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RESEARCH ARTICLE

Effect of vigorous-intensity physical activity on incident cognitive impairment in high-risk hypertension

Richard Kazibwe[1] | **Christopher L. Schaich**[2] | **Ahmad Imtiaz Muhammad**[3] | **Isabella Epiu**[4] | **Juliana H. Namutebi**[5] | **Parag A. Chevli**[1] | **Joseph Kazibwe**[6] | **Timothy Hughes**[7] | **Rishi R. Rikhi**[8] | **Michael D. Shapiro**[8] | **Joseph Yeboah**[8]

[1]Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[2]Hypertension and Vascular Research Center, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[3]Department of Medicine, Section on Hospital Medicine, Wisconsin College of Medicine, Milwaukee, Wisconsin, USA

[4]Prince of Wales Clinical School, University of New South Wales Sydney, Sydney, New South Wales, Australia

[5]Wake Forest University, School of Graduate Studies, Winston-Salem, North Carolina, USA

[6]Department of Cardiology, Sheffield Teaching Hospital, Sheffield, UK

[7]Department of Medicine, Section on Cardiovascular Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[8]Department of Internal Medicine, Section on Gerontology and Geriatrics Medicine & Sticht Center for Healthy Aging and Alzheimer's Prevention, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

Correspondence
Richard Kazibwe, Department of Internal Medicine,Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA.
Email: rkazibwe@wakehealth.edu

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Abstract

INTRODUCTION: We investigated the effect vigorous physical activity (VPA) on the risk of incident mild cognitive impairment (MCI) and probable dementia among individuals with high-risk hypertension.

METHODS: Baseline self-reported frequency of VPA was categorized into low VPA (<1 session/week), and high VPA (≥1 session/week). We used multivariate Cox regression analysis to examine the association of VPA categories with incident MCI and probable dementia events.

RESULTS: Participants in the high VPA category, compared with low VPA, experienced lower events rates (per 1000 person-years) of MCI (13.9 vs 19.7), probable dementia (6.3 vs 9.0), and MCI/probable dementia (18.5 vs 25.8). In the multivariate Cox regression model, high VPA, compared with low VPA, was associated with lower risk of MCI, probable dementia, and MCI/probable dementia (HR [95% CI]: 0.81 [0.68–0.97], 0.80 [0.63–1.03], and 0.82 [0.70–0.96]), respectively.

DISCUSSION: This study provides evidence that VPA may preserve cognitive function in high-risk patients with hypertension.

KEYWORDS
cognitive impairment, dementia, hypertension, mild cognitive impairment, physical activity

Highlights

- Hypertension is associated with an increased risk of cognitive impairment
- Physical activity (PA) is associated with a lower risk of decline in cognition
- The effect of ≥1 sessions of vigorous-intensity PA (VPA) per week was assessed
- This analysis included SPRINT MIND trial participants with high-risk hypertension
- ≥1 VPA sessions/week was associated with lower risk of future cognitive impairment

1 | BACKGROUND

Hypertension is a highly prevalent condition affecting one-third of adults globally and is an established risk factor for cardiovascular (CV) and cerebrovascular disease.[1–3] Additionally, it is estimated that more than 65 million people live with dementia worldwide, with this number projected to exceed 175 million by 2050.[4] Individuals with hypertension are at an increased risk of developing cognitive impairment including mild cognitive impairment (MCI), Alzheimer's dementia, and vascular dementia.[2,3] Hypertension is viewed as a key modifiable risk factor for cognitive impairment, Alzheimer's disease, and related dementias.[5] Evidence from the Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND) study showed intensive blood pressure control to be effective in preventing incident cases of cognitive impairment as a composite outcome.[6]

Previous studies have shown that physical activity (PA) can slow cognitive decline.[7–9] Multidomain intervention study protocols involve strategies such as blood pressure control, promotion of PA, and management of other risk factors to assess their combined impact on reducing the risk of dementia.[10–12] Yet the optimal volume and intensity of PA required for this benefit remain unclear.[8] Furthermore, uncertainties persist regarding the combined impact of PA intensity levels, the influence of baseline PA, and the shape of the dose-response curve on the protective effects of PA on cognition.[9,13,14] Crucially, focused research is necessary to identify the specific types of PA that effectively reduce the risk of dementia in high-risk older individuals.[14]

The present study aims to assess the impact of habitual vigorous physical activity (VPA) in the context of varied degrees of blood pressure control, as investigated in the SPRINT MIND study.[6] Additionally, this analysis facilitates a comparison of how VPA affects cognitive health among individuals with hypertension across diverse trial subgroups, including age (<75 vs ≥75 years), Black versus non-Black participants, severity of baseline hypertension, and the status of preexisting cardiovascular disease (CVD) and chronic kidney disease (CKD).[15] Therefore, the findings from this analysis could help fill various gaps in the existing literature regarding the effect of VPA on cognitive impairment among older and high-risk individuals with hypertension.

2 | METHODS

2.1 | Study design and population

In this post hoc analysis, we used data from the previously published SPRINT MIND study,[6] which was part of the SPRINT trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT01206062).[16,17] Briefly, SPRINT was a randomized, controlled, open-label trial that included 9361 nondiabetic U.S. adults at least 50 years of age, at high CVD risk, with hypertension and systolic blood pressure (SBP) between 130 and 180 mmHg at enrollment. SPRINT was conducted to test the effect of intensive (target SBP <120 mm Hg) versus standard (target SBP <140 mm Hg) treatment on a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from CV causes (the primary outcome), as well as renal and cognitive outcomes in individuals without diabetes or preexisting stroke. Individuals with a diagnosis of dementia (based on medical record review) or being treated with medications primarily used for dementia therapy were excluded. The trial was stopped early due to the analysis of the primary outcome showing a significant benefit of intensive SBP treatment compared to the standard treatment.[15] The SPRINT MIND study aimed to describe the effect of intensive blood pressure treatment on the rate of MCI and probable dementia compared with standard blood pressure treatment.[6] Enrollment began on November 8, 2010, and ended in March 2013. The study's design included planned cognitive assessments at baseline and at 2 and 4 years of follow-up, and at study closeout if it was over 1 year removed from the 4-year follow-up visit. However, at the time of the discontinuation of the SPRINT trial on August 20, 2015, many scheduled cognitive assessments for the fourth year had not been completed. These assessments were subsequently completed at the study's closeout and during the extended follow-up visits.[6]

The identified dataset was obtained from the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center. All participants provided written informed consent for participation in the trial. The trial was approved by the institutional review board (IRB) at each site. 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. The primary endpoint for our analysis was

adjudicated MCI and probable dementia, and our secondary endpoint was the composite of composite of MCI/probable dementia.

2.2 | Assessment of vigorous-intensity physical activity

Using a self-administered questionnaire, participants at enrollment were asked about their frequency of vigorous-intensity PA over the past 12 months 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 participate in vigorous activities." Then the following options were provided: (1) rarely or never, (2) 1 to 3 times per month, (3) 1 time per week, (4) 2 to 4 times per week, and (5) 5+ times per week. We categorized VPA into two groups, that is, <1 sessions/week (low VPA group) and ≥1 sessions/week (high VPA group).

2.3 | Ascertainment of cognitive impairment

A rigorous adjudication process for probable dementia at baseline and follow-up has been previously described in detail.[17] Briefly, trained and certified personnel administered in-person cognitive assessments that included the Montreal Cognitive Assessment (MoCA), a brief test of global cognitive function (range 0 to 30).[18] A preidentified proxy was administered the Functional Activities Questionnaire (FAQ), a 10-item assessment of functional abilities (range 0 to 30) for White participants with a MoCA score of <19 (for years of education < 12) or MoCA score < 21 (for years of education ≥ 12), or for non-White individuals with MoCA score < 17 (for years of education < 12) or MoCA score < 19 (for years of education ≥ 12), or those with a ≥5-point decrease in the MoCA score from a previous test. Individuals with scores of >0 on the FAQ or a 5-point Delayed Recall component on the MoCA score of ≤1 further tested using an extended cognitive battery that assessed attention/concentration, verbal and nonverbal memory, language, and executive functions. Additionally, all participants were assessed for depressive symptoms, perceived health status, and quality of life.[6]

2.4 | Covariates

Trained SPRINT MIND study personnel ascertained baseline sociodemographic data including age, sex, self-reported race/ethnicity, highest level of education attained, and health habits including smoking and alcohol use, medical history, and self-rated health. We categorized level of education into the following categories: (1) less than high school, (2) high school, (3) bachelor's degree, and (4) graduate degree or higher. Smoking was categorized into never, former, and current smoking status. Alcohol use was categorized based on the average number of drinks per day in the past 12 months as none, ≤1 drink per day (light drinking) or >1 drink per day (moderate to heavy drinking). Self-reported baseline moderate PA was categorized based on the average time spent per day doing moderate-intensity physical activities (eg, walking, vacuuming, or climbing a flight of stairs) into less versus more than 15 minutes per day. Participants also self-reported information on medical problems and current medications, including the number and classes of antihypertensive agents. During the study visit, participants' blood pressure, body weight, and height were measured by study personnel. All assays for laboratory data were performed at the single-site SPRINT central laboratory.[1]

RESEARCH CONTEXT

1. **Systematic review**: The authors reviewed the available literature using traditional (eg, PubMed) sources and meeting abstracts and presentations. The protective effect of physical activity (PA) on cognition has been studied and we have provided the relevant citations. Hypertension is associated with an increased risk of decline in cognition. However, research gaps remain regarding the adequate amount and volume of PA necessary for preserving cognition in this patient population.
2. **Interpretation**: Among individuals with high-risk hypertension, participation in at least one session of vigorous PA (VPA) per week was associated with lower risk of mild cognitive impairment and probable dementia. These results can help in public health messaging regarding the benefit of VPA, particularly in patients with hypertension who are at increased risk of cognitive decline.
3. **Future directions**: The manuscript highlights the need for additional prospective cohort studies and randomized trials with device-based PA measurement, and longer follow-up, to confirm and extend these findings.

2.5 | Inclusion and exclusion

We excluded participants who reported significant limitations in physical function, being confined in bed, being unable to perform self-care, or who reported inability to do usual activities (eg, work, study, housework family or leisure activities) ($n = 999$), those with missing VPA data ($n = 18$) or those missing any cognitive assessments ($n = 674$). After all exclusions ($n = 1691$), a total of 7670 participants were included in the final analysis.

2.6 | Statistical analysis

First, we compared demographic and clinical characteristics of participants in the low (<1 session/week) and high (≥1 session/week) VPA

groups using *t*-tests for continuous variables or chi-square tests for categorical variables.

We then used multivariable-adjusted Cox proportional hazards models with inverse probability weighting for exclusion to examine the association between VPA and incident-adjudicated cognitive outcomes (MCI, probable dementia, and MCI/probable dementia composite). We report the hazard ratio (HR) associated with the high VPA group relative to the low VPA group. We fit two Cox models: a minimally adjusted model (Model 1) that included age, sex, race/ethnicity, and level of education; and a second model (Model 2) additionally adjusted for smoking status, moderate physical exercise, alcohol use, depression, history of CVD, baseline SBP, baseline body mass index (BMI), number of antihypertensive medications at baseline, and study arm assignment. We imputed missing covariate data (≤1.1% for each variable) using multiple imputations by chained equations. Results from 10 iterations of 20 imputed datasets generated by predictive mean matching were combined for validity. Stabilized inverse probability weights conditioned on Model 2 covariates were generated by logistic regression for participants who were included in the analysis relative to those who were excluded based on criteria described above.

We additionally stratified results by the following prespecified groups: age (<75 vs ≥75 years), sex, race (Black vs non-Black participants), baseline SBP tertiles (≤132, >133 to <145, and ≥145 mm Hg), and status of preexisting CVD and CKD at baseline.

2.6.1 | Sensitivity analysis

We assessed the impact of VPA on cognitive impairment while accounting for the competing risk of death using Fine-Gray subdistribution hazard models. Furthermore, to mitigate the potential bias of nonparticipation in VPA due to poor physical function or health status, we adjusted for additional documented comorbidities in the SPRINT cohort, including osteoarthritis, chronic lower back pain, history of cancer, chronic liver disease or hepatitis, and overall self-rated general health (excellent, very good, good, or fair/poor). Finally, we excluded cases of MCI and probable dementia diagnosed during the first 2 years of follow-up to ensure that the observed association with cognitive impairment was not driven by undetected MCI events, particularly considering that baseline MCI in SPRINT MIND was not adjudicated.

A two-sided *P*-value of <0.05 was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc.) and the R statistical computing environment (version 4.1.2; http://www.r-project.org). Multiple imputations were completed with the mice package (version 3.15.0) for R.

2.6.2 | Data availability and ethics statement

We obtained the publicly available deidentified SPIRINT MIND data from the National Heart, Lung, and Blood Institute, https://biolincc.nhlbi.nih.gov/studies/sprint/. All participants provided written informed consent for participation in the trial. The SPRINT trial was approved by the institutional review board (IRB) at each site. The present analysis was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Wake Forest University School of Medicine.

3 | RESULTS

Overall, participants were aged 70.0 (9.2) years, 34.5% were women, 59.4% were White, and 59.3% reported engaging in VPA at least once weekly (high VPA category). Compared with the high VPA category, participants in the low VPA group were more likely to be female, current smokers, have less education, higher BMI, higher prevalence of CKD, and use more antihypertensive medications (Table 1).

Over a maximum follow-up of 7.4 (median [25%, 75%] = 4.5 [3.6, 5.9]) years, 570, 273 and 759 MCI, probable dementia, and MCI/probable dementia events were adjudicated, respectively. The incidence of MCI, probable dementia, and MCI/probable dementia among participants in the high VPA group compared with the low VPA group were 6.5% versus 8.8%, 3.1% versus 4.3%, and 8.7% versus 11.7%, respectively. Similarly, compared to participants in the low VPA group, those in the high VPA group experienced lower event rates (per 1000 person-years) of MCI (13.9 vs 19.7), probable dementia (6.3 vs 9.0), and MCI/probable dementia (18.5 vs 25.8) (Figure 1). The cumulative incidence rate of cognitive impairment outcomes was found to be significantly higher in the low VPA group when compared to the high VPA group (Supplement Figure).

After adjusting Cox regression models for sociodemographic factors (Model 1), the high VPA group had a significantly lower risk of MCI (HR [95% CI] = 0.80 [0.67–0.95]) and MCI/probable dementia (HR [95% CI] = 0.82 [0.70–0.94]) compared with the low VPA group (Figure 2). Higher VPA was similarly associated with lower risk of probable dementia, though the confidence interval prevented it from reaching statistical significance (HR [95% CI] = 0.80 [0.63–1.02]). Further adjustment for moderate PA, alcohol use, depression, and CV risk factors had minimal effect on the association of high VPA and cognitive impairment (Figure 2).

The analysis stratified by SPRINT randomization into standard and intensive treatment of SBP produced comparable results regarding the association of VPA and risk of cognitive outcomes, and there was no significant heterogeneity by treatment group assignment (Table 2). However, there was significant heterogeneity in associations with MCI and MCI/probable dementia by age group (<75 vs ≥75 years) and race (Black vs non-Black participants).

For example, the association with the MCI/probable dementia composite was moderately stronger among participants <75 years of age at baseline (HR [95% CI] = 0.77 [0.60–0.97] vs 0.89 [0.73–1.09]; interaction $P = 0.021$) and was driven exclusively by Black participants (HR [95% CI] = 0.63 [0.48–0.83] vs 0.98 [0.81–1.18]; interaction $P = 0.011$) (Table 3).

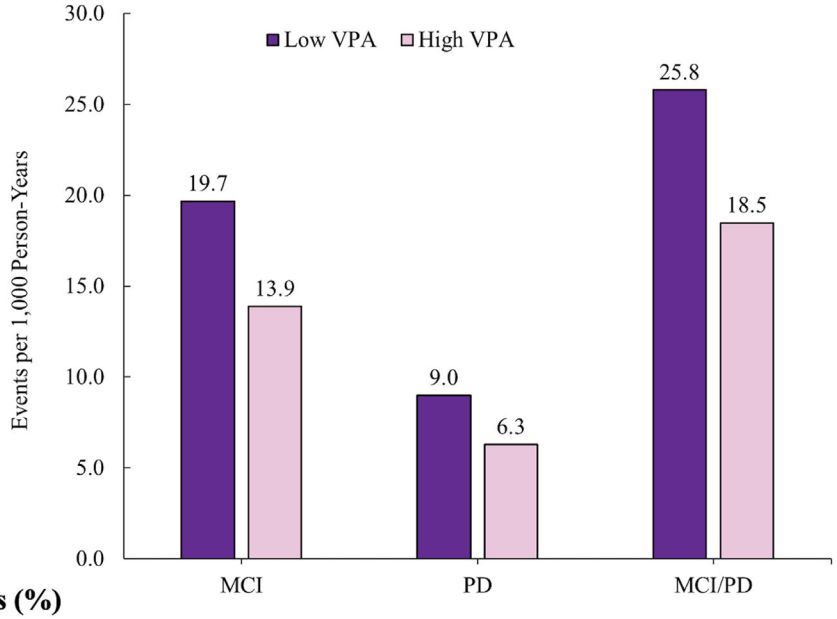
Participants included in and excluded from the analysis demonstrated similar age, blood pressure, and randomization to the intensive SBP lowering trial arm. However, excluded participants were more

TABLE 1 Baseline characteristics and study outcomes of the 7670 SPRINT MIND study participants by category of self-reported vigorous-intensity physical activity (VPA).

Variable	Full Cohort ($n = 7670$)	Low VPA (<1 times weekly) ($n = 3119$)	High VPA (≥1 times weekly) ($n = 4551$)	*P*-value*
Age, years, mean (SD)	68.0 (9.2)	68.2 (9.4)	67.8 (9.1)	0.100
Age ≥75 years, *n* (%)	2147 (28.0)	905 (29.0)	1242 (27.3)	0.104
Female, *n* (%)	2644 (34.5)	1282 (41.1)	1362 (29.9)	<0.001
Race or ethnic group, *n* (%)				<0.001
Non-Hispanic Black	2158 (28.1)	957 (30.7)	1201 (26.4)	
Hispanic	825 (10.8)	383 (12.3)	442 (9.7)	
Non-Hispanic White	4573 (59.6)	1741 (55.8)	2832 (62.2)	
Other	114 (1.5)	38 (1.2)	76 (1.7)	
Education level				<0.001
Less than high school	636 (8.3)	327 (10.5)	309 (6.8)	
High school	3891 (50.7)	1657 (53.1)	2234 (49.1)	
Bachelor's degree	1783 (23.2)	693 (22.2)	1090 (24.0)	
Graduate degree or higher	1360 (17.7)	442 (14.2)	918 (20.2)	
Smoking status, *n* (%)				0.002
Never	3465 (45.2)	1424 (45.7)	2041 (44.8)	
Former	3246 (42.3)	1263 (40.5)	1983 (43.6)	
Current	959 (12.5)	432 (13.9)	527 (11.6)	
Alcohol use, past 12 months, *n* (%)				<0.001
None	2564 (33.5)	1163 (37.4)	1401 (30.8)	
≤1 drink/day	3926 (51.3)	1534 (49.3)	2392 (52.7)	
>1 drink/day	1162 (15.2)	412 (13.3)	750 (16.5)	
Depression, *n* (%)	1255 (16.4)	551 (17.7)	704 (15.5)	0.012
Moderate-intensity PA, average duration				<0.001
<15 min/day	1276 (16.7)	894 (28.7)	382 (8.4)	
≥15 min/day	6384 (83.3)	2220 (71.3)	4164 (91.6)	
BMI, kg/m^2, mean (SD)	29.7 (5.6)	30.3 (6.0)	29.3 (5.2)	<0.001
Average SBP, mmHg, mean (SD)	145.2 (11.2)	145.5 (11.0)	145.0 (11.3)	0.070
Average DBP, mmHg, mean (SD)	80.2 (11.5)	80.0 (11.6)	80.4 (11.4)	0.160
Framingham Risk Score, mean (SD)	17.4 (2.5)	17.5 (2.5)	17.3 (2.5)	<0.001
History of cardiovascular disease, *n* (%)	1473 (19.2)	617 (19.8)	856 (18.8)	0.302
Chronic kidney disease, *n* (%)	2111 (27.5)	950 (30.5)	1161 (25.5)	<0.001
Creatinine, (mg/dL), mean (SD)	1.1 (0.3)	1.1 (0.4)	1.1 (0.3)	0.848
Estimated GFR, (mL/min/1.73 m^2)	71.8 (20.2)	71.4 (21.2)	72.1 (19.4)	0.185
Aspirin use, *n* (%)	3952 (51.5)	1558 (50.0)	2394 (52.6)	0.023
Randomized to intervention group, *n* (%)	3814 (49.7)	1540 (49.4)	2274 (50.0)	0.628
No. of antihypertensive medication classes, mean (SD)	1.8 (1.0)	1.8 (1.0)	1.7 (1.0)	<0.001

Note: Continuous variables are presented as means and standard deviations. Categorical variables are presented as counts and corresponding percentages.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; PA, physical activity; SBP, systolic blood pressure; SD, standard deviation; SPRINT MIND, Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension; VPA, vigorous-intensity physical activity.

**P*-value is for the comparison between the two categories of VPA, tested with the chi-square test for categorical variables and ANOVA for interval variables.



No. Events (%)	MCI	PD	MCI/PD
Low VPA	275 (8.8)	134 (4.3)	365 (11.7)
High VPA	295 (6.5)	139 (3.1)	394 (8.7)

FIGURE 1 Rate of cognitive impairment events by category of vigorous-intensity physical activity (VPA). Low VPA denotes VPA <1 session/week. High VPA denotes ≥1 session/week. MCI, mild cognitive impairment; PD, probable dementia.

likely to be female, have lower educational attainment, report current smoking status, and experience a higher prevalence of depression, and prevalent CKD and CVD. In contrast, included participants reported higher levels of alcohol consumption and reported engaging in more moderate-intensity PA (Supplemental Table S1).

The hazard ratios, factoring in the competing risk of death, remained consistent with our main analysis in both direction and magnitude (Supplement Table S2). Additional adjustments for comorbidities in Model 2 (Supplement Table S3) and the exclusion of MCI cases identified in the first two years (n = 205) did not significantly change the results (Supplement Table S4).

Different self-reported frequencies of VPA were associated with a lower risk of cognitive impairment outcomes (Supplement Table S5).

4 | DISCUSSION

In this post hoc analysis of the SPRINT MIND study, we investigated the association of self-reported VPA at a threshold of ≥1 session per week on MCI and probable dementia among individuals with high-risk hypertension undergoing blood pressure control. Our findings show that individuals who reported engaging in VPA at a frequency of one or more sessions per week had a lower risk of MCI and probable dementia when compared to those who reported engaging in less than one session of VPA per week. Importantly, this association remained significant regardless of the intensity of SBP treatment. The results were also consistent across all the subgroups we included, with some heterogeneity by age and race for both MCI and probable dementia.

The benefit of PA in the management of hypertension is well-documented and is a vital component of treatment.[19,20] Additionally, PA has been identified as a key modifiable factor for delaying cognitive impairment including dementia; however, the required quantity of PA is unknown.[8] Health-conscious individuals frequently embrace an active lifestyle to enhance their well-being. It is therefore crucial to explore the diverse facets of PA that may decrease the risk of cognitive impairment. A previous study showed that engaging in moderate-intensity PA once a week is associated with a reduced incidence of dementia among those 50 years and older.[21] It has been suggested that vigorous-intensity PA may confer even higher risk reduction than moderate-intensity PA.[8] Furthermore, an inverse dose-response association between PA and incidence of dementia has been previously reported.[21,22] However, most of the existing studies included heterogeneous quantification of PA needed for prevention of cognitive decline.[7–9] In this analysis, we characterized the frequency of VPA associated with a lower risk of future cognitive impairment. While research focusing on the potential protective benefit of VPA on cognition is currently limited, our findings are consistent with a previous study that found VPA corresponding to 9 metabolic equivalents (METs) for 1.3 hours weekly was associated with a reduction in the risk of developing dementia among older individuals.[23]

Due to the relatively lower cases of probable dementia, our study likely lacked the adequate statistical power to detect the benefit of VPA on the risk of probable dementia. However, the point estimates for probable dementia we found were similar to results for MCI and the composite of the MCI/probable dementia, which were robust and imply clinical significance. MCI represents an intermediate state

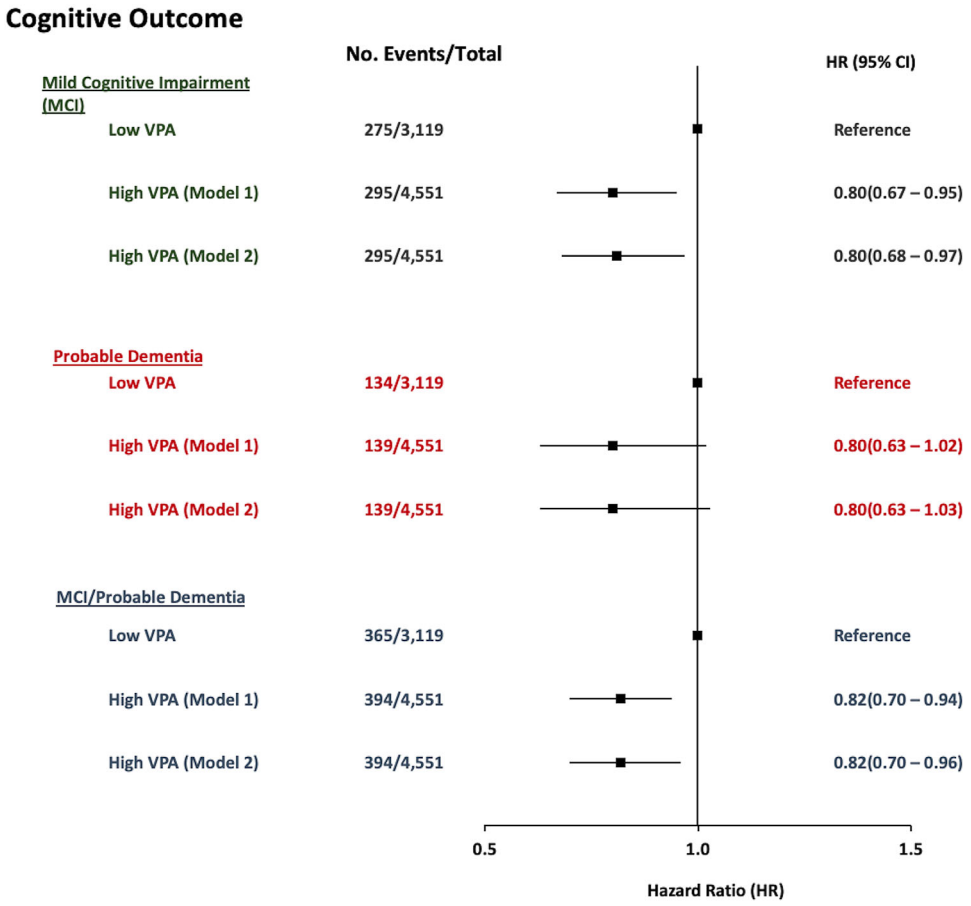


FIGURE 2 Vigorous-intensity physical activity (VPA) and risk of cognitive impairment outcomes. Low VPA denotes VPA frequency of <1 session/week. High VPA denotes VPA frequency of ≥ 1 session/week. Model 1 adjusted for age, sex, race/ethnicity, and level of education (<high school, high school, college degree, graduate degree). Model 2 adjusted for Model 1 plus smoking status (never/former/current), moderate physical exercise, alcohol use (none, moderate, heavy), depression, history of cardiovascular disease, baseline average systolic blood pressure, baseline body mass index, number of classes of antihypertensive medications at baseline, and study arm assignment. CI, confidence interval.

between cognitive decline as part of the aging process and dementia or Alzheimer's disease.[24] The overall rate of progression from MCI has been estimated to be 20%–40%, [25,26] but reversion of MCI to normal cognition is also possible in some individuals.[27]

The most recent (2018) U.S PA guidelines recommend a weekly minimum of 150 min of moderate-intensity or 75 min of VPA,[28] and adherence to these guidelines is associated with reduced incidence of dementia.[29] However, these guidelines have been criticized for being arbitrary, with the suggestion that levels lower than these thresholds may be sufficient to confer health benefits.[30–32] Yet, only about one in five US adults meet these minimum recommended levels of PA.[33] It is therefore notable that almost 60% of the participants in our study reported engaging in VPA at least once a week, even among the subgroup of those aged ≥75 years. This suggests that older individuals, upon recognizing the advantages of VPA, may become more inclined to engage in regular higher-intensity exercise.

The mechanisms through which PA may lead to protection against cognitive decline involve increased production of ketone bodies and lactate, and myokines from the muscles, as well as promoting neurotrophic factors such as the brain-derived neurotrophic factor, all of which may be protective against cognitive decline.[34] Other mechanisms involve the salutary effect of PA on hippocampal neurogenesis, synaptic plasticity, and oxidative stress.[29] A combination of these exercise-induced physiologic changes has a protective effect on the pathogenesis of dementia by reducing the deposition of amyloid beta deposition.[34] Moreover, PA has a blood pressure-lowering effect among those with hypertension in addition to improving CV health via its effect on serum glucose, heart rate, endothelial function, and parasympathetic tone.[35]

In SPRINT MIND, the benefit of VPA did not differ based on intensity of SBP treatment. While intensive SBP treatment compared to standard treatment was associated with reduced CV risk in SPRINT, it did not result in a significant reduction in the risk of probable dementia.[6,15] PA stands out as a cost-effective and low-risk intervention that can potentially help in delaying cognitive decline in those with hypertension.[2] In our subgroup analysis according to the SPRINT subgroups, the effect of VPA for reduced risk of cognitive impairment was retained with varying strengths. For instance, despite comparable baseline participation in VPA in both those with and without prior CVD, among individuals with prior CVD, VPA appeared to have stronger

TABLE 2 Risk of cognitive impairment and vigorous-intensity physical activity (VPA) by treatment assignment reference: VPA frequency <1/week.

Cognitive impairment outcome	Standard treatment (SBP goal <140 mm Hg) (*n* = 3856)				Intensive treatment (SBP goal <120 mm Hg) (*n* = 3814)			Interaction *P*-value[a]
	No. Event/ Total (%)	Model	HR (95% CI)	*P*-value	No. Event/ Total (%)	HR (95% CI)	*P*-value	
MCI	570 (7.4%)	Model 1	0.84 (0.67–1.06)	0.145	252 (6.6%)	0.75 (0.58–0.96)	0.025	0.286
		Model 2	0.87 (0.68–1.11)	0.257		0.78 (0.59–1.02)	0.065	
Probable dementia	273 (3.6%)	Model 1	0.77 (0.56–1.06)	0.110	118 (3.1%)	0.84 (0.58–1.23)	0.370	0.801
		Model 2	0.73 (0.53–1.01)	0.061		0.97 (0.65–1.44)	0.873	
Composite of MCI/ probable dementia	759 (9.9%)	Model 1	0.83 (0.68–1.02)	0.073	341 (8.9%)	0.80 (0.64–1.00)	0.048	0.500
		Model 2	0.84 (0.68–1.03)	0.097		0.85 (0.67–1.08)	0.176	

Note: Model 1 adjusted for age, sex, race/ethnicity, and level of education (<high school, high school, college degree, graduate degree).
Model 2 adjusted for Model 1 plus smoking status (never/former/current), moderate physical exercise, alcohol use (none, moderate, heavy), depression, history of cardiovascular disease, baseline average systolic blood pressure, baseline body mass index, number of classes of antihypertensive medications at baseline, and study arm assignment.
Abbreviations: CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; SBP, systolic blood pressure.
[a]Interaction *P* for treatment assignment and physical activity category was calculated using Model 2.

association with reduced risk of cognitive impairment. Although the reasons for this is unclear, this result is consistent with data from the English Longitudinal Study of Ageing (ELSA) that showed among older individuals that the risk of dementia associated with CV risk factors was reduced by PA.[36] Additionally, there was significant heterogeneity in our results by age group and race, which showed that associations were driven primarily by those <75 years of age and those of Black race. Possible explanations for the difference we observed in the above subgroups may include survivor bias among those older than 75 years, and higher prevalence of risk factors for cognitive impairment among low VPA Black participants. Notably, the protective impact of VPA was more pronounced for participants <75 years of age (where VPA was highest) and for the prevention of MCI. More studies are needed to investigate the differential association of PA with cognitive impairment in these subgroups.

Strengths of our study include its large sample size, prospective study design, rigorously adjudicated cognitive impairment outcomes in the setting of a randomized clinical trial, and the use of statistical techniques to mitigate bias resulting from differential attrition or missing data. However, some limitations should be considered. First, self-reported VPA is a crude measure and is prone to misclassification, and to recall and social desirability biases. Additionally, various confounding factors exist in the association between VPA and cognitive impairment. Although we made every effort to address and control these factors in our analysis, the potential for confounding still persists. Nevertheless, we believe robust conclusions can be drawn from our study. Notably, self-reported PA is often the only information available to clinicians. Thus, given that we still found strong associations between self-reported VPA and cognitive impairment, it clearly has at least some clinical relevance. Future studies would be strengthened by the use of objective measures of PA, such as accelerometers or other devices. Secondly, our analysis was based on baseline VPA data and does not take into account changes in the level of participation in VPA during follow-up which may impact cognitive outcomes. Third, our analysis did not include the potential benefit of light and moderate PA or the potential negative effect of sedentary behavior on cognitive status. Fourth, while SPRINT MIND excluded individuals with prevalent dementia, prevalent MCI at the time of enrollment was not adjudicated. Finally, the results from this study cannot be generalized to populations not represented in SPRINT such as those with diabetes mellitus, stroke, or without hypertension.

In conclusion, this study provides evidence that self-reported VPA may preserve cognitive function in high-risk patients with hypertension. To validate and expand upon these findings, future prospective cohort studies and randomized trials incorporating device-based PA measurements, longer observational periods, and more diverse participant populations are needed.

AUTHOR CONTRIBUTIONS

Dr. Kazibwe, Dr. Shapiro, and Dr. Yeboah conceived and designed the study, and also conducted the preparing, reviewing, and editing the original manuscript draft. Dr. Kazibwe and Dr. Schaich performed statistical analysis and accept full responsibility for the work and/or the

TABLE 3 Association of incident cognitive impairment and vigorous physical activity in the SPRINT MIND study by subgroup.

	MCI				Probable dementia				MCI/Probable dementia			
Subgroups	Low VPA No. Events/N	High VPA No. Events/N	HR (95% CI)	Interaction *P*-value[a]	Low VPA No. Events/N	High VPA No. Events/N	HR (95% CI)	Interaction *P*-value[a]	Low VPA No. Events/N	High VPA No. Events/N	HR (95% CI)	Interaction *P*-value[a]
Age, years												
<75, *n* = 5523	136 /2214	125 /3309	**0.76 (0.58, 0.99)**	0.033	52 /2214	45 /3309	0.69 (0.45, 1.05)	0.207	169 /2214	158 /3309	**0.77 (0.60, 0.97)**	0.021
≥75, *n* = 2147	139 /905	170 /1242	0.91 (0.72, 1.15)		82 /905	94 /1242	0.83 (0.62, 1.12)		196 /905	236 /1242	0.89 (0.73, 1.09)	
Sex												
Male, *n* = 5026	173 /1837	204 /3189	**0.79 (0.64, 0.98)**	0.630	68 /1837	96 /3189	0.94 (0.68, 1.30)	0.124	216 /1837	273 /3189	0.84 (0.70, 1.02)	0.770
Female, *n* = 2644	102 /1282	91 /1362	0.87 (0.63, 1.19)		66 /1282	43/1362	**0.60 (0.40, 0.90)**		149 /1282	121 /1362	0.79 (0.60, 1.03)	
Race												
Black, *n* = 2269	120 /1015	88 /1254	**0.65 (0.48, 0.89)**	0.031	47 /1015	24 /1254	**0.52 (0.31, 0.85)**	0.071	151 /1015	103 /1254	**0.63 (0.48, 0.83)**	0.011
Non-Black, *n* = 5401	155 /2104	207 /3297	0.97 (0.77, 1.21)		87 /2104	115 /3297	0.91 (0.67, 1.22)		214 /2104	291 /3297	0.98 (0.81, 1.18)	
Prior CKD												
Yes, *n* = 2111	106 /950	93 /1161	0.84 (0.62, 1.14)	0.884	68 /950	53/1161	0.69 (0.47, 1.02)	0.229	150 /950	134 /1161	0.83 (0.64, 1.07)	0.839
No, *n* = 5559	169 /2169	202 /3390	0.82 (0.66, 1.02)		66 /2169	86 /3390	0.91 (0.65, 1.28)		215 /2169	260 /3390	0.83 (0.68, 1.02)	
Prior Clinical CVD												
Yes, *n* = 1222	50 /498	41 /724	**0.59 (0.37, 0.95)**	0.174	25 /498	27 /724	0.83 (0.47, 1.47)	0.936	69 /498	63 /724	0.67 (0.46, 0.98)	0.233
No, *n* = 6448	225 /2621	254 /3827	0.87 (0.72, 1.06)		109 /2621	112 /3827	0.77 (0.59, 1.02)		296 /2621	331 /3827	0.87 (0.73, 1.03)	
SBP Tertile, mm Hg												
<132, *n* = 2573	91 /1039	86 /1534	0.81 (0.59, 1.13)	0.274	41 /1039	34 /1534	0.82 (0.49, 1.36)	0.177	118 /1039	111 /1534	0.85 (0.63, 1.13)	0.187
>132 to <145, *n* = 2492	76 /985	103 /1507	0.97 (0.70, 1.34)		31 /985	47 /1507	0.99 (0.62, 1.58)		96 /985	134 /1507	0.98 (0.74, 1.31)	
≥145, *n* = 2605	108 /1095	106 /1510	0.75 (0.56, 1.00)		62 /1095	58 /1510	**0.64 (0.44, 0.93)**		151 /1095	149 /1510	**0.73 (0.57, 0.93)**	

Note: Boldface shows *P*-values of <0.05. Reference group in each subgroup is low VPA, which is defined as VPA frequency <1/week. High VPA is defined as VPA frequency ≥1/week.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; MCI, mild cognitive impairment; SBP, systolic blood pressure; VPA, vigorous physical activity.

[a]Interaction *P* for treatment assignment and physical activity category was calculated using Model 2, which adjusted for age, sex, race/ethnicity, and level of education (<high school, high school, college degree, graduate degree), smoking status (never/former/current), moderate physical exercise, alcohol use (none, moderate, heavy), depression, history of cardiovascular disease, baseline average systolic blood pressure, baseline body mass index, number of classes of antihypertensive medications at baseline, and study arm assignment.

conduct of the study. All authors were involved in writing the paper and gave final approval for the submitted and published versions.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest related to this manuscript. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided written informed consent for participation in the trial. The trial was approved by the institutional review board (IRB) at each site.

ORCID

Richard Kazibwe https://orcid.org/0000-0001-7085-3373

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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