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Gender, Race, Age, and Regional Differences in the Association of Pulse Pressure with Atrial Fibrillation: The Reasons for Geographic and Racial Differences in Stroke Study

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Abstract

Background—Pulse pressure (PP) has been associated with atrial fibrillation (AF) independent of other measures of arterial pressure, and other AF risk factors. However, the impact of gender, race, age, and geographic region on the association between PP and AF is unclear.

Method—A cross-sectional study of data from 25,109 participants (65±9 years of age), 54% women, 40% black) from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study recruited between 2003 and 2007 were analyzed. AF was defined as a self-reported history of a previous physician diagnosis, or presence of AF on ECG. Multivariable logistic regression models were used to calculate the odds ratio for AF. Interactions for age (< and ≥ 75 years), gender, race, and region were examined in the multivariable adjusted model.

Results—The prevalence of AF increased with widening PP (7.9%, 7.9%, 8.4%, and 11.6%, for PP <45, 45-54.9, 55-64.9, and ≥ 65 mm Hg, respectively, [p for trend <0.001]), but attenuated with adjustment. No differences by gender, race, and region were observed. However, there was evidence of significant effect modification by age (interaction p=0.0002). For those <75 years of age, PP ≥ 65 mm Hg compared to PP <45 mm Hg was significantly associated with higher risk of AF in both the unadjusted and multivariable adjusted models (Odds Ratio 1.66 [95% CI 1.42-1.94] and 1.32 [95% CI 1.03-1.70], respectively). In contrast, higher PP (55-64.9 mm Hg) among those ≥ 75 years of age was significantly associated with a lower risk of AF.

Conclusion—The relationship between PP and AF may differ for older vs. younger individuals.

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Keywords

atrial fibrillation; pulse pressure; age

Pulse pressure (PP) is a surrogate measure of arterial stiffness, and both have been linked to cardiovascular disease (CVD) outcomes¹⁻⁷. Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia in adults and is associated with adverse CVD events⁸⁻¹⁰. In the US, AF prevalence is expected to increase from 2.3 million currently to 5.6 million by the year 2050 and thereby require more healthcare utilization irrespective of gender or race^{8, 11}. In some studies, PP has been associated with new onset AF independent of other measures of arterial pressure and other previously recognized AF risk factors^{12, 13}. In the Framingham Heart Study, each 20 mm Hg increase in the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP) was associated with a 24% increase in the risk of developing AF, even after adjusting for average arterial pressure and AF risk factors¹². Elevated PP is associated with increased aortic stiffness which increases with age and appears to be modifiable^{14, 15}. These findings suggest that PP may represent a potentially modifiable risk factor, and that lifestyle modifications, including weight loss, exercise, salt reduction, moderate alcohol consumption¹⁶, or therapy aimed specifically at reducing or limiting the increase in PP with advancing age has the potential to reduce the substantial and rapidly growing incidence of AF in our aging society.

Studies that have addressed the risk of AF in African Americans (AAs) suggest that they have a lower prevalence of AF compared to whites, despite higher prevalence of AF risk factors. This is referred to as the AF paradox, and no good explanation has been elucidated, although detection bias, survival bias, and differential susceptibility have been suggested¹⁷. In the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, the relative risk of AF in AA versus whites differed according to the approach to detect AF. Adding electrocardiographically detected AF to self-report diminished the association between race and AF¹⁸. Our aim was to better understand if the AF paradox holds true when studying the association between PP and AF, or if this paradox could be explained by PP differences by race¹⁸. Prior studies have shown that gender is related to risk of developing AF. AF prevalence increases with age, but after adjusting for AF risk factors including age, men compared to women had a 1.5 fold increased risk of developing AF¹⁹. Furthermore, women develop AF at an older age than men and have high CVD risk once AF develops including greater rates of stroke and lower quality of life than men²⁰⁻²³. Moreover, evidence from population studies that evaluated gender, race, age, or regional differences in the relationship between AF and PP in a cohort that includes a large number of AA and women is lacking. Therefore, we examined the cross-sectional association between PP and AF in the REGARDS study.

METHODS

Study Population and Design

Details of the REGARDS study have been published previously²⁴. Briefly, the REGARDS study was designed to understand mechanisms leading to regional and racial disparities in

stroke mortality. The study over-sampled AA and residents of the stroke belt (North Carolina, South Carolina, Georgia, Alabama, Mississippi, Tennessee, Arkansas, and Louisiana). Between January 2003 and October 2007, participants were recruited from a commercially available list of residents using postal mailings and telephone data. Trained interviewers used a computer-assisted telephone interview (CATI) system to obtain demographic information and medical histories. An in-home physical examination including blood pressure measurements, electrocardiogram recording, information on medications, blood and urine samples was performed 3-4 weeks after the telephone interview.

For this study, 5130 of the study's 30,239 participants were excluded because of missing baseline covariates (n=4372) or participants missing AF data (n=702). The remaining 25,109 participants were included in the final analysis (Figure 1).

Pulse Pressure

Similar to other published studies, PP was divided into 4 groups: < 45 mm Hg, 45–54.9 mm Hg, 55–64.9 mm Hg, and ≥ 65 mm Hg.⁶ SBP and DBP were measured by trained technicians using an aneroid sphygmomanometer. The SBP and DBP was recorded as the average of two measurements taken according to the recommendations of the seventh Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC 7).²⁵

Atrial Fibrillation

Details on AF ascertainment have been published previously²⁶. Briefly, AF was identified from a self-reported history of a physician diagnosis of AF obtained during CATI surveys and by the study-scheduled ECG recorded during the in-home visit that was then read centrally by trained ECG technicians blinded to the clinical data.

Covariates

Age, gender, race, income, education, region, alcohol habits, and smoking status were self-reported. Annual household income was dichotomized at \$35,000, and education was dichotomized as achieving at least a high school diploma vs. less than a high school education. Cigarette smokers were categorized into never, past (at least 100 cigarettes in their lifetime), and current. Alcohol use was classified as heavy (>2 drinks/day for men and >1 drink/day for women), moderate (1 to 2 drinks/day for men and 1 drink/day for women), and none²⁷. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, respectively, or self-reported use of anti-hypertensive medications, which were classified according to the Medispan Therapeutic Classification system²⁸. Vascular disease was defined as self-reported history of stroke, peripheral artery disease or aortic aneurysm. Coronary heart disease was defined by self-reported history of myocardial infarction (MI), coronary artery bypass grafting, coronary angioplasty or stenting, or evidence of MI on the baseline electrocardiogram. Left ventricular hypertrophy was defined by the Sokolow-Lyon Criteria²⁹. Diabetes was defined as fasting glucose level ≥ 126 mg/dL (non-fasting glucose, ≥ 200 mg/dL) or a history of taking diabetes medications. Renal function was assessed using urinary albumin to creatinine ratio (ACR). ACR levels >30mg/g were considered as renal dysfunction³⁰. Blood and urine markers included levels of total cholesterol, high-density

lipoprotein (HDL) cholesterol, and high-sensitivity C-reactive protein (CRP). Body mass index (BMI) was calculated from height and weight measured during the in-home visit using a standardized protocol. Data on antihypertensive drug use was based on self-report, while use of digoxin, Coumadin, and statins were based on pill-bottle review. Digoxin was used as a proxy for heart failure as currently the only clinical indication for digoxin are heart failure and atrial fibrillation and digoxin use has a specificity of approximately 99% and sensitivity of 28% in heart failure diagnosis³¹. The CHADS2 score (congestive heart failure; hypertension; age, ≥ 75 years; diabetes mellitus; and prior stroke) was calculated using 1 point for each category except for prior stroke, which was given 2 points^{32, 33}.

Statistical Analysis

Characteristics of the study sample were contrasted by PP categories at baseline. Logistic regression was used to calculate the odds ratio (OR) and 95% confidence intervals (CI) for the association between PP and AF. Multivariable models were adjusted as follows: Model 1 was the unadjusted model; Model 2 adjusted for age, gender, race, region, education, and income; Model 3 adjusted for Model 2 covariates plus history of vascular disease, history of coronary heart disease, left ventricular hypertrophy, diabetes, hypertension, heart failure, SBP, ACR, total cholesterol, HDL, log of hsCRP, BMI, smoking status, alcohol use. Model 4 adjusted for Model 3 covariates and antihypertensive medication use, and statin use. Additionally, tests of effect modification by age (dichotomized at 75), race (black vs white), gender (men vs. women), and region (stroke belt, stroke buckle, non-belt) were carried out. Statistical significance for all comparisons was defined as $p < 0.05$. SAS version 9.4 (SAS, Cary, NC) was used for all the analyses.

RESULTS

Of the 25109 participants included in the analysis; 8440 (33.6%), 8194 (32.6%), 5041 (20.1%), and 3434 (13.7%) participants had PP < 45 mm Hg, 45-45.9 mm Hg, 55-64.9 mm Hg and 65.0+ mm Hg, respectively. Baseline characteristics for study participants stratified by PP group are shown in Table 1(A/B/C). The prevalence of AF increased with widening PP (7.9%, 7.9%, 8.4%, and 11.6% of the sample had AF for PP < 45 , 45-54.9, 55-64.9, and 65 mm Hg, respectively; p for trend < 0.001) even in those receiving antihypertensive treatment (Table 1A).

The associations between PP and AF are shown in Table 2. In the unadjusted model, every 10 mmHg increase in PP was associated with greater prevalence of AF, especially for a PP ≥ 65 mmHg (OR=1.53 [95% CI 1.34-1.75]). The association between PP and AF attenuated with full adjustment (Table 2).

In the analyses testing for effect modification of PP by age, gender, and region, only age was found to be a significant effect modifier (p interaction=0.0002). The results of the age-stratified analyses are presented in Table 3. For those < 75 years of age, PP ≥ 65 mmHg was significantly associated with higher risk of AF in both unadjusted and multivariable adjusted models. In contrast, higher PP (55-64.9 mmHg) was significantly associated with a lower risk of AF among those ≥ 75 years of age.

Discussion

In this analysis from the REGARDS study, higher PP was associated with a greater prevalence of AF. However, the association between PP and AF was attenuated after adjustment for sociodemographic factors, medical conditions, and physiological markers. However, the association between PP and AF was stronger in adults <75 compared to those who were ≥75 years old.

The Framingham study reported that PP was associated with increased risk of AF¹². It has also been reported that age is an independent clinical risk factor for AF³⁴. PP serves as a surrogate measure of arterial stiffness and vascular aging and contributes to AF development.^{35, 36} A significant correlation between PP and left atrial size independent of age, sex, and body surface area, was found in the Lifestyle Interventions and Independence for Elders (LIFE) sub study³⁷. Furthermore, PP is associated with cardiovascular morbidity and mortality; and, this effect increases with age³⁸⁻⁴¹. Our study found that the association between AF and PP was age dependent. Interestingly, adults <75 compared to ≥75 years of age with higher PP had a greater risk of AF even after adjusting for all clinically significant variables including antihypertensive medications (Table 3). The explanation for this is not apparent, however, previous studies have speculated that the underlying mechanism between PP and AF is related to arterial stiffness that increases with age resulting in increased pulsatile load of blood on the heart⁴², promotion of left ventricular hypertrophy⁴³, impairment of left ventricular diastolic relaxation^{44, 45}, and enlargement of left atrium⁴². Left atrial enlargement is an independent risk factor for AF resulting from fibrosis and remodeling of the atrium^{34, 46}. In a prospective study by Conan et al⁴⁷, in individuals with normal left atrial size, age, height, hypertension, and exercise were significantly associated with incident AF. On the other hand, in individuals with left atrial enlargement only age and body weight were associated with incident AF. A study including participants from the Multi-Ethnic Study of Atherosclerosis, showed that for every 1 standard deviation increase in PP there was a 29% increased AF risk¹³. Magnetic resonance imaging based aortic distensibility (as a measure of aortic stiffness) was not consistently associated with risk of AF. Based on these results they suggested that different mechanisms other than aortic stiffness may explain the PP and AF association, (eg left ventricular structural change and myocardial fibrosis). Therefore, the difference seen in our study between individuals <75 and ≥75 years and the PP-AF association may be due to mechanisms other than left atrial enlargement and stiffness. Those mechanisms still need to be further elucidated in future studies. Moreover, the association between higher PP and lower risk of AF in those ≥75 does not hold true in the group with a PP>65 mmHg after multivariable adjustment (Table 3). We do not have any clear explanation for this inconsistency.

The strength of this study is that we used a large national cohort that included a good representation of women and blacks as well as different socioeconomic status, assessed by income and education. To our knowledge, this is the first study showing that the association between PP and AF did not differ by race, gender, or region. Our study's limitations include the self-report of some variables (such as prior CHD and smoking, which is common in epidemiologic studies), relying on resting electrocardiograms and a participant's self-reported history of AF (likely underestimating the prevalence of AF e.g. we likely missed

paroxysmal cases), diagnosis of heart failure based on digoxin (we might have excluded patients with diastolic heart failure), and the statistical use of multiple testing. Given the cross-sectional nature of our analysis, we could not establish the temporal relationship between AF and PP. Also, although we adjusted for several potential confounders, residual confounding remains a possibility.

In conclusion, in the REGARDS study PP was independently associated with AF, and the association of PP and AF differed by age; but after adjustment these associations were attenuated. Since PP increases with age, and PP is a potentially modifiable risk factor,¹³ targeted interventions to reduce PP particularly in adults <75 years has the potential to decrease AF risk, but longitudinal studies are needed to evaluate these observations.

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Highlights

- There are no racial, gender or regional differences in the relationship between pulse pressure and atrial fibrillation.
- In participants <75 years compared to those ≥ 75 years, pulse pressure was associated with higher risk of atrial fibrillation
- Pulse pressure is a potentially modifiable risk factor

Figure 1. Exclusion cascade

Table 1A

Baseline demographics of REGARDS participants by pulse pressure categories. N=25,109

Pulse Pressure	<45mmHg	45-54.9mmHg	55-64.9 mmHg	65.0+ mmHg	P-value
	N=8440	N=8194	N=5041	N=3434	
Demographics:					
Age, years, Mean (SD)	61.7±9.0	64.4±9.0	67.0±8.9	70.0±8.8	<.0001
African Americans (%)	2993(35.5)	3239(39.5)	2166(42.9)	1580(46.0)	<.0001
Females (%)	4831(57.2)	4326(52.8)	2660(52.8)	1730(50.4)	<.0001
Region:					
Stroke Belt (%)	2764(32.8)	2895(35.3)	1749(34.7)	1252(36.5)	<.0001
Stroke Buckle (%)	1969(23.3)	1706(20.8)	975(19.3)	651(18.9)	
Non belt (%)	3707(43.9)	3593(43.8)	2317(45.9)	1531(44.6)	
Socioeconomic status:					
Income < \$ 35k (%)	2960(35.1)	3246(39.6)	2380(47.2)	1815(52.8)	<.0001
Education<High school (%)	710(8.4)	925(11.3)	716(14.2)	650(18.9)	<.0001
Smoking:					
Never(%)	4078(48.3)	3723(45.4)	2183(43.3)	1452(42.3)	<.0001
Past (%)	3146(37.3)	3329(40.6)	2105(41.8)	1452(42.3)	
Currently (%)	1216(14.4)	1142(13.9)	753(14.9)	507(14.8)	
Alcohol Use (NIAAA):					
Heavy (%)	318(3.8)	327(3.9)	234(4.6)	128(3.7)	<.0001
Moderate (%)	3193(37.8)	2788(34.0)	1526(30.3)	1030(29.9)	
None(%)	4929(58.4)	5079(61.9)	3281(65.1)	2276(66.3)	
Prevalence of Atrial Fibrillation (AF)					
AF (%)	665(7.9)	653(7.9)	423(8.4)	398(11.6)	<.0001
AF among participants not taking anti-HTN drugs (%)	311(6.2)	244(6.0)	122(6.2)	95(8.8)	.0083
AF among participants on anti-HTN drugs (%)	354(10.4)	409(9.9)	301(9.9)	303(12.9)	.0006

NIAAA: National Institute on Alcohol Abuse and Alcoholism, HTN: Hypertension

Table 1B

Baseline characteristics of REGARDS participants by pulse pressure categories. N=25,109

<u>Pulse Pressure</u>	<u><45mmHg</u>	<u>45-54.9mmHg</u>	<u>55-64.9 mmHg</u>	<u>65.0+ mmHg</u>	<u>P-value</u>
	N=8440	N=8194	N=5041	N=3434	
<u>Baseline medical conditions:</u>					
Hypertension (%)	3586(42.5)	4467(54.5)	3649(72.4)	3099(90.2)	<.0001
Stroke, PAD or aortic aneurysm (%)	510(6.0)	650(7.9)	498(9.9)	443(12.9)	<.0001
Coronary Heart Disease (%)	1081(12.8)	1334(16.3)	1027(20.4)	869(25.3)	<.0001
Left Ventricular Hypertrophy (%)	595(7.1)	799(9.8)	551(10.9)	493(14.4)	<.0001
Diabetes (%)	1127(13.4)	1610(19.7)	1277(25.3)	1118(32.6)	<.0001
<u>Physiologic Markers</u>					
SBP, mmHg, Mean (SD)	114±10	126±10	136±11	151 ±16	<.0001
DBP, mm Hg, Mean (SD)	76±9	77±9	77±10	76±12	0.01
Renal Function: ACR >30 (%)	769(9.1)	1045(12.8)	932(18.5)	948(27.6)	<.0001
Total Cholesterol , mg/dL	193.5±39.1	191.9±39.7	191.0±40.0	190.0±42.3	<.0001
HDL, mg/dL	52.9±16.3	51.3±15.8	51.3±16.2	50.9±16.2	<.0001
hsCRP, mg/L	4.1±8.6	4.4±7.4	4.9±8.3	5.3±9.0	<.0001
BMI, kg/m ²	28.6±6.0	29.4±6.0	29.7±6.2	29.5±6.3	<.0001
<u>Medications:</u>					
Antihypertensive Drugs (%)	3401(40.3)	4137(50.5)	3056(60.6)	2349(68.4)	<.0001
Statins (%)	2281(27.0)	2606(31.8)	1748(34.7)	1246(36.3)	<.0001
Digoxin (%)	156(1.9)	181(2.2)	124(2.5)	147(4.3)	<.0001

PAD: peripheral arterial disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, ACR: albumin to creatinine ratio, HDL: high-density lipoprotein, hsCRP: high sensitivity C - reactive protein, BMI: body mass index

Table 1C

CHADS2 score for each pulse pressure category

<u>Pulse Pressure</u>	<u><45mmHg</u>	<u>45-54.9mmHg</u>	<u>55-64.9 mmHg</u>	<u>65.0+ mmHg</u>	<u>P-value</u>
	N=8440	N=8194	N=5041	N=3434	
<u>CHADS2 Score for participants with Atrial Fibrillation , n=2139</u>					
(C: Congestive heart failure H: Hypertension A:Age 75 years D: Diabetes Mellitus S2: Prior Stroke or TIA or thromboembolism)					
0 (%)	186(27.9)	120(18.4)	42(9.9)	9(2.3)	<.0001
1 (%)	211(31.7)	231(35.4)	141(33.3)	109(27.4)	
2 (%)	268(40.3)	302(46.2)	240(56.7)	280(70.4)	

HTN: Hypertension

Table 2
Crude and Multivariable Adjusted Association of Atrial Fibrillation with Pulse Pressure

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
<u>Pulse Pressure</u>				
<45 mmHg	REF	---	---	---
45-54.9 mmHg	1.01(0.91-1.13)	0.93(0.83-1.05)	0.90(0.79-1.03)	0.91(0.80-1.03)
55-64.9 mmHg	1.07(0.94-1.22)	0.90(0.79-1.03)	0.86(0.73-1.01)	0.86(0.73-1.01)
65.0+ mmHg	1.53(1.34-1.75)	1.18(1.03-1.36)	1.06(0.85-1.31)	1.07(0.86-1.33)

OR: odds ratio, REF: reference

Model 1 includes pulse pressure

Models 2 adjusts for age, gender, race, region, education, income

Model 3 adjusts for model 2 covariates and cardiovascular disease, coronary heart disease, left ventricular hypertrophy, diabetes, digoxin use, systolic blood pressure, albumin to creatinine ratio, total cholesterol, high-density lipoprotein, statins, log of high sensitivity C-reactive protein, body mass index, smoking, alcohol use

Model 4 adjusts for model 3 covariates and anti-hypertensive medications and baseline hypertension

Table 3
Association of Prevalent Atrial Fibrillation with Pulse Pressure stratified by age, younger (<75) vs. older (>75)

	Model 1	Model 2	Model 3	Model 4
	OR, (95% CI)	OR, (95% CI)	OR, (95% CI)	OR, (95% CI)
Age (<75 years) n=20893				
<u>Pulse Pressure</u>				
<45mmHg	REF	---	---	---
45-54.9mmHg	0.96(0.84-1.09)	0.91(0.80-1.03)	0.89(0.77-1.03)	0.89(0.77-1.04)
55-64.9 mmHg	1.07(0.93-1.25)	0.97(0.84-1.13)	0.94(0.78-1.13)	0.93(0.77-1.13)
65.0+ mmHg	1.66(1.42-1.94)	1.43(1.21-1.68)	1.31(1.02-1.68)	1.32(1.03-1.70)
Age (≥75 years) n=4216				
<u>Pulse Pressure</u>				
<45mmHg	REF	---	---	---
45-54.9mmHg	0.96(0.75-1.22)	0.97(0.76-1.25)	0.94(0.71-1.24)	0.94(0.71-1.25)
55-64.9 mmHg	0.69(0.53-0.89)	0.70(0.54-0.91)	0.66(0.47-0.91)	0.65(0.47-0.90)
65.0+ mmHg	0.76(0.59-0.98)	0.78(0.60-1.02)	0.70(0.46-1.05)	0.69(0.46-1.04)

OR: odds ratio, Ref: Reference

Model 1 includes pulse pressure

Models 2 adjusts for age, gender, race, region, education, income

Model 3 adjusts for model 2 covariates and cardiovascular disease, coronary heart disease, left ventricular hypertrophy, diabetes, digoxin use, systolic blood pressure, albumin to creatinine ratio, total cholesterol, high-density lipoprotein, statins, log of high sensitivity C-reactive protein, body mass index, smoking, alcohol use

Model 4 adjusts for model 3 covariates and anti-hypertensive medications and baseline hypertension