Nature and Science of Sleep

Elevate Series

Open Access Full Text Article

ORIGINAL RESEARCH

Impact of Replacing Sedentary Behavior with Physical Activity and Sleep on Stroke Risk: A Prospective Cohort Study

Xiao-Fang Dong[1], Qiang Zhang[2], Jia-Ning Wei[2], Qian-Yu Zhou[3], Fan-Jia-Yi Yang[2], Yan-Jin Liu[4], Yu-Sheng Li[5], Chang-Qing Sun[2,3]

[1]Department of Endocrinology and Metabolic Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [2]School of Nursing and Health, Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [3]Department of Epidemiology and Biostatistics, Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [4]Department of Nursing, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China; [5]Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, People's Republic of China

Correspondence: Chang-Qing Sun, School of Nursing and Health, Zhengzhou University, NO. 101 Kexue Road, High-Tech Development Zone of District, Zhengzhou, Henan, People's Republic of China, Email suncq@zzu.edu.cn

Objective: Our research explores how leisure-time sedentary behavior (SB) correlates with stroke risk. Additionally, we utilize the isotemporal substitution model (ISM) to examine how replacing brief durations of leisure-time SB with light physical activity (LPA), moderate physical activity (MPA), vigorous physical activity (VPA), and sleep might influence the risk of stroke.

Methods: This investigation tracked 478,198 participants from the UK Biobank. Data regarding individual leisure-time SB and PA were collected through a standardized questionnaire. A Cox proportional hazards model, alongside an isotemporal substitution model (ISM), was utilized.

Results: We identified 10,003 cases of incident stroke over 12.7 years. When compared to participants who engaged in leisure-time SB for less than 4 hours per day, the hazard ratios (HRs) for stroke incidence increased with more prolonged leisure-time SB: HRs were 1.06 (95% CI: 1.01 to 1.11) for 4–6 h/d, 1.16 (95% CI: 1.10 to 1.23) for 6–8 h/d, and 1.24 (95% CI: 1.15 to 1.33) for over 8 h/d. According to the ISM analysis, substituting leisure-time SB with various forms of PA could markedly reduce stroke risk. For individuals sleeping ≤8h/d, replacing one hour of leisure-time SB with an equivalent duration of LPA, VPA, or sleep corresponded to a 3.0%, 7.0%, and 22.0% decrease in stroke risk, respectively. Meanwhile, for those already sleeping more than 8h/d, substituting one hour of leisure-time SB with an equivalent duration of LPA or VPA resulted in a notable decrease in the risk of stroke by 6.0% and 18.0%, respectively.

Conclusion: The findings demonstrate that leisure-time SB and unhealthy sleep durations are confirmed risk factors for stroke. For individuals sleeping 8 hours or less per day, and for those who sleep more than 8 hours, substituting SB with an adequate amount of sleep or engaging in VPA, respectively, emerges as an effective strategy for reducing stroke risk.

Keywords: stroke, isotemporal substitution model, physical activity, sedentary behavior, sleep

Introduction

Stroke represents a significant global health challenge, known for its high rates of occurrence, re-occurrence, mortality, morbidity, and overall impact on health systems. As of 2019, stroke ranks as the third leading cause of combined death and disability worldwide and is the second leading cause of death globally.[1] Forecasts indicate that by 2030, there will be an increase of 3.4 million US adults aged 18 and older who have experienced a stroke, equating to 3.9% of the adult population. This marks a 20.5% rise in the incidence rate compared to 2012.[2] Thus, it is essential to identify cost-effective methods to minimize the widespread impact of stroke.

Sedentary behavior (SB), identified as any activity performed while awake involving sitting, reclining, or lying down positions that require minimal energy expenditure,[3] has seen a marked increase in the United States throughout the past twenty years.[4,5] Given its widespread nature, the WHO recently updated its PA and SB guidelines to include advice on decreasing SB.[3] Moreover, it has been suggested that extended periods of SB are associated with an elevated risk of all-cause mortality.[6]

Received: 2 July 2024
Accepted: 1 October 2024
Published: 13 October 2024

SB has been recognized as a distinct risk factor for various chronic conditions independently of PA, such as cardiovascular disease (CVD),[7] diabetes,[8] irritable bowel syndrome,[9] and cognitive decline.[10] Recent systematic reviews also signify that lengthy sedentary duration correlate with an elevated risk of stroke.[11–13] Nevertheless, the connections between SB and stroke were previously recognized only in past cross-sectional studies. Therefore, any potential reductions in risk associated with decreasing SB are contingent upon what activity replaces SB, such as specific forms of PA or sleep. Considering the close ties between sleep duration and stroke risk,[14] an intriguing question emerges about whether adequate sleep could serve as a more effective alternative to SB in diminishing stroke risk. Currently, public health guidelines are promoting the idea that individuals should sit less, move more and sleep well, comprehensive evidence regarding the impact of replacing SB with varying intensities of PA and sleep on stroke risk remains scarce, especially in large longitudinal studies and among individuals not meeting recommended sleep durations.[15]

The isotemporal substitution model (ISM) has recently emerged as a pivotal methodology for evaluating the health impact of displacing a specific duration of leisure-time SB with an equivalent amount of PA, while keeping overall discretionary time constant.[16] This innovative approach offers the possibility to quantify the health benefits of reallocating time normally spent in sedentary pursuits to different forms of PAs, providing valuable insights that could inform public health guidelines. A recent systematic review, analyzing compositional data from one prospective and seven cross-sectional studies, identified notable associations between sleep, SB, and PA concerning health outcomes among adults.[17] Similarly, findings from a study utilizing data from the UK Biobank have illustrated significant cardiovascular health benefits when SB is replaced with various everyday activities or structured exercises.[18] Despite these advances, data exploring the use of the ISM to specifically investigate the potential advantages of substituting SB with different intensities of PA or sleep for reducing stroke risk remains scant, especially in the context of a prospective cohort study with a large participant pool. This gap highlights a crucial area for future research, emphasizing the need for comprehensive studies to elucidate the impact of such behavioral modifications on stroke prevention.

To augment the current evidence regarding the impact of SB and to support the creation and assessment of PA interventions, our research investigated the forward-looking associations between the length of leisure-time SB and the risk of stroke, utilizing data from the UK Biobank. Our goal was to ascertain if the risk of stroke could be affected by SB. Specifically, we prospectively analyzed the potential decrease in stroke risk that could be achieved by replacing brief intervals of leisure-time SB with light physical activity (LPA), moderate physical activity (MPA), vigorous physical activity (VPA), and sleep using the ISM.

Methods

Study Design and Participants

This research employed a prospective, population-based cohort approach, incorporating individuals from the UK Biobank. Recruitment occurred from March 2006 through December 2010, during which time 502,413 adults aged between 40 and 69 years from the broader UK population were enlisted.[19] These participants contributed detailed health information via questionnaires, underwent physical examinations, and provided biological samples at one of 22 assessment centers located throughout England, Scotland, and Wales. Comprehensive details regarding the study's methodology and measurements have been detailed in prior publications.[19]

From the initial cohort of the UK Biobank's 502,413 participants, exclusions were made as follows: 1,283 participants who withdrew from the study during the follow-up period, 7,741 individuals diagnosed with stroke either at the baseline or within the initial two years, 1,682 participants lacking reliable SB data, 9,441 individuals without dependable PA data, and 4068 participants missing sleep data. Following these exclusions, the main analysis was conducted with a remaining cohort of 478,198 participants.

Exposure Variables

Leisure-time SB were assessed through self-reporting using questionnaires at the study's baseline. Participants provided details on their typical daily time allocation for three prevalent leisure-time SB among adults: watching television, using a computer, and driving. The aggregate duration spent on these three activities constituted the total length of SB. This

total SB time was then classified into four distinct categories: less than 4.0 hours per day, 4.0 to 6.0 hours per day, 6.0–8.0 hours per day, and more than 8.0 hours per day.

For PA, the baseline questionnaire of the UK Biobank incorporated adaptations from the short form of the International Physical Activity Questionnaire (IPAQ).[20]

The questions captured the frequency and duration of three different intensity of activities (light, moderate, and vigorous). The number of days per week that participants engaged in each level of physical activity was multiplied by the number of minutes spent per day doing that activity. This gave the total number of minutes spent per week engaged in each activity category, then we calculate the mean hours spent per day.

It included items that measured the frequency and duration of engagement in activities of three different intensities: walking for pleasure, moderate activity, and vigorous activity.

Sleep duration was also determined via self-report. Participants answered the question, "About how many hours of sleep do you get in every 24h?". Sleep data were segmented based on guidelines recommending 8 hours as the healthy sleep duration threshold.[21]

Outcome Ascertainment

This study included three outcomes: stroke, ischemic stroke (IS), and hemorrhagic stroke (HS). The diagnosis of all outcomes was obtained through linkage with hospital inpatient records, death registers, primary care records, and self-reported. All outcome events were diagnosed according to their International Classification of Diseases 10th revision code. Follow-up time was started from the date at first attendance to the assessment center to the earliest date of stroke, IS and HS diagnosis, death or the censor date, whichever occurred first. This study was performed in complied with the STROBE protocol.

Covariates

The analysis took into account the following potential confounding factors: age, gender, ethnicity, education, income, employment status, Townsend Index, smoking status, alcohol consumption, body mass index, triglycerides, blood glucose, systolic and diastolic blood pressure, diabetes, cancer, broad depression, and hypertension.

Statistical Analysis

We summarized baseline characteristics by leisure-time SB using descriptive statistics, reporting means and standard deviations (SDs) for continuous variables with a normal distribution, and medians with interquartile ranges for those with a non-normal distribution.

To investigate the relationship between leisure-time SB and the incidence of stroke, we employed Cox proportional hazards models. These models allowed us to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs), comparing groups with different levels of leisure-time SB. Specifically, participants who reported less than 4 hours of leisure-time SB per day were used as the reference group for our analyses. Model 1 was adjusted for age, gender, ethnicity, and BMI. Model 2 included additional adjustments for TDI, education, average household income, employment status, smoking status, alcohol intake, PA, sleep duration, and major diseases. To explore the potential non-linear relationships between leisure-time SB and the incidence of stroke, we utilized restricted cubic spline functions.

Second, An ISM analysis was employed to assess how substituting leisure-time SB with various intensities of PA and different sleep durations might impact stroke risk. The ISM was also evaluated separately according to sex, age, BMI, ethnic background, and sleep duration to explore whether the isotemporal effects of PA and sleep varied among different subgroups.

Additionally, to ensure the reliability of the primary results, a sensitivity analysis was performed. To mitigate the impact of reverse causality, we repeated the main stroke incidence outcomes models after excluding participants who had a stroke within the first two years of follow-up. To address the competing risk of mortality, the Fine and Gray subdistribution model was used to explore the association between SB and outcome incidence. Competing risk of mortality refers to a situation in which there are multiple different events or conditions that can independently lead to death, and these events compete with each other.

All analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing). A p value < 0.05 was considered statistically significant (two-sided).

Results

Study Sample

Over an average follow-up period of 12.7 years, 10,003 stroke cases were recorded among 478,198 participants in the UK Biobank study. The overall response rate was 99.7% (478,198/479,481). Responder bias was assessed by examining age, gender, smoking, drinking and BMI. Respondents did not differ from non-respondents in these demographics and health factors. As detailed in Table 1, Participants who engaged in high levels of leisure-time SB (>8 h/d) tended to be

Table 1 UK Biobank Participant Characteristics by Leisure-Time SB Time (n=478,198)

Characteristic	Total n=478,198	<4.0 n=231,075	4.0 to <6.0 n=153,461	6.0 to <8.0 n=60,131	>8.0 n=33,531	*P*
Age (year)	56.5 (8.1)	55.9 (8.1)	57.3 (7.9)	57.4 (8.0)	55.4 (8.1)	<0.001
Gender						<0.001
Female	262,896 (54.9%)	144,757 (62.6%)	80,499 (52.4%)	26,248 (43.6%)	11,392 (33.9%)	
Male	215,302 (45.1%)	86,318 (37.4%)	72,962 (47.6%)	33,883 (56.4%)	22,139 (66.1%)	
Average household income						<0.001
<18,000	110,738 (23.2%)	48,567 (21.0%)	36,819 (23.9%)	16,417 (27.3%)	8,935 (26.6%)	
18,000 to 30,999	122,147 (25.5%)	56,294 (24.3%)	40,971 (26.7%)	16,266 (27.0%)	8,616 (25.6%)	
31,000 to 51,999	123,682 (25.8%)	60,213 (26.0%)	39,978 (26.0%)	15,085 (25.0%)	8,406 (25.0%)	
52,000 to 100,000	96,112 (20.0%)	50,785 (21.9%)	29,020 (18.9%)	10,164 (16.9%)	6,143 (18.3%)	
≥100,000	25,519 (5.5%)	15,216 (6.8%)	6,673 (4.5%)	2,199 (3.8%)	1,431 (4.5%)	
Ethnic background						<0.001
White	433,830 (90.7%)	207,194 (89.6%)	141,573 (92.2%)	55,104 (91.6%)	29,959 (89.3%)	
Other ethic group	44,368 (9.3%)	23,881 (10.4%)	11,888 (7.8%)	5,027 (8.4%)	3,572 (10.7%)	
Employed status						<0.001
Working	278,117 (58.1%)	144,514 (62.5%)	82,173 (53.5%)	30,365 (50.5%)	21,065 (62.8%)	
Retired	160,913 (33.6%)	69,126 (29.9%)	59,549 (38.8%)	23,808 (39.5%)	8,430 (25.1%)	
Unemployed	7,754 (1.8%)	2,827 (1.3%)	2,434 (1.7%)	1,431 (2.5%)	1,062 (3.3%)	
Others	31,414 (6.5%)	14,608 (6.3%)	9,305 (6.0%)	4,527 (7.5%)	2,974 (8.8%)	
TDI	−1.4 (3.06)	−1.3 (3.07)	−1.6 (2.9)	−1.3 (3.1)	−0.76 (3.3)	<0.001
BMI (kg/m^2)	27.4 (4.8)	26.5 (4.5)	27.8 (4.7)	28.7 (4.9)	29.3 (5.3)	<0.001
Smoking						
Never	263,789 (55.2%)	136,887 (59.2%)	81,867 (53.3%)	29,327 (48.8%)	15,708 (46.8%)	
Previous	165,406 (34.5%)	73,274 (31.7%)	56,018 (36.5%)	23,434 (38.9%)	12,680 (37.8%)	
Current	49,003 (10.3%)	20,914 (9.1%)	15,576 (10.2%)	7,370 (12.3%)	5,143 (15.4%)	
Drinking						<0.001
Never	20,627 (4.3%)	11,281 (4.9%)	5,517 (3.6%)	2,330 (3.9%)	1,499 (4.5%)	
Previous	16,553 (3.5%)	7,708 (3.3%)	4,931 (3.2%)	2,338 (3.9%)	1,576 (4.7%)	
Current	441,018 (92.2%)	212,086 (91.8%)	143,013 (93.2%)	55,463 (92.2%)	30,465 (90.8%)	
Sleep duration (h/day)						<0.001
≤8 hours	303926 (63.6%)	147,981 (64.1%)	96,088 (62.5%)	37,640 (62.6%)	22,217 (66.3%)	
>8 hours	174,272 (36.4%)	83,094 (35.9%)	57,373 (37.5%)	22,491 (37.4%)	11,314 (33.7)	
Physical activity (min/day)						
LPA	34.3 (24.1,29.8)	34.3 (17.2,68.6)	34.3 (17.2,68.6)	30.00 (14.3,68.6)	22.3 (11.4,51.4)	
MPA	22.9 (8.6,51.4)	25.7 (8.9,51.4)	22.9 (8.6,51.4)	21.4 (8.6,51.4)	17.1 (8.6,35.7)	
VPA	8.6 (4.3,22.9)	8.6 (4.3,25.7)	8.6 (4.3,21.4)	8.6 (4.3,19.2)	8.6 (2.9,17.1)	
Major diseases						
Hypertension	113,767 (23.8%)	47,410 (20.1%)	39,133 (25.5%)	17,239 (28.7%)	9,985 (29.7%)	<0.001
Diabetes	24,104 (5.0%)	8,541 (3.7%)	8,148 (5.3%)	4,359 (7.2%)	3,056 (9.1%)	<0.001
Cancer	110,444 (23.1%)	51,049 (22.1%)	37,267 (24.3%)	14,919 (24.8%)	7,209 (21.5%)	<0.001
Depression	111,880 (23.4%)	52,137 (22.5%)	34,797 (22.6%)	15,270 (25.4%)	9676 (28.8%)	<0.001
Education (year)	9.6 (3.7,20.5)	8.3 (3.0,18.7)	9.9 (3.9,20.7)	11.1 (4.6,23.3)	12.8 (5.3,26.4)	<0.001
Blood glucose (mmol/d)	5.1 (1.2)	5.0 (1.1)	5.1 (1.2)	5.2 (1.4)	5.2 (1.5)	<0.001
Systolic blood pressure (mm Hg)	139.6 (19.7)	136.5 (20.0)	140.7 (19.5)	141.4 (19.3)	140.2 (18.9)	<0.001
Diastolic blood pressure (mm Hg)	82.2 (10.7)	80.4 (10.8)	82.6 (10.6)	83.3 (10.6)	83.7 (10.8)	<0.001
Triglycerides (mmol/d)	1.73 (1.0)	1.6 (0.9)	1.79 (1.0)	1.9 (1.1)	1.9 (1.1)	<0.001

Abbreviations: TDI, Townsend Index; BMI, body mass index; LPA, light physical activity; MPA, moderate physical activity; VPA, vigorous physical activity.

predominantly male and have a higher prevalence of overweight or obesity. This group was also more inclined to be current alcohol consumers and to have chronic health issues.

Association Between Different Leisure-Time SB with Stroke, is and HS Incidence

Our analysis revealed a clear connection between increased duration of leisure-time SB and a heightened risk of stroke as shown in Table 2. In Model 1, when comparing participants with the lowest level of leisure-time SB (<4 h/d) to those with higher levels, the hazard ratios (HRs) for stroke escalated progressively: 1.06 (95% CI: 1.01 to 1.11) for those engaging in 4 to 6 hours/day, 1.16 (95% CI: 1.10 to 1.23) for 6 to 8 h/d, and 1.24 (95% CI: 1.15 to 1.33) for over 8 h/d of SBs. Specifically, for those in the leisure-time SB categories of 4 to 6 h/d, 6 to 8 h/d, and over 8 h/d, the adjusted HRs for stroke were 1.04 (95% CI: 1.00 to 1.09), 1.11 (95% CI: 1.04 to 1.18), and 1.14 (95% CI: 1.05 to 1.23) respectively, compared to the lowest SB category (<4 h/d).Divergent patterns emerged when examining the outcomes for IS and HS independently, as detailed in Table 3.

Replacing Leisure-Time SB with PAs and Healthy Sleep Using the ISM

Across the whole population, as shown in Table 4, substituting 1 h/d of SB with an equivalent duration of PA was associated with a notable reduction in stroke risk, varying by the intensity of the activity: LPA yielded a 4% risk reduction, MPA a 1% reduction, and VPA a 9% reduction. Specifically, substituting 1 hour of SB with LPA resulted in reduced stroke risk (HR=0.96, 95% CI: 0.94 to 0.98), highlighting the importance of the PA's intensity.

Table 2 Association Between Leisure-Time SB and the Incidence of Stroke

Sedentary Time (h/d)	Case/n	Model 1		Model 2	
		HR (95% CI)	*P*	HR (95% CI)	*P*
<4	231,075	1 (reference)		1 (reference)	
4–6	153,461	**1.06 (1.01,1.11)**	**0.01**	1.04 (1.00,1.09)	0.064
6–8	60,131	**1.16 (1.10,1.23)**	**<0.001**	**1.11 (1.04,1.18)**	**<0.001**
≥8	33,531	**1.24 (1.15,1.33)**	**<0.001**	**1.14 (1.05,1.23)**	**<0.001**

Notes: Model 1: age, gender, ethnicity and body mass index. Model 2: Model 1 plus Townsend deprivation index, education, average household income, employed status, smoking status, alcohol intake, physical activity, sleep duration, major diseases. Bold text means that *P*< 0.05.

Table 3 Association Between Leisure-Time SBs and the Incident of is and HS

Sedentary Time (h/d)	Case/n	Model 1		Model 2	
		HR (95% CI)	*P*	HR (95% CI)	*P*
IS					
<4	231,075	1 (reference)		1 (reference)	
4–6	153,461	**1.06 (1.01,1.12)**	**0.03**	1.04 (0.99,1.10)	0.11
6–8	60,131	**1.18 (1.10,1.26)**	**<0.001**	**1.12 (1.05,1.20)**	**<0.001**
≥8	33,531	**1.28 (1.18,1.39)**	**<0.001**	**1.17 (1.08,1.27)**	**<0.001**
IH					
<4	231,075	1(reference)		1 (reference)	
4–6	153,461	0.97 (0.87,1.09)	0.613	0.97 (0.87,1.08)	0.556
6–8	60,131	1.02 (0.88,1.19)	0.758	1.00 (0.86,1.16)	0.969
≥8	33,531	1.07 (0.88,1.30)	0.505	1.02 (0.84,1.25)	0.809

Notes: Model 1: age, gender, ethnicity and body mass index. Model 2: Model 1 plus Townsend deprivation index, education, average household income, employed status, smoking status, alcohol intake, physical activity, sleep duration, major diseases. Bold text means that *P*< 0.05.
Abbreviations: HR, hazard ratio; IS, ischemic stroke; HS, hemorrhagic stroke.

Table 4 ISM of the Association of Time Reallocation in SB to PA and Sleep and the Risk of Stroke

Whole Population	HR (95% CI)	*P*
≤8 h/d	**0.82 (0.79,0.92)**	**<0.001**
>8 h/d	**1.02 (1.00,1.04)**	**0.02**
LPA	**0.96 (0.94,0.98)**	**<0.001**
MPA	0.99 (0.97,1.00)	0.270
VPA	**0.91 (0.86,0.97)**	**0.002**
Sleep duration≤8 h/d		
LPA	**0.97 (0.95,0.98)**	**<0.001**
MPA	1.01 (0.99,1.03)	0.535
VPA	**0.93 (0.89,0.98)**	**0.007**
Sleep duration	**0.78 (0.74,0.83)**	**<0.001**
Sleep duration>8 h/d		
LPA	**0.94 (0.90,0.99)**	**0.03**
MPA	0.99 (0.96,1.02)	0.521
VPA	**0.82 (0.79,0.85)**	**<0.001**
Sleep duration	1.02 (0.99,1.04)	0.19

Note: Bold text means that *P*< 0.05.

Further analyses revealed that the beneficial effect of substituting sleep for leisure-time SB was especially significant for individuals with ≤8 h/d of sleep, showing a striking 22% lower stroke risk (95% CI: 0.74 to 0.83). For those not getting enough sleep, replacing 1 h/d of leisure-time SB with LPA, VPA, and sleep led to a 3.0% (95% CI: 0.95 to 0.98), 7.0% (95% CI: 0.89 to 0.98), and 22.0% (95% CI:0.74 to 0.83) decreased risk of stroke, respectively. Among participants already sleeping more than 8 h/d, reallocating 1 hour of leisure-time SB to LPA or VPA showed a significant association with a 6.0% (95% CI: 0.90 to 0.99) and 18.0% (95% CI: 0.79 to 0.85) reduction in stroke risk, respectively. The substitution with MPA provided a positive but slight benefit (HR=0.99, 95% CI: 0.96 to 1.02).

In terms of secondary outcomes like IS and HS, reallocating 1 h/d of leisure-time SB with equivalent durations of sleep, LPA, MPA, and VPA showed protective effects against IS incidence, as detailed in Table 5.

Sensitivity Analysis

Upon adjusting for all factors in model 2, a cubic spline model revealed a significant non-linear J-shaped relationship between age and the risk of stroke (Figure 1). The risk was found to be lowest at the age of 58. Individuals below the age of 58 exhibited a reduced stroke risk, with a HR of 0.31 (95% CI: 0.29 to 0.32) (Figure 2). Specifically, the stroke risk was 18% lower in individuals with a BMI under 27 kg/m^2 in comparison to individuals with a BMI over 27 kg/m^2 (Figure 3).

Table 5 ISM of the Association of Time Reallocation in SB to PA and Sleep and the Risk of is and HS

Whole Population	IS		HS	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
≤8 h/d	**0.89 (0.87,0.94)**	**<0.001**	0.94 (0.83, 1.06)	0.28
>8 h/d	**1.04 (1.03,1.05)**	**<0.001**	1.11 (0.81,1.53)	0.51
LPA	**0.96 (0.92,0.99)**	**0.009**	1.13 (0.85, 1.50)	0.390
MPA	1.00 (0.98,1.03)	0.827	1.11 (0.81, 1.53)	0.515
VPA	**0.92 (0.87,0.98)**	**0.007**	0.84 (0.61, 1.46)	0.789

Note: Bold text means that *P*< 0.05.
Abbreviations: IS, ischemic stroke; HS, hemorrhagic stroke (HS).

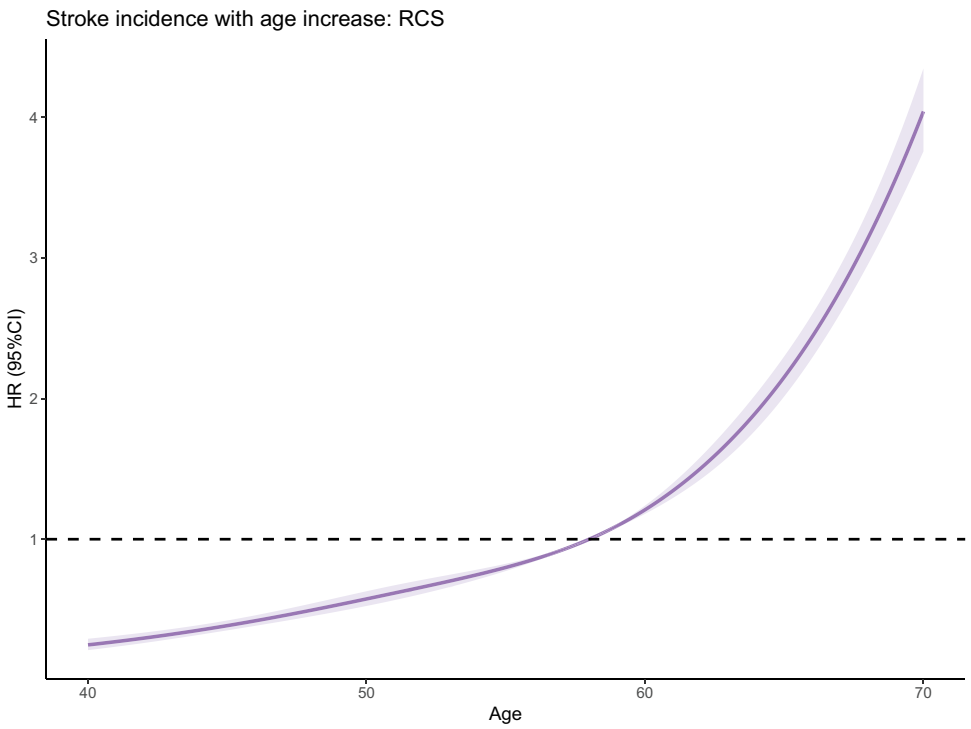

Figure 1 Dose-response association between age and stroke incidence.

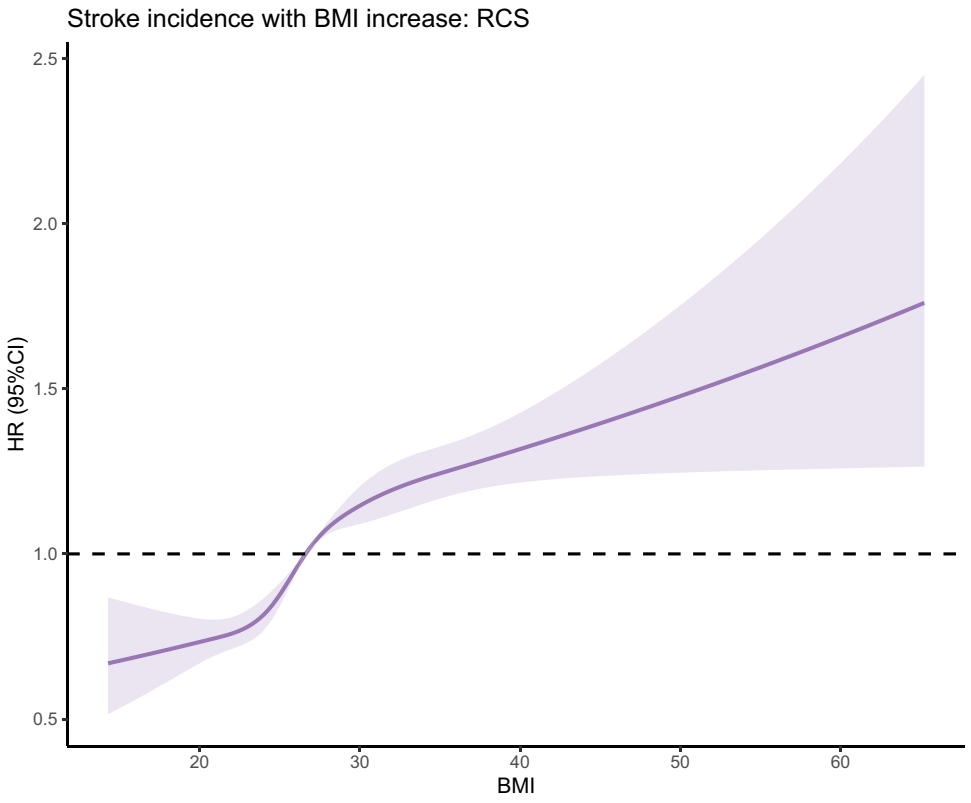

Figure 2 Dose-response association between BMI and stroke incidence.

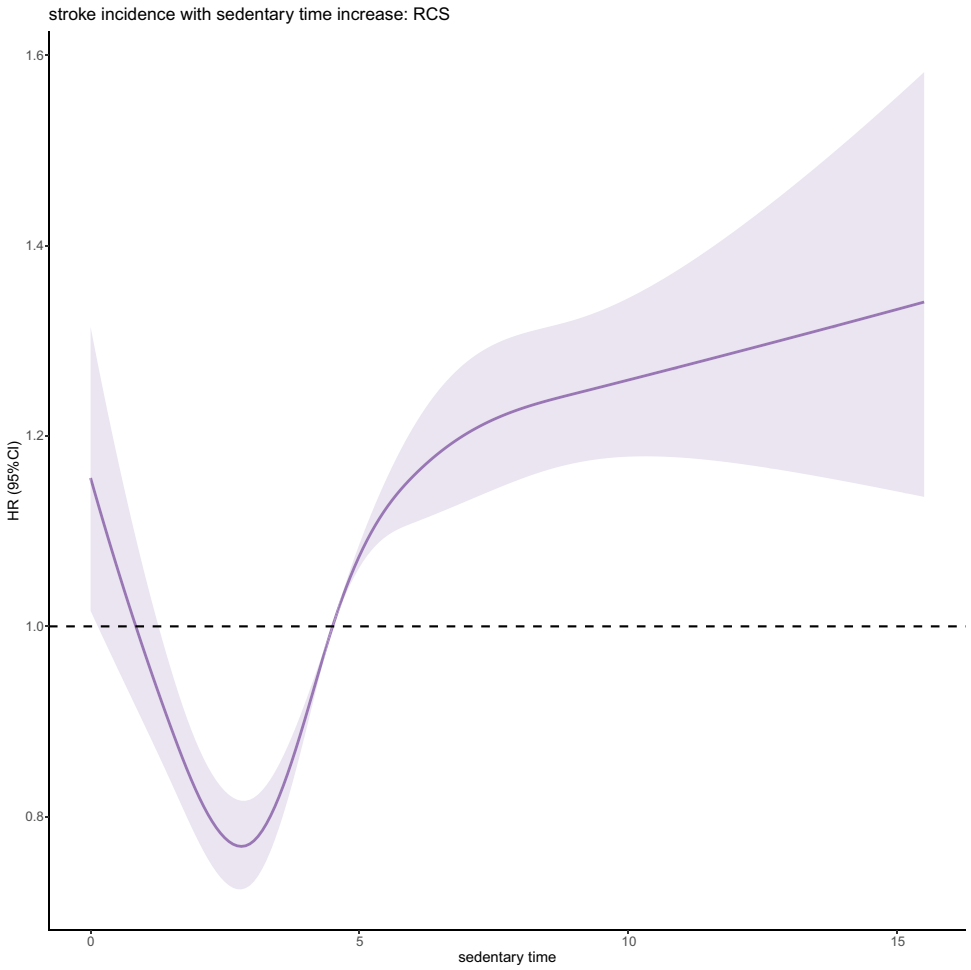

Figure 3 Dose-response association between leisure-time sedentary behavior and stroke incidence.

Discussion

This extensive cohort research, involving close to 500,000 participants across a follow-up period of 12 years, has produced substantial results. Firstly, it was observed that extended periods of leisure-time SB were linked to an increased risk of stroke. Secondly, substituting 1 h/d of leisure-time SB with an equivalent duration of PAs resulted in a 4–9% reduction in stroke risk, underscoring the importance of the PA's intensity in its effectiveness. Thirdly, for those averaging less than 8 hours of sleep nightly, replacing leisure-time SB with sleep resulted in the most substantial decrease in stroke risk. Conversely, for individuals sleeping more than 8 hours per day, engaging in VPA emerged as the optimal strategy for minimizing stroke risk. These insights strongly emphasize the benefits of adopting an active lifestyle through either an increase in PA or enhancement of sleep quality as strategic preventive measures against stroke.

The association identified in our study, linking increased leisure-time SB with a heightened risk of stroke, echoes findings from previous research.[22] These congruent findings underscore the potential of non-pharmacological interventions, focused on elevating daily PA levels and reducing SB, to significantly lower the risk of stroke. In the pursuit of effective interventions, the past decade has seen various randomized controlled trials and qualitative studies aiming to establish physical treatment protocols specifically for stroke rehabilitation.[23–27] However, the widespread application and generalizability of such interventions in clinical practice remain uncertain. Further research is crucial to validate these interventions across different populations and settings, considering the diverse climatic, socioeconomic, and cultural factors that might affect their effectiveness.

Sleep serves as a fundamental aspect of human health,[28] playing a critical role in reducing mortality rates associated with various conditions including all-cause mortality, CVD, cancer, and other major chronic illnesses.[21,29] Consistent with findings from a prior review,[30,31] we discovered that among individuals not getting enough sleep, substituting leisure-time SB with sleep resulted in the most significant decrease in the risk of stroke. The interplay between the duration of sleep and the risk of stroke is multifaceted. Our research underscores the importance of maintaining a healthy sleep pattern, not only to support overall well-being but as a preventative measure against future stroke risk. Sleep and PA are not isolated behaviors but may influence one another. When assessing the health benefits of PA, many studies group MPA and VPA into moderate-to-vigorous physical activity (MVPA). In our analysis, VPA was more effective in reducing stroke risk compared to MPA, particularly among individuals who already get sufficient sleep. The complexities of the relationship between sleep and stroke may be further elucidated by findings from a prior investigation,[32] which suggested a connection between VPA and enhanced sleep quality among elderly individuals. Our age group-specific sensitivity analysis also corroborated this finding.

Various mechanisms might account for the protective link observed with PA in the ISM analyses. An expanding corpus of research indicates that PA is associated with traditional modifiable risk factors.[33,34] Moreover, substituting leisure-time SB with PA contributes to a range of cardiometabolic health advantages,[35–37] such as lower BMI, reduced visceral fat, decreased insulin resistance and triglyceride levels.[38] This suggests that engaging in regular PA contributes to lowering the risk of stroke through mechanisms that extend beyond the mitigation of these conventional risk factors.[39] Our research further supported this observation. Therefore, the advantageous effects of PA extend beyond the modification of risk factors. It has been discovered that increased levels of PA positively influence carotid artery flexibility, the availability of nitric oxide, and endothelial dysfunction.[40,41] These biological mechanisms enhance cardiovascular health by boosting cerebral blood flow and brain volume, concurrently slowing down the natural reduction in the density of cerebral tissue.[42] Also, excessive leisure-time SB, on the other hand, has been linked with a rise in inflammatory markers, including adipokines and C-reactive protein (CRP).[43]

Clinical Implications

The study reveals critical insights with profound implications for clinical practice and public health strategies aimed at the primary prevention of stroke. It challenges existing assumptions regarding the limited options for counteracting non-modifiable risk factors. By demonstrating the tangible benefits of interventions such as regular PA, this research opens new avenues for reducing stroke risk that transcend traditional beliefs about the immutable nature of certain risk factors. This underscores the potential for lifestyle modifications to play a crucial role in stroke prevention, even in the presence of non-modifiable risk elements. Encouraging a shift towards a more active lifestyle, with decreased SB and increased daily activities, could serve as practical clinical advice. Everyday activities such as gardening, cutting the grass, and along with deliberate physical activities such as dancing, jogging, and rope skipping can have a favorable impact. The reality faced by the majority of stroke survivors includes dealing with lasting impairments such as hemiparesis, spasticity, cognitive dysfunction, and aphasia, with only a fraction achieving full recovery. These impairments often lead to activity limitations and a chronic sedentary lifestyle.[44] Our findings emphasize the potential of even modest increases in PA, such as replacing 1 h/d of leisure-time SB with LPA, to reduce stroke risk by 4%. This highlights the importance of incorporating more PA into daily routines for stroke prevention in clinical settings. Considering the perspective of public health, converting these epidemiological insights into practical measures involves promoting specific types of PAs and ensuring adequate sleep as part of daily routines. Since leisure-time SB, PAs, and sleep are integral components of everyone's life, the implementation primarily involves reallocating time rather than introducing entirely new behaviors. This transition towards increasing VPA or enhancing sleep quality and duration, based on individual needs, is not only manageable but also cost-effective. Such interventions offer a practical and accessible method for reducing the risk of stroke across the population, emphasizing the significance of lifestyle modifications in preventative health strategies.

Limitations

Our study boasts several strengths, including a large cohort design, consistent collection of variable information, and the utilization of an ISM. These aspects make the epidemiological findings easily understandable and applicable from a public health standpoint. Nonetheless, the study is subject to several potential limitations. Firstly, owing to the study's

observational design, caution should be exercised when drawing exact conclusions about causality, as we cannot entirely rule out residual confounding. Second, the measurements of leisure-time SB, PAs, and sleep were assessed through subjective reporting, a method that is widely recognized for its potential to introduce measurement bias. Recently, the UK Biobank has commenced objective measurement of activity levels using 7-day accelerometers in a subset of participants.[45] Although the accelerometer data provides valuable insights, the follow-up period subsequent to data collection is markedly short, limiting a comprehensive assessment of various health conditions. Furthermore, the relatively small sample size constrains the robustness of the findings. Third, our study's definition of leisure-time SB was limited to television watching, computer use, and driving. Other significant contributors to daily sedentary time, such as occupational SB, were not considered, which limits the generalizability of our conclusions to total SB. Future research should aim to include these aspects by expanding the analysis to encompass total SB, ideally incorporating accelerometer data. Fourth, leisure-time SB, PAs, and sleep patterns were exclusively evaluated at the initial stage of the study. The lack of subsequent data on how these behaviors evolved over the follow-up period limits our ability to determine the impact of any changes in these behaviors on health outcomes. Fifth, our findings were derived from hypothetical modeling based on existing cohort data. While ISM presents a more realistic approach compared to some traditional methods, it remains a mathematical technique that cannot replace experimental evidence. Finally, the predominance of volunteers of European ancestry and a higher socioeconomic status within the UK Biobank cohort narrows the representation of the broader population. This limitation underscores the pressing need for additional research that includes well-designed studies encompassing more diverse populations, thereby broadening the scope and applicability of these findings.

Conclusion

This prospective, population-based study demonstrated a positive correlation between leisure-time SB and the incidence of stroke risk. Furthermore, it demonstrated that substituting leisure-time SB with PA and maintaining healthy sleep duration could significantly reduce the risk of stroke. These findings suggest practical and achievable strategies for the general population to decrease time spent in leisure-time SB as a means to prevent or delay the onset of stroke. These findings underscore the necessity for future studies that not only engage larger participant groups but also implement advanced precision tools, such as wearable monitors or accelerometers, to accurately measure activity levels. Undertaking such research is paramount to fully comprehend how healthy behaviors, notably consistent exercise and quality sleep, contribute to the prevention of stroke.

Data Sharing Statement

The data for this study are housed in a public, open access repository. Specifically, the data utilized originated from the freely accessible UK Biobank Resource, with access granted through application number 71051. However, these data are not permitted to be shared directly with other researchers.

Ethical Approval and Consent to Participate

This research includes human subjects and utilized data obtained from the publicly accessible UK Biobank Resource, with the permission granted under application number 71051. The UK Biobank is approved as a research tissue bank by the North West Multicentre Research Ethics Committee, which also oversaw this study. Before taking part in the study, all participants gave their written informed consent, affirming their agreement to participate in the research.

Acknowledgments

This research was conducted utilizing data from the UK Biobank Resource, under application number 71051. Our gratitude extends to both the participants and the researchers of the UK Biobank for their contributions. This paper has been uploaded to ResearchSquare as a preprint: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4796043.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

The study received financial support from several sources, including the National Natural Science Foundation of China (Grant No. 72274179), the Medical Science and Technology Project of Henan Province (Grant No. LHGJ20220430), and the Nursing Science Foundation of the First Affiliated Hospital of Zhengzhou University (Grant No. HLKY2023017). It should be emphasized that the funding organizations played no role in any phase of the research, including its conception and implementation, the gathering, handling, analysis, or understanding of the data, or in the creation, revision, or endorsement of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Collaborators GS. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. 2021;20:795–820. doi:10.1016/s1474-4422(21)00252-0
2. Ovbiagele B, Goldstein LB, Higashida RT, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke*. 2013;44:2361–2375. doi:10.1161/STR.0b013e31829734f2
3. Bull FC, Al-Ansari SS, Biddle S, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med*. 2020;54:1451–1462. doi:10.1136/bjsports-2020-102955
4. Lavie CJ, Ozemek C, Carbone S, et al. Sedentary behavior, exercise, and cardiovascular health. *Circ Res*. 2019;124:799–815. doi:10.1161/circresaha.118.312669
5. Omura JD, Whitfield GP, Chen TJ, et al. Surveillance of physical activity and sedentary behavior among youth and adults in the United States: history and opportunities. *J Phys Act Health*. 2021;18:S6–s24. doi:10.1123/jpah.2021-0179
6. Ekelund U, Tarp J, Steene-Johannessen J, et al. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ*. 2019;366:l4570. doi:10.1136/bmj.l4570
7. Del Pozo Cruz B, Ahmadi M, Inan-Eroglu E, et al. Prospective associations of accelerometer-assessed physical activity with mortality and incidence of cardiovascular disease among adults with hypertension: the UK Biobank study. *J Am Heart Assoc*. 2022;11:e023290. doi:10.1161/jaha.121.023290
8. Patterson R, McNamara E, Tainio M, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol*. 2018;33:811–829. doi:10.1007/s10654-018-0380-1
9. Gao X, Tian S, Huang N, et al. Associations of daily sedentary behavior, physical activity, and sleep with irritable bowel syndrome: a prospective analysis of 362,193 participants. *J Sport Health Sci*. 2023;13:72–80. doi:10.1016/j.jshs.2023.02.002
10. Sun Y, Chen C, Yu Y, et al. Replacement of leisure-time sedentary behavior with various physical activities and the risk of dementia incidence and mortality: a prospective cohort study. *J Sport Health Sci*. 2023;12:287–294. doi:10.1016/j.jshs.2022.11.005
11. Wang Z, Jin X, Liu Y, et al. Sedentary behavior and the risk of stroke: a systematic review and dose-response meta-analysis. *Nutr Metab Cardiovasc Dis*. 2022;32:2705–2713. doi:10.1016/j.numecd.2022.08.024
12. Patel AV, Maliniak ML, Rees-Punia E, et al. Prolonged leisure time spent sitting in relation to cause-specific mortality in a large US cohort. *Am J Epidemiol*. 2018;187:2151–2158. doi:10.1093/aje/kwy125
13. Ikehara S, Iso H, Wada Y, et al. Television viewing time and mortality from stroke and coronary artery disease among Japanese men and women—The Japan Collaborative Cohort Study. *Circ J*. 2015;79:2389–2395. doi:10.1253/circj.CJ-14-1335
14. Mc Carthy CE, Yusuf S, Judge C, et al. Sleep patterns and the risk of acute stroke: results from the INTERSTROKE international case-control study. *Neurology*. 2023;100:e2191–e2203. doi:10.1212/wnl.0000000000207249
15. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA*. 2018;320:2020–2028. doi:10.1001/jama.2018.14854
16. Dumuid D, Pedišić Ž, Stanford TE, et al. The compositional isotemporal substitution model: a method for estimating changes in a health outcome for reallocation of time between sleep, physical activity and sedentary behaviour. *Stat Methods Med Res*. 2019;28:846–857. doi:10.1177/0962280217737805
17. Janssen I, Clarke AE, Carson V, et al. A systematic review of compositional data analysis studies examining associations between sleep, sedentary behaviour, and physical activity with health outcomes in adults. *Appl Physiol Nutr Metab*. 2020;45:S248–s257. doi:10.1139/apnm-2020-0160
18. Li X, Ma H, Zhou T, et al. Replacing sedentary behavior time with physical activities, recommended physical activity, and incident coronary heart disease. *Mayo Clin Proc*. 2023;98:111–121. doi:10.1016/j.mayocp.2022.06.031
19. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12:e1001779. doi:10.1371/journal.pmed.1001779
20. Lee PH, Macfarlane DJ, Lam TH, et al. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. *Int J Behav Nutr Physl Act*. 2011;8:115. doi:10.1186/1479-5868-8-115
21. Lloyd-Jones DM, Allen NB, Anderson CAM, et al. Life's essential 8: updating and enhancing the American Heart Association's construct of cardiovascular health: a presidential advisory from the American Heart Association. *Circulation*. 2022;146:e18–e43. doi:10.1161/cir.0000000000001078
22. Peter-Marske KM, Evenson KR, Moore CC, et al. Association of accelerometer-measured physical activity and sedentary behavior with incident cardiovascular disease, myocardial infarction, and ischemic stroke: the Women's health study. *J Am Heart Assoc*. 2023;12:e028180. doi:10.1161/jaha.122.028180

23. Ashizawa R, Honda H, Take K, et al. Approaches to promote reduction in sedentary behavior in patients with minor ischemic stroke: a randomized controlled trial. *Arch Phys Med Rehabil*. 2022;103:255–262.e254. doi:10.1016/j.apmr.2021.08.019
24. Kerr A, Dawson J, Robertson C, et al. Sit to stand activity during stroke rehabilitation. *Topic Stroke Rehabilitat*. 2017;24:562–566. doi:10.1080/10749357.2017.1374687
25. Ashizawa R, Yamashita K, Take K, et al. Nonleisure-time physical activity guidance following minor ischemic stroke: a randomized clinical trial. *Adapt Phys Activ Q*. 2021;38:329–347. doi:10.1123/apaq.2020-0029
26. Grau-Pellicer M, Lalanza JF, Jovell-Fernández E, et al. Impact of mHealth technology on adherence to healthy PA after stroke: a randomized study. *Topic Stroke Rehabilitat*. 2020;27:354–368. doi:10.1080/10749357.2019.1691816
27. Stefanick ML, Kooperberg C, LaCroix AZ. Women's Health Initiative Strong and Healthy (WHISH): a pragmatic physical activity intervention trial for cardiovascular disease prevention. *Contemp Clin Trials*. 2022;119:106815. doi:10.1016/j.cct.2022.106815
28. Grandner MA, Fernandez FX. The translational neuroscience of sleep: a contextual framework. *Science*. 2021;374:568–573. doi:10.1126/science.abj8188
29. Baillieul S, Dekkers M, Brill AK, et al. Sleep apnoea and ischaemic stroke: current knowledge and future directions. *Lancet Neurol*. 2022;21:78–88. doi:10.1016/s1474-4422(21)00321-5
30. Titova OE, Michaëlsson K, Larsson SC. Sleep duration and stroke: prospective cohort study and Mendelian randomization analysis. *Stroke*. 2020;51:3279–3285. doi:10.1161/strokeaha.120.029902
31. Khot SP, Morgenstern LB. Sleep and stroke. *Stroke*. 2019;50:1612–1617. doi:10.1161/strokeaha.118.023553
32. Alnawwar MA, Alraddadi MI, Algethmi RA, et al. The effect of physical activity on sleep quality and sleep disorder: a systematic review. *Cureus*. 2023;15:e43595. doi:10.7759/cureus.43595
33. Hamer M, Stamatakis E, Steptoe A. Effects of substituting sedentary time with physical activity on metabolic risk. *Med Sci Sports Exerc*. 2014;46:1946–1950. doi:10.1249/mss.0000000000000317
34. Helmerhorst HJ, Wijndaele K, Brage S, et al. Objectively measured sedentary time may predict insulin resistance independent of moderate- and vigorous-intensity physical activity. *Diabetes*. 2009;58:1776–1779. doi:10.2337/db08-1773
35. Mekary RA, Willett WC, Hu FB, et al. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol*. 2009;170:519–527. doi:10.1093/aje/kwp163
36. Healy GN, Winkler EA, Owen N, et al. Replacing sitting time with standing or stepping: associations with cardio-metabolic risk biomarkers. *Eur Heart J*. 2015;36:2643–2649. doi:10.1093/eurheartj/ehv308
37. Ryan DJ, Wullems JA, Stebbings GK, et al. Segregating the distinct effects of sedentary behavior and physical activity on older adults' cardiovascular profile: part 2-isotemporal substitution approach. *J Phys Act Health*. 2018;15:537–542. doi:10.1123/jpah.2017-0326
38. Kinoshita K, Ozato N, Yamaguchi T, et al. Association of sedentary behaviour and physical activity with cardiometabolic health in Japanese adults. *Sci Rep*. 2022;12:2262. doi:10.1038/s41598-022-05302-y
39. Willey JZ, Voutsinas J, Sherzai A, et al. Trajectories in leisure-time physical activity and risk of stroke in women in the California teachers study. *Stroke*. 2017;48:2346–2352. doi:10.1161/strokeaha.117.017465
40. Taddei S, Galetta F, Virdis A, et al. Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation*. 2000;101:2896–2901. doi:10.1161/01.cir.101.25.2896
41. Quan HL, Blizzard CL, Sharman JE, et al. Resting heart rate and the association of physical fitness with carotid artery stiffness. *Am J Hypertens*. 2014;27:65–71. doi:10.1093/ajh/hpt161
42. Ainslie PN, Cotter JD, George KP, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *J Physiol*. 2008;586:4005–4010. doi:10.1113/jphysiol.2008.158279
43. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4. doi:10.1161/jaha.115.002014
44. Billinger SA, Arena R, Bernhardt J, et al. Physical activity and exercise recommendations for stroke survivors: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2532–2553. doi:10.1161/str.0000000000000022
45. Walmsley R, Chan S, Smith-Byrne K, et al. Reallocation of time between device-measured movement behaviours and risk of incident cardiovascular disease. *Br J Sports Med*. 2021;56:1008–1017. doi:10.1136/bjsports-2021-104050