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Occupational and leisure-time physical activity differentially predict 6-year incidence of stroke and transient ischemic attack in women

by Hall C, Heck JE, Sandler DP, Ritz B, Chen H, Krause N

The results of this study show that high levels of occupational physical activity increase the risk of stroke and transient ischemic attack in women, while high levels of leisure-time physical activity decrease risk for these diseases. These findings corroborate the physical activity health paradox for the first time with respect to cerebrovascular disease.

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Key terms: cerebrovascular disease; cohort; epidemiology; incidence; ischemic heart disease; leisure-time physical activity; occupational physical activity; physical activity; physical activity health paradox; prospective; stroke; transient ischemic attack; women; work posture

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Occupational and leisure-time physical activity differentially predict 6-year incidence of stroke and transient ischemic attack in women

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Objectives Recent meta-analyses suggest a physical activity health paradox: high levels of occupational physical activity (OPA) increase cardiovascular disease (CVD) risk, while leisure-time physical activity (LTPA) decreases risk. However, studies of women and cerebrovascular disease are limited. This report examines physical activity effects on stroke and transient ischemic attack (TIA) among working women in the United States.

Methods OPA history, health status, and lifestyle were assessed by baseline interviews of 31 270 employed Sister Study participants aged 35–74 years. OPA was assessed at six intensity levels (lowest: "mostly sitting"); the highest three were combined as "high intensity work." Independent OPA and LTPA effects on 6-year cerebrovascular disease incidence were estimated in adjusted Cox proportional hazard models.

Results Stroke (N=441) and TIA (N=274) risk increased with more standing and higher intensity work at current and longest held job. Compared with mostly sitting, high intensity work at the current job increased TIA risk by 57% [hazard ratio (HR) 1.57, 95% confidence interval (CI) 1.04–2.38]. High intensity OPA at the longest held job increased risk for stroke by 44% (HR 1.44; 95% CI 1.08–1.93). Among women with CVD, sitting and standing equally, especially at the current job, increased risks up to two-fold (TIA HR 1.98, 95% CI 1.10–3.55) compared with mostly sitting at work. LTPA showed inverse associations.

Conclusions Higher intensity levels of OPA increased stroke and TIA risks, while LTPA decreased risks; results corroborate the physical activity health paradox for women and cerebrovascular disease. More standing at work increased cerebrovascular disease risks, especially for women with CVD.

Key terms cerebrovascular disease; cohort; epidemiology; ischemic heart disease; occupational physical activity; physical activity health paradox; prospective; work posture

In the United States, stroke is the leading cause of long-term disability and one of the leading causes of death (1). Stroke and transient ischemic attack (TIA) partially share a similar pathophysiology and are mostly distinguished by the duration and severity of clinical symptoms; TIA symptoms last <24 hours, while stroke symptoms last ≥24 hours and can lead to permanent disability or death (2, 3). Like cardiovascular disease (CVD), stroke occurrence is associated with sociodemographic, lifestyle, and environmental factors (2). Although men have a higher risk for stroke than women of the same age, more women than men are affected by stroke due to their average longer lifespan (1, 2).

Risk factors for stroke include CVD, atrial fibrillation, hypertension, smoking, high cholesterol, heavy alcohol consumption, and obesity (2, 4, 5). In contrast, diet high in fish, grains, fruits, and vegetables, and high levels of leisure-time physical activity (LTPA), are associated with lower stroke risk (6–8). Occupational risk factors for stroke include heavy physical work (9, 10), long working hours (11), night shifts (12), job stress (13), discrimination (14), and professional driving (15).

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Some risk factors for stroke have been confirmed as risk factors for TIA, but the strength of associations may differ between these cerebrovascular diseases (2, 16); to our knowledge, none of the aforementioned occupational risk factors have been evaluated for TIA.

While the protective role of LTPA is well-documented, the role of occupational physical activity (OPA) in the etiology of stroke and TIA is less clear, especially in women. No studies have examined the relationship between OPA and TIA, and few have examined stroke as an outcome (7, 9, 17–21), with five providing sex-specific results (7, 9, 19–21). In women, lower OPA was associated with higher risk for stroke (7, 9, 19, 20); however, some studies lacked the statistical power to investigate higher levels of OPA (9, 20). Only one study used a validated questionnaire (22) to assess OPA, which found higher levels of OPA to increase stroke risk in women (21). Additionally, only one study adjusted for other types of physical activity (LTPA, commuting), and reported protective OPA effects on women's stroke risk (7).

Recent reviews of the epidemiological literature suggest paradoxical health effects for physical activity, with OPA being positively related to CVD incidence and mortality, and LTPA being inversely related (23–29) or having no effect at all after adjustment for OPA (30–32). A similar paradoxical effect was reported for Parkinson's disease (33). The most recent meta-analysis of 17 prospective cohort studies showed an 18% increased mortality risk for high levels of OPA among men [hazard ratio (HR) 1.18, 95% confidence interval (CI) 1.05–1.34], but a 10% decreased risk among women (HR 0.90, 95% CI 0.80–1.01) (28). The contrasting effects of OPA and LTPA on CVD and mortality may be in part explained by sustained inflammatory responses and prolonged elevation of heart rate and blood pressure, which are associated with OPA but not LTPA (24). Additionally, OPA is structurally different than LTPA because workers typically lack control over activity and recovery time and work tasks; this can result in exhaustion and fatigue, which are associated with progression of atherosclerosis (34) and elevated CVD and stroke risks (35–37).

The current study investigates the relationships between OPA and incident stroke and TIA, separately for current and longest held job. We originally hypothesized that higher intensity levels of OPA in general, and more standing at work specifically, increase risk for cerebrovascular diseases compared with more sitting, since both high relative aerobic workloads and occupational standing have been previously associated with increased risks for atherosclerosis and CVD (30–32, 38, 39). This study overcomes several methodological limitations of previous analyses by using a sufficiently large cohort and employing a finely graded, six-level intensity-ranked OPA measure anchored in common descriptive indicators of work intensity, including work postures, body movements, perceived heart rate increases during work, and perceived heaviness of work. We intentionally retained the original questionnaire items referring to working postures because earlier research has shown that a standing working posture is strongly related to progression of atherosclerosis (30, 39), the main underlying pathological process of cerebrovascular diseases. This study comprehensively adjusts for potentially confounding factors, including LTPA.

Methods

Study population

Subjects were participants in the Sister Study, a prospective cohort study designed to assess genetic and environmental risk factors for breast cancer (40). Between 2003 and 2009, the Sister Study enrolled 50 884 women aged 35–74 who resided in the United States or Puerto Rico and were breast cancer-free at enrollment but had a sister with breast cancer. At baseline, written informed consent was obtained and interviews were conducted. Excluded from analyses were unemployed women or homemakers (N=18 039), those who did not report OPA for their current job (N=63), and women who completed a non-comparable version of the occupational questionnaire (N=1512), resulting in an analytic sample of 31 270 women. The Internal Review Boards at the National Institute of Environmental Health Sciences and Copernicus Group approved the original study; the University of California, Los Angeles approved this secondary analysis.

Outcome assessment

Incident stroke and TIA cases were self-reported doctor's diagnoses ascertained by follow-up health surveys between 2005 and 2015. If a participant died, next of kin were asked about diagnosed diseases. Eight fatal stroke cases were confirmed via the National Death Index and/or the individual's death certificate and analyzed together with non-fatal cases. Subsequent events were not excluded, but a supplementary analysis combining stroke and TIA was restricted to first events. Women with stroke or TIA before enrollment were excluded from analyses of incident stroke and TIA, respectively. Missing event dates were replaced by the midpoint of the last event-free survey and the first survey with an event.

Assessment of occupational physical activity

At baseline, computer-assisted telephone interviews solic-

ited detailed information for all jobs, military service, and volunteer work performed after age 18 for ≥10 hours per week. For each job, participants were asked, "Which of the following best describes your usual physical activity while on the job?" The possible responses were: (i) mostly sitting, with some standing and/or walking; (ii) sitting and standing equally (may include some walking); (iii) mostly standing with some walking; (iv) continuous walking or other movements that increase your heart rate slightly; (v) heavy manual labor that causes sweating or increases your heart substantially; and (vi) sporadic heavy manual labor. Due to small numbers, the latter two categories were collapsed in preliminary analyses into a group labeled "heavy manual labor." However, this exposure group still contained few events so it was further combined with "continuous walking or other movements" into a category labeled "high intensity work," resulting in a four-level exposure variable for OPA: mostly sitting, sitting and standing equally, mostly standing, and high intensity work. If OPA at the longest held job was not reported (N=225), the response for current job was used. This report primarily uses the four-level OPA measure and separately assesses OPA for participants' current job and longest held job in order to determine if timeframe of exposure differentially impacts cerebrovascular disease risk.

Selection and assessment of covariates

Potential confounders were identified using *a priori* knowledge and change-in-estimate criteria. Traditional cardiovascular risk factors such as age, body mass index (BMI), smoking status, alcohol intake, and LTPA were selected for inclusion due to their strong influence on stroke risk (2) and association with OPA (41). Work-related factors, like night work and perceived discrimination at work, were selected for adjustment because they have been shown to increase CVD or stroke risk in other studies (12, 14). Heart rate and systolic and diastolic blood pressure are independent hemodynamic risk factors for CVD (42–44); however, these factors may also be considered mediators of the OPA–CVD relationship. Therefore, most analyses were performed both with and without adjustment for these hemodynamic factors operationalized as rate pressure product, ie, the product of heart rate and pulse pressure (systolic minus diastolic blood pressure). Pulse pressure and rate pressure product are independent predictors of CVD risk (45, 46).

Socioeconomic factors including race/ethnicity, income, and education level were examined as potential confounders but not included in final models because they did not change effect estimates by >5%. For the same reason, a simple sum diet score (based on participants' responses to an extensive food frequency questionnaire) and job strain (derived from a 17-item Job Content Questionnaire) (47), were not included in final models. We assessed the role of both mistreatment/harassment at work and discrimination at work but adjusted only for the latter as it was a more inclusive and predictive measure of stroke risk. Heart rate, systolic blood pressure, and diastolic blood pressure were explored individually as potential confounders, but the combined measure (rate pressure product) better controlled confounding.

LTPA was assessed using metabolic equivalent task (MET) hours per week in concordance with established guidelines. Participants were asked about all sport/exercise activities performed during the last 12 months, including the number of hours spent per week on each activity. Weekly energy expenditures were determined using published MET values for each activity (48). Each participant's LTPA was classified based on the World Health Organization (WHO) guidelines for adults: (i) ≥150 minutes of moderate-intensity physical activity (3–<6 MET) per week or (ii) ≥75 minutes of vigorous physical activity (≥6 MET) per week (49). Those who met both requirements were classified in the latter category to reflect more intense LTPA. Women who participated in moderate-intensity or vigorous LTPA, but not for the recommended amount of time per week, were classified as "insufficient activity time to meet requirements." Women who only participated in LTPA at MET values of <3 were categorized as such, as were study participants who did not partake in any LTPA. This categorization better controlled for confounding by LTPA than explored alternatives that used both raw and corrected (50) MET values.

Participants were categorized into never, former, and current smokers based on lifetime smoking history. Alcohol consumption over the past year was ascertained and individuals were categorized into never drinkers, former drinkers, 1–3 drinks/day, and >3 drinks/day, following the current alcohol–CVD literature (51, 52).

Height, weight, heart rate, and systolic and diastolic blood pressure were measured during home visits by trained study personnel. BMI in kg/m^2 was categorized according to WHO definitions: underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese (30–34.9), severely obese (35–39.9), and morbidly obese (≥40). Blood pressure was measured after participants sat and rested for a few minutes. Three measurements of systolic and diastolic pressure were taken 1–2 minutes apart following a left-right-left protocol (53) and then averaged. Heart rate was measured via palpation of the radial pulse for 60 seconds after ≥5 minutes rest.

Night shift work (ever versus never) was assessed at baseline, while discrimination at work was assessed approximately two years later by a stress and coping follow-up questionnaire. Separate questions asked if participants had "ever been treated unfairly in job hiring, promotion or firing due to" sex, age, race/ethnicity,

sexual orientation, or illness/medical condition. One or more "yes" response was classified as ever experiencing discrimination at work. Missing values (N=3421) were analyzed as a separate category.

Statistical analyses

Multivariable-adjusted Cox regression models estimated HR and 95% CI for OPA and LTPA as predictors of stroke or TIA, with days since study enrollment as the timescale. Follow-up was censored at first cerebrovascular event or at 14 August 2015, whichever came first. Analyses were incrementally adjusted for (i) age; (ii) age and behavioral factors (smoking, alcohol consumption, BMI, and LTPA); (iii) age, behavioral factors, and work-related factors (discrimination, night work); and (iv) fully-adjusted for age, behavioral factors, work-related factors, and potentially mediating hemodynamic factors (rate pressure product). The proportionality assumption was assessed by Schoenfeld residuals; if violated, an interaction term (time×covariate) was added to the model (54).

Sensitivity analyses stratified by pre-existing CVD because previous studies have noted differences in disease risk by baseline cardiovascular health status (30, 32, 34, 55). CVD was assessed by self-reported doctor's diagnosis of previous myocardial infarction, angina, congestive heart failure, or arrhythmia; stroke was included as a pre-existing condition in analyses of TIA, and TIA in analyses of stroke. All analyses used Sister Study data release 5.0.2 and SAS, Version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

During an average of 5.7 (range, 2.3–10.8) years of follow-up, 441 stroke and 274 TIA diagnoses were reported, resulting in incidence rates of 221 and 141 per 100 000 person-years, respectively. A total of 148 participants experienced both a stroke and TIA. Population characteristics, stratified by outcome, are shown in table 1. Compared with event-free women, those with a cerebrovascular event during follow-up were older at baseline, more often smokers, less often current drinkers, less likely to participate in any LTPA, more likely to report OPA involving continuous walking/movements for both current and longest held job, and more likely to ever work night shifts or experience discrimination at work. All hemodynamic measures were higher among those with events. Supplementary table S1 (www.sjweh.fi/show_abstract.php?abstract_id=3787) shows population characteristics stratified by baseline CVD status.

Table 2 displays HR for OPA and stroke incidence with incremental adjustment for potential confounders (models 1–4), separately for current and longest held job. Compared with women mostly sitting at their current job, women sitting and standing equally had a 15% higher risk for stroke in age-adjusted model 1. Women with high intensity work at their longest held job experienced a 56% higher risk for stroke compared with those mostly sitting. This association was driven by women who reported continuous walking or other movements that raised their heart rate slightly (age-adjusted HR 1.62, 95% CI 1.21–2.18), and not by the few women with heavy manual labor jobs (age-adjusted HR 1.04; 95% CI 0.43–2.53). Further adjustment for behavioral, work-related, and hemodynamic factors only slightly attenuated these risks.

Table 3 displays HR for OPA and TIA incidence. Compared with mostly sitting at current job, all other levels of OPA were associated with higher risks for TIA and showed a strong monotonic positive association with TIA incidence across OPA intensity levels, up to a 71% increased risk for high intensity work. For the longest held job, age-adjusted models showed a 41% increased risk for TIA with high intensity work (driven by those who reported OPA involving continuous walking or other movements that slightly raise heart rate). Associations were moderately attenuated in fully-adjusted models.

Supplementary table S2 (www.sjweh.fi/show_abstract.php?abstract_id=3787) shows HR for OPA and any incident cerebrovascular event (stroke or TIA). For current job, increased risks were observed for all levels of OPA other than mostly sitting, ranging from 13–17% in fully-adjusted models. For longest held job, only high intensity OPA was associated with an increased risk for any cerebrovascular event (fully-adjusted HR 1.27, 95% CI 0.98–1.65), driven by risks associated with continuous walking or moving (fully-adjusted HR 1.35, 95% CI 1.03–1.76).

Table 4 displays the number of incident stroke cases for each OPA level by baseline CVD status with fully-adjusted HR and 95% CI. Among women *without* CVD at baseline, risks increased monotonically with OPA intensity, with those reporting high intensity work for their longest held job at the highest risk (HR 1.65, 95% CI 1.17–2.33). Among women *with* CVD at baseline, the highest risks for stroke were observed among those who reported sitting and standing equally in their current job (HR 1.56, 95% CI 1.06–2.31).

For TIA, supplementary table S3 (www.sjweh.fi/show_abstract.php?abstract_id=3787) shows substantially increased risks for women *without* CVD, specifically for those who reported mostly standing (HR 1.46, 95% CI 1.01–2.11) or high intensity work (HR 1.52, 95% CI 0.95–2.42) at the current job. Respective risk estimates based on the longest held job were much lower, and sitting and standing equally was associated

Table 1. Characteristics of the study population, stratified by cerebrovascular disease event status. Sister Study, 2004–2015, N=31 270. [SD=standard devation; MET=metabolic equivalent task.]

Characteristics	No cerebrovascular event reported (N=30 703)				Cerebrovascular event reported [a] (N=567)			
	N	%	Mean	SD	N	%	Mean	SD
Age			53.0	7.6			57.7	8.0
Race/ethnicity								
Non-Hispanic White	25 295	82.4			452	79.7		
Non-Hispanic Black	3146	10.3			74	13.1		
Hispanic	1450	4.7			24	4.2		
Other	802	2.6			17	3.0		
Missing	10	0.0			0	0.0		
Occupational physical activity (OPA), current job								
Mostly sitting	16 808	54.7			282	49.7		
Sitting and standing equally	6546	21.3			132	23.3		
Mostly standing	4790	15.6			97	17.1		
Continuous walking/movements [b]	2292	7.5			50	8.8		
Heavy manual labor [c]	261	0.9			6	1.1		
Sporadic heavy manual labor	6	0.0			0	0.0		
Occupational physical activity, longest held job								
Mostly sitting	14 895	48.5			267	47.1		
Sitting and standing equally	6766	22.0			115	20.3		
Mostly standing	5704	18.6			106	18.7		
Continuous walking/movements [b]	2910	9.5			73	12.9		
Heavy manual labor [c]	424	1.4			6	1.1		
Sporadic heavy manual labor	4	0.0			0	0.0		
Leisure-time physical activity								
None	5311	17.3			130	22.9		
Insufficient activity time to meet requirements	18 106	59.0			321	56.6		
All activity <3 MET	1108	3.6			28	4.9		
3–<6 MET for ≥150 minutes/week	1527	5.0			34	6.0		
≥6 MET for ≥75 minutes/week	4651	15.2			54	9.5		
Alcohol consumption								
Never drinker	933	3.0			29	5.1		
Former drinker	4124	13.4			112	19.8		
<1–3 drinks/day	25414	82.8			422	74.4		
>3 drinks/day	190	0.6			1	0.2		
Missing	42	0.1			3	0.5		
Smoking status								
Never smoker	17 820	58.0			282	49.7		
Former smoker	10 287	33.5			221	40.0		
Current smoker	2583	8.4			64	11.3		
Missing	13	0.0			0	0.0		
Body mass index (kg/m^2)								
<18.5	315	1.0			8	1.4		
18.5–24.9	11 578	37.7			148	26.1		
25.0–29.9	9576	31.2			167	29.5		
30.0–34.9	5239	17.1			147	25.9		
35.0–39.9	2456	8.0			62	10.9		
≥40.0	1530	5.0			35	6.2		
Missing	9	0.0			0	0.0		
Ever face discrimination at work								
Yes	7077	23.1			180	31.8		
No	20 272	66.0			320	56.4		
Missing	3354	10.9			67	11.8		
Ever work night shifts								
Yes	9432	30.7			195	34.4		
No	21 271	69.3			372	65.6		
Resting heart rate			69.0	8.2			70.2	8.5
Systolic blood pressure			114.0	13.3			119.7	14.9
Diastolic blood pressure			72.6	8.8			74.5	8.8
Pulse pressure			41.4	9.1			45.2	11.2
Rate pressure product [d]			2862.4	730.8			3178.7	930.5

[a] Defined by reported stroke or transient ischemic attack during follow-up.
[b] Self-reported OPA as "continuous walking or other movements that increase your heart rate slightly".
[c] Self-reported OPA as "heavy manual labor that causes sweating or increases your heart substantially".
[d] Rate pressure product defined as the product of pulse pressure and resting heart rate.

Table 2. Occupational physical activity and incident stroke (N=441). Hazard ratios (HR) and 95% confidence intervals (CI) from Cox regression analyses with incremental adjustment for potential confounders. Sister Study, 2004–2015, N=31 270.

Occupational physical activity	N Case/ Exposed	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Current job									
Mostly sitting	221/16287	1.00		1.00		1.00		1.00	
Sitting and standing equally	103/6386	1.15	0.91–1.45	1.18	0.93–1.49	1.19	0.94–1.51	1.18	0.93–1.49
Mostly standing	67/4656	1.03	0.78–1.35	1.04	0.79–1.36	1.06	0.80–1.39	1.05	0.80–1.39
High intensity work	40/2477	1.24	0.88–1.73	1.12	0.80–1.56	1.11	0.79–1.56	1.11	0.79–1.56
Continuous walking/movements	35/2225	1.20	0.84–1.72	1.10	0.77–1.57	1.10	0.77–1.57	1.10	0.77–1.57
Heavy manual labor	5/252	1.52	0.63–3.68	1.27	0.52–3.08	1.24	0.51–3.02	1.21	0.50–2.95
Longest held job									
Mostly sitting	194/14444	1.00		1.00		1.00		1.00	
Sitting and standing equally	94/6586	1.01	0.79–1.29	1.03	0.80–1.32	1.03	0.80–1.32	1.02	0.80–1.31
Mostly standing	80/5549	1.05	0.81–1.36	1.03	0.79–1.34	1.04	0.80–1.35	1.04	0.80–1.35
High intensity work	63/3227	1.56	1.17–2.07	1.46	1.09–1.94	1.45	1.08–1.94	1.44	1.08–1.93
Continuous walking/movements	58/2821	1.62	1.21–2.18	1.54	1.15–2.07	1.53	1.14–2.07	1.53	1.13–2.06
Heavy manual labor	5/406	1.04	0.43–2.53	0.88	0.36–2.15	0.89	0.36–2.16	0.87	0.36–2.13

[a] Model 1 adjusts for age.
[b] Model 2 adjusts for age, leisure-time physical activity, alcohol, smoking, and body mass index.
[c] Model 3 adjusts for age, leisure-time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work.
[d] Model 4 adjusts for age, leisure-time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product.

Table 3. Occupational physical activity and incident transient ischemic attack (N=274). Hazard ratios (HR) and 95% confidence intervals (CI) from Cox regression analyses with incremental adjustment for potential confounders. Sister Study, 2004–2015, N=31 270.

Occupational physical activity	N Case/ Exposed	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Current job									
Mostly sitting	122/16119	1.00		1.00		1.00		1.00	
Sitting and standing equally	64/6338	1.29	0.96–1.75	1.30	0.96–1.77	1.31	0.97–1.78	1.37	1.01–1.88
Mostly standing	50/4612	1.39	1.00–1.93	1.37	0.98–1.90	1.40	1.01–1.96	1.51	1.08–2.12
High intensity work	31/2453	1.71	1.15–2.54	1.55	1.04–2.31	1.52	1.02–2.27	1.57	1.04–2.38
Continuous walking/movements	28/2207	1.72	1.14–2.59	1.56	1.03–2.36	1.53	1.00–2.33	1.60	1.04–2.45
Heavy manual labor	3/246	1.64	0.52–5.15	1.49	0.47–4.71	1.43	0.45–4.51	1.36	0.43–4.35
Longest held job									
Mostly sitting	127/14315	1.00		1.00		1.00		1.00	
Sitting and standing equally	48/6525	0.79	0.57–1.10	0.82	0.59–1.14	0.82	0.59–1.15	0.84	0.60–1.17
Mostly standing	54/5485	1.08	0.79–1.49	1.01	0.74–1.40	1.03	0.75–1.42	0.88	0.62–1.24
High intensity work	38/3197	1.41	0.98–2.03	1.32	0.92–1.90	1.28	0.88–1.86	1.26	0.86–1.82
Continuous walking/movements	36/2795	1.52	1.05–2.20	1.43	0.99–2.07	1.39	0.95–2.03	1.37	0.93–2.00
Heavy manual labor	2/402	0.62	0.15–2.51	0.56	0.14–2.25	0.54	0.13–2.18	0.52	0.13–2.10

[a] Model 1 adjusts for age.
[b] Model 2 adjusts for age, leisure-time physical activity, alcohol, smoking, and body mass index.
[c] Model 3 adjusts for age, leisure-time physical activity, alcohol, smoking, body mass index, discrimination at work, and night work.
[d] Model 4 adjusts for age, leisure-time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product.

with a decreased risk for TIA (HR 0.68, 95% CI 0.46–1.03). Among women *with CVD,* sitting and standing equally at the current job increased TIA risk two-fold (HR 1.98, 95% CI 1.10–3.55), followed by 36% and 33% increases for mostly standing and high intensity work, respectively. For the longest held job, sitting and standing equally and high intensity work were associated with 44% and 75% increased risks, respectively.

Analyses stratified by CVD *without* adjustment by potentially mediating hemodynamic factors (ie, rate pressure product) showed similar risk patterns for stroke and TIA, with the exception of TIA where women with CVD had consistently higher risks. For example, removing rate pressure product from fully-adjusted models changed the highest TIA risks from 98% to 127% (HR 2.27, 95% CI 1.28–4.04) for sitting and standing equally at the current job, and from 45% to 105% (HR 2.05, 95% CI 0.95–4.42) for high intensity OPA at the longest held job (other results not shown).

LTPA was inversely associated with both stroke and TIA risk (table 5). For stroke, this inverse relationship was monotonic, with the strongest protective effect for LTPA at >6 MET for ≥75 minutes each week (HR 0.64, 95% CI 0.44–0.94) compared with no LTPA. Similar inverse associations were observed between LTPA and TIA. Associations were similar or stronger when limited to women without CVD at baseline (results not shown).

Table 4. Occupational physical activity and incident stroke (N=441) by baseline cardiovascular disease (CVD). Hazard ratios (HR) and 95% confidence intervals (CI) from fully-adjusted Cox regression models. Sister Study, 2004–2015, N=31 270.

Occupational physical activity	Cardiovascular disease status at baseline					
	Without CVD (N=24 974)			With CVD [a] (N=6076)		
	N Case/Exposed	HR [b]	95% CI	N Case/Exposed	HR [b]	95% CI
Current job						
Mostly sitting	147/13 078	1.00		74/3209	1.00	
Sitting and standing equally	63/5154	1.06	0.79–1.43	40/1232	1.56	1.06–2.31
Mostly standing	49/3751	1.16	0.84–1.60	18/905	0.95	0.56–1.61
High intensity work	27/1975	1.22	0.80–1.84	13/502	1.18	0.65–2.15
Longest held job						
Mostly sitting	125/11 648	1.00		69/2796	1.00	
Sitting and standing equally	59/5278	1.01	0.74–1.38	35/1308	1.24	0.82–1.88
Mostly standing	56/4444	1.15	0.84–1.58	24/1105	0.97	0.60–1.55
High intensity work	46/2588	1.65	1.17–2.33	17/639	1.17	0.68–2.03

[a] Defined by self-reported doctor's diagnosis of congestive heart failure, mitral valve prolapse, arrhythmia, TIA, angina, or myocardial infarction at baseline.
[b] Models adjust for age, leisure time physical activity, alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product.

Table 5. Leisure-time physical activity (LTPA) and incident stroke and transient ischemic attack. Hazard ratios (HR) and 95% confidence intervals (CI) from fully-adjusted Cox regression analyses. Sister Study, 2004–2015, N=31 270. [MET=metabolic equivalent task.]

LTPA [a]	Stroke (N=441)			TIA (N=274)		
	N Case/Exposed	HR [b]	95% CI	N Case/Exposed	HR [b]	95% CI
No LTPA	103/5099	1.00		65/5061	1.00	
All activity <3 MET	24/1072	0.97	0.62–1.51	13/1050	0.76	0.41–1.42
Insufficient activity to meet requirements	247/17 603	0.82	0.65–1.04	145/17 421	0.87	0.64–1.19
Meets requirement of 3–<6 MET at ≥150 minutes/week	19/1499	0.72	0.44–1.19	19/1489	0.80	0.46–1.40
Meets requirement of ≥6 MET at ≥75 minutes/week	38/4533	0.64	0.44–0.94	25/4501	0.69	0.42–1.13

[a] LTPA categorized according to WHO recommendation-based categories; those who met both requirements listed were classified in the latter category in order to reflect more intense LTPA
[b] Models adjust for age, occupational physical activity (current job), alcohol, smoking, body mass index, discrimination at work, night work, and rate pressure product

Discussion

Summary of main findings

Overall, OPA intensity was positively associated with risks for both stroke and TIA, even after comprehensive control for confounding factors. Effect estimates varied by specific exposures, outcomes, and CVD status at baseline. Risks increased with both more standing and more intense work in a pattern compatible with a positive, monotonic dose-response relationship between exposure at current job and TIA, and between exposure at longest held job and stroke. In general, those *without* CVD at baseline showed monotonic increases in risk, while those *with* CVD showed highest increases in risk with partially standing work and high intensity OPA. LTPA was inversely associated with both stroke and TIA. Overall, results were consistent with our hypothesis of detrimental effects for high intensity OPA and standing work postures and with protective effects for LTPA; our findings provide further evidence for the physical activity health paradox.

Comparison with the literature

Only one prospective study previously reported a positive association between OPA and stroke in women (21). No studies have investigated the role of OPA for TIA, nor have any specifically examined prolonged standing at work with regard to cerebrovascular disease. However, our results are consistent with recent prospective cohort studies reporting increased CVD mortality and all-cause mortality risks with high intensity OPA (23, 25, 28, 30–32). Our observation that standing work is associated with higher risks than sitting work is consistent with our hypothesis and with the hemodynamic theory of atherosclerosis, which posits increases in venous pooling, heart rate, and blood pressure as pathophysiological pathways (39, 56). Previous prospective cohort studies have linked prolonged standing at work to varicose vein diseases (57, 58), accelerated progression of atherosclerosis (39), and to a two-fold risk for incident ischemic heart disease (38). While sitting may impose greater risks than recumbent postures (59), and while sitting at home and total sitting time during the day have also been associated with increased CVD risks, it is important to note that sitting at work has not been

shown to increase risks compared with standing work postures (60).

The physical activity health paradox

This concept asserts that high LTPA is beneficial to cardiovascular health, while high OPA is detrimental (23). Our findings provide, for the first time, empirical epidemiological evidence for the physical health paradox with regard to cerebrovascular diseases.

Several plausible explanations for this paradox have been suggested (24), including sustained inflammatory responses and prolonged elevations of heart rate and blood pressure, all of which are typically associated with OPA but not with LTPA. Inflammation markers (eg, C-reactive protein) increase during all types of physical activity in the short-term and remain elevated until the body has recovered (61). High levels of OPA for prolonged periods during the work day—or over several days—result in elevations of average daily heart rate, mean blood pressure, and pulse pressure, leading to increases in cyclical pressure- and stretching-induced arterial wall stress. This results in cumulative arterial endothelial and medial injury that can lead—especially without sufficient recovery time for repair—to denudation of the endothelium and trigger small muscle cell proliferation, one of the proposed mechanisms in the development of atherosclerosis underlying CVD (30, 56, 62, 63). Additionally, elevated resting and average 24-hour heart rate and blood pressure are known independent risk factors for CVD (64–67). High OPA over extended periods of time has been shown to increase 24-hour heart rate, an effect not observed with shorter duration high levels of LTPA (24). For instance, the Belgian Physical Fitness Study reported a more than 3-fold increased all-cause mortality risk among working men in the upper tertile of ambulatory 24-hour heart rate (HR=3.21, 95% CI 1.22–8.44) (68). Likewise, prolonged static OPA and heavy lifting have been shown to elevate blood pressure, even after working hours, in contrast to LTPA (69). LTPA may also involve heavy lifting, however, it usually occurs for short periods of time and under controlled conditions, resulting in little impact on 24-hour blood pressure. Moreover, short-term high intensity physical training can increase cardiorespiratory fitness, in turn lowering heart rate during rest and work. This increased fitness reduces relative aerobic workload (energy expenditure at work expressed as percent of cardiorespiratory fitness) which has been shown to be a stronger predictor of CVD than absolute measures of energy expenditure (30, 32).

LTPA also differs from OPA in that LTPA is voluntary and participants are generally in control of their actions, including how much to do and when and how long to rest. Conversely, OPA is an employment requirement and employees typically have little control over work tasks, work hours, work speed, and other psychosocial, organizational, or ergonomic stressors that may be present in the work environment and determine the type, intensity, and duration of OPA. Furthermore, OPA is usually performed for longer time periods and with much less recovery time between and after activities than LTPA. All of these factors can result in worker exhaustion and fatigue, which are associated with progression of atherosclerosis (34) and increases in CVD and stroke risk (35–37).

Healthy worker effects

It is important to acknowledge the possible impact of various forms of the so-called "healthy worker effect," including the "healthy worker survivor effect," in analyses of occupational exposures and health (70). These effects can be described as a continuous selection process in which healthier workers enter and remain in the workforce while unhealthier workers select out of the workforce, or certain jobs or job tasks. This typically results in a conservative bias, ie, attenuation of the effect of any occupational exposure (70, 71). For this reason, we expect our reported hazard ratios to underestimate the true effect of OPA on stroke and TIA incidence.

In our study, the healthy worker survivor effect is operating in two main ways. First, we assume this effect because only women employed at baseline were included in this study. Women with no occupational history were not eligible for this analysis, and those who already left the workforce (possibly due to health reasons related to stroke or TIA risk) were excluded in order to assure direct comparability of OPA exposure assessment based on both current and longest held job, as previously employed women who were not working at baseline could only be considered in analyses based on exposure in their longest held job. Moreover, including these women would introduce misclassification of health behaviors that are influenced by employment status (72, 73); when analyzing the impact of OPA at times of employment, adjusting for baseline behaviors (eg, LTPA) reported at times of unemployment or after retirement could bias adjusted effect estimates in an unpredictable direction. Our exclusion of women not working at baseline likely resulted in a conservative bias because the unhealthiest and most at-risk women had already left the workforce before baseline.

Second, sensitivity analyses stratified by baseline CVD status revealed different risk patterns that are reflective of an additional healthy worker survivor effect. Individuals with CVD at baseline – who did not leave the workforce entirely because of their disease – may have instead transitioned from more demanding high intensity work to less demanding, more sitting work,

resulting in an apparent higher risk for cerebrovascular disease in the subgroups currently working jobs with lower-middle levels of OPA. Results from Supplementary Table 4 support this notion: A larger percentage of individuals reported higher intensity levels of OPA for their longest held job than for their current job, while a smaller percentage of women reported lower intensity OPA at their longest held job and higher intensity OPA at their current job. These patterns were similar or even stronger when restricted to women with CVD at baseline (Supplementary Table 5), and specifically confirm the transition of women with CVD from high to low OPA in this population, consistent with a healthy worker survivor effect. At the same time, women without CVD at baseline were able to perform at higher OPA levels and constitute a highly selected group of the most resilient women with lower *a priori* risk for stroke and TIA, resulting in a downward conservative bias for cerebrovascular disease risks associated with high levels of OPA.

Consideration of these healthy worker effects is important when interpreting the results of this study. We reason that the exclusion of women not working at baseline, and the inclusion of women with pre-existing CVD, led to a conservative bias in effect estimates because the first group was never in or already left the workforce and the second group was more likely to change from high to low intensity jobs while being at high risk for cerebrovascular events. Subsequent cerebrovascular events in women who migrated to lower OPA jobs would inflate the risk in lower OPA categories while deflating the risk in higher OPA categories. We therefore believe the true impact of higher intensity OPA on stroke and TIA risk to be greater than estimated in this study.

Strengths and limitations. Key strengths of this study include large sample size as well as detailed and complete information on occupational history and most relevant risk factors including socio-demographic, behavioral, work-related, and hemodynamic characteristics. Potential bias from exposure misclassification was reduced by the availability and use of relatively detailed and specific OPA exposure measures. Though this exposure assessment tool has not been externally validated, its specific and rank-ordered categories are an improvement over previous studies that relied on non-specific categorizations such as "high" and "low" OPA that were not clearly linked to specific job characteristics (eg, work postures). Using two different exposures (current and longest held job) to assess OPA allowed for differentiating the impact of more recent current and longer-term past exposures on stroke and TIA risk. Although there is substantial overlap in participant's reported OPA for current and longest held job (see Supplementary Tables 4–5), the observed differences can explain the respective differential results for stroke and TIA.

Detailed information on important risk factors allowed us to rule out any substantial confounding by a wide array of covariates that we examined and controlled for in our fully-adjusted statistical models. Of note, further adjustment for indicators of socioeconomic status (SES) (ie, race/ethnicity, income, and education) did not substantially change effect estimates when added to models individually or in various combinations, despite the known association between SES and cerebrovascular disease (2). While residual confounding by SES cannot be ruled out completely, our adjustment for confounders closely related to SES – such as smoking status, alcohol consumption, BMI, and LTPA – reduces the possibility of such confounding. Adjustment for blood pressure and heart rate in fully-adjusted models did attenuate risks and might be considered over-adjustment; hemodynamic factors need to be considered as both confounders and mediators in the relationship between OPA and cerebrovascular disease. Mutual adjustment for LTPA and OPA is another important strength of our study shared by only one other study on physical activity and cerebrovascular disease (7). By including both LTPA and OPA simultaneously in our analytic models, we were able to confirm their independent and differential effects are compatible with the physical activity health paradox, which had not been previously examined for cerebrovascular diseases.

The self-reported nature of OPA exposures and disease outcome is an important limitation. Specifically, we could not explore the extent to which physical activities differently impact ischemic and hemorrhagic stroke because self-report on these subtypes was deemed unreliable and therefore not collected. However, non-fatal stroke cases are more likely to be ischemic than hemorrhagic and, given the few fatal cases in our sample (N=8), we assume that most reported stroke cases were ischemic (2, 4). While we were able to confirm a possible mediating role of hemodynamic factors by examining models with and without adjustment for the rate pressure product, lack of repeated measures of heart rate and blood pressure prevented formal mediation analyses. Finally, stroke and TIA are rare diseases and, despite our large sample size, the relatively short follow-up time (6 years) limited statistical power and therefore precision of risk estimates. However, our short follow-up time is also a strength because it minimized the potential for misclassification bias due to unmeasured changes in exposure and covariates after baseline.

Incidence rates of stroke in our study population are similar to those seen in comparable populations (74), supporting the generalizability of our results. Yet, studies of other populations are needed to confirm our findings and to investigate specific dose-response relationships and thresholds. This requires more comprehensive exposure assessments with repeated measures of duration, intensity, and the actual combination of different

occupational physical activities, including information on static workloads such as constrained postures, carrying, lifting, and holding tools, and both upper and lower body movements to assess static and dynamic OPA intensities. Repeat objective measures based on accelerometers and heart rate monitors could allow continuous measurement of relative aerobic workloads that consider the cardiorespiratory fitness of the individual worker as well as changes over time. Though it may not be feasible to implement observational tools in large cohort studies spanning several geographic regions, many different workplaces, and repeat assessments over several years, such observational tools could be used to validate respective self-report measures. Access to medical records would be desirable in order to avoid outcome misclassification and to perform stratified analyses by stroke subtype.

Concluding remarks

This study provides further support for the physical activity health paradox and suggests that higher levels of OPA intensity and prolonged standing at work increase risks for both stroke and TIA among working women, while WHO recommended levels of LTPA appear to decrease risks for these cerebrovascular diseases.

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