Healthy Lifestyle Factors and Risk of Cardiovascular Events and Mortality in Treatment-Resistant Hypertension

The Reasons for Geographic and Racial Differences in Stroke Study

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Abstract—Few data exist on 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=2043) from the population-based Reasons for Geographic and Racial Differences in Stroke (REGARDS) study with apparent treatment-resistant hypertension (blood pressure ≥140/90 mm Hg despite the use of 3 antihypertensive medication classes or the 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, nonsmoking, moderate alcohol consumption, high Dietary Approaches to Stop Hypertension diet score, and low sodium-to-potassium intake ratio) were examined. A greater number of healthy lifestyle factors were associated with lower risk for cardiovascular events (n=360) during a mean follow-up of 4.5 years. Multivariable-adjusted hazard ratios [HR (95% confidence interval)] for cardiovascular events comparing individuals with 2, 3, and 4 to 6 versus 0 to 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 nonsmoking 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 nonsmoking, are associated with a lower risk for cardiovascular events and mortality among individuals with apparent treatment-resistant hypertension. (Hypertension. 2014;64:00-00.) ● Online Data Supplement

Key Words: diet ■ hypertension ■ lifestyle ■ smoking

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 subclass 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 3 or more classes, or the use of 4 or more classes to achieve BP control. The prevalence of apparent treatment-resistant hypertension (aTRH) in the 2005 to 2008 National Health and Nutrition Examination Survey was estimated to be 11.8% among the US adults with hypertension, an increase from 5.5% in 1998–1994 and 8.5% in 1999 to 2004; indicating that a growing proportion of the 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 3 medications. Other longitudinal studies have yielded similar results for cardiovascular outcomes and all-cause mortality. 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. However, few data exist on 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 previously. Briefly, REGARDS is a population-based cohort study of 30,239 white and black adults ≥45 years of age from across the contiguous United States 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, 2043 individuals with aTRH were available for analyses (Figure S1 in the online-only Data Supplement). 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, 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 protocol. BP was measured 2 times by a trained examiner using an aneroid sphygmomanometer after 5 minutes of seated rest. Based on the average of 2 measurements, uncontrolled hypertension was defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. During the in-home examination, medications taken in the past 2 weeks were recorded and subsequently coded into drug classes. Single-pill combinations were classified into their respective classes as individual components. aTRH was defined as: (1) taking 3 or more antihypertensive medication classes with uncontrolled BP; or (2) taking 4 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, nonsmoking status, moderate alcohol consumption, high DASH diet score, and low Na/K intake were considered to be healthy lifestyle factors. The 6 healthy lifestyle factors were adapted from lifestyle modifications recommended for the treatment of hypertension. Moderate alcohol consumption was considered to be a healthy lifestyle factor as prior studies have shown reduced cardiovascular risk associated with moderate versus heavy or no alcohol consumption.

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 standing. 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). 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 4 or more times/week. Smoking status was determined by responses to 2 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 following the in-home study visit to estimate average dietary intake for the previous year. Nutrient analysis was conducted by NutritionQuest. A DASH dietary score was created using methods described by Fung et al. 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 Food Frequency Questionnaire are provided in the online-only Data Supplement.

Outcomes

The primary outcome was combined fatal and nonfatal 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. Nonfatal cardiovascular events were defined as nonfatal 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 biannual 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 Food Frequency Questionnaire-derived variables (DASH diet score and Na/K intake) were because of participants not returning the questionnaire. Missing data were imputed with 10 data sets using chained equations. For primary analyses, participants were grouped according to the number of healthy lifestyle factors: 0 to 1, 2, 3, or 4 to 6. Participant characteristics were calculated by the 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 to 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 <60 mL/min/1.73 m², albuminuria, atrial fibrillation, left ventricular hypertrophy on ECG, diabetes mellitus, statin use, history of coronary heart disease, 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 coronary heart disease (yes vs no). Also, HRs were calculated in subgroups defined by race and history of stroke or coronary heart disease.

Three sensitivity analyses were conducted. First, analyses were repeated using participants with complete data (ie, without imputation; n=1300). Second, as the use of a diuretic has been suggested to be required for diagnosis of aTRH, we repeated analyses restricting the study population to participants on a diuretic (n=1809).
Finally, as aTRH may be partially explained by reduced medication adherence, 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 online-only 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 the 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 examined. Data analyses were conducted using STATA/IC version 12.1 (StataCorp, College Station, TX).

Results

Participant Characteristics

Among the 2043 participants with aTRH, 662 (32.4%) had 0 to 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 to 6 healthy lifestyle factors. Overall, 658 participants (32.2%) did not have abdominal obesity, 453 (22.2%) engaged in physical activity ≥4 times/week, 1797 (88.0%) were nonsmokers, 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 mellitus, estimated glomerular filtration rate <60 mL/min/1.73 m², 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 were 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 coronary heart disease (*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 were 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 were also associated with a lower risk of cardiovascular events; the fully adjusted HR (95% confidence interval) comparing participants with 2, 3, and 4 to 6 versus 0 to 1 healthy lifestyle factors were 0.92 (0.67–1.26), 0.80 (0.55–1.16), and

| Table 1. Characteristics of Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study Participants (n=2043) With Apparent Treatment-Resistant Hypertension Stratified by the Number of Healthy Lifestyle Factors |
|-------------------------------|---------------------|-------------------|-------------------|------------------|-------------------|
| Variable                      | 0–1 (n=662)        | 2 (n=671)         | 3 (n=430)         | 4–6 (n=280)      | *P*-Trend         |
| Age, y                        | 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 and nonbuckle, %     | 35.1               | 36.8              | 33.7              | 30.9             | 1 (ref)           |
| Residence in stroke belt, %   | 22.9               | 18.6              | 22.0              | 18.6             | 0.197             |
| Residence in stroke buckle, % | 42.1               | 44.6              | 44.3              | 50.5             | 0.086             |
| Diabetes mellitus, %          | 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/1.73 m² (%)  | 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±SE or percentage. BP indicates blood pressure; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; and HDL, high-density lipoprotein.
lower risk for all-cause mortality, and 50% and 53% lower risk for cardiovascular events, 42% and 47% were individual healthy lifestyle factors associated with a 33% lower mortality. Furthermore, physical activity and nonsmoking were significant associated with a lower risk for cardiovascular events and all-cause and cardiovascular mortality in unadjusted and adjusted models (Table S8). Higher levels of physical activity and nonsmoking status were significantly associated with a lower risk for cardiovascular mortality (Table 2).

When the association of each healthy lifestyle factor with cardiovascular events was examined, higher levels of physical activity and nonsmoking 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 were 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, nonsmoking 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 were significantly associated with a lower risk for cardiovascular mortality (Table S7). Higher levels of physical activity and nonsmoking 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 nonsmoking 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 increase, 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 baroreceptor 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. These recommendations, in part, stem from studies which have demonstrated an association between lifestyle factors and morbidity/mortality among hypertensive individuals. 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 were 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 the 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 4 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 hypertension. The low prevalence of healthy lifestyle factors in this study highlights a great potential to reduce the increased morbidity and mortality risk associated with aTRH through multifaceted 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 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 to 12 weeks of aerobic exercise reduced daytime systolic and diastolic ambulatory BP by 5.9 and 3.3 mm Hg, respectively.20

Alternatively, the association between physical activity and outcomes in aTRH could also be attributed to the non-BP effects of increased physical activity (eg, insulin sensitivity, lipid metabolism, endothelial function, immune function).21

Table 3. Hazard Ratios for Cardiovascular Events Associated With Individual Lifestyle Factors in Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study Participants With Apparent Treatment-Resistant Hypertension

<table>
<thead>
<tr>
<th>Lifestyle Factor</th>
<th>No. of Events</th>
<th>Person Years at Risk</th>
<th>Unadjusted Hazard Ratio (95% Confidence Interval)</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>224</td>
<td>6294.9</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>No</td>
<td>136</td>
<td>2985.9</td>
<td>1.28 (1.04–1.59)</td>
<td>1.05 (0.83–1.32)</td>
<td>1.12 (0.89–1.42)</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>186</td>
<td>3812.6</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>1–3 times/wk</td>
<td>113</td>
<td>3280.9</td>
<td>0.72 (0.57–0.91)</td>
<td>0.70 (0.56–0.89)</td>
<td>0.82 (0.65–1.04)</td>
</tr>
<tr>
<td>≥4 times/wk</td>
<td>61</td>
<td>2187.4</td>
<td>0.58 (0.43–0.77)</td>
<td>0.55 (0.40–0.74)</td>
<td>0.67 (0.50–0.91)</td>
</tr>
<tr>
<td>P-trend</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Current smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>66</td>
<td>1016.2</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>No</td>
<td>294</td>
<td>8264.6</td>
<td>0.55 (0.42–0.71)</td>
<td>0.47 (0.35–0.61)</td>
<td>0.54 (0.41–0.72)</td>
</tr>
<tr>
<td>Alcohol consumption*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>7</td>
<td>285.6</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Moderate</td>
<td>90</td>
<td>2624.6</td>
<td>0.88 (0.53–1.45)</td>
<td>0.90 (0.55–1.48)</td>
<td>0.94 (0.57–1.57)</td>
</tr>
<tr>
<td>None</td>
<td>263</td>
<td>6364.6</td>
<td>1.06 (0.66–1.69)</td>
<td>1.15 (0.71–1.87)</td>
<td>1.10 (0.67–1.80)</td>
</tr>
<tr>
<td>DASH diet score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (&lt;20)</td>
<td>82</td>
<td>2386.7</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Quartile 2 (&lt;20–&lt;23)</td>
<td>96</td>
<td>2420.1</td>
<td>1.16 (0.82–1.64)</td>
<td>1.06 (0.76–1.48)</td>
<td>1.07 (0.77–1.48)</td>
</tr>
<tr>
<td>Quartile 3 (&lt;23–&lt;26)</td>
<td>89</td>
<td>2126.7</td>
<td>1.20 (0.86–1.69)</td>
<td>1.09 (0.78–1.53)</td>
<td>1.08 (0.77–1.52)</td>
</tr>
<tr>
<td>Quartile 4 (&gt;26)</td>
<td>93</td>
<td>2347.3</td>
<td>1.14 (0.82–1.60)</td>
<td>1.03 (0.73–1.43)</td>
<td>1.06 (0.75–1.50)</td>
</tr>
<tr>
<td>P-trend</td>
<td>=0.423</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na/K intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4 (&gt;0.71)</td>
<td>98</td>
<td>2461.6</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Quartile 3 (&gt;0.71–&lt;0.88)</td>
<td>103</td>
<td>532.6</td>
<td>1.08 (0.80–1.47)</td>
<td>1.01 (0.74–1.37)</td>
<td>1.01 (0.73–1.38)</td>
</tr>
<tr>
<td>Quartile 2 (&gt;0.88–&lt;1.08)</td>
<td>83</td>
<td>2310.3</td>
<td>0.90 (0.62–1.29)</td>
<td>0.83 (0.57–1.20)</td>
<td>0.86 (0.58–1.27)</td>
</tr>
<tr>
<td>Quartile 1 (&gt;1.08)</td>
<td>76</td>
<td>2125.9</td>
<td>0.89 (0.64–1.24)</td>
<td>0.82 (0.59–1.16)</td>
<td>0.82 (0.57–1.18)</td>
</tr>
<tr>
<td>P-trend</td>
<td>=0.344</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Model 1: adjusted for age, race, sex, education, and geographic region of residence. Model 2: adjusted for covariates in Model 1 plus total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate <60 mL/min/1.73 m², albuminuria, atrial fibrillation, left ventricular hypertrophy, diabetes mellitus, statin use, history of coronary heart disease, and history of stroke. DASH indicates Dietary Approaches to Stop Hypertension.

*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.

Our study also found that nonsmoking 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 treatment.22 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 this 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 nonfatal cardiovascular events with consumption of a DASH-like diet, whereas other studies have reported a reduced risk for all-cause mortality, but not cardiovascular mortality.

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 monounsaturated and polyunsaturated fats.

It has been previously reported in a study of 12 participants with aTRH that a low-salt diet compared with high-salt diet reduced systolic and diastolic BP by 22.7 and 9.1 mm Hg, respectively. 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 aTRH. In this 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, Food Frequency Questionnaire data to derive the DASH diet score and ratio of sodium-to-potassium intake were not available on 699 (34.2%) of 2043 participants. Nonetheless, dietary data were available for 1344 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 United States and includes a biracial sample of participants recruited from across the United States. Therefore, results of this study may be highly generalizable to the US adult population. Second, BP was measured by trained technicians using a standardized protocol. 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 the US adults with aTRH, a greater number of healthy lifestyle factors were associated with a lower risk of cardiovascular events, all-cause mortality, and cardiovascular mortality. Among the individual healthy lifestyle factors investigated, physical activity and nonsmoking 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.

**Acknowledgments**

We thank the staff, participants, and other investigators of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org.
Sources of Funding

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Disclosures

None.

References


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.

What Is Relevant?

• Among individuals with apparent treatment-resistant hypertension, having more healthy lifestyle factors was associated with a lower risk for cardiovascular events and mortality. Physical activity and nonsmoking 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 apparent treatment-resistant hypertension.
Healthy Lifestyle Factors and Risk of Cardiovascular Events and Mortality in Treatment-Resistant Hypertension: The Reasons for Geographic and Racial Differences in Stroke Study
Keith M. Diaz, John N. Booth III, David A. Calhoun, Marguerite R. Irvin, George Howard, Monika M. Safford, Paul Muntner and Daichi Shimbo

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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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Supplemental Methods

Data Collected at Baseline: REasons for Geographic And Racial Differences in Stroke (REGARDS) study data were collected via a computer-assisted telephone interview, a self-administered questionnaire, and in-home examination. Trained health professionals conducted in-home examinations which included anthropometric and blood pressure (BP) measurements, electrocardiogram (ECG), collection of blood and spot urine samples, and a review of medication pill bottles for medications taken in the prior 2 weeks. History of coronary heart disease (CHD) was defined as a self-reported or ECG evidence of myocardial infarction (MI) or a self-reported coronary revascularization procedure. History of stroke was defined on the basis of self-report. Atrial fibrillation was defined as self-reported history or evidence on ECG using standardized procedures. Left ventricular hypertrophy was defined by ECG using Sokolow-Lyon criteria. Diabetes was defined as a serum glucose $\geq 126$ mg/dL for participants who had fasted $\geq 8$ hours prior to their blood draw, a serum glucose $\geq 200$ mg/dL for those who had not fasted, or a self-report of a prior diagnosis of diabetes with use of insulin or oral hypoglycemic medications. Chronic kidney disease was defined by the presence of a reduced estimated glomerular filtrate rate (eGFR, $<60$ ml/min/1.73 m$^2$) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and/or albuminuria (urinary albumin to urinary creatinine ratio $\geq 30$ mg/g). Medication adherence was assessed by summing each point assigned for responding “yes” (totaling 0-4) to each of the 4-items on the Morisky Medication Adherence Scale (MMAS), with a higher score indicating worse adherence.

Validity and Reproducibility of Physical Activity and Food Frequency Questionnaires: The physical activity question (How many times per week do you engage in intense physical activity, enough to work up a sweat?) used in REGARDS is a widely used measure of physical activity that has been validated against maximum aerobic capacity, has moderate reproducibility (0.60-0.70), can include either aerobic or resistance training, and has been used in similar studies, such as the National Health And Nutrition Examination Survey (NHANES). For dietary intake assessment, versions of the Block Food Frequency Questionnaire have been extensively validated against 24-hour recalls and 4-day food records among diverse populations of adults, have been demonstrated to have moderate to high reproducibility (0.57-0.90), and have been used in several other population-based studies including NHANES.

Outcome Ascertainment: For the current study, cardiovascular events, all-cause mortality, and cardiovascular mortality were evaluated as primary, 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. Trained experts adjudicated all cardiovascular events and deaths (described below) using information retrieved from interviewing the participant, proxy, or next-of-kin; and by reviewing autopsy reports, death certificates, medical records and administrative databases (e.g. Social Security Death Index, National Death Index) for the circumstances surrounding each event. Agreement on independent review for all endpoints had $\kappa > 0.80$.

Cardiovascular events: Cardiovascular events included combined fatal and non-fatal cardiovascular events. Fatal cardiovascular events were defined as death within 28 days of a definite or probable MI, or sudden death; or death within 28 days of a confirmed ischemic, hemorrhagic or clinical (defined below) stroke event. Non-fatal cardiovascular events were
defined as a non-fatal definite or probable MI or a non-fatal confirmed stroke. Cardiovascular events occurring through December 31, 2010 were available for the current analysis.

Cardiovascular events were adjudicated using published guidelines\textsuperscript{12,13}. MI was determined using a combination of clinical signs and symptoms consistent with ischemia, imaging/ECG findings, and a characteristic rising and falling pattern of cardiac biomarkers (usually troponin, but in the absence of troponin, creatine phosphokinase-MB fraction) over 6 or more hours to a peak of at least twice the upper limit of normal. The interpretation of ECG was guided by the Minnesota code to classify ECGs as evolving diagnostic, positive, non-specific or not consistent with ischemia\textsuperscript{14,15}.

For stroke events, a panel of neurologists used the World Health Organization (WHO) definition\textsuperscript{16} to adjudicate stroke events based on self-reported hospitalizations or physician evaluations of stroke, and newly reported stroke symptoms detected on the Questionnaire for Verifying Stroke-Free Status that resulted in a medical evaluation\textsuperscript{17}. Events not meeting the WHO definition were classified as clinical strokes if symptoms lasted <24 hours and neuroimaging was consistent with acute infarct or hemorrhage. We included both WHO and clinic strokes.

\textit{All-Cause Mortality:} All-cause mortality was defined as any REGARDS participant who died after enrollment regardless of the cause of death. Dates of death were confirmed through review of death certificates, medical records, and administrative databases (e.g. Social Security Death Index, National Death Index). Deaths occurring through March 29, 2012 were included in the current analysis.

\textit{Cardiovascular Mortality:} For cardiovascular mortality, the cause of death was adjudicated as caused by a definite, probable or possible MI; sudden death; heart failure; stroke; or other cardiovascular cause including ruptured aortic aneurysm, pulmonary embolism or other heart-related condition. Deaths from cardiovascular-related causes occurring through December 31, 2010 were available for the current analysis.
SUPPLEMENTAL REFERENCES


**Table S1:** Characteristics of REGARDS participants included and not included in the present analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Included (n=2,043)</th>
<th>Excluded(^a) (n=28,196)</th>
<th>P-difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.6 ± 0.2</td>
<td>64.7 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>49.2</td>
<td>44.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black (%)</td>
<td>60.5</td>
<td>40.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education &lt; High School (%)</td>
<td>19.2</td>
<td>12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-belt &amp; non-buckle (%)</td>
<td>34.8</td>
<td>34.6</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Residence in stroke belt (%)</td>
<td>20.7</td>
<td>20.9</td>
<td>0.824</td>
</tr>
<tr>
<td>Residence in stroke buckle (%)</td>
<td>44.5</td>
<td>44.5</td>
<td>0.929</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>45.7</td>
<td>20.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>180.3 ± 0.9</td>
<td>192.9 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>48.3 ± 0.3</td>
<td>52.1 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR &lt; 60 ml/min1.73m(^2) (%)</td>
<td>27.6</td>
<td>10.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td>33.6</td>
<td>14.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial Fibrillation (%)</td>
<td>15.4</td>
<td>8.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left Ventricular Hypertrophy (%)</td>
<td>18.5</td>
<td>9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>142.0 ± 0.4</td>
<td>126.6 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78.0 ± 0.1</td>
<td>76.3 ± 0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of antihypertensive medications</td>
<td>3.6 ± 0.0</td>
<td>1.0 ± 0.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>52.1</td>
<td>29.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of CHD (%)</td>
<td>36.0</td>
<td>16.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>13.6</td>
<td>5.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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.

\(^a\)Participants were excluded if they were missing blood pressure measurements or data on antihypertensive medications at baseline, did not have aTRH, or were missing outcome data during follow-up.
### Table S2: Hazard ratios for cardiovascular events associated with cumulative number of healthy lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension stratified by race.

<table>
<thead>
<tr>
<th>Number of Healthy Lifestyle Factors</th>
<th>No. of events</th>
<th>Person years at Risk</th>
<th>Hazard Ratioa (95% CI)</th>
<th>P-Interaction (Blacks vs. Whites)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blacks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>82</td>
<td>1,976.2</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>1,975.3</td>
<td>0.94 (0.67–1.34)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>1,060.1</td>
<td>0.83 (0.52–1.34)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>13</td>
<td>549.9</td>
<td>0.59 (0.52–1.34)</td>
<td>P-trend=0.118</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.934</td>
</tr>
<tr>
<td><strong>Whites</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>40</td>
<td>893.1</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>1,119.3</td>
<td>0.85 (0.53–1.36)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>941.1</td>
<td>0.72 (0.44–1.18)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>26</td>
<td>766.9</td>
<td>0.60 (0.35–1.04)</td>
<td>P-trend=0.050</td>
</tr>
</tbody>
</table>

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.

aAdjusted for the following covariates: age, sex, education, and geographic region of residence, 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 S3: Hazard ratios for cardiovascular events associated with cumulative number of healthy lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension stratified by history of stroke or coronary heart disease (CHD).

<table>
<thead>
<tr>
<th>Number of Healthy Lifestyle Factors</th>
<th>No. of events</th>
<th>Person years at Risk</th>
<th>Hazard Ratio&lt;sup&gt;a&lt;/sup&gt; (95% CI)</th>
<th>P-Interaction (No stroke or CHD history vs. stroke or CHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No history of stroke or CHD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>52</td>
<td>1,699.0</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>54</td>
<td>1,740.5</td>
<td>0.96 (0.64–1.45)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>1,213.8</td>
<td>0.78 (0.45–1.34)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>15</td>
<td>756.6</td>
<td>0.52 (0.27–1.00)</td>
<td>P-trend=0.040</td>
</tr>
<tr>
<td><strong>History of stroke or CHD</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.628</td>
</tr>
<tr>
<td>0-1</td>
<td>70</td>
<td>1,170.3</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>74</td>
<td>1,353.0</td>
<td>0.88 (0.57–1.36)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>787.4</td>
<td>0.84 (0.54–1.31)</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>24</td>
<td>560.2</td>
<td>0.71 (0.42–1.20)</td>
<td>P-trend=0.189</td>
</tr>
</tbody>
</table>

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 (4<sup>th</sup>) for DASH diet score, lowest (1<sup>st</sup>) quartile for Na/K intake ratio.

<sup>a</sup>Adjusted for the following covariates: age, race, sex, education, and geographic region of residence, total cholesterol, HDL-cholesterol, eGFR < 60 ml/min/1.73 m<sup>2</sup>, albuminuria, atrial fibrillation, left ventricular hypertrophy, diabetes, and statin use.
Table S4: Hazard ratios for cardiovascular events associated with cumulative number of healthy lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension restricted to individuals with complete data for the healthy lifestyle factors (n=1,300).

<table>
<thead>
<tr>
<th>Number of Healthy Lifestyle Factors</th>
<th>No. of events</th>
<th>Person years at Risk</th>
<th>Hazard Ratio (95% CI) for Cardiovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>0-1</td>
<td>78</td>
<td>2,011.4</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>2,211.7</td>
<td>1.10 (0.81–1.48)</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>1,225.0</td>
<td>0.76 (0.51–1.13)</td>
</tr>
<tr>
<td>4-6</td>
<td>19</td>
<td>629.4</td>
<td>0.78 (0.47–1.29)</td>
</tr>
</tbody>
</table>

P-trend = 0.095  P-trend = 0.001  P-trend = 0.007

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 S5: Hazard ratios for all-cause mortality associated with cumulative number of healthy lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension restricted to individuals with complete data for the healthy lifestyle factors (n=1,300).

<table>
<thead>
<tr>
<th>Number of Healthy Lifestyle Factors</th>
<th>No. of events</th>
<th>Person years at Risk</th>
<th>Hazard Ratio (95% CI) for All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>0-1</td>
<td>100</td>
<td>2,369.1</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>95</td>
<td>2,621.2</td>
<td>0.84 (0.63–1.11)</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>1,458.9</td>
<td>0.76 (0.54–1.08)</td>
</tr>
<tr>
<td>4-6</td>
<td>19</td>
<td>750.8</td>
<td>0.58 (0.35–0.94)</td>
</tr>
</tbody>
</table>

P-trend=0.016  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.
<table>
<thead>
<tr>
<th>Lifestyle Factor</th>
<th>No. of Events</th>
<th>Person years at Risk</th>
<th>Hazard Ratio (95% CI) for All-Cause Mortality</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Model 1</td>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td>Abdominal Obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>271</td>
<td>7,402.8</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>181</td>
<td>3,562.8</td>
<td>1.38 (1.14–1.66)</td>
<td>1.05 (0.86–1.29)</td>
<td>1.10 (0.89–1.35)</td>
<td></td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
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<td>None</td>
<td>258</td>
<td>4,533.6</td>
<td>1 (ref)</td>
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<tr>
<td>1-3 times/week</td>
<td>117</td>
<td>3,854.3</td>
<td>0.51 (0.41–0.64)</td>
<td>0.50 (0.40–0.62)</td>
<td>0.58 (0.46–0.73)</td>
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</tr>
<tr>
<td>≥ 4 times/week</td>
<td>77</td>
<td>2,577.8</td>
<td>0.51 (0.39–0.65)</td>
<td>0.48 (0.37–0.61)</td>
<td>0.58 (0.45–0.75)</td>
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<td>Yes</td>
<td>79</td>
<td>1,212.6</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>No</td>
<td>373</td>
<td>9,953.1</td>
<td>0.57 (0.45–0.73)</td>
<td>0.45 (0.35–0.59)</td>
<td>0.53 (0.40–0.69)</td>
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<tr>
<td>Alcohol Consumption&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Heavy</td>
<td>10</td>
<td>340.6</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>Moderate</td>
<td>114</td>
<td>3,054.6</td>
<td>0.66 (0.44–0.99)</td>
<td>0.67 (0.45–0.99)</td>
<td>0.80 (0.44–1.49)</td>
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<tr>
<td>None</td>
<td>328</td>
<td>7,570.5</td>
<td>0.78 (0.54–1.14)</td>
<td>0.79 (0.55–1.14)</td>
<td>0.98 (0.79–1.22)</td>
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<tr>
<td>DASH diet score</td>
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<td></td>
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<td></td>
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<tr>
<td>Quartile 1 (&lt;20)</td>
<td>118</td>
<td>2,767.3</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>Quartile 2 (&lt;20≤23)</td>
<td>132</td>
<td>2,848.1</td>
<td>1.10 (0.84–1.45)</td>
<td>0.96 (0.73–1.25)</td>
<td>0.97 (0.74–1.28)</td>
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<tr>
<td>Quartile 3 (&lt;23≤26)</td>
<td>101</td>
<td>2,489.2</td>
<td>0.95 (0.69–1.32)</td>
<td>0.82 (0.60–1.12)</td>
<td>0.78 (0.57–1.07)</td>
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<tr>
<td>Quartile 4 (&gt;26)</td>
<td>101</td>
<td>2,861.1</td>
<td>0.82 (0.60–1.13)</td>
<td>0.69 (0.51–0.95)</td>
<td>0.72 (0.53–0.98)</td>
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<tr>
<td>P-trend=0.158</td>
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<td>Na/K intake</td>
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<td></td>
</tr>
<tr>
<td>Quartile 4 (&lt;0.71)</td>
<td>128</td>
<td>2,911.2</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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</tr>
<tr>
<td>Quartile 3 (&gt;0.71≤0.88)</td>
<td>123</td>
<td>2,890.4</td>
<td>0.98 (0.74–1.31)</td>
<td>0.91 (0.69–1.19)</td>
<td>0.92 (0.70–1.20)</td>
<td></td>
</tr>
<tr>
<td>Quartile 2 (&gt;0.88≤1.08)</td>
<td>100</td>
<td>2,665.0</td>
<td>0.84 (0.61–1.15)</td>
<td>0.76 (0.54–1.05)</td>
<td>0.78 (0.55–1.11)</td>
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<tr>
<td>Quartile 1 (&gt;1.08)</td>
<td>101</td>
<td>2,559.2</td>
<td>0.90 (0.66–1.21)</td>
<td>0.81 (0.60–1.08)</td>
<td>0.80 (0.59–1.08)</td>
<td></td>
</tr>
</tbody>
</table>

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 m<sup>2</sup>, albuminuria, atrial fibrillation, left ventricular hypertrophy, diabetes, statin use, history of coronary heart disease, and history of stroke.

<sup>a</sup>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.
Table S7: Hazard ratios for cardiovascular mortality associated with cumulative number of healthy lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension.

<table>
<thead>
<tr>
<th>Number of Healthy Lifestyle Factors</th>
<th>No. of events</th>
<th>Person years at Risk</th>
<th>Hazard Ratio (95% CI) for Cardiovascular Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td>0-1</td>
<td>66</td>
<td>3,064.0</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>3,294.9</td>
<td>0.83 (0.58–1.19)</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>2,138.9</td>
<td>0.62 (0.38–1.01)</td>
</tr>
<tr>
<td>4-6</td>
<td>17</td>
<td>1,408.9</td>
<td>0.54 (0.30–0.96)</td>
</tr>
</tbody>
</table>

P-trend=0.009  P-trend <0.001  P-trend=0.004

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 S8: Hazard ratios for cardiovascular mortality associated with individual lifestyle factors in REGARDS study participants with apparent treatment resistant hypertension.

<table>
<thead>
<tr>
<th>Lifestyle Factor</th>
<th>No. of Events</th>
<th>Person years at Risk</th>
<th>Hazard Ratio (95% CI) for Cardiovascular Mortality</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Model 1</td>
<td>Model 2</td>
<td></td>
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<tr>
<td>Abdominal Obesity</td>
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<tr>
<td>Yes</td>
<td>107</td>
<td>6,680.9</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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</tr>
<tr>
<td>No</td>
<td>67</td>
<td>3,225.7</td>
<td>1.30 (0.96–1.76)</td>
<td>1.01 (0.74–1.41)</td>
<td>1.08 (0.77–1.51)</td>
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<tr>
<td>Physical Activity</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>97</td>
<td>4,111.4</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td></td>
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<tr>
<td>1-3 times/week</td>
<td>53</td>
<td>3,476.1</td>
<td>0.60 (0.43–0.84)</td>
<td>0.59 (0.42–0.82)</td>
<td>0.72 (0.51–1.00)</td>
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<tr>
<td>≥ 4 times/week</td>
<td>24</td>
<td>2,319.2</td>
<td>0.42 (0.27–0.66)</td>
<td>0.40 (0.25–0.62)</td>
<td>0.50 (0.32–0.80)</td>
<td>P-trend &lt;0.001</td>
</tr>
<tr>
<td>Current Smoking</td>
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<tr>
<td>Yes</td>
<td>35</td>
<td>1,104.3</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>No</td>
<td>139</td>
<td>8,802.4</td>
<td>0.49 (0.34–0.71)</td>
<td>0.39 (0.27–0.58)</td>
<td>0.47 (0.31–0.70)</td>
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<tr>
<td>Alcohol Consumption a</td>
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<td></td>
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<tr>
<td>Heavy</td>
<td>4</td>
<td>309.8</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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</tr>
<tr>
<td>Moderate</td>
<td>43</td>
<td>2,746.2</td>
<td>0.67 (0.35–1.31)</td>
<td>0.69 (0.36–1.35)</td>
<td>0.76 (0.39–1.51)</td>
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<tr>
<td>None</td>
<td>127</td>
<td>6,850.6</td>
<td>0.81 (0.44–1.51)</td>
<td>0.83 (0.44–1.58)</td>
<td>0.82 (0.42–1.58)</td>
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<tr>
<td>DASH diet score</td>
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<td>Quartile 1 (≤ 20)</td>
<td>40</td>
<td>2,541.6</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>Quartile 2 (20–23)</td>
<td>47</td>
<td>2,561.2</td>
<td>1.05 (0.63–1.75)</td>
<td>0.93 (0.55–1.59)</td>
<td>0.95 (0.56–1.62)</td>
<td></td>
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<tr>
<td>Quartile 3 (23–26)</td>
<td>48</td>
<td>2,267.3</td>
<td>1.27 (0.73–2.19)</td>
<td>1.11 (0.63–1.95)</td>
<td>1.09 (0.63–1.88)</td>
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</tr>
<tr>
<td>Quartile 4 (26+)</td>
<td>39</td>
<td>2,536.5</td>
<td>0.85 (0.51–1.41)</td>
<td>0.73 (0.44–1.23)</td>
<td>0.79 (0.46–1.34)</td>
<td>P-trend=0.741</td>
</tr>
<tr>
<td>Na/K intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4 (≤ 0.71)</td>
<td>45</td>
<td>2,677.7</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
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<tr>
<td>Quartile 3 (0.71–0.88)</td>
<td>48</td>
<td>2,535.9</td>
<td>1.21 (0.67–2.17)</td>
<td>1.12 (0.62–2.01)</td>
<td>1.13 (0.64–1.99)</td>
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<td>Quartile 2 (0.88–1.08)</td>
<td>41</td>
<td>2,400.9</td>
<td>1.00 (0.62–1.61)</td>
<td>0.90 (0.54–1.47)</td>
<td>0.96 (0.59–1.58)</td>
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<tr>
<td>Quartile 1 (&gt;1.08)</td>
<td>42</td>
<td>2,292.1</td>
<td>1.03 (0.62–1.70)</td>
<td>0.92 (0.54–1.56)</td>
<td>0.93 (0.54–1.57)</td>
<td>P-trend=0.870</td>
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</tbody>
</table>

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.

aP-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.
Figure S1. Inclusion criteria for examining the association of healthy lifestyle factors with cardiovascular events, all-cause mortality, and cardiovascular mortality among individuals with apparent treatment resistant hypertension (aTRH) in the REGARDS study.