Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed Methods

Baseline measures: Reasons for Geographic And Racial Differences in Stroke (REGARDS) study data were collected via a computer-assisted telephone interview (CATI) and an in-home examination. Trained health professionals conducted the in-home examination which included an electrocardiogram (ECG) and collection of blood and spot urine samples. For the present analyses, demographic factors (age, sex, race, geographic region of residence, education), cancer risk factors (current smoking, heavy alcohol use, body mass index), and chronic disease status/medical history (diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke) collected during the baseline examination period were included as covariates.

Region of residence was classified as stroke buckle (coastal plain region of North Carolina, South Carolina, and Georgia), stroke belt (remainder of North Carolina, South Carolina, and Georgia, plus Alabama, Mississippi, Tennessee, Arkansas, and Louisiana) or non-belt/buckle. Smoking status was determined by responses to two questions during the CATI-assisted interview: "Have you smoked at least 100 cigarettes in your lifetime?" and "Do you smoke cigarettes now, even occasionally?" Current smoking was defined as a positive response to both questions. Self-reported heavy alcohol consumption, assessed during the CATI-assisted interview, was categorized as none (no weekly alcohol consumption), moderate (1-14 and 1-7 alcoholic beverages/week for men and women, respectively) or heavy (>14 and >7 alcoholic beverages/week for men and women, respectively). Weight, and height were measured during the in-home visit following a standardized protocol. Body mass index was calculated as weight in kilograms divided by height (in meters) squared. Diabetes mellitus was defined as fasting plasma glucose of 126 mL/dL or more (or ≥200 mL/dL for those who did not fast) or self-report of current use of medications for glucose control. Blood pressure was determined as the mean of two measurements taken after 5 minutes of seated rest, and hypertension was defined as systolic blood pressure of 140 mmHg or greater, diastolic blood pressure of 90 mmHg or greater, or self-reported current use of antihypertensive medication. Dyslipidemia was defined as fasting total cholesterol of 240 mg/dL or greater, fasting low-density lipoprotein cholesterol of 160 mg/dL or greater, fasting high-density lipoprotein cholesterol of 40 mg/dL or less, or self-reported current use of lipid-lowering medications. History of coronary heart disease was defined as a self-reported or ECG evidence of myocardial infarction or a self-reported coronary revascularization procedure. History of stroke was defined on the basis of self-report.

Isotemporal substitution models: Standard regression models are limited in their ability to evaluate the health benefits/harms associated with movement behaviors (e.g. sedentary behavior, light intensity physical activity [LIPA], and moderate-vigorous intensity physical activity [MVPA]) as such models do not take into consideration that movement behaviors are inherently co-dependent. One movement behavior cannot be changed without a ripple effect on the remaining movement behaviors that comprise the physical activity profile. Instead, time-use epidemiology statistics are recommended.[1] The isotemporal substitution model was proposed by Mekarky et al as a method for evaluating the displacement of one movement-related behavior time-use component with another, while allowing for adjustment for the confounding effect of the remaining time-use components.[2] Since its first application in physical activity epidemiology research in 2009, isotemporal substitution has become widely adopted as a means to account for time displacement and estimate the health benefits incurred when reallocating time from one

activity to another, keeping time in other activities fixed.[3] It is considered by some to be the gold standard time-use statistical method for physical activity epidemiology research.[4]

The isotemporal substitution model estimates the effect of replacing one physical activity type with another physical activity type for the same amount of time (e.g., replacing sedentary time with LIPA, by taking sedentary time out of the model). In the present analyses, isotemporal substitution modeling was used to estimate the theoretical effect of substituting total sedentary time with another type of activity (LIPA, MVPA) for the same amount of time while holding accelerometer wear time constant. Our isotemporal model was expressed as follows:

$$Cancer\ Mortality\ Risk = h_0(t) \times \exp(B_1X_i[LIPA] + B_2X_i[MVPA] + B_3X_i[Weartime] + B_4X_i \dots [covariates])$$

where h_0 represents the baseline hazard, t represents the survival time and B_1-B_4 are the hazards of respective activities or covariates. Each given type of activity was expressed in 30-minute units. By eliminating sedentary time from the model (i.e. it is "dropped"), the resulting hazard ratios for LIPA and MVPA represent the consequences of replacing 30 minutes of sedentary time with an equal amount of time in a given type of activity (LIPA or MVPA).

To better understand results from the isotemporal analyses, we also fitted Cox regression models that represented the association of each intensity category (sedentary time, LIPA, MVPA) with cancer mortality 1) without mutual adjustment for other activity categories (single-factor models), 2) with adjustment for selected activity categories (2-factor models), and 3) with mutual adjustment for all activity categories simultaneously (3-factor models or Partition models). As described by Mekary[2], the partition model partitions "total activity" among its components and was expressed as follows:

$$Cancer\ Mortality\ Risk = h_0(t) \times \exp(B_1X_i[Sedentary\ Time] + B_2X_i[LIPA] + B_3X_i[MVPA] + B_4X_i \dots [covariates]).$$

In this model, the hazards for one type of activity represents the effect of increasing this type of activity while holding other activity types constant. Therefore, it represents the effect of "adding" rather than substituting an activity type. It should be noted that total time for physical activity is not held constant, so this model is not isotemporal.

The single activity model, also not an isotemporal model, assesses each activity component separately (e.g., sedentary time), without taking into account the other activity types, and was expressed as follows:

$$Cancer\ Mortality\ Risk = h_0(t) \times \exp(B_1X_i[Sedentary\ Time] + B_4X_i \dots [covariates])$$

eTable 1: Hazard ratios for risk of cancer mortality by sedentary breaks tertiles in the REGARDS study
(n=8,002).

	Tertile 1 *(n=2667)*	**Tertile 2** *(n=2668)*	**Tertile 3** *(n=2667)*	**P-Trend**[a]
No. of Deaths	120	85	63	
Unadjusted	1.00 (ref)	0.83 (0.63-1.10)	0.70 (0.51-0.96)	0.025
Model 1[b]	1.00 (ref)	0.82 (0.62-1.09)	0.72 (0.52-0.99)	0.039
Model 2[c]	1.00 (ref)	0.92 (0.69-1.23)	0.82 (0.59-1.13)	0.230

Data presented as hazard ratio (95% confidence interval).

[a]p-value from linear trend test when tertiles were treated as an ordinal variable in the Cox model.

[b]Adjusted for age, race, sex, region of residence, education, and season the accelerometer was worn.

[c]Adjusted for covariates in model 1 plus current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, stroke, and MVPA.

The tertile cutoff points were <68.3, ≥68.3 to <83.5, ≥83.5 breaks/16-h day.

eTable 2: Hazard ratios for risk of cancer mortality by total sedentary time tertiles in the REGARDS study Stratified by Moderate-Vigorous Intensity Physical Activity Category (n=8,002).				
	Tertile 1	**Tertile 2**	**Tertile 3**	**P-Trend[a]**
MVPA <150 min/week				
No. of Deaths/N	26/1467	84/2198	126/2583	
HR (95% CI)[b]	1.00 (ref)	1.83 (1.17-2.85)	1.94 (1.24-3.04)	0.009
MVPA ≥150 min/week				
No. of Deaths	20/1200	9/470	3/84	
HR (95% CI)[b]	1.00 (ref)	0.95 (0.41-2.20)	1.39 (0.38-5.06)	0.771
Data presented as hazard ratio (95% confidence interval).				
[a]p-value from linear trend test when tertiles were treated as an ordinal variable in the Cox model.				
[b]Adjusted for age, race, sex, region of residence, education, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, and stroke.				
The tertile cutoff points were <709.7, ≥709.7 to <782.6, ≥782.6 min/16-h day.				

eTable 3: Hazard ratios for risk of cancer mortality by sedentary bout duration tertiles in the REGARDS study Stratified by Moderate-Vigorous Intensity Physical Activity Category (n=8,002).				
	Tertile 1	**Tertile 2**	**Tertile 3**	**P-Trend[a]**
MVPA <150 min/week				
No. of Deaths/N	38/1783	77/2039	121/2426	
HR (95% CI)[b]	1.00 (ref)	1.51 (1.02-2.24)	1.70 (1.16-2.50)	0.009
MVPA ≥150 min/week				
No. of Deaths	17/884	11/629	4/241	
HR (95% CI)[b]	1.00 (ref)	0.84 (0.37-1.87)	0.64 (0.20-2.02)	0.426
Data presented as hazard ratio (95% confidence interval).				
[a]p-value from linear trend test when tertiles were treated as an ordinal variable in the Cox model.				
[b]Adjusted for age, race, sex, region of residence, education, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, and stroke.				
The tertile cutoff points were <8.3, ≥8.3 to <11.3, and ≥11.3 min/bout.				

eTable 4. Hazard ratios for cancer mortality by total sedentary time levels in the REGARDS study (n=8,002)	
Total Sedentary Time *(h/16-h day)*	**HR (95% CI)**
9.0	0.74 (0.58-0.94)
9.5	0.80 (0.66-0.96)
10.0	0.86 (0.76-0.97)
10.5	0.93 (0.87-0.99)
11.0	1.00 (ref)
11.5	1.08 (1.02-1.15)
12.0	1.16 (1.03-1.31)
12.5	1.25 (1.05-1.50)
13.0	1.35 (1.06-1.72)
13.5	1.46 (1.08-1.97)
14.0	1.57 (1.09-2.26)
14.5	1.70 (1.11-2.59)
15.0	1.83 (1.13-2.97)
Model adjusted for age, race, sex, region of residence, education, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke, and MVPA	

eTable 5. Hazard ratios for cancer mortality by mean sedentary bout duration levels in the REGARDS study (n=8,002)	
Mean Sedentary Bout Duration *(min/bout)*	**HR (95% CI)**
5.0	0.98 (0.96-1.00)
6.0	0.99 (0.98, 1.00)
7.0	1.00 (ref)
8.0	1.01 (1.00-1.02)
9.0	1.02 (1.00-1.04)
10.0	1.03 (1.00-1.06)
15.0	1.08 (1.00-1.17)
20.0	1.13 (1.00-1.29)
25.0	1.19 (0.99-1.42)
30.0	1.25 (0.99-1.57)
35.0	1.31 (0.99-1.73)
40.0	1.37 (0.99-1.91)
45.0	1.44 (0.99-2.11)
Model adjusted for age, race, sex, region of residence, education, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke, and MVPA	

eTable 6. Hazard Ratios for Risk Of Cancer by Sedentary Time, Light Intensity Physical Activity, and Moderate-Vigorous Intensity Physical Activity (Expressed in 10-minute Units) With and Without Adjustment for Each Activity Variable in the REGARDS Study (N=8,002).

Model	Sedentary Time	LIPA	MVPA
Single-Factor Models[a]	1.04 (1.02-1.06)	0.96 (0.94-0.98)	0.84 (0.75-0.94)
2-Factor Models[b]	1.03 (1.01-1.05)	0.97 (0.95-0.99)	-
2-Factor Models[c]	1.13 (1.01-1.27)	-	0.88 (0.79-0.99)
Partition Models[d]	0.99 (0.98-1.01)	0.96 (0.94-0.99)	0.88 (0.78-0.98)
Isotemporal Models[e]	-	0.97 (0.95-0.99)	0.88 (0.79-0.99)

LIPA, light intensity physical activity; MVPA, moderate-vigorous intensity physical activity.

Data presented as hazard ratio (95% CI).

All models adjusted for age, race, sex, region of residence, education, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, history of stroke, and accelerometer wear time.

All variables expressed in 10 min units.

[a]Results from separate models for each activity variable (sedentary time, LIPA, MVPA), adjusted for covariates.

[b]Results from separate models for each activity variable, adjusted for covariates and MVPA.

[c]Results from separate models for each activity variable, adjusted for covariates and LIPA.

[d]Results from a single model that includes sedentary time, LIPA, MVPA, and covariates

[e]Results from a single model wherein sedentary time is omitted from the model (but LIPA, MVPA, and wear time are included along with covariates); thus resulting HRs estimate associations for replacing 30 minutes of sedentary time with an equal amount in a given type of activity (LIPA or MVPA).

eTable 7. Hazard ratios for risk of cancer mortality by sedentary time and sedentary bout duration tertiles in the REGARDS study Stratified by Deaths in First Year vs Later Years

(n=8,002).

	Tertile 1	Tertile 2	Tertile 3	
Total Sedentary Time				
First Year	1.00 (ref)	1.49 (1.02-2.18)	1.49 (0.99-2.23)	
Later Years	1.00 (ref)	1.05 (0.43-2.53)	1.87 (0.98-3.56)	
Mean Sedentary Bout Duration				
First Year	1.00 (ref)	1.31 (0.93-1.86)	1.33 (0.94-1.91)	
Later Years	1.00 (ref)	0.79 (0.31-2.02)	1.61 (0.87-3.00)	

Data presented as hazard ratio (95% confidence interval).

Models adjusted for age, race, sex, region of residence, education, season the accelerometer was worn, current smoking, alcohol use, body mass index, diabetes, hypertension, dyslipidemia, history of coronary heart disease, and stroke, and mean MVPA.

The tertile cutoff points were <709.7, ≥709.7 to <782.6, ≥782.6 min/16-h day for total sedentary time and <8.3, ≥8.3 to <11.3, and ≥11.3 min/bout for sedentary bout duration.

eReferences.

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