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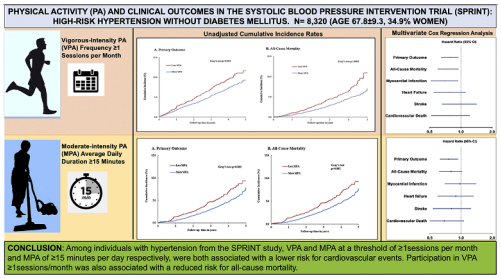
Association between physical activity and clinical outcomes in high-risk hypertension: Post-hoc analysis of SPRINT

Richard Kazibwe [a,*], Matthew J. Singleton [b], Parag A. Chevli [a], Arnaud D. Kaze [c], Juliana H. Namutebi [d], Michael D. Shapiro [e], Joseph Yeboah [e]

[a] Department of Medicine, Section on Hospital Medicine, Wake Forest University School of Medicine, 1 Medical Center Blvd, Winston-Salem, NC 27157, USA
[b] Department of Medicine, Section on Cardiovascular Medicine, WellSpan Health, York, PA, USA
[c] Department of Medicine, Sovah Health, Danville, VA, USA
[d] School of Graduate Studies, Wake Forest University, Winston-Salem, NC, USA
[e] Center for the Prevention of Cardiovascular Disease Section on Cardiovascular Medicine, Wake Forest University School of Medicine, Winston-Salem, NC, USA

GRAPHICAL ABSTRACT



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ABSTRACT

Objective: Engaging in physical activity (PA) is recommended to reduce the risk of morbidity and mortality in patients with hypertension. However, the association between PA and clinical outcomes in individuals with high-risk hypertension is understudied. We examined the relationship between PA and clinical outcomes in the Systolic Blood Pressure Intervention Trial (SPRINT). SPRINT investigated the benefit of intensive (vs. standard) blood pressure treatment in patients with high-risk hypertension.

Methods: Baseline data on PA was self-reported. Vigorous-intensity PA (VPA) was categorized into 2 groups based on frequency of "Rarely or Never" and 1 or more sessions/month. Moderate-intensity PA (MPA) was also categorized into 2 groups based on average duration/day of <15 min and 15 or more minutes. Using multivariable Cox regression, we estimated the associations between PA the primary outcome which was a composite of cardiovascular events, and all-cause mortality.

Results: A total of 8,320 (age 67.8 ± 9.3, 34.9% women) of SPRINT participants with data on PA were included. During a median follow-up of 3.8 years, 619 primary outcome, and 419 all-cause mortality events occurred. Compared to not engaging in VPA, the risk of the primary outcome, myocardial infarction, and all-cause mortality (HR 95% CIs) associated with VPA of ≥1sessions/month was 0.79(0.65–0.94; p=0.009), 0.70(0.52–0.93; p=0.014) and 0.75(0.60–0.94; p=0.011), respectively. Similarly, the risk of the primary outcome and all-cause

* Corresponding author.
E-mail address: rkazibwe@wakehealth.edu (R. Kazibwe).

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mortality (HR 95% CI) associated with engaging in MPA for ≥15 min/day, relative to <15 min/day was 0.76 (0.63–0.93; p=0.008) and 0.80(0.62–1.02; p=0.066), respectively.
Conclusion: Among individuals with hypertension from the SPRINT study, VPA and MPA at a threshold of ≥1sessions/month and MPA of ≥15 min/day respectively, were both associated with a lower risk for cardiovascular events, and VPA was also associated with a reduced risk for all-cause mortality. Further studies are required to identify the optimal volume and intensity of PA in high-risk hypertension.

1. Introduction

Hypertension affects an estimated 31.1% of adults (1.39 billion) worldwide and is a leading cause of cardiovascular disease (CVD) and mortality [1,2]. Engaging in physical activity (PA) and avoiding sedentary behavior are important modifiable risk factors for CVD and mortality in hypertension [1,3]. Therefore, it is critical to identify and emphasize effective strategies that can increase PA in order to reduce the burden of hypertension and its associated morbidity [4].

The current U.S guidelines recommend 150–300 min per week of moderate-intensity, or 75–150 min a week of vigorous-intensity aerobic physical exercise [5]. Yet, only about 20 percent of US adults meet these recommended levels of PA [6]. Furthermore, the recommended PA levels have been criticized for being arbitrary and with substantial limitations [7]. There is some evidence to suggest that lower levels of PA than those currently recommended may be sufficient to provide significant health benefits [8–10].

However, few studies have examined the association between levels of PA and clinical outcomes in high-risk individuals with hypertension [11–13]. The Systolic Blood Pressure Intervention Trial (SPRINT) enrolled older individuals (age ≥ 50 years) who had hypertension but without diabetes mellitus and an increased risk of cardiovascular events to compare the safety and efficacy of systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment) [14,15]. Therefore, the aim of this post-hoc analysis was to examine the association of self-reported levels of vigorous-intensity PA (VPA) and moderate-intensity PA (MPA) and clinical outcomes in the SPRINT trial population. We hypothesized that both a daily average minimum of 15 min of MPA and one (1) or more sessions of VPA per month would be associated with lower risk of cardiovascular events and all-cause mortality.

2. Methods

2.1. Study design and population

The rationale, protocol, and primary results of SPRINT have been previously published [14]. Briefly, SPRINT was a randomized, controlled, open-label trial, including 9361 non-diabetic U.S. adults who were at least 50 years of age, at high cardiovascular risk, with hypertension and systolic blood pressure between 130 to180 mmHg at enrollment. Increased cardiovascular risk was defined by one or more of the following: clinical or subclinical CVD other than stroke; chronic kidney disease (excluding polycystic kidney disease), with an estimated glomerular filtration rate (eGFR) of 20 to less than 60 ml per minute per 1.73 m^2 of body surface area, calculated with the use of the four variable Modification of Diet in Renal Disease equation [16]. A 10-year risk of CVD of 15% or greater on the basis of the Framingham risk score [17] or an age of 75 years or older. Individuals with unintentional weight loss greater than 10% in the last six (6) months were excluded. SPRINT trial participants were allocated into intensive treatment arm with target systolic blood pressure <120 mmHg or standard treatment arm with target systolic blood pressures <140 mmHg. The primary efficacy endpoint was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes. Secondary efficacy endpoints comprised the individual components of the primary endpoint (stroke, acute decompensated heart failure, and cardiovascular death) and death from any cause. A structured interview was used in both groups every three (3) months to obtain self-reported CVD outcomes. The results from the SPRINT trial have been published [15]. All participants provided written informed consent for participation in the trial. The trial was approved by the institutional review board at each site and was registered with ClinicalTrials.gov. The primary endpoint of this study was the SPRINT primary efficacy endpoint (composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes) and all-cause mortality.

2.2. Vigorous-Intensity physical activity (VPA)

Using a self-administered "SPRINT My Health" questionnaire, participants were asked about their frequency of VPA over the last year with the following question: "…. When we say "vigorous" we mean activities that make you sweat, increase your heart rate or increase your breathing. Please think about vigorous activities that you may have done at home or at places of work other than your home, as well as vigorous recreational activities or conditioning exercises. Please think over the last year and indicate how often you participated in vigorous activities." Then the following options were provided: a) rarely or never b) 1–3 times per month c) 1 time per week d) 2–4 times per week and e) 5+ times per week. These activities are similar to vigorous-intensity activities included in the current U.S guidelines [5].

2.3. Moderate-Intensity physical activity (MPA)

As part of the same questionnaire, each participant was asked to indicate their daily average time spent doing less vigorous PA over the past 12 months. Specifically, a modified Saltin-Grimby Physical Activity Level Scale (SGPALS) questionnaire was used [18].

The following question was asked: "Now let us think about less vigorous activities like brisk walking, climbing stairs or vacuuming floors. Do not include activities like standing still or walking slowly. Again, include work time, free time, and time at home." The question then provided options for the average duration per day that the respondent spent participating in these less vigorous activities as follows: a) 0–15 min b) 15 to 30 min, c) 30 to 60 min d) 1–4 h and e) 4 or more hours. These activities are consistent with moderate-intensity activities in the current guidelines [5].

2.4. Exclusion

Using a self-administered questionnaire at baseline, participants were asked about their health in various domains including overall general health, limitation in doing moderate activities (such as moving a table, pushing a vacuum cleaner, bowling, or playing golf), mobility and ability to care for self. For this analysis, we excluded participants who reported being significantly limited in doing moderate activities (n=971), being confined in bed or being unable to perform self-care (n=13), inability to do usual activities (e.g., work study, housework, family, or leisure activities) (n=73) or those with missing covariates (n=42). After all exclusions (n = 1041), a total of 8320 participants remained and were included in the final analysis.

Table 1
Baseline characteristics and study outcomes according to self-reported vigorous-intensity physical activity.

Variable	Overall (n=8320)	Less VPA (VPA = "Rarely or Never") (n=2056)	More VPA (VPA ≥1 /Month) (n=6264)	P-value
Age, years, mean (SD)	67.9 ± 9.3	69.2 ± 9.6	67.6 ± 9.2	<0.0001
Age ≥75 years, n (%)	2345(28.2)	667(32.4)	1678(26.8)	<0.0001
Female, n (%)	2904(34.9)	947(46.1)	1957(31.2)	<0.0001
Race or Ethnic group, n (%)	–	–	–	<0.0001
Non-Hispanic black	2381(28.6)	647(31.5)	1734(27.7)	
Hispanic	909(10.9)	287(14.0)	622(9.9)	
Non-Hispanic White	4873(58.6)	1082(52.6)	3791(60.5)	
Other	1,57(1.9)	40(2.0)	117(1.9)	
Smoking Status, n (%)	–	–	–	0.007
Never Smoker	3721(45.2)	933(46.0)	2788(45.0)	
Former Smoker	3486(42.4)	811(40.0)	2675(45.2)	
Current Smoker	1022(12.4)	286(14.1)	736(11.9)	
College Degree, n (%)	8086 (97.2)	1954(95.0)	6132(97.9)	<0.0001
Married, n (%)	7123(85.6)	1708 (83.1)	5415(86.5)	<0.001
Uninsured, n (%)	853(10.3)	208 (10.1)	645(10.3)	0.815
BMI, kg/m^2, mean (SD)	29.7 ± 5.6	30.2 ± 6.2	29.5 ± 5.3	<0.0001
Average SBP, mmHg, mean (SD)	145.2 ± 11.2	145.4 ± 11.0	1,45.2 ± 11.3	0.076
Average DBP, mmHg, mean (SD)	80.3 ± 11.6	79.2 ± 11.6	80.6 ± 11.6	<0.0001
Framingham Risk Score, mean (SD)	17.4 ± 2.5	16.6 ± 2.5	17.3 ± 2.5	<0.0001
History of CVD, n (%)	1616(19.4)	410(19.9)	1206(19.3)	0.493
Chronic Kidney Disease, n (%)	2310(27.8)	694(33.8)	1616(25.8)	<0.0001
Creatinine, (mg/dL), mean (SD)	1.1 ± 0.3	1.1 ± 0.4	1.1 ± 0.3	0.166
Estimate GFR, (ml/min/1.73 m^2)	71.8 ± 20.3	70.5 ± 22.1	72.2 ± 19.7	0.001
Ratio of urinary albumin to Creatinine	41.2 ± 166.1	51.7 ± 205.9	37.7 ± 150.6	0.001
Aspirin use	4247(51.1)	1027(50.2)	3220(51.4)	0.359
Randomized to intervention group	4142(49.8)	1038(50.5)	3104(49.6)	0.463
Not using of anti-hypertensive agents	821(9.9)	182(8.9)	639(10.2)	0.075
Using Statin	3591(43.4)	907(44.5)	2684(43.1)	0.273
No. of antihypertensive medication classes	1.8 ± 1.0	1.9 ± 1.0	1.7 ± 1.0	<0.0001
Fasting Glucose, (mg/dL), mean (SD)	98.8 ± 13.3	98.8 ± 13.3	98.8 ± 13.3	0.952
HDL-C, (mg/dL), mean (SD)	52.9 ± 14.4	53.0 ± 14.6	52.9 ± 14.4	0.812
LDL-C, (mg/dL), mean (SD)	112.7 ± 34.8	111.6 ± 34.8	113.0 ± 34.8	0.120
Total Cholesterol (mg/dL), mean (SD)	190.3 ± 40.8	189.5 ± 40.4	190.6 ± 40.9	0.292
Triglycerides (mg/dL), mean (SD)	125.6 ± 91.1	126.2 ± 75.3	125.4 ± 95.8	0.738
Study Outcomes, n (%)				
Primary Outcome*	619(7.4)	183(8.9)	436(7.0)	0.004
All-Cause Mortality	419(5.0)	138(6.7)	281(4.5)	<0.0001
Myocardial Infarction	238(2.9)	77(3.8)	161(2.6)	0.006
Heart Failure	168(2.0)	57(2.8)	111(1.8)	0.005
Stroke	149(1.8)	40(2.0)	109(1.7)	0.542
Cardiovascular Mortality	121(1.5)	35(1.7)	86(1.4)	0.279

VPA, vigorous-intensity physical activity; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SD, standard deviation. Continuous variables are presented as means and standard deviations. Categorical variables are presented as counts and corresponding percentages.

* Primary outcome was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes.

2.5. Covariates

In the SPRINT study, trained study personnel ascertained baseline sociodemographic data, comorbid conditions, and use of antihypertensive medications during the screening or randomization visit. Fasting blood and urine samples were collected at that time. Serum and urine creatinine were measured using an enzymatic procedure and an auto-analyzer. Urine albumin was measured using an immuneturbidometric method on an auto-analyzer. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) formula [16]. All assays were performed in a single SPRINT central laboratory [14].

2.6. Statistical analysis

The baseline demographic, risk factors, and clinical characteristics were assessed according to two categories of self-reported frequency of VPA, i.e., "rarely or never" ("Less VPA" group) and ≥1 sessions of vigorous physical activity per month ("More VPA" group). Mean and standard deviation or percent were reported for continuous and categorical variables, respectively. P-values were determined by analysis of variance for continuous variables or chi-square for categorical variables.

We constructed curves for cumulative incidence rates for all-cause mortality and the primary outcomes by the two categories of VPA. We used Cox proportional hazards analysis to examine the association between VPA and our outcomes of interest, using self-reported nonparticipation in VPA as the reference. We chose this reference point to examine the potential clinical benefit of at least one session of VPA in our study population.

Next, we examined the effect of MPA using self-reported daily average time spent of <15 min as the reference. We did this to investigate the association of clinical outcomes at a threshold of 15 min of MPA per day. Finally, we performed additional exploratory analysis to examine the effect of joint participation in at least one (1) of VPA and at least 15 min of MPA. We did this to investigate the potential synergistic effect of participation in both VPA and MPA at our minimum threshold of ≥ 1 per month and ≥ 15 min per day, respectively.

All predictor variables were introduced into our models as categorical variables, consistent with the available SPRINT data on PA. Three models were used, with model 1 adjusting for age, sex, and race/ethnicity; model 2 adjusting model 1 plus health insurance status, education, clinical trial site and marital status, and model 3 adjusting model 2 plus baseline covariates including history of CVD, smoking status, use of antihypertensive medications, use of statin, average

systolic blood pressure, body mass index (BMI), total cholesterol, high-density lipoprotein cholesterol (HDL-C), serum triglycerides and urine albumin-creatinine ratio, glomerular filtration rate (GFR) and study arm assignment. We performed additional analysis by SPRINT subgroups including age (<75 versus ≥75 years), sex, race (black versus non-Black), prior clinical CVD, and prior CKD, defined eGFR <60 mL/min per 1.73 m^2 of body-surface area). Finally, we examined the association of PA and safety outcomes including hypotension, syncope, bradycardia, electrolyte abnormalities, acute kidney injury and injurious falls.

A two-sided P-value < 0.05 was considered statistically significant, and all statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 8320 (mean age ± SD, 67.9 ± 9.3 years, 34.9% women, 58.6% Non-Hispanic White) of the SPRINT participants were included in this analysis (Table 1). Participants who reported rarely or never participating in VPA (Less VPA group), compared to those who participated in at least one VPA per month (More VPA group), were more likely to be older, female, current cigarette smokers, and have baseline CKD, and have higher BMI, FRS, and average diastolic blood pressure. There was no significant difference in baseline average systolic BP, history of CVD, use of aspirin and baseline serum levels of total cholesterol, HDL-C, LDL-C, and triglycerides between the two groups (Table 1). Baseline characteristic by category of MPA of daily average of <15 min and ≥15 min, as well as by category of joint participation in both predefined minimum VPA and MPA, were also compared (Supplement Table S1 and Supplement Table S2).

After a median follow-up of about 3.8 years, 619 (7.4%) and 419 (5.0%) participants had adjudicated primary outcome (a composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes) and all-cause mortality, respectively. During the same follow-up period the individual event rates for heart failure, myocardial infarction, stroke, and death from a cardiovascular cause were 168(2.0%), 238(2.9%), 149 (1.8%) and 121(1.5%), respectively. Compared to participants with more VPA, those with less VPA experienced higher event rates of the primary outcome, all-cause mortality, heart failure and myocardial infarction (Table 1).

During the follow-up period, the unadjusted cumulative incidence rates of both all-cause mortality and the primary composite cardiovascular outcome were higher among those who reported performing less VPA (Fig. 1). Similarly, those who reported participation in less than 15 min of MPA, compared to those who reported participating in at least 15 min per day, had a higher incidence of all-cause mortality and the primary composite cardiovascular outcome (Fig. 2). Furthermore, those who reported joint participation in the above minimum levels of VPA and MPA, compared to those who did not, had lower unadjusted incidence rate for both all-cause mortality and the primary outcomes (Supplement Fig. S1).

In the fully adjusted Cox models, self-reported participation in VPA at a threshold of one session per month, was significantly associated with reduced risk of the primary outcomes, myocardial infarction and all-cause mortality [Hazard Ratio (HR) (95% CI)]: 0.79(0.65–0.94; P=0.009), 0.70(0.52–0.93; P=0.014) and 0.75(0.60–0.94; P=0.011) respectively. However, the risk of heart failure, stroke and cardiovascular mortality did not significantly differ between the two categories of VPA (Table 2).

Self-reported participation in MPA for a daily average minimum of 15 min, compared to less than 15 min, was associated with lower risk of the primary outcome of 0.76(0.63–0.93; P=0.008). A similar threshold of MPA was also weakly associated with a lower risk of all-cause mortality (HR 95% CI) 0.80(0.62–1.02; P=0.066). However, the risk of myocardial infarction, heart failure, stroke or cardiovascular mortality did not significantly differ between the two categories of MPA (Table 3).

Similarly, self-reported joint participation in both above minimum levels of VPA and MPA, compared to not, was associated with lower risk of the primary outcome and all-cause mortality of 0.68(0.52 – 0.89; p=0.005) and 0.65(0.49– 0.92; p=0.010) respectively. However, the risk of myocardial infarction, heart failure, stroke or cardiovascular mortality did not significantly differ between the two categories (Table 4).

Fig. 3 depicts the dose-response curves of VPA and MPA and primary outcome and all-cause mortality expressed as unadjusted event rates per 1000 person-years of follow-up. Increasing amount of PA was more

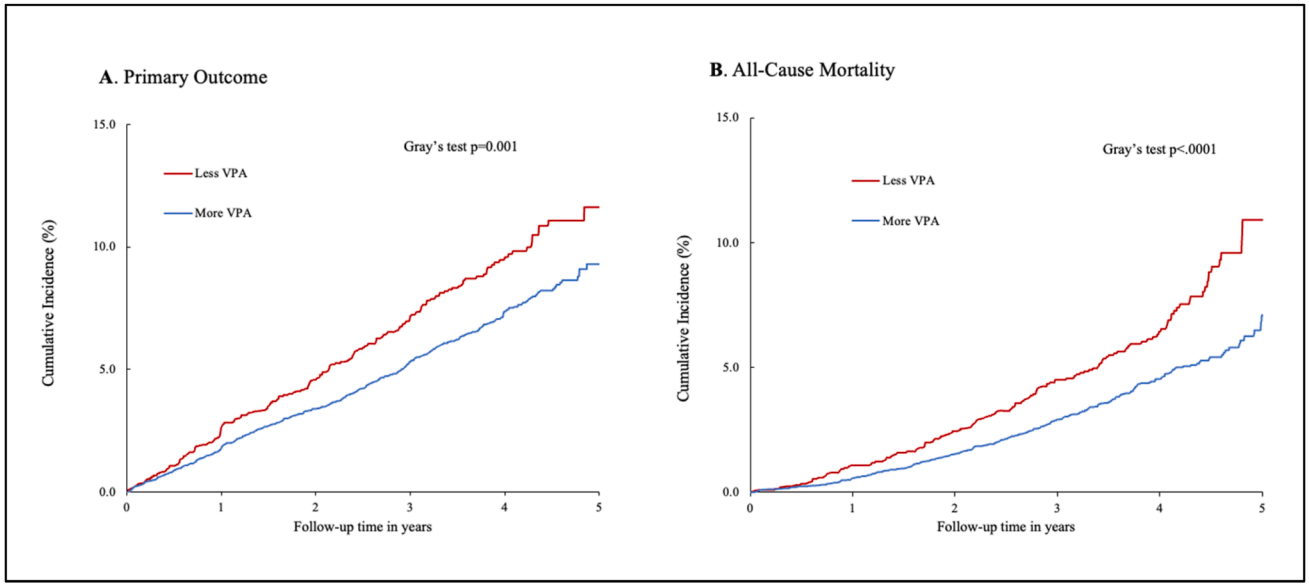

Fig. 1. Cumulative incidence rate of all-cause mortality and primary outcome by stratified by category of self-reported vigorous-intensity physical activity.
VPA denotes vigorous-intensity physical activity.
Less VPA = Self-reported VPA frequency of "Rarely or Never"; More VPA = Self-reported VPA frequency of 1 time or more per month.
Primary Outcomes was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes.

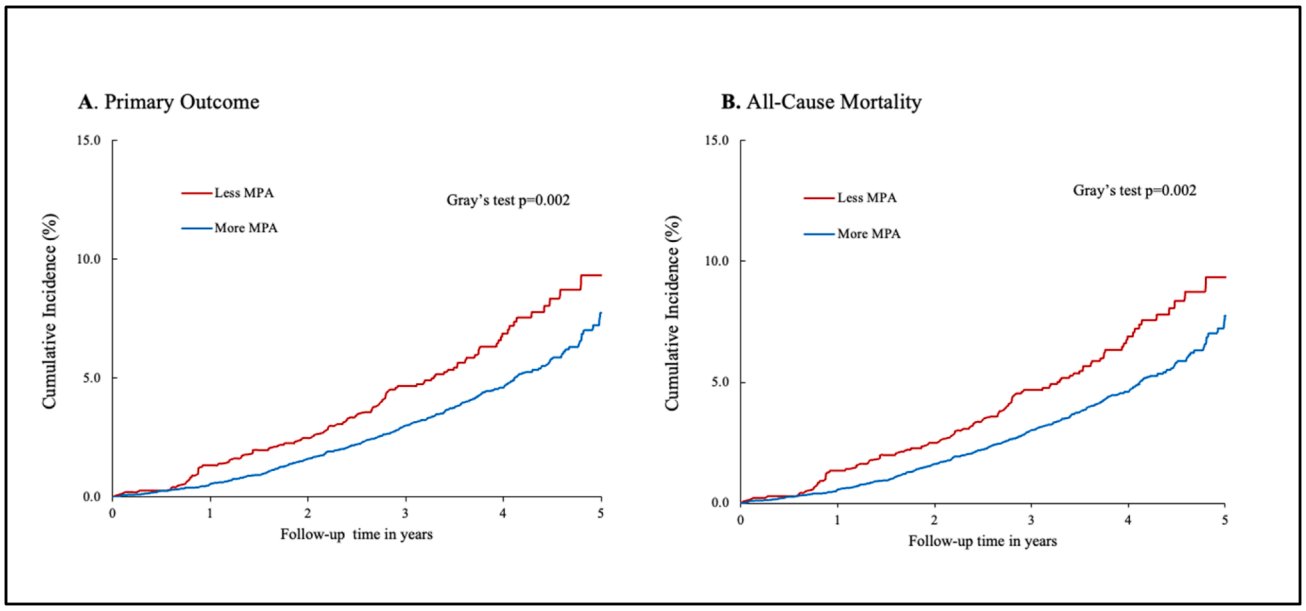

Fig. 2. Cumulative incidence rate of all-cause mortality and primary outcome by stratified by category of self-reported moderate-intensity physical activity. MPA denotes moderate-intensity physical activity.
Less MPA = daily average MPA duration of <15minuntes. More MPA = daily average MPA duration of ≥15 min.
Primary Outcomes was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes.

Table. 2
Risk of outcomes according to frequency of vigorous-intensity physical activity (VPA) per month.

Outcome	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary Outcome*	0.78(0.65–0.93)	0.005	0.77(0.65–0.92)	0.005	0.79(0.65–0.94)	0.009
All-cause death	0.70(0.57–0.86)	<0.0001	0.72(0.59–0.89)	0.003	0.75(0.60–0.94)	0.011
Myocardial Infarction	0.67(0.51–0.88)	0.005	0.70(0.53–0.92)	0.012	0.70(0.52–0.93)	0.014
Heart failure	0.69(0.50–0.96)	0.026	0.69(0.50–0.97)	0.030	0.78(0.55–1.10)	0.158
Stroke	0.96(0.67–1.39)	0.838	0.93(0.64–1.35)	0.709	0.96(0.66–1.41)	0.843
Cardiovascular death	0.84(0.57–1.26)	0.403	0.86(0.57–1.29)	0.459	0.79(0.52–1.21)	0.281

Reference: VPA frequency of "rarely or never".
HR, Hazard Ratio; CI, Confidence Interval.
* Primary outcome was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes.
Model 1 adjusted for age, sex and race/ethnicity.
Mode 2 adjusted for model 1 and health insurance status, education, site and marital status.
Model 3 adjusted for model 2 and history of clinical CVD, smoking status, use of antihypertensive medications, use of statin, baseline average systolic blood pressure, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, urine albumin-creatinine ratio, and study arm assignment.

consistently associated with lower event rate for all-cause mortality, but the association with the primary outcome was less consistent. Fig. 4 shows association of VPA with the primary outcome and all-cause mortality by subgroups (female vs male, age <75 vs ≥75 years, Black vs non-Black, prior CVD status, and prior CKD status). Supplement Fig. S2 shows subgroups results for participation in MPA. Finally, as shown in Supplement Table S3, participants who reported engaging in more VPA and MPA had a lower risk of safety events and injurious falls.

4. Discussion

In this post-hoc analysis of a large randomized cardiovascular outcomes trial of high-risk older individuals with hypertension, we examined the association between self-reported PA and a composite of cardiovascular outcomes and all-cause mortality. First, we found that self-reported vigorous-intensity PA at a threshold of one session per month was significantly associated with lower risk of the cardiovascular events, and myocardial infarction all-cause mortality. Similarly, an average self-reported moderate-intensity PA of 15 min or more per day was associated with lower risk of cardiovascular events and was also weakly associated with improved risk of all-cause mortality. Second, participants who engaged in both these thresholds of vigorous-intensity PA and moderate-intensity PA, compared to those who did not, also had reduced risk of cardiovascular events and all-cause mortality. Finally, the risk of safety adverse events and injurious falls were also lower in participants who reported higher levels of VPA and MPA.

Our study contributes to the much-needed evidence regarding the beneficial associations between the levels of PA and important clinical outcomes in a unique population of high-risk older individuals with hypertension. These findings may assist in informing public health messages aimed at motivating older patients with hypertension to adopt a more active lifestyle to reduce morbidity and mortality.

Among patients with hypertension, the blood pressure-lowering effect of physical activity is well-documented [1,11]. Other mechanisms

Table. 3
Risk of outcomes according to duration of moderate-intensity physical activity (MPA) per day.

Outcome	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary Outcome	0.76(0.63–0.92)	0.005	0.74(0.61–0.90	0.003	0.76(0.63–0.93)	0.008
All-cause death	0.76(0.60–0.95)	0.016	0.78(0.62–0.98)	0.036	0.80(0.62–1.02)	0.066
Myocardial Infarction	0.93(0.67–1.29)	0.650	0.92(0.66–1.28)	0.628	0.98(0.70–1.39)	0.922
Heart failure	0.81(0.56–1.17)	0.255	0.83(0.57–1.20)	0.320	0.89(0.60–1.31)	0.544
Stroke	0.82(0.55–1.22)	0.323	0.80(0.53–1.19)	0.268	0.81(0.54–1.23)	0.323
Cardiovascular death	0.71(0.47–1.08)	0.110	071(0.46–1.09)	0.121	0.68(0.44–1.06)	0.086

Reference: MPA duration of <15 min.
HR, Hazard Ratio; CI, Confidence Interval.
*Primary outcome was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes.
Model 1 adjusted for age, sex and race/ethnicity.
Mode 2 adjusted for model 1 and health insurance status, education, site and marital status.
Model 3 adjusted for model 2 and history of clinical CVD, smoking status, use of antihypertensive medications, use of statin, baseline average systolic blood pressure, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, urine albumin-creatinine ratio, and study arm assignment.

Table 4
Risk of outcomes according to combined participation in ≥ 1 VPA sessions per month and ≥ 15 min MPA per day.

Outcome	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary Outcome*	0.63(0.49 – 0.82)	<0.001	0.65(0.50 – 0.84)	0.001	0.68(0.52 – 0.89)	0.005
All-Cause Mortality	0.60(0.45 – 0.81)	<0.001	0.64(0.47 – 0.87)	0.004	0.65(0.47– 0.90)	0.010
Myocardial Infarction	0.64(0.42 – 0.96)	0.032	0.68(0.45 – 1.04)	0.074	0.72(0.46 – 1.11)	0.134
Heart failure	0.59(0.37 – 0.94)	0.026	0.63(0.39 – 1.03)	0.065	0.77(0.46 – 1.29)	0.327
Stroke	0.75(0.44 – 1.29)	0.300	0.73(0.42 – 1.26)	0.256	0.77(0.44 – 1.34)	0.346
Cardiovascular death	0.65(0.38 – 1.33)	0.130	0.69(0.39 – 1.22)	0.201	0.71(0.39 – 1.30)	0.266

Reference group: Joint group of VPA "Rarely or Never" and MPA<15 min per day.
HR, Hazard Ratio; CI, Confidence Interval.
* Primary outcome was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes.
Model 1 adjusted for age, sex and race/ethnicity.
Mode 2 adjusted for model 1 and health insurance status, education, site and marital status.
Model 3 adjusted for model 2 and history of clinical CVD, smoking status, use of antihypertensive medications, use of statin, baseline average systolic blood pressure, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, urine albumin-creatinine ratio, and study arm assignment.

through which physical activity improves health in those at risk of CVD include its salutary effects on plasma glucose and lipid concentrations level, resting heart rate, endothelial function, parasympathetic tone, and a reduction in the risk of thrombosis [19].

Therefore, PA is recommended as an essential component in the management of hypertension [1,3]. However, the amount of PA that is sufficient for health benefits in various populations is still debated and is the subject of ongoing research [7]. The most recent (2018) U.S physical activity guidelines recommend a weekly minimum of 150 min of moderate-intensity or 75 min of VPA [5]. Although these minimum thresholds remain uncertain, there is evidence to support the stipulation in the guidelines that some physical activity is better than none and additional benefits occur with more physical activity [5]. Engaging in PA below these thresholds may actually be sufficient [8,9]. Studies have shown that in those with hypertension a minimum of 15 min per day or 105 min per week of MPA was associated with substantial benefits [10]. While one study suggested a possible U-shaped relationship between the amount of PA and clinical outcomes in hypertension [12]. most of the existing literature demonstrates a more linear, inverse dose-response pattern [10,20,21]. Among participants in the Multi-Ethnic Study of Atherosclerosis (MESA), there was no increased risk of cardiovascular outcomes with high levels of PA, even among individuals at high risk of CVD [22].

Nonetheless, existing misconceptions about the amount of PA necessary to obtain significant health benefits may be demotivating for some patients [7]. Our analysis shows that the health benefits of maintaining an active lifestyle are not attenuated in individuals ≥ 75 years of age. Older individuals often have physical limitations which can further impede their participation in PA. Therefore, it is important to develop more individualized PA recommendations to aid in counselling patients with hypertension regarding optimal levels of PA.

In recognition of these challenges, both the World Health Organization's physical activity and sedentary behavior Guidelines Development Group in 2020 and the 2018 US Physical Activity Guidelines Advisory Committee recommended initiating studies that examine the relationship between minimum PA thresholds and key clinical end points in individuals with hypertension [23,24].

Results from our study suggest that participation in at least one VPA per month, or at least 15 min per day of MPA may provide significant benefits in a population of high-risk older individuals with hypertension. Consistent with existing literature [25]. participation in both vigorous-intensity and moderate-intensity PA appeared to have incremental beneficial effect on cardiovascular outcomes and mortality. However, in our results the dose-response effect was more consistent with all-cause mortality than with the primary outcome, due to limited power and other confounding factors in our data.

Furthermore, due to safety concerns clinicians may be hesitant to make the necessary adjustments in anti-hypertensive medications to achieve recommended blood pressure goals in high-risk patients. Our results show that maintaining an active lifestyle may have the additional benefit of reducing the risk of safety adverse events and injurious falls among those receiving treatment for hypertension.

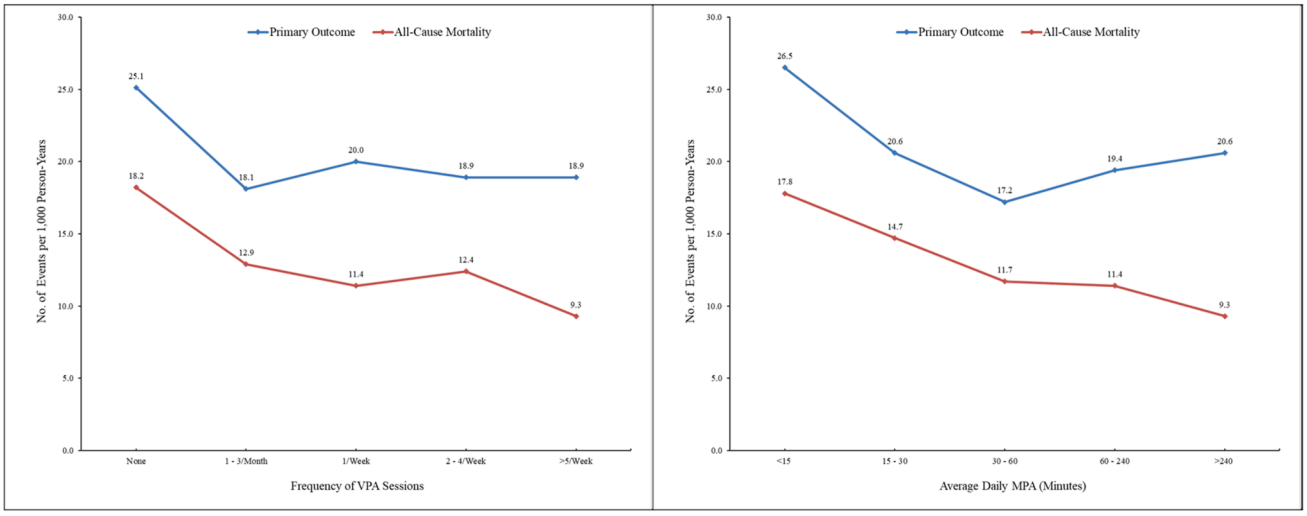

Fig. 3. The Dose-response curves of physical activity and clinical outcomes.
VPA denotes vigorous-intensity physical activity. MPA denotes moderate-intensity physical activity.
Primary Outcomes was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular cause.

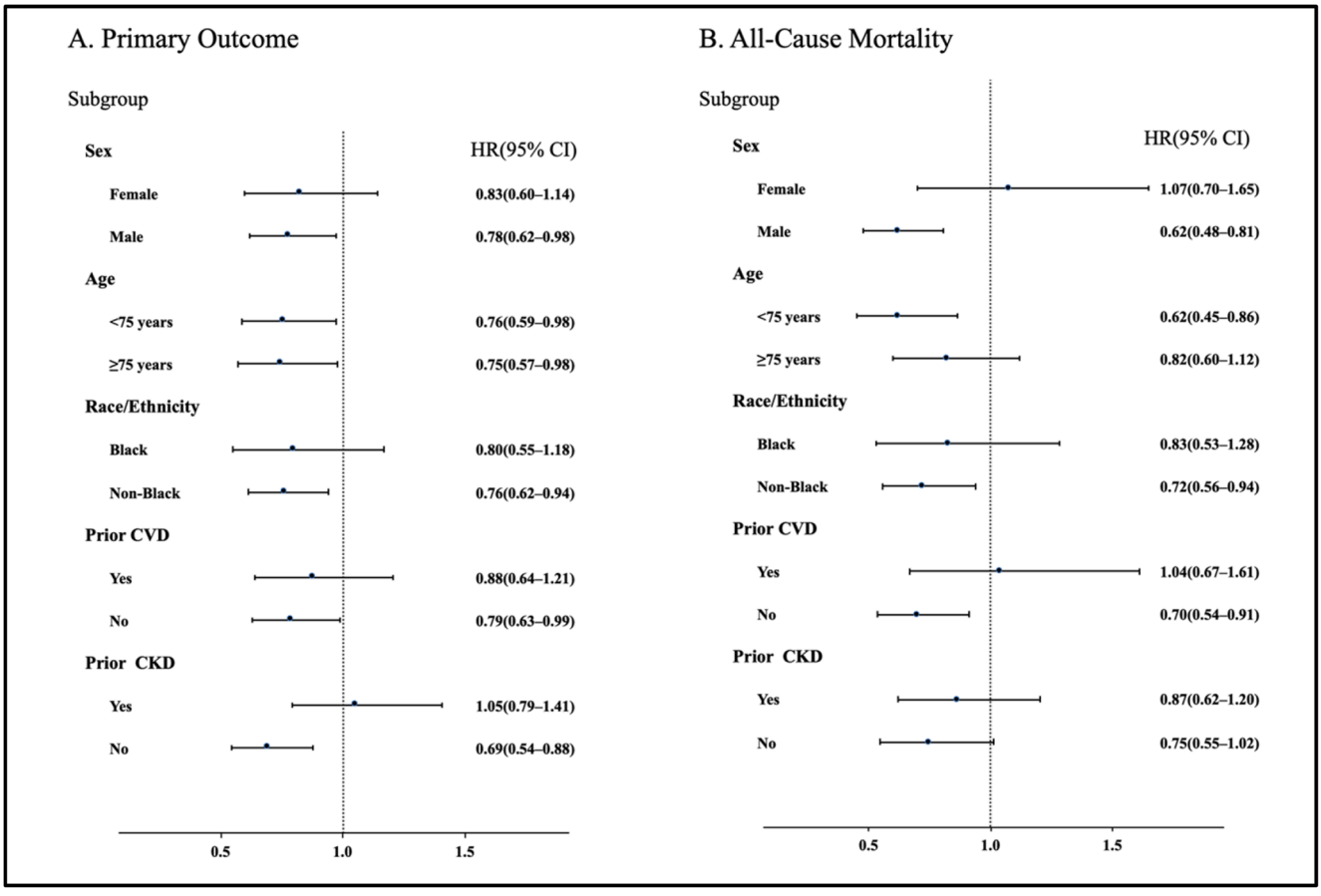

Fig. 4. Risk of primary outcome and all-cause mortality associated with engaging in ≥1 vigorous-intensity sessions per month by subgroups.
HR, hazard ration; CI, confidence interval; CVD, cardiovascular disease; CKD, chronic kidney disease.
Primary Outcomes was the composite of myocardial infarction, other acute coronary syndromes, stroke, acute decompensated heart failure, or death from cardiovascular causes.
Model adjusted for age, sex and race/ethnicity, health insurance status, education, site and marital status, history of clinical CVD, smoking status, use of antihypertensive medications, use of statin, baseline average systolic blood pressure, body mass index, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, urine albumin-creatinine ratio, and study arm assignment.

The strength of our study is the use of a large sample size of a high-risk cohort of older participants with hypertension. The data was well-collected using a standardized process in the context of a clinical trial. Despite this, certain limitations in our study exist. First, data on PA that we analyzed was self-reported, which is prone to recall and social desirability biases. Second, we only used baseline PA data and did not consider changes in PA during the follow-up period. Third, our analysis did not examine the potentially beneficial effect of light physical activity [26] or the negative effects of sedentary behavior [27]. In this patient population even lower levels of physical activity than those we examined could have a significant health benefit. Finally, despite our effort to adjust for confounders, the possibility of other residual confounding remains.

5. Conclusion

Among high-risk older individuals with hypertension but without DM, one or more sessions of VPA per month or an average of 15 min or more per day of MPA were both significantly associated with lower risk for major adverse cardiovascular events, and similar level of VPA was also associated with a lower risk of all-cause mortality. These benefits occurred without an increase in risk of safety adverse events and falls. Further studies are required to identify the minimum amount of PA sufficient to reduce morbidity and mortality in this patient population.

Statement of ethics

All participants provided written informed consent, and Institutional Review Boards of all participating institutions approved the study. The present study was conducted in accordance with the Declaration of Helsinki and was also approved by the Institutional Review Board of Wake Forest University School of Medicine.

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Data availability

The datasets generated during analysis during the current study are available in the National Heart, Lung, and Blood Institute BioLINCC repository, https://biolincc.nhlbi.nih.gov/studies/sprint/.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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RK and JY conceived and designed the study, preparing, reviewing, and editing the original manuscript draft. RK and JY performed statistical analysis and accept responsibility for the work and/or the study's conduct. MS, PC, AK, JN and MS were all involved in writing, reviewing, and editing the manuscript. All authors had final approval of the submitted manuscript. The authors would like to recognize the SPRINT participants, without whom this study would not have been possible. Thank you for your contributions to science. The authors also would like to recognize the SPRINT trial team. A full list of contributors to SPRINT can be found at ClinicalTrials.gov Identifier: NCT01206062.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2023.100524.

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