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Healthy Lifestyle Factors and Risk of Cardiovascular Events and Mortality in Treatment-Resistant Hypertension: The Regards Study

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Abstract

Few data exist regarding whether healthy lifestyle factors are associated with better prognosis among individuals with apparent treatment-resistant hypertension, a high-risk phenotype of hypertension. The purpose of this study was to assess the association of healthy lifestyle factors with cardiovascular events, all-cause mortality, and cardiovascular mortality among individuals with apparent treatment-resistant hypertension. We studied participants (n=2,043) from the population-based REasons for Geographic And Racial Differences in Stroke (REGARDS) study with apparent treatment-resistant hypertension (blood pressure $\geq 140/90$ mmHg despite use of ≥ 3 antihypertensive medication classes or use of ≥ 4 classes of antihypertensive medication regardless of blood pressure control). Six healthy lifestyle factors adapted from guidelines for the management of hypertension (normal waist circumference, physical activity ≥ 4 times/week, non-smoking, moderate alcohol consumption, high Dietary Approaches to Stop Hypertension (DASH) diet score, and low sodium-to-potassium intake ratio) were examined. A greater number of healthy

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lifestyle factors was associated with lower risk for cardiovascular events (n=360) over a mean follow-up of 4.5 years. Multivariable adjusted hazard ratios [HR (95% CI)] for cardiovascular events comparing individuals with 2, 3, and 4-6 versus 0-1 healthy lifestyle factors were 0.91 (0.68-1.21), 0.80 (0.57-1.14), and 0.63 (0.41-0.95), respectively (P-trend=0.020). Physical activity and non-smoking were individual healthy lifestyle factors significantly associated with lower risk for cardiovascular events. Similar associations were observed between healthy lifestyle factors and risk for all-cause and cardiovascular mortality. In conclusion, healthy lifestyle factors, particularly physical activity and non-smoking, are associated with a lower risk for cardiovascular events and mortality among individuals with apparent treatment-resistant hypertension.

Keywords

hypertension; lifestyle; physical activity; smoking; diet

Introduction

Despite the use of antihypertensive medications, inadequately controlled blood pressure (BP) remains a challenge in the management of hypertension for many patients. In 2008, the American Heart Association published a scientific statement on a sub-class of hypertensive patients considered to have treatment-resistant hypertension. In this statement, treatment-resistant hypertension was defined as uncontrolled BP despite the use of antihypertensive medications from three or more classes, or the use of four or more classes to achieve BP control¹. The prevalence of apparent treatment-resistant hypertension (aTRH) in the 2005-2008 National Health and Nutrition Examination Survey (NHANES) was estimated to be 11.8% among US adults with hypertension, an increase from 5.5% in 1998-1994 and 8.5% in 1999-2004²; indicating that a growing proportion of US adults with hypertension are resistant to antihypertensive medication regimens.

Data from the Cardiovascular Research Network has shown that patients with aTRH had an almost 50% higher risk for cardiovascular events compared with patients whose BP had been controlled on three medications³. Other longitudinal studies have yielded similar results for cardiovascular outcomes and all-cause mortality^{4,5}. Taken together, available data suggest that individuals with aTRH are at high risk for adverse cardiovascular events and mortality, highlighting a need for efforts toward improving outcomes in this population.

Guidelines endorse lifestyle changes, including weight loss, regular exercise, smoking cessation, moderation of alcohol consumption, and a high-fiber, low-fat, and low-salt diet, for individuals with hypertension^{6,7}. However, few data exist regarding whether these lifestyle factors, either individually or combined as part of an overall healthy lifestyle, are associated with better prognosis among individuals with aTRH. If lifestyle factors are associated with better outcomes in aTRH, it will highlight the need to invest more resources in developing and testing behavioral interventions to mitigate their elevated risk. The purpose of this study, therefore, was to investigate the associations of healthy lifestyle factors with cardiovascular events, all-cause mortality, and cardiovascular mortality among

individuals with aTRH in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

Methods

Study Population

The REGARDS study has been described previously⁸. Briefly, REGARDS is a population-based cohort study of 30,239 white and black adults ≥45 years of age from across the contiguous US who were enrolled between 2003 and 2007. The current analysis was restricted to individuals with aTRH (defined below). After excluding participants without BP measurements or data on antihypertensive medications at baseline, without aTRH, and who were missing outcome data during follow-up, 2,043 individuals with aTRH were available for analyses (Figure S1). Characteristics of participants included and excluded from analyses are presented in Table S1. The REGARDS study protocol was approved by Institutional Review Boards at participating centers. All participants provided informed consent.

Data Collected at Baseline

Data were collected via a telephone interview, self-administered questionnaires, and an in-home examination. The in-home examination was conducted by trained health professionals during a single visit and included anthropometrics, BP measurements, electrocardiogram (ECG), collection of blood and urine samples, and review of medication pill bottles. A detailed summary of baseline measures are provided in the online-only Data Supplement.

BP Measurement, Medication Use, and aTRH Definition

BP was measured during the in-home examination using a standardized protocol⁸. BP was measured two times by a trained examiner using an aneroid sphygmomanometer after five minutes of seated rest. Based on the average of two measurements, uncontrolled hypertension was defined as systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. During the in-home examination, medications taken in the past two weeks were recorded and subsequently coded into drug classes⁶. Single-pill combinations were classified into their respective classes as individual components. aTRH was defined as: (1) taking three or more antihypertensive medication classes with uncontrolled BP; or (2) taking four or more classes regardless of BP control.

Healthy Lifestyle Factors

Six lifestyle factors were evaluated: waist circumference, physical activity, cigarette smoking, alcohol consumption, Dietary Approaches to Stop Hypertension (DASH) diet score, and sodium-to-potassium (Na/K) intake. Normal waist circumference, physical activity ≥4 days/week, non-smoking status, moderate alcohol consumption, high DASH diet score, and low Na/K intake were considered to be healthy lifestyle factors. The six healthy lifestyle factors were adapted from lifestyle modifications recommended for the treatment of hypertension^{6,7}. Moderate alcohol consumption was considered to be a healthy lifestyle factor as prior studies have shown reduced cardiovascular risk associated with moderate vs. heavy or no alcohol consumption⁹.

Consistent with World Health Organization recommendations, waist circumference was measured using a tape measure midway between the lowest rib and iliac crest with the participant standing¹⁰. Waist circumference was dichotomized as normal (≤ 102 cm in men; ≤ 88 cm in women) or abdominal obesity (>102 cm in men; >88 cm in women)¹¹. Physical activity was assessed during the telephone interview using the question: “How many times per week do you engage in intense physical activity, enough to work up a sweat?” with response options of “none”, “1 to 3 times/week” and “four or more times/week”. Smoking status was determined by responses to two questions during the telephone interview: “Have you smoked at least 100 cigarettes in your lifetime?” and “Do you smoke cigarettes now, even occasionally?” Current smoking was defined as a positive response to both questions. Self-reported alcohol consumption, assessed during the telephone interview, was categorized as none (no weekly alcohol consumption), moderate (1-14 and 1-7 alcoholic beverages/week for men and women, respectively) or heavy (>14 and >7 alcoholic beverages/week for men and women, respectively). Participants completed a self-administered Block Food Frequency Questionnaire (FFQ) following the in-home study visit to estimate average dietary intake over the previous year. Nutrient analysis was conducted by NutritionQuest. A DASH dietary score was created using methods described by Fung et al¹². Using the distribution of DASH dietary scores from participants with aTRH, a high DASH diet score was defined as being in the highest quartile (≥ 27). Similar methods were used to dichotomize Na/K intake, with low Na/K intake defined as being in the lowest quartile (≤ 0.71). Information on the validation and reproducibility of the physical activity questionnaire and Block FFQ are provided in the online-only Data Supplement.

Outcomes

The primary outcome was combined fatal and non-fatal cardiovascular events. Fatal cardiovascular events were defined as death within 28 days of a definite or probable myocardial infarction, or sudden death; or death within 28 days of a confirmed stroke. Non-fatal cardiovascular events were defined as non-fatal definite or probable myocardial infarction or stroke. All-cause mortality and cardiovascular mortality were secondary and tertiary outcomes, respectively. Vital status and cardiovascular events were ascertained during bi-annual telephone follow-up interviews of the participant, proxy, or next-of-kin. Report of a potential event triggered medical record retrieval followed by expert adjudication. A detailed description of the identification and adjudication of outcomes is provided in the online-only Data Supplement.

Statistical Analysis

We accounted for missing data in the lifestyle factors (waist circumference: $n=11$; physical activity: $n=33$; smoking: $n=4$; alcohol use: $n=43$; DASH diet score and Na/K intake: $n=699$) using multiple imputation. Almost all of the data missing for the FFQ-derived variables (DASH diet score and Na/K intake) were due to participants not returning the questionnaire. Missing data were imputed with 10 data sets using chained equations¹³. For primary analyses, participants were grouped according to number of healthy lifestyle factors: 0-1, 2, 3, or 4-6. Participant characteristics were calculated by number of healthy lifestyle factors. Cox proportional-hazards regression models were then used to calculate the hazard ratio (HR) for cardiovascular events associated with the number of healthy lifestyle factors (2, 3,

or 4-6) in comparison to participants with 0-1 healthy lifestyle factors. Crude HRs were initially calculated. Subsequently, HRs were calculated with adjustment for age, race, sex, education, and geographic region of residence (Model 1) and further adjustment for total cholesterol, high-density lipoprotein (HDL)-cholesterol, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², albuminuria, atrial fibrillation, left ventricular hypertrophy on ECG, diabetes, statin use, history of coronary heart disease (CHD), and history of stroke (Model 2). P-trend tests were conducted by including the number of lifestyle factors for each participant as an ordinal variable in regression models. Analyses were then repeated in a fully adjusted model testing interactions for race (black vs. white) and history of stroke or CHD (yes vs. no). Also, HRs were calculated in sub-groups defined by race and history of stroke or CHD.

Three sensitivity analyses were conducted. First, analyses were repeated using participants with complete data (i.e., without imputation; n=1300). Second, as use of a diuretic has been suggested to be required for diagnosis of aTRH¹, we repeated analyses restricting the study population to participants on a diuretic (n=1809). Finally, as aTRH may be partially explained by reduced medication adherence¹⁴, we restricted the study population to participants who reported a high level of medication adherence (n=1364), defined as a Morisky Medication Adherence Scale score of 0 (see Data Supplement).

To evaluate the association of each individual healthy lifestyle factor with cardiovascular events, Cox proportional-hazards regression models were repeated, testing each lifestyle factor separately. P-trend tests were conducted for lifestyle factors with more than 2 levels that we hypothesized would have a linear association with outcomes (physical activity, DASH diet score, Na/K intake).

The association between number of healthy lifestyle factors and all-cause mortality, a secondary outcome, was examined. This association was also examined in a sensitivity analysis without imputation. Next, the association of each individual healthy lifestyle factor with all-cause mortality was tested. Finally, associations between the number of healthy lifestyle factors and, separately, each healthy lifestyle factor and cardiovascular mortality was examined. Data analyses were conducted using STATA/IC version 12.1 (StataCorp, College Station, Texas).

Results

Participant Characteristics

Among the 2,043 participants with aTRH, 662 (32.4%) had 0-1 healthy lifestyle factors, 671 (32.8%) had 2 healthy lifestyle factors, 430 (21.0%) had 3 healthy lifestyle factors, and 280 (13.7%) had 4-6 healthy lifestyle factors. Overall, 658 participants (32.2%) did not have abdominal obesity, 453 (22.2%) engaged in physical activity 4 times/week, 1,797 (88.0%) were non-smokers, and 539 (26.4%) were moderate alcohol drinkers. The mean DASH diet score and Na/K intake ratio were 23.7±0.1 and 0.92±0.01, respectively. Participants with more healthy lifestyle factors were, on average, older, more likely to be male, white, and graduate high school, less likely to have diabetes, eGFR<60 ml/min/1.73m², and

albuminuria, were taking fewer classes of antihypertensive medications, and had lower total cholesterol and diastolic BP (Table 1).

Cardiovascular Events

There were 360 (17.6%) cardiovascular events during a mean follow-up of 4.5 years (maximum: 7.8 years). In unadjusted and adjusted models, a greater number of healthy lifestyle factors was associated with a lower risk for cardiovascular events (Table 2). The association between the number of healthy lifestyle factors and risk of cardiovascular events did not vary by race (p -interaction=0.934) or history of stroke or CHD (p -interaction=0.628) (Tables S2 and S3).

In a sensitivity analysis restricted to participants with complete data, a greater number of healthy lifestyle factors was associated with a lower risk of cardiovascular events (Table S4). In a second sensitivity analysis excluding participants not taking a diuretic, a greater number of healthy lifestyle factors was also associated with a lower risk of cardiovascular events; the fully adjusted HR (95% CI) comparing participants with 2, 3, and 4-6 versus 0-1 healthy lifestyle factors were 0.92 (0.67-1.26), 0.80 (0.55-1.16), and 0.59 (0.37-0.92), respectively (P -trend=0.017). In a third sensitivity analysis, associations were similar after restricting the sample to participants who had a high level of medication adherence; the fully adjusted HR (95% CI) for cardiovascular events comparing participants with 2, 3, and 4-6 versus 0-1 healthy lifestyle factors were 0.88 (0.62-1.26), 0.71 (0.47-1.09), and 0.54 (0.33-0.90), respectively (P -trend =0.010).

When the association of each healthy lifestyle factor with cardiovascular events was examined, higher levels of physical activity and non-smoking status were significantly associated with a reduced risk for cardiovascular events in unadjusted and adjusted models (Table 3). No other healthy lifestyle factor was associated with risk of cardiovascular events.

All-Cause Mortality

There were 452 (22.1%) deaths during a mean follow-up of 5.4 years (maximum: 9.0 years). A greater number of healthy lifestyle factors was associated with a lower risk for all-cause mortality (Table 4). This association remained significant in a sensitivity analysis restricted to participants with complete data (Table S5). When each healthy lifestyle factor was examined, physical activity, non-smoking status, and a high DASH diet score were significantly associated with a lower risk for all-cause mortality in adjusted models (Table S6).

Cardiovascular Mortality

There were 174 (8.5%) cardiovascular deaths during follow-up. A greater number of healthy lifestyle factors was significantly associated with a lower risk for cardiovascular mortality (Table S7). Higher levels of physical activity and non-smoking status were each associated with a significantly lower risk for cardiovascular mortality in unadjusted and adjusted models (Table S8).

Discussion

In this population-based study of individuals with aTRH, having more healthy lifestyle factors was associated with a lower risk for cardiovascular events and all-cause and cardiovascular mortality. Furthermore, physical activity and non-smoking were individual healthy lifestyle factors associated with a 33% and 46% lower risk for cardiovascular events, 42% and 47% lower risk for all-cause mortality, and 50% and 53% lower risk for cardiovascular mortality, respectively. Finally, a higher DASH diet score was associated with a 28% lower risk for all-cause mortality. To our knowledge, this is the first study to examine the association of healthy lifestyle factors with outcomes among individuals with aTRH.

As the prevalence of aTRH is expected to increase¹, effective treatments to improve outcomes among individuals with aTRH are needed. Treatment methods being explored for the management of aTRH include invasive, irreversible procedures or implantable devices such as renal denervation and carotid baro receptor stimulation. However, it is important to determine the efficacy of less invasive approaches to spare individuals the inconvenience and possible complications that come from these procedures. Hypertension guidelines generally recommend lifestyle modification, including weight reduction, increasing physical activity, moderation of alcohol consumption, adoption of the DASH diet, dietary salt reduction, and smoking cessation, as adjunctive therapy to antihypertensive medication^{6,7}. These recommendations, in part, stem from studies which have demonstrated an association between lifestyle factors and morbidity/mortality amongst hypertensive individuals^{15,16}. However, it was previously unknown whether lifestyle factors are associated with better prognosis specifically in individuals with aTRH. In our study of individuals with aTRH, having a greater number of healthy lifestyle factors was associated with a lower risk for cardiovascular events and mortality. These findings suggest that lifestyle interventions may be beneficial for reducing morbidity and mortality risk in individuals with aTRH. As there was a graded inverse association between number of healthy lifestyle factors and risk for cardiovascular events and mortality, there may be incremental benefits to increasing the number of healthy lifestyle factors among individuals with aTRH. Moreover, only a small percentage of individuals had four or more healthy lifestyle factors (13.7%); a finding that corresponds to the low percentage of individuals with multiple healthy lifestyle factors reported for general population-based samples and populations with hypertension¹⁷⁻¹⁹. The low prevalence of healthy lifestyle factors in the present study highlights a great potential to reduce the increased morbidity and mortality risk associated with aTRH through a multi-faceted lifestyle intervention.

In our study, higher levels of physical activity were associated with a lower risk of cardiovascular events, all-cause mortality, and cardiovascular mortality. This finding may provide support for implementation of regular exercise and/or increased physical activity as a treatment modality for aTRH. Notably, there was a linear association between higher levels of physical activity and lower risk of clinical outcomes, suggestive that even modest amounts of physical activity may be beneficial for individuals with aTRH. Mechanisms underlying this association, however, are unknown. One possible explanation is the effect of physical activity on BP. Recently, in a study of 50 participants with aTRH, Dimeo et al.

showed that 8-12 weeks of aerobic exercise reduced daytime systolic and diastolic ambulatory BP by 5.9 and 3.3 mmHg, respectively²⁰. Alternatively, the association between physical activity and outcomes in aTRH could also be attributed to the non-BP effects of increased physical activity (e.g. insulin sensitivity, lipid metabolism, endothelial function, immune function, etc.²¹).

Our study also found that non-smoking was associated with a lower risk of cardiovascular events, all-cause mortality, and cardiovascular mortality in individuals with aTRH. Previous findings from observational studies have suggested that smoking cessation may have a larger effect on reducing the risk of morbidity and mortality than any other intervention or treatment²². Our findings remain consistent with previous findings and reinforce the role of cigarette smoking as a major health hazard that is pertinent even to individuals with aTRH.

Adoption of the DASH diet, a diet rich in fruits, vegetables, low-fat dairy products, and low in saturated and total fat; has been recommended as an important lifestyle modification to lower morbidity and mortality risk among individuals with hypertension^{6,7}. In the present study, a high DASH diet score was associated with a lower risk for all-cause mortality; suggestive that adoption of a DASH-like diet may reduce mortality risk for individuals with aTRH. However, caution is warranted in interpreting this finding as the association was not significant when risks for cardiovascular events or cardiovascular mortality were assessed. Results from previous observational studies are conflicting. Some have reported a reduced risk of fatal and non-fatal cardiovascular events with consumption of a DASH-like diet¹², whereas other studies have reported a reduced risk for all-cause mortality, but not cardiovascular mortality²³. Reasons for the lack of association between consumption of a DASH-like diet and risk for cardiovascular-related outcomes are unclear, but have been attributed to several factors related to macronutrient composition of the DASH diet and blood lipid changes that occur with adoption of the DASH diet including: a reduction in HDL-cholesterol, higher consumption of carbohydrates, and less consumption of mono- and polyunsaturated fats²³.

It has been previously reported in a study of 12 participants with aTRH that a low-salt diet compared to high-salt diet reduced systolic and diastolic BP by 22.7 and 9.1 mm Hg, respectively²⁴. These striking BP reductions have led some to suggest that emphasis be placed on sodium reduction to control BP and reduce cardiovascular risk in individuals with aTRH²⁵⁻²⁶. In the present study, however, the ratio of sodium-to-potassium intake was not associated with a significant reduction in clinical outcomes. Rigorous studies are needed to determine whether dietary sodium reduction and the concomitant BP reductions it induces can translate to mitigating morbidity/mortality risk in aTRH.

Several limitations must be noted when interpreting our findings. First, medication dosing is not available in the REGARDS study. Thus, we were unable to confirm optimal dosing of antihypertensive medications. Second, BP levels were defined by readings during a single visit. Third, physical activity, cigarette smoking, dietary measures, and alcohol use were assessed via self-report. Fourth, FFQ data to derive the DASH diet score and ratio of sodium-to-potassium intake were not available on 699 (34.2%) of 2,043 participants. Nonetheless, dietary data were available for 1,344 participants, which is still a sizable

cohort. Also, results were similar when analyses were conducted among participants with complete data. Fifth, it is possible that some individuals with a history of aTRH undertook several lifestyle modifications, lowered their BP, and were no longer classified as having aTRH at the REGARDS baseline visit. As these individuals may have a low risk for outcomes, the protective association of healthy lifestyle factors with risk of outcomes in our study may have been underestimated. Finally, the study was observational; therefore the causal nature of the associations cannot be established.

Despite these limitations, there are several strengths to our study. First, the REGARDS study is one of the largest population-based studies conducted in the US and includes a biracial sample of participants recruited from across the US. Therefore, results of this study may be highly generalizable to the US adult population. Second, BP was measured by trained technicians using a standardized protocol⁸. Third, medication usage was recorded through direct inspection of medication pill bottles. Finally, all outcomes were adjudicated by a centralized events committee.

Perspectives

In a geographically diverse, biracial population-based sample of US adults with aTRH, a greater number of healthy lifestyle factors was associated with a lower risk of cardiovascular events, all-cause mortality, and cardiovascular mortality. Among the individual healthy lifestyle factors investigated, physical activity and non-smoking status were each associated with a decreased risk for cardiovascular events, all-cause mortality, and cardiovascular mortality. A higher DASH diet score was also associated with a decreased risk for all-cause mortality. These data support the concept that the prognosis among individuals with aTRH may be improved by interventions targeting healthy lifestyle factors. Future randomized controlled trials are warranted to examine whether lifestyle interventions lower morbidity and mortality risk among adults with aTRH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What is new? This is the first study to examine whether healthy lifestyle factors are associated with better prognosis among individuals with apparent treatment-resistant hypertension (aTRH).

What is relevant? Among individuals with aTRH, having more healthy lifestyle factors was associated with a lower risk for cardiovascular events and mortality. Physical activity and non-smoking were individual healthy lifestyle factors associated with a lower risk for these outcomes.

Summary: Lifestyle modification interventions may be beneficial for reducing morbidity and mortality risk in individuals with aTRH.

Characteristics of REGARDS study participants (n=2,043) with apparent treatment resistant hypertension stratified by number of healthy lifestyle factors.

Table 1

Variable	Number of Healthy Lifestyle Factors				P-trend
	0-1 (n=662)	2 (n=671)	3 (n=430)	4-6 (n=280)	
Age (years)	66.1 ± 0.4	67.2 ± 0.4	68.7 ± 0.4	70.3 ± 0.5	<0.001
Male (%)	38.3	50.4	56.1	59.5	<0.001
Black (%)	69.7	63.7	52.9	42.5	<0.001
Education < High School (%)	24.5	19.7	17.3	8.7	<0.001
Region of residence					
Non-belt & non-buckle (%)	35.1	36.8	33.7	30.9	1 (ref)
Residence in stroke belt (%)	22.8	18.6	22.0	18.6	0.197
Residence in stroke buckle (%)	42.1	44.6	44.3	50.5	0.086
Diabetes (%)	53.6	47.5	39.8	32.1	<0.001
Total Cholesterol (mg/dL)	182.5 ± 1.8	181.4 ± 1.7	178.1 ± 2.0	176.2 ± 2.7	0.031
HDL-cholesterol (mg/dL)	48.0 ± 0.7	47.8 ± 0.6	48.1 ± 0.8	50.2 ± 1.0	0.071
eGFR < 60 ml/min/1.73m ² (%)	29.1	29.4	26.2	22.3	<0.001
Albuminuria (%)	36.3	35.4	29.6	28.9	<0.001
Atrial Fibrillation (%)	17.0	15.0	14.0	15.1	0.369
Left Ventricular Hypertrophy (%)	21.7	17.0	16.3	17.7	0.128
Systolic BP (mmHg)	142.2 ± 0.8	141.7 ± 0.8	141.1 ± 1.1	143.3 ± 1.1	0.606
Diastolic BP (mmHg)	80.0 ± 0.5	79.6 ± 0.5	79.2 ± 0.6	75.0 ± 0.1	0.048
No. of antihypertensive medications	3.7 ± 0.0	3.6 ± 0.0	3.7 ± 0.0	3.6 ± 0.0	0.028
Statin use (%)	51.9	48.9	52.5	59.5	0.061
History of CHD (%)	35.2	35.3	37.0	38.7	0.508
History of stroke (%)	15.5	14.6	11.5	9.9	0.557

Data are presented as mean ± standard error or percentage.

BP, blood pressure; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

Hazard ratios for cardiovascular events associated with cumulative number of healthy lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension.

Table 2

Number of Healthy Lifestyle Factors		No. of events	Person years at Risk	Hazard Ratio (95% CI) for Cardiovascular Events		
				Unadjusted	Model 1	Model 2
0-1		122	2,869.3	1 (ref)	1 (ref)	1 (ref)
2		128	3,093.5	0.98 (0.74–1.29)	0.87 (0.66–1.15)	0.91 (0.68–1.21)
3		71	2,001.2	0.84 (0.59–1.18)	0.69 (0.49–0.98)	0.80 (0.57–1.14)
4-6		39	1,316.8	0.70 (0.47–1.03)	0.54 (0.36–0.80)	0.63 (0.41–0.95)
				P-trend=0.042	P-trend=0.001	P-trend=0.020

Healthy lifestyle factors: waist circumference < 102 cm in men and < 88 cm in women, physical activity 4 times/week, non-smoking, moderate alcohol consumption, highest quartile (4th) for DASH diet score, lowest (1st) quartile for Na/K intake ratio.

Model 1: Adjusted for age, race, sex, education, and geographic region of residence.

Model 2: Adjusted for covariates in model 1 plus total cholesterol, HDL-cholesterol, eGFR < 60 ml/min/1.73 m², albuminuria, atrial fibrillation, left ventricular hypertrophy, diabetes, statin use, history of coronary heart disease, and history of stroke.

Table 3

Hazard ratios for cardiovascular events associated with individual lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension.

Lifestyle Factor	No. of Events	Person years at Risk	Hazard Ratio (95% CI) for Cardiovascular Events		
			Unadjusted	Model 1	Model 2
Abdominal Obesity					
Yes	224	6,294.9	1 (ref)	1 (ref)	1 (ref)
No	136	2,985.9	1.28 (1.04–1.59)	1.05 (0.83–1.32)	1.12 (0.89–1.42)
Physical Activity					
None	186	3,812.6	1 (ref)	1 (ref)	1 (ref)
1–3 times/week	113	3,280.9	0.72 (0.57–0.91)	0.70 (0.56–0.89)	0.82 (0.65–1.04)
4 times/week	61	2,187.4	0.58 (0.43–0.77)	0.55 (0.40–0.74)	0.67 (0.50–0.91)
			P-trend <0.001	P-trend <0.001	P-trend=0.006
Current Smoking					
Yes	66	1,016.2	1 (ref)	1 (ref)	1 (ref)
No	294	8,264.6	0.55 (0.42–0.71)	0.47 (0.35–0.61)	0.54 (0.41–0.72)
Alcohol Consumption ^a					
Heavy	7	285.6	1 (ref)	1 (ref)	1 (ref)
Moderate	90	2,624.6	0.88 (0.53–1.45)	0.90 (0.55–1.48)	0.94 (0.57–1.57)
None	263	6,364.6	1.06 (0.66–1.69)	1.15 (0.71–1.87)	1.10 (0.67–1.80)
DASH diet score					
Quartile 1 (20)	82	2,386.7	1 (ref)	1 (ref)	1 (ref)
Quartile 2 (>20– 23)	96	2,420.1	1.16 (0.82–1.64)	1.06 (0.76–1.48)	1.07 (0.77–1.48)
Quartile 3 (>23– 26)	89	2,126.7	1.20 (0.86–1.69)	1.09 (0.78–1.53)	1.08 (0.77–1.52)
Quartile 4 (>26)	93	2,347.3	1.14 (0.82–1.60)	1.03 (0.73–1.43)	1.06 (0.75–1.50)
			P-trend=0.423	P-trend=0.864	P-trend=0.746
Na/K intake					
Quartile 4 (0.71)	98	2,461.6	1 (ref)	1 (ref)	1 (ref)
Quartile 3 (>0.71– 0.88)	103	532.6	1.08 (0.80–1.47)	1.01 (0.74–1.37)	1.01 (0.73–1.38)
Quartile 2 (>0.88– 1.08)	83	2,310.3	0.90 (0.62–1.29)	0.83 (0.57–1.20)	0.86 (0.58–1.27)
Quartile 1 (>1.08)	76	2,125.9	0.89 (0.64–1.24)	0.82 (0.58–1.16)	0.82 (0.57–1.18)

Hazard Ratio (95% CI) for Cardiovascular Events				
Lifestyle Factor	No. of Events	Person years at Risk	Unadjusted	Model 1 Model 2
			P-trend=0.344	P-trend=0.171 P-trend=0.221

Model 1: Adjusted for age, race, sex, education, and geographic region of residence.

Model 2: Adjusted for covariates in model 1 plus total cholesterol, HDL-cholesterol, eGFR< 60 ml/min/1.73 m², albuminuria, atrial fibrillation, left ventricular hypertrophy, diabetes, statin use, history of coronary heart disease, and history of stroke.

^a P-trend values for alcohol consumption are not presented as we hypothesized that the association between alcohol consumption and outcomes would not be linear given that moderate alcohol consumption (the middle category) was considered to be a healthy lifestyle factor in our analyses.

Hazard ratios for all-cause mortality associated with cumulative number of healthy lifestyle factors in REasons for Geographic And Racial Differences in Stroke study participants with apparent treatment resistant hypertension.

Table 4

Number of Healthy Lifestyle Factors	No. of Deaths	Person years at Risk	Hazard Ratio (95% CI) for All-cause Mortality		
			Unadjusted	Model 1	Model 2
0-1	161	3,364.8	1 (ref)	1 (ref)	1 (ref)
2	146	3,646.1	0.82 (0.64 – 1.04)	0.71 (0.55 – 0.91)	0.71 (0.55 – 0.93)
3	96	2,361.3	0.82 (0.62 – 1.10)	0.63 (0.47 – 0.86)	0.70 (0.52 – 0.94)
4-6	49	1,593.5	0.62 (0.44 – 0.88)	0.46 (0.33 – 0.66)	0.54 (0.37 – 0.77)
			P-trend = 0.009	P-trend <0.001	P-trend = 0.001

Healthy lifestyle factors: waist circumference <102 cm in men and <88 cm in women, physical activity 4 times/week, non-smoking, moderate alcohol consumption, highest quartile (4th) for DASH diet score, lowest (1st) quartile for Na/K intake ratio.

Model 1: Adjusted for age, race, sex, education, and geographic region of residence.

Model 2: Adjusted for covariates in model 1 plus total cholesterol, HDL-cholesterol, eGFR<60 ml/min/1.73 m², albuminuria, atrial fibrillation, left ventricular hypertrophy, diabetes, statin use, history of coronary heart disease, and history of stroke.