and 90,870 which resulted in incidence rates of dementia (per 1000 person-years) of 3.2, 6.1, 5.0, and 6.7, respectively (**Table 4**).

Cox Proportional Hazards Regression Models on Binary Categorizations

To evaluate the effect of having hypertension or not on incident dementia, non-hypertensive categories (normal and prehypertension for JNC7 guidelines, normal and elevated for ACC/AHA guidelines) were combined, and hypertensive categories (stage 1 and stage 2 hypertension for both sets of guidelines) were combined. The same Cox proportional hazards regression model was run for each set of guidelines, using no hypertension as the reference for each model.

The HR according to the JNC7 guidelines was 1.19 (95% CI: 1.06, 1.34). The number of incident dementia cases per category were 772 and 609 for no hypertension and hypertension, respectively. The number of person-years contributed to each category was 192,453 and 90,870 which resulted in incidence rates of dementia (per 1000 person-years) of 4.0 and 6.7, respectively (**Table 5**).

The HR according to the ACC/AHA guidelines was 1.22 (95% CI: 1.08, 1.37). The number of incident dementia cases per category were 572 and 809 for no hypertension and hypertension, respectively. The number of person-years contributed to each category was 152,623 and 130,700 which resulted in incidence rates of dementia (per 1000 person-years) of 3.8 and 6.2, respectively (**Table 5**).

Stratified Cox Proportional Hazards Regression Models on Non-Binary Categorizations

Separate Cox proportional hazards regression models were stratified on sex and race to determine if there was a significant interaction between these variables and BP categories. These models adjusted for the same covariates listed above. The normal BP category was used as a reference for the other BP categories.

Overall, we did not find evidence of effect modification by sex or race. When stratified by sex for the JNC7 guidelines, the corresponding p-value for interaction between sex and BP categories was 0.72. When stratified by race, the corresponding p-value for interaction between race and BP categories was 0.33 (**Table 6**).

When stratified by sex for the ACC/AHA guidelines, the corresponding p-value for interaction between sex and BP categories was 0.73. When stratified by race, the corresponding p-value for interaction between race and BP categories was 0.37 (**Table 6**).

Stratified Cox Proportional Hazards Regression Models on Binary Categorizations

As with the other binary BP categorization analyses, Cox proportional hazards regression models adjusted for the same covariates listed above. No hypertension and hypertension categories were categorized using the same method when analyzing non-stratified binary Cox proportional hazards regression models. No hypertension was used as a reference for each model.

When stratified by sex, the HRs according to the JNC7 guidelines were 1.21 (95% CI: 1.04, 1.41) and 1.14 (95% CI: 0.95, 1.37) for females and males, respectively. The corresponding p-value for interaction between sex and hypertension was 0.58. The HRs according to the JNC7 guidelines, when stratified by race, were 1.21 (95% CI: 1.05, 1.41) and 1.13 (95% CI: 0.93, 1.38) for whites and blacks, respectively. The corresponding p-value for interaction between race and hypertension was 0.27 (**Table 7**).

When stratified by sex, the HRs according to the ACC/AHA guidelines were 1.28 (95% CI: 1.09, 1.50) and 1.13 (95% CI: 0.94, 1.35) for females and males, respectively. The corresponding p-value for interaction between sex and hypertension was 0.29. The HRs according to the ACC/AHA guidelines, when stratified by race, were 1.24 (95% CI: 1.08, 1.43) and 1.13 (95% CI: 0.90, 1.41) for whites and blacks, respectively. The corresponding p-value for interaction between race and hypertension was 0.21 (**Table 7**).

Population Attributable Factor (PAF) on Non-Binary Categorizations

As previously mentioned, PAF was calculated using the equation pd [(RR – 1)/RR], where pd is equal to the proportion of cases exposed to hypertension.[21,22] Poisson regression was used to obtain risk ratios (RR) required to calculate the PAF for each BP category. The normal BP category was used as a reference for RRs and for the PAF calculations.

According to the JNC7 guidelines, the PAF of dementia from hypertension categories were 6.3% (95% CI: 2.9%, 9.1%), 0.1% (95% CI: -1.6%, 1.5%), and 9.4% (95% CI: 5.1%, 13.2%) for prehypertension, stage 1 hypertension, and stage 2 hypertension, respectively. According to the ACC/AHA guidelines, the PAF were 3.1% (95% CI: 1.3%, 4.7%), 3.1% (95% CI: 0.9%, 4.9%), and 9.1% (95% CI: 4.0%, 13.7%) for elevated, stage 1 hypertension, and stage 2 hypertension, respectively (**Table 8**).

Population Attributable Factor (PAF) on Binary Categorizations

No hypertension and hypertension categories were categorized using the same method when analyzing non-stratified binary Cox proportional hazards regression models. No hypertension was used as the reference category for the RRs.

According to the JNC7 guidelines, the RR of dementia was 1.11 (95% CI: 0.98, 1.24) and the PAF of dementia was 4.4% (95% CI: -0.9%, 8.5%). According to the ACC/AHA guidelines, the RR was 1.16 (95% CI: 1.03, 1.30) and the PAF was 8.1% (95% CI: 1.7%, 13.5%) (**Table 9**).

Discussion

This study showed that hypertension defined with the new ACC/AHA guidelines was associated with an increased risk of dementia compared to the JNC7 guidelines. Overall, the hazard ratios using BP categories according to the ACC/AHA guidelines were more often higher than those obtained when using the JNC7 guidelines for all categorizations of BP (i.e. stratified and non-stratified binary and non-binary categorizations). The PAF of dementia according to the ACC/AHA guidelines was similar to the PAF of dementia according to the JNC7 guidelines.

This analysis supports previous findings that, in general, high BP is associated with a higher risk of incident dementia.[2-9] The SPRINT-MIND randomized clinical trial lends more evidence that interventions to control dementia have proven to be successful. In this trial, 9361 participants were randomized to an intensive treatment group (those with a goal of SBP less than 120 mm Hg) or a standard treatment group (those with a goal of less than 140 mm Hg) to determine if these interventions reduced the occurrence of adjudicated probable dementia, adjudicated mild cognitive impairment, and a composite outcome of either cognitive outcome.[21] The intensive treatment group vs the standard treatment group saw a decreased rate of adjudicated probable dementia although these results were not significant (HR 0.83; 95% CI: 0.67, 1.04); however, the intensive treatment group significantly reduced the risk of mild cognitive impairment alone (HR 0.81; 95% CI: 0.69, 0.95) and the combined outcomes of mild cognitive impairment or probable dementia (HR 0.85; 95% CI: 0.74, 0.97).[13] This clinical trial adds support to the literature that treating hypertension can reduce the risk of cognitive decline and probable dementia.

Although the new ACC/AHA guidelines recategorized more participants from prehypertension/elevated BP categories into stage 1 and stage 2 hypertension categories, results of the JNC7 and ACC/AHA guidelines yielded similar (although overall, ACC/AHA generally yielded slightly higher HRs) results when analyzed using non-binary categories, binary categories, and stratified non-

binary and binary analyses. In non-binary category analyses, results follow a similar trend where the HRs are high for prehypertension/elevated categories, fall to a varying degree for stage 1 hypertension, then increase again for stage 2 hypertension, generally to a higher value than the HR for the prehypertension/elevated categories. This trend can be explained due to the difference in the BP cutoffs between the two sets of guidelines. With the JNC7 guidelines for stage 2 hypertension set at SBP ≥160 or DBP ≥100, participants in this category were generally more at risk for incident dementia due to their higher BP than if they were classified according to the ACC/AHA guidelines (SBP ≥140 or DBP ≥90).

Results from this analysis indicate that associations between hypertension and dementia risk were stronger in women compared to men, and in whites compared to blacks, using both sets of guidelines. The stratified results of BP guidelines by race are inconsistent with previous studies which concluded that blacks experience higher rates of dementia compared to whites.[9,14,15] Interaction tests between BP categories and sex or race were not statistically significant.

PAF on dementia incidence using ACC/AHA guidelines is only slightly higher than the impact of the JNC7 guidelines. This suggests that the new criteria for the diagnosis of hypertension will only have a limited impact on the number of people in whom hypertension could be labeled as risk for dementia. However, the impact of interventions targeting incident dementia according to the new ACC/AHA guidelines appears to be larger due to the higher prevalence of hypertension when participants were recategorized under these guidelines. This analysis suggests that the lower cutoffs under the new guidelines could be used to more accurately identify people who are at a higher risk for incident dementia by treating their hypertension.

Strengths and Limitations

Our analysis has some important strengths, such as a large and racially diverse sample size that had a long follow-up of decades. Careful adjudication of dementia allowed for the inclusion of deceased participants as identified through hospitalization and death certificate codes, and through informant

interviews for deceased participants who were highly suspected to have dementia. Informant interviews were also used to identify dementia cases in participants who were too cognitively impaired to attend a clinic visit or complete neuropsychological testing.

Our study, however, has important limitations. Many of the covariates used in this study were based on self-reported data, which may introduce residual confounding when assessing the association between hypertension and incident dementia. Cases of dementia that were identified through hospitalization codes may be incorrect or more frequent in participants who have numerous vascular comorbidities. If many cases of dementia were misclassified, the association between hypertension and other vascular risk factors on incident dementia may be underestimated.[9] Estimates of the onset of dementia may also be imprecise as dementia often has an onset of years before a diagnosis is made. Black participants have higher mortality rates than whites in the ARIC cohort, leading to less of these participants surviving to visit 5. The decreased susceptibility of black participants developing incident dementia could underestimate the effect of hypertension on dementia among this population.

Issues with generalizability arise from this study as the ARIC study was initiated in the late 1980s and focused on only 4 communities and 2 races. These results would be more generalizable to the general population if participants were sampled from communities across the country and large enough sample sizes of all races were recruited. Lastly, this analysis serves as an exploratory analysis to determine if the new guidelines would have had a different association with incident dementia. The ARIC-NCS data was based on the JNC7 guidelines, therefore results based on the ACC/AHA guidelines cannot be used to fully estimate causal effects of the new categorization of BP and hypertension on incident dementia.

Conclusions

The association of midlife hypertension and BP categories defined according to the new ACC/AHA guidelines generally resulted in an increased risk of incident dementia than the old JNC7

guidelines. Although this increased risk was not as pronounced among the black population as hypothesized, the association of stage 2 hypertension with dementia was stronger than for stage 1 hypertension when compared to normal BP. The PAF of hypertension and of BP categories according to the new guidelines were only slightly larger than those with the old BP guidelines. Future studies need to further evaluate the impact of the new BP categories and definition of hypertension on incident dementia.

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Table 1. Categories of Hypertension Established by the JNC7 (Old) and ACC/AHA (New) Guidelines

JNC7 (SBP and/or DBP, mm Hg)		ACC/AHA (SBP and/or DBP, mm Hg)	
Normal	<120 and <80	Normal	<120 and <80
Prehypertension	120-139 or 80-89	Elevated	120-129 and <80
Hypertension Stage 1	140-159 or 90-99	Hypertension Stage 1	130-139 or 80-89
Hypertension Stage 2*	≥160 or ≥100	Hypertension Stage 2*	≥140 or ≥90

* Participants using antihypertensive medication were included in the hypertension stage 2 category.

Table 2. Demographic Characteristics of Atherosclerosis Risk in Communities (ARIC) Participants by JNC7 (Old) Hypertension Guidelines

	Normal	Prehypertension	Stage 1	Stage 2	Total
No., n (%)	5793 (41.5)	3369 (24.1)	1000 (7.2)	3809 (27.3)	13971 (100)
Female, n (%)	3362 (58.0)	1665 (49.4)	493 (49.3)	2191 (57.5)	7711 (55.2)
White, n (%)	4978 (85.9)	2521 (74.8)	625 (62.5)	2114 (55.5)	10238 (73.3)
Field center, n (%)					
Forsyth County, North Carolina	1836 (31.7)	864 (25.7)	227 (22.7)	772 (20.3)	3699 (26.5)
Jackson, Mississippi	683 (11.8)	751 (22.3)	343 (34.3)	1501 (39.1)	3278 (23.5)
Minneapolis, Minnesota	1766 (30.5)	979 (29.1)	245 (24.5)	684 (18.0)	3674 (26.3)
Washington County, Maryland	1508 (26.0)	775 (23.0)	185 (18.5)	852 (22.4)	3320 (23.8)
Age, y, mean (SD)	52.3 (5.5)	54.5 (5.8)	55.3 (5.7)	55.6 (5.6)	54.1 (5.8)
Education level, n (%)					
Grade school or 0 years	327 (5.6)	293 (8.7)	147 (14.7)	537 (14.1)	1304 (9.3)
High school, no degree	628 (10.8)	460 (13.7)	144 (14.4)	707 (18.6)	1939 (13.9)
High school graduate	1898 (32.8)	1112 (33.0)	310 (31.0)	1185 (31.1)	4505 (32.3)
Vocational school	529 (9.1)	308 (9.1)	83 (8.3)	278 (7.3)	1198 (8.6)
College	1724 (29.8)	874 (25.9)	235 (23.5)	794 (20.9)	3627 (26.0)
Graduate or professional school	687 (11.9)	322 (9.6)	81 (8.1)	308 (8.1)	1398 (10.0)
Smoking status					
Current	1678 (29.0)	809 (24.0)	241 (24.1)	927 (24.3)	3655 (26.2)
Former	1809 (31.2)	1173 (34.8)	317 (31.7)	1228 (32.2)	4527 (32.4)
Never	2306 (39.8)	1387 (41.2)	442 (44.2)	1654 (43.4)	5789 (41.4)
Alcohol consumption, g/wk, mean (SD)	37.2 (79.5)	48.1 (100.5)	58.1 (130.6)	39.8 (98.9)	42.0 (94.8)
Physical activity score, mean (SD)	2.5 (0.8)	2.5 (0.8)	2.4 (0.8)	2.3 (0.8)	2.4 (0.8)
BMI, kg/m^2, mean (SD)	26.0 (4.3)	27.8 (5.2)	28.5 (5.8)	29.8 (5.9)	27.7 (5.4)

Systolic blood pressure, mmHg, mean (SD)	106.3 (8.4)	126.2 (6.5)	144.1 (8.2)	133.4 (22.2)	121.2 (18.8)
Diastolic blood pressure, mmHg, mean (SD)	66.4 (7.1)	76.2 (7.6)	84.3 (9.2)	79.7 (12.7)	73.7 (11.3)
Total cholesterol, mmol/L, mean (SD)	5.4 (1.0)	5.6 (1.1)	5.6 (1.1)	5.7 (1.2)	5.5 (1.1)
HDL cholesterol, mmol/L, mean (SD)	1.4 (0.4)	1.3 (0.5)	1.4 (0.5)	1.3 (0.4)	1.3 (0.4)
Diabetes, n (%)	339 (5.9)	317 (9.4)	120 (12.0)	869 (22.8)	1645 (11.8)
Prevalent coronary heart disease, n (%)	203 (3.5)	112 (3.3)	23 (2.3)	329 (8.6)	667 (4.8)
Prevalent heart failure, n (%)	90 (1.6)	58 (1.7)	13 (1.3)	488 (12.8)	649 (4.7)
Prevalent stroke, n (%)	82 (1.4)	42 (1.3)	20 (2.0)	109 (2.9)	253 (1.8)
APOE ε4 genotype, n (%)					
0 alleles	4072 (70.3)	2361 (70.1)	681 (68.1)	2541 (66.7)	9655 (69.1)
1 allele	1604 (27.7)	904 (26.8)	291 (29.1)	1149 (30.2)	3948 (28.3)
2 alleles	117 (2.0)	104 (3.1)	28 (2.8)	119 (3.1)	368 (2.6)
Antihypertensive use, n (%)	0	0	0	3505 (92.0)	3505 (25.1)

Table 3. Demographic Characteristics of Atherosclerosis Risk in Communities (ARIC) Participants by ACC/AHA (New) Hypertension Guidelines

	Normal	Elevated	Stage 1	Stage 2	Total
No., n (%)	5793 (41.5)	1433 (10.3)	1936 (13.9)	4809 (34.4)	13971 (100)
Female, n (%)	3362 (58.0)	755 (52.7)	910 (47.0)	2684 (55.8)	7711 (55.2)
White, n (%)	4978 (85.9)	1168 (81.5)	1353 (69.9)	2739 (57.0)	10238 (73.3)
Field center, n (%)					
Forsyth County, North Carolina	1836 (31.7)	448 (31.3)	416 (21.5)	999 (20.8)	3699 (26.5)
Jackson, Mississippi	683 (11.8)	217 (15.1)	534 (27.6)	1844 (38.3)	3278 (23.5)
Minneapolis, Minnesota	1766 (30.5)	404 (28.2)	575 (29.7)	929 (19.3)	3674 (26.3)
Washington County, Maryland	1508 (26.0)	364 (25.4)	411 (21.2)	1037 (21.6)	3320 (23.8)
Age, y, mean (SD)	52.8 (5.5)	55.4 (5.7)	53.9 (5.8)	55.5 (5.6)	54.1 (5.8)
Education level, n (%)					
Grade school or 0 years	327 (5.6)	117 (8.2)	176 (9.1)	684 (14.2)	1304 (9.3)
High school, no degree	628 (10.8)	195 (13.6)	265 (13.7)	851 (17.7)	1939 (13.9)
High school graduate	1898 (32.8)	497 (34.7)	615 (31.8)	1495 (31.1)	4505 (32.3)
Vocational school	529 (9.1)	128 (8.9)	180 (9.3)	361 (7.5)	1198 (8.6)
College	1724 (29.8)	362 (25.3)	512 (26.5)	1029 (21.4)	3627 (26.0)
Graduate or professional school	687 (11.9)	134 (9.4)	188 (9.7)	389 (8.1)	1398 (10.0)
Smoking status					
Current	1678 (29.0)	375 (26.2)	434 (22.4)	1168 (24.3)	3655 (26.2)
Former	1809 (31.2)	485 (33.9)	688 (35.5)	1545 (32.1)	4527 (32.4)
Never	2306 (39.8)	573 (40.0)	814 (42.1)	2096 (43.6)	5789 (41.4)
Alcohol consumption, g/wk, mean (SD)	37.2 (79.5)	45.9 (91.3)	49.7 (106.8)	43.6 (106.5)	42.0 (94.8)
Physical activity score, mean (SD)	2.5 (0.8)	2.5 (0.8)	2.4 (0.8)	2.3 (0.8)	2.4 (0.8)
BMI, kg/m^2, mean (SD)	26.0 (4.3)	27.5 (5.0)	28.1 (5.4)	29.5 (5.9)	27.7 (5.4)

Systolic blood pressure, mmHg, mean (SD)	106.3 (8.4)	123.9 (2.8)	128.0 (7.7)	135.6 (20.5)	121.2 (18.8)
Diastolic blood pressure, mmHg, mean (SD)	66.4 (7.1)	71.4 (6.2)	79.7 (6.6)	80.7 (12.2)	73.7 (11.3)
Total cholesterol, mmol/L, mean (SD)	5.4 (1.0)	5.6 (1.0)	5.6 (1.1)	5.7 (1.1)	5.5 (1.1)
HDL cholesterol, mmol/L, mean (SD)	1.4 (0.4)	1.3 (0.4)	1.3 (0.5)	1.3 (0.4)	1.3 (0.4)
Diabetes, n (%)	339 (5.9)	135 (9.4)	182 (9.4)	989 (20.6)	1645 (11.8)
Prevalent coronary heart disease, n (%)	203 (3.5)	52 (3.6)	60 (3.1)	352 (7.3)	667 (4.8)
Prevalent heart failure, n (%)	90 (1.6)	26 (1.8)	32 (1.7)	501 (10.4)	649 (4.7)
Prevalent stroke, n (%)	82 (1.4)	19 (1.3)	23 (1.2)	129 (2.7)	253 (1.8)
APOE ε4 genotype, n (%)					
0 alleles	4072 (70.3)	1020 (71.2)	1341 (69.3)	3222 (67.0)	9655 (69.1)
1 allele	1604 (27.7)	366 (25.5)	538 (27.8)	1440 (29.9)	3948 (28.3)
2 alleles	117 (2.0)	47 (3.3)	57 (2.9)	147 (3.1)	368 (2.6)
Antihypertensive use, n (%)	0	0	0	3505 (72.9)	3505 (25.1)

Table 4: Cox Proportional Hazards Regression Model of Time to Incident Dementia Based on JNC7 (Old) and ACC/AHA (New) Hypertension Guideline Categories (Non-Binary Categories)

JNC7 (Old) Guidelines	**Normal**	**Prehypertension**	**Hypertension Stage 1**	**Hypertension Stage 2**
No. of incident dementia cases	396	376	96	513
Person-years	123571	68882	19501	71369
Incidence rate (per 1000 person-years)	3.2	5.5	4.9	7.2
Hazard Ratio (95% CI)*	1 [Reference]	1.31 (1.13, 1.51)	1.12 (0.89, 1.41)	1.44 (1.24, 1.66)
ACC/AHA (New) Guidelines	**Normal**	**Elevated**	**Hypertension Stage 1**	**Hypertension Stage 2**
No. of incident dementia cases	396	176	200	609
Person-years	123571	29053	39830	90871
Incidence rate (per 1000 person-years)	3.2	6.1	5.0	6.7
Hazard Ratio (95% CI)*	1 [Reference]	1.35 (1.12, 1.61)	1.28 (1.07, 1.52)	1.36 (1.18, 1.57)

* Cox proportional hazards model adjusted for age, sex, field center, education level, APOE ε4 genotype, smoking status, alcohol consumption, physical activity, total cholesterol, HDL cholesterol, BMI, diabetes, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

Table 5: Cox Proportional Hazards Regression Model of Time to Incident Dementia Based on JNC7 (Old) and ACC/AHA (New) Hypertension Guideline Categories (Binary Categories)

JNC7 (Old) Guidelines	**No Hypertension**	**Hypertension**
No. of incident dementia cases	772	609
Person-years	192454	90871
Incidence rate (per 1000 person-years)	4.0	6.7
Hazard Ratio (95% CI)*	1 [Reference]	1.19 (1.06, 1.34)
ACC/AHA (New) Guidelines	**No Hypertension**	**Hypertension**
No. of incident dementia cases	572	809
Person-years	152624	130701
Incidence rate (per 1000 person-years)	3.7	6.2
Hazard Ratio (95% CI)*	1 [Reference]	1.22 (1.08, 1.37)

* Cox proportional hazards model adjusted for age, sex, field center, education level, APOE ε4 genotype, smoking status, alcohol consumption, physical activity, total cholesterol, HDL cholesterol, BMI, diabetes, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

Table 6: Time to Incident Dementia Hazard Ratios* Based on JNC7 (Old) and ACC/AHA (New) Hypertension Guideline Categories Stratified by Sex and Race (Non-Binary Categories)

JNC7 (Old) Guidelines	**Normal**	**Prehypertension**	**Hypertension Stage 1**	**Hypertension Stage 2**	**p-value for Interaction**
Female	1 [Reference]	1.37 (1.13, 1.68)	1.22 (0.90, 1.66)	1.47 (1.21, 1.79)	0.72
Male	1 [Reference]	1.23 (0.99, 1.52)	1.00 (0.71, 1.42)	1.36 (1.08, 1.71)	
White	1 [Reference]	1.35 (1.14, 1.60)	1.16 (0.87, 1.54)	1.48 (1.24, 1.77)	0.33
Black	1 [Reference]	1.10 (0.81, 1.49)	0.97 (0.66, 1.44)	1.25 (0.95, 1.64)	
ACC/AHA (New) Guidelines	**Normal**	**Elevated**	**Hypertension Stage 1**	**Hypertension Stage 2**	**p-value for Interaction**
Female	1 [Reference]	1.36 (1.07, 1.74)	1.38 (1.08, 1.76)	1.42 (1.18, 1.71)	0.73
Male	1 [Reference]	1.33 (1.02, 1.75)	1.16 (0.90, 1.49)	1.26 (1.02, 1.57)	
White	1 [Reference]	1.38 (1.13, 1.68)	1.32 (1.07, 1.63)	1.40 (1.18, 1.66)	0.37
Black	1 [Reference]	1.13 (0.74, 1.73)	1.08 (0.78, 1.50)	1.20 (0.91, 1.56)	

* Cox proportional hazards model adjusted for age, sex, field center, education level, APOE ε4 genotype, smoking status, alcohol consumption, physical activity, total cholesterol, HDL cholesterol, BMI, diabetes, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

Table 7: Time to Incident Dementia Hazard Ratios* Based on JNC7 (Old) and ACC/AHA (New) Hypertension Guideline Categories Stratified by Sex and Race (Binary Categories)

JNC7 (Old) Guidelines	**No Hypertension**	**Hypertension**
Female	1 [Reference]	1.21 (1.04, 1.41)
Male	1 [Reference]	1.14 (0.95, 1.37)
p-value for Interaction	-	0.58
White	1 [Reference]	1.21 (1.05, 1.41)
Black	1 [Reference]	1.13 (0.93, 1.38)
p-value for Interaction	-	0.27
ACC/AHA (New) Guidelines	**No Hypertension**	**Hypertension**
Female	1 [Reference]	1.28 (1.09, 1.50)
Male	1 [Reference]	1.13 (0.94, 1.35)
p-value for Interaction	-	0.29
White	1 [Reference]	1.24 (1.08, 1.43)
Black	1 [Reference]	1.13 (0.90, 1.41)
p-value for Interaction	-	0.21

* Cox proportional hazards model adjusted for age, sex, field center, education level, APOE ε4 genotype, smoking status, alcohol consumption, physical activity, total cholesterol, HDL cholesterol, BMI, diabetes, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

Table 8. Risk Ratios of Incident Dementia and Population Attributable Fraction of Dementia for Hypertension Based on JNC7 (Old) and ACC/AHA (New) Hypertension Guidelines Categories (Non-Binary Categories)

JNC7 (Old) Guidelines	**Normal**	**Prehypertension**	**Hypertension Stage 1**	**Hypertension Stage 2**
Risk Ratio (95% CI)*	1 [Reference]	1.30 (1.12, 1.50)	1.02 (0.81, 1.28)	1.34 (1.16, 1.55)
PAF % (95% CI)	-	6.3 (2.9, 9.1)	0.1 (-1.6, 1.5)	9.4 (5.1, 13.2)
ACC/AHA (New) Guidelines	**Normal**	**Elevated**	**Hypertension Stage 1**	**Hypertension Stage 2**
Risk Ratio (95% CI)*	1 [Reference]	1.32 (1.11, 1.59)	1.27 (1.07, 1.51)	1.26 (1.10, 1.45)
PAF % (95% CI)	**-**	3.1 (1.3, 4.7)	3.1 (0.9, 4.9)	9.1 (4.0, 13.7)

* Poisson regression model adjusted for age, sex, field center, education level, APOE ε4 genotype, smoking status, alcohol consumption, physical activity, total cholesterol, HDL cholesterol, BMI, diabetes, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.

Table 9. Risk Ratios of Incident Dementia and Population Attributable Fraction of Dementia for Hypertension Based on JNC7 (Old) and ACC/AHA (New) Hypertension Guidelines Categories (Binary Categories)

JNC7 (Old) Guidelines	**No Hypertension**	**Hypertension**
Risk Ratio (95% CI)*	1 [Reference]	1.11 (0.98, 1.24)
PAF % (95% CI)	-	4.4 (-0.9, 8.5)
ACC/AHA (New) Guidelines	**No Hypertension**	**Hypertension**
Risk Ratio (95% CI)*	1 [Reference]	1.16 (1.03, 1.30)
PAF % (95% CI)	-	8.1 (1.7, 13.5)

* Poisson regression model adjusted for age, sex, field center, education level, APOE ε4 genotype, smoking status, alcohol consumption, physical activity, total cholesterol, HDL cholesterol, BMI, diabetes, prevalent coronary heart disease, prevalent heart failure, and prevalent stroke.