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### Physical Activity Frequency and Risk of Incident Stroke in a National US Study of Blacks and Whites

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#### Abstract

**Background and Purpose**—Regular physical activity is an important recommendation for stroke prevention. We compared the associations of self-reported physical activity (PA) with incident stroke in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study.

**Methods**—REGARDS recruited 30,239 US blacks (42%) and whites, aged 45 with follow-up every six months for stroke events. Excluding those with prior stroke, analysis involved27,348participants who reported their frequency of moderate-vigorous intensity PA at baseline according to three categories: none (physical inactivity), 1–3 times/week and 4 times/ week. Stroke and TIA cases were identified during an average of 5.7 years of follow-up. Cox proportional hazards models were constructed to examine whether self-reported PA was associated with risk of incident stroke.

**Results**—Physical inactivity was reported by 33% of participants and was associated with a hazard ratio (HR) of 1.20 ([95% confidence intervals 1.02–1.42], p = 0.035). Adjustment for demographic and socioeconomic factors did not affect HR, but further adjustment for traditional stroke risk factors (diabetes, hypertension, body mass index, alcohol use and smoking) partially attenuated this risk (HR 1.14 [0.95–1.37], p = 0.17). There was no significant association between PA frequency and risk of stroke by sex groups although there was a trend towards increased risk for men reporting PA 0–3 times a week compared to 4 or more times a week.

**Conclusions**—Self-reported low PA frequency is associated with increased risk of incident stroke. Any effect of PA is likely to be mediated through reducing traditional risk factors.

Disclosures None.

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#### Keywords

stroke; physical exercise; stroke prevention

Stroke is a leading cause of disability in the United States and the fourth leading cause of mortality<sup>1</sup> with total incidence expected to escalate in the coming decades with the rapidly ageing population<sup>2</sup>. Adults who make healthy lifestyle choices have an 80% lower risk of stroke when compared to those who do not<sup>3</sup>, indicating that advances can still be made in primary prevention of stroke. An important component of a healthy lifestyle is regular physical activity (PA), as recommended by the "Physical Activity Guidelines for Americans"<sup>4</sup>, which is associated with lower risk of stroke<sup>5, 6</sup>. Recent data from the 2010 National Health Interview Survey revealed that 49% of Americans do not meet these Physical Activity Guidelines<sup>7</sup>. There is considerable evidence from prospective and case-controlled studies that higher self-reported PA levels are associated with a reduced risk of stroke<sup>1, 8</sup>.

Physical inactivity has been identified as the second leading risk factor for stroke following hypertension in a multinational case-control study (INTERSTROKE), finding a population-attributable risk of 28.5%<sup>9</sup>. Although the precise amounts and type of exercise required to prevent stroke are unclear, meta-analyses conclude that "regular" PA reduces the risk of stroke by 25–30% when compared with the least active people<sup>8, 10</sup>. Recent evidence is emerging that there may be differences between sexes with vigorous PA associated with decreased risk of stroke in men<sup>11</sup> but not women<sup>12</sup>. Many large prospective studies investigating the association between PA and stroke have involved only women or men, and often only in limited locations or professions<sup>13–16</sup>. The aim of this study was to investigate the potential for PA to reduce incident stroke in a large, national multi-racial prospective cohort study of men and women.

#### Materials and Methods

The REasons for Geographic and Racial Differences in Stroke (REGARDS) study, a national, population based, longitudinal study of 30 239 Americans, was designed to determine the causes for the excess stroke mortality in African Americans and those living in the Southeastern US<sup>17</sup>. Participants aged 45 years and over were recruited by mail and telephone between 2003 and 2007 from a commercially available list of residents with over sampling of blacks and residents of the southeastern Stroke Belt, an area with higher stroke mortality rates than the remaining United States<sup>18</sup>. Within the Stroke Belt, there is a region along the coastal plain of North Carolina, South Carolina and Georgia that has even higher stroke mortality than the remainder of the Stroke Belt, and this area is identified as the Stroke Buckle<sup>19</sup>. Demographic information and medical history were obtained by telephone interview followed by an in-home visit to obtain physical measurements. Cerebrovascular disease risk factors were body mass index, smoking status (never versus past versus current use of cigarettes), alcohol use (heavy: 7 drinks/week for women, 14 per week for men; moderate: 1-7 for women, 1-14 for men; and none), diabetes (fasting glucose >126 ml/dL or non-fasting glucose >200 ml/dL, or self-reported use of oral hypoglycemic medications or insulin) and hypertension (systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg or self-reported use of antihypertensive medications). Participants are contacted every 6 months by telephone to assess potential stroke, with retrieval and central physician adjudication of medical charts of suspected strokes. Consent was obtained verbally and later in writing. All involved Institutional Review Boards approved the study methods.

Of the 30 239 REGARDS participants, follow up data were available for 29 643. Of these, we excluded 1 854 participants due to prevalent stroke, and 441 who had not answered the PA question.

#### Assessment of physical activity

At enrollment, participants reported their usual PA frequency using the following question: "How many times per week do you engage in intense physical activity, enough to work up a sweat?" Physical activity, in this context, could involve leisure time, commuting and occupational PA. Responses were categorized into 3 groups: 1 = no times per week, 2 = 1 to 3 times per week, 3 = 4 or more times per week. Although geographic region and season may influence the intensity of PA required to work up a sweat, this widely used measure of PA is well validated<sup>20, 21</sup>, can include either aerobic or resistance training and has been used in similar studies such as the National Health And Nutrition Examination Survey<sup>22</sup> and similar questions have been used in other longitudinal cohort studies<sup>13, 23</sup>. The "sweat question" has been shown to correlate with measures of physical fitness, such as maximal oxygen uptake and treadmill time during a maximal exercise fitness test<sup>24, 25</sup>. This categorization of PA is appropriate because the effects of PA on stroke risk are more pronounced with moderate-vigorous rather than light PA<sup>8, 11</sup> and allows analysis of the dose-response relationship between PA frequency and risk of stroke.

#### Stroke events

Incidence of stroke is confirmed in a three-stage process which has been described previously<sup>26</sup>. Briefly, reports of possible stroke during follow-up result in the retrieval of medical records that are centrally adjudicated by at least 2 physician members of a committee of stroke experts to confirm that the case meets the WHO definition<sup>27</sup>. Events not meeting this definition due to a duration of symptoms <24 hours and neuroimaging consistent with acute ischemia or hemorrhage were classified as "clinical strokes", or "probable strokes" if adjudicators agreed that event was likely a stroke or death related to stroke but information was incomplete for WHO or clinical classification. Strokes were further classified as ischemic or hemorrhagic. Participants who reported a diagnosis of TIA were also included in this analysis as a stroke-event.

#### Statistical analysis

Cox proportional hazards analysis was used to determine the hazard ratios (HR) and 95% confidence intervals (CIs) for the association between PA and incident stroke/TIA. Models were initially adjusted for age, sex, race and age-race interaction, then for socioeconomic factors (income and education). An additional model was adjusted for stroke risk factors (diabetes, hypertension, body mass index, alcohol use and smoking status). A final model took into account the effect of physical health limitations on incident stroke for those people who answered yes to either one or both of the following questions: "Does your health limit moderate activities such as moving a table, pushing a vacuum cleaner, bowling or playing golf?", "Does your health limit you climbing several flights of stairs?"

The protective level of PA was defined as taking part in exercise 4 times or more per week, in accordance with the INTERSTROKE study<sup>9</sup>.

#### Results

Table 1 shows the baseline characteristics of the REGARDS participants by PA category. Participants who were more physically active tended to be male, white, have higher levels of education, higher income and had lower BMI and prevalence of diabetes.

Participants were followed for a mean of 5.7 years, and there were 918 confirmed incident stroke and TIA cases. There was a significant association between PA and incident stroke/ TIA as demonstrated in Figure 1. After adjustment for age, sex, race and age-race interaction, the HR for stroke/TIA for those undertaking no PA was 1.20 (95% confidence interval [CI]: 1.02 to 1.42) and for PA1-3x/wk, the HR was 1.16 (95% CI: 0.98 to 1.42). After adjustment for region, urban/rural residence and socioeconomic status (SES), the significant association remained with similar HR of 1.20(95% CI: 1.01 to 1.42) for no PA and 1.14 (95% CI: 0.96 to 1.35) for 1-3x/wk. There was a dose dependent relationship, with PA 1-3x/wk offering less protection against stroke than 4x/wk. Further adjustment for stroke risk factors attenuated the effect by 30% to 1.14 (95% CI: 0.95 to 1.37), making the association statistically insignificant. The final adjustment for physical limitations did not change the HRs further.

The association between PA frequency and incident stroke/TIA was further investigated by comparing the risk of incident stroke in those who report being physically active 4x/wk to those reporting PA 0–3x/wk. After adjustment for age, sex, race and age-race interaction, the HR for stroke/TIA was 1.18 (95% CI: 1.01, 1.36). This was partially attenuated after adjustment for region, urban/rural residence and SES (HR 1.17;95% CI (0.99, 1.36) and the associations were statistically insignificant after further adjustment.

Analyses were repeated separately for stroke type (ischemic versus haemorrhagic), with no difference in the results obtained [data not shown].

The protective effect of PA has been reported to differ between men and women<sup>28</sup> but the interaction between sex and PA was not significant in this analysis (p = 0.22), perhaps due to insufficient power. To investigate this further we stratified our results by sex to investigate whether this revealed a difference in risk of incident stroke in our cohort (see Table 2). Men who took part in PA 1-3x/wk compared with 4x/wk had greater incidence of stroke. This relationship was significant for the demographic model with a hazard ratio of 1.30 (95% CI: 1.05 to 1.61) and also for the SES model with a hazard ratio of 1.26 (95% CI: 1.00 to 1.59). Further adjustment for stroke risk factors and physical limitations did not attenuate the effect for men (adjustment for physical limitations not shown, results are identical to the risk factor model for men). These findings contrast with those observed in women, with no significant association between PA and incident stroke although there was a trend towards a similar reduction in risk for PA 1-3 times/week and 4 or more times a week compared to none. Additional analysis was performed combining both 1-3 and 4x/wkcategories to compare any PA to none. This demonstrated a lack of association between PA frequency and incident stroke, with the demographic model demonstrating no effect of PA on stroke (women, hazard ratio 1.15 (95% CI: 0.95 to 1.39); men, hazard ratio 1.05 (95% CI: 0.86 to 1.29).

There was no significant interaction between race and physical activity therefore results were not stratified for race.

#### Discussion

The results of this large, population-based prospective cohort study confirm that regular PA is associated with a decreased risk of incident stroke and TIA. This effect was seen for 4x/ wk compared to no PA, with 1-3x/wk showing a trend toward being less protective than 4x/wk although not significantly different. This confirms previous reports suggesting that exercising four times a week is associated with a reduced risk of stroke<sup>9</sup> and other meta-analyses which suggest that moderate intensity PA reduces the risk of stroke<sup>8</sup>. <sup>11</sup>.To the best of our knowledge, this is the first study to quantify the protective effect of PA on incident

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stroke in such a large multiracial cohort with equal representation of men and women in the US.

The association between PA and incident stroke was present after adjustment for demographic and SES factors, but further adjustment for stroke risk factors attenuated the relationship somewhat. This suggests that PA interacts with stroke risk factors, such as diabetes, hypertension, body mass index, alcohol use and smoking status. In our cohort, there was an unexpected finding in the prevalence of risk factors amongst the groups: those who regularly participated in PA were more likely to be moderate or heavy consumers of alcohol. Both PA groups were, however, less likely to smoke, have hypertension or have a high BMI, and had significantly less diabetes than the non-exercisers. Thus, reduced stroke risk in the exercisers is likely to be explained for the most part by the positive effect that PA has on BMI, hypertension and diabetes, although PA also has the potential to reduce stroke risk due to other biological actions (e.g. improving endothelial function<sup>29</sup> and reducing platelet activity<sup>30</sup>).

Consistent with a previous report<sup>28</sup>, we found a difference between PA and risk reduction when results were stratified according to sex. There was no protective effect of 1-3x/wk or 4x/wk on incident stroke/TIA in women, which was confirmed by collapsing both activity categories and still finding no association. The opposite was true for men, with increased hazard ratios for 1-3x/wk (but not 0 times per week) compared with 4x/wk, although this trend was not significant (p = 0.09). Combining both PA categories for men attenuated the association completely, confirming that PA 4x/wk is required to reduce the risk of incident stroke in men.

Our PA measure enabled us to classify participants based on the frequency of moderate to vigorous PA rather than duration. Nevertheless, there was a significant difference in stroke risk between those individuals reporting PA1–3 or 4 times per week, confirming that regular moderate to heavy intensity PA is protective against stroke and TIA<sup>11</sup>. This was further substantiated with subsequent analysis which compared PA 4x/wk to 0–3 x/wk and found a significant association with a HR of 1.18; exercising "intensely" at least four times a week was required for PA have a protective effect in this cohort, as previously reported<sup>11</sup>. Separate analyses by stroke subtype showed similar results. This is consistent with other reports that have considered risk of stroke separately for all stroke, as well as haemorrhagic and ischaemic strokes with similar findings<sup>8, 9, 12, 31</sup>.

An important consideration in the interpretation of these results is the potential limitation of our measurement of PA. Although the "sweat question" is a valid tool to assess PA in large cohort studies such as REGARDS, it does not include certain key elements to consider when quantifying PA. Firstly, asking specifically about intense PA which works up a sweat may prevent participants from including activities with a light or moderate intensity such as walking or cycling, which may underestimate the amounts of PA actually performed. Secondly, our measure of PA does not quantify the duration or type of PA, nor the precise number of sessions: responses for those who reported exercising once per week were included in the same category as those exercising three times per week. It is possible that the inability to find an association between PA and incident stroke in women in our sample is due to the limitation of our PA measure to capture walking and other low intensity PA; it has previously been reported that walking, but not vigorous PA, is associated with reduced stroke risk in women<sup>12</sup>. Future large-scale cohort studies should consider incorporating measures of PA that allow quantification of intensity, duration and frequency, such as the International Physical Activity Questionnaire<sup>32</sup> or accelerometry.

Another limitation of the study was that the classification of PA category was performed at entry into the study, with stroke events occurring several years later. While participants may have changed their PA habits during this time, the advantage of this method is that responses are not influenced by recall bias if they were asked to report their usual PA habits soon after diagnosis of stroke, which frequently leads to overestimating of PA<sup>5</sup>. Another potential limitation is that stroke cases could have been missed if participants did not seek medical care or report a suspected stroke. However, medical records were obtained for 89% of potential stroke events, including those instances where participants sought medical attention for stroke-like symptoms. It is possible that incident stroke may have been underreported, but few stroke events are likely to have been missed. The strengths of this study include the rigorous confirmation of stroke incidence with review of medical records with stroke experts, and participation in follow up interviews was very high. Furthermore, other strengths include the large sample size representative of blacks and whites, with greater reported to those in areas of high stroke mortality.

In conclusion, regular moderately-vigorous self-reported PA is associated with a reduced risk of stroke and TIA in this large multi-racial prospective cohort study. When considering men, exercising at an intensity sufficient to work up a sweat at least 4 times a week is more protective than exercising 1–3 times per week. Any effect of PA is likely to be mediated through reduction of traditional risk factors such as body mass index and diabetes.

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#### Figure 1.

PA frequency and risk of incident stroke/TIA. The initial regression model included adjustment for demographics (age, sex, race and age-race interaction) and then further adjustments were performed for 3 additional models: SES (including region, urban/rural residence); stroke risk factors (diabetes, hypertension, BMI, alcohol use, smoking); presence of physical limitations (unable to climb stairs, perform moderate physical activities). \* denotes significant association between PA and stroke (P<sub>trend</sub> < 0.05).

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# Table 1

Baseline Characteristics of Study Participants by Physical Activity Frequency

	All N=27348	4x/wk n=8187	1–3x/wk n=10003	None n=9158	p- value <sup>*</sup>
Age, mean (SD)	64.6(9.39)	64.8(9.13)	63.6(9.22)	65.6(9.71)	<0.0001
Black, %	40.4	36.1	40.5	44.2	<0.0001
Female, %	55.5	46.1	55.0	64.3	<0.0001
Region, %					
Belt	34.7	34.9	34.5	34.7	0.3899
Buckle	21.0	21.6	21.0	20.6	
Nonbelt	44.3	43.5	44.5	44.7	
Urban Group, %					
Urban	78.1	75.1	78.7	80.1	<0.0001
Mixed	11.0	12.2	10.8	10.2	
Rural	10.9	12.7	10.5	9.7	
Annual Income, %					
Less than 20K	17.1	15.2	14.2	22.1	<0.0001
20–34K	23.9	23.2	23.1	25.4	
35-74K	30.5	31.3	32.6	27.3	
75K and above	16.5	18.2	19.2	12.1	
Refused	12.0	12.1	10.9	13.1	
Highest Education, %					
Less than HS	11.6	11.0	9.5	14.6	<0.0001
HS graduate	25.7	25.5	23.4	28.3	
Some college	26.9	25.9	27.1	27.5	
College Grad and above	35.8	37.6	40.0	29.6	
BMI kg/m <sup>2</sup> , mean(SD)	29.3(6.18)	28.2(5.44)	29.3(5.95)	30.3(6.86)	<0.0001
Smoke, %					
Current	14.2	12.7	13.0	16.7	<0.0001
Never	45.8	44.4	48.4	44.2	
Past	40.0	42.9	38.6	39.1	
Alcohol Use, %					

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	All N=27348	4x/wk n=8187	1-3x/wK n=10003	None n=9158	p- value <sup>*</sup>
Heav	y 4.1	5.2	3.7	3.6	<0.0001
Modera	e 34.1	36.8	36.6	28.8	
Nor	le 61.8	58.0	59.7	67.6	
Diabetes, %	21.0	17.5	19.7	25.4	<0.0001
Hypertension, %	57.8	53.2	56.1	63.9	<0.0001

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È -m \* p-values based on ANOVA tests for mean differences and Chi-square tests for differences in proportions

#### Table 2

Association between PA frequency and incident stroke/TIA in women and men

	No. of cases	Demographic model	SES model	Risk factor model
Women				
4x/wk (n = 3777)	105	1	1	1
1-3x/wk (n = 5498)	146	1.00 (0.78–1.28)	0.99 (0.76–1.29)	0.99 (0.75–1.30)
None (n = 5890)	198	1.15 (0.91–1.46)	1.19 (0.93–1.52)	1.10 (0.85–1.43)
p-value for trend		0.20	0.12	0.40
Men				
4x/wk (n = 4410)	149	1	1	1
1-3x/wk (n = 4505)	188	1.30 (1.05–1.61)	1.26 (1.00–1.59)	1.29 (1.02–1.64)
None (n = 3268)	132	1.21 (0.95–1.53)	1.16 (0.90–1.49)	1.13 (0.87–1.47)
p-value for trend		0.09	0.21	0.35