RESEARCH ARTICLE

Use of the Brain Care Score to Estimate the Risk of Incident Cerebrovascular Events in Middle-Aged Women

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Abstract

Background and Objectives

In the United States, stroke is the third leading cause of death among women, with 1 in 5 women aged 55 to 75 years expected to experience a stroke. The Brain Care Score (BCS) is an evidence-based tool designed to motivate lifestyle changes, with higher scores associated with reduced risk of stroke, dementia, and depression. We aim to measure the association of the BCS and incident cerebrovascular events (CVEs), including stroke and transient ischemic attack (TIA), in the Women's Health Study (WHS).

Methods

The WHS comprises women health professionals aged 45 and older in the United States. Participants without history of CVE and complete data available to calculate a BCS and covariates 5 years after enrollment were included. Higher BCS reflects better risk factor control, with the minimum score being 0 and the maximum score being 20. Cox proportional hazard models examined the association between BCS and incident CVE adjusted for potential confounders.

Results

A total of 21,271 women were eligible with a median age of 57.9 years (interquartile range: 53.9–63.8) and median BCS of 15 (interquartile range [IQR]:13–16). There were 1,294 incident CVE cases (6.1%) during a median follow-up of 22.4 (IQR: 15.9–23.5) years. A five-point higher baseline BCS was associated with a 37% decrease in the risk of incident CVE after adjusting for age, menopausal status, use of hormonal replacement therapy, and other known cardiovascular disease risk factors (hazard ratio [HR] 0.63, 95% CI 0.56–0.71). This association remained significant after adjusting for race, educational attainment, and income (HR 0.64, 95% CI 0.57–0.72). There was a 28% decreased risk of incident CVE among those with a BCS equal to or above the median compared with those with a BCS below the median, in a fully adjusted model (HR 0.72, 95% CI 0.64–0.80).

Discussion

Higher baseline BCS was associated with a decreased risk of incident CVE in the WHS. Future studies are needed to study the BCS in more diverse populations and to investigate how changes in BCS across the lifespan affect risk of CVE.

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Glossary

BCS = Brain Care Score; **CVE** = cerebrovascular event; **HR** = hazard ratio; **HRT** = hormone replacement therapy; **IQR** = interquartile range; **RN** = registered nurse; **SDOH** = social determinants of health; **VIF** = variance inflation factor; **WHS** = Women's Health Study.

Introduction

Stroke is the second leading cause of death and disability worldwide.[1] In the United States, stroke is the third leading cause of death among women, and it is estimated that 1 in 5 women between 55 and 75 years will have a stroke.[2-4] Existing evidence suggests that stroke risk can be reduced by addressing modifiable risk factors through primary prevention strategies.[5,6] However, the ability to modify the risk factors also depends on the social determinants of health (SDOH)—the environments where people are born, live, learn, work, play, worship, and age.[7] Previous studies have shown that these determinants can further influence stroke risk[8,9] and disproportionately affect minoritized populations, further exacerbating disparities in stroke.[10,11]

The Brain Care Score (BCS) was developed in partnership with patients and clinicians as an evidence-based, multidimensional, and quantitative score to engage patients in lifelong modification of established clinical, lifestyle, and social-emotional risk factors of stroke, dementia, and late-life depression.[12-14] While the BCS has been validated in the UK Biobank, the external validity of this tool in an American population remains unknown.[13]

The primary aim of this study was to measure the association between the BCS at baseline and future incident cerebrovascular events (CVEs) in the Women's Health Study (WHS). Given the complex relationship of lifestyle factors and CVE risk, a secondary aim was to explore the impact of SDOH on the association between BCS and incident CVE in this cohort. We hypothesize that higher BCS will be associated with lower rates of incident CVE, independent of adverse SDOH.

Methods

Study Population

The WHS is a large, randomized placebo-controlled trial designed to test the effects of aspirin and vitamin E on the primary prevention of cardiovascular disease and cancer in women.[15,16] Since the conclusion of the clinical trial, observational follow-up has been ongoing among consenting participants. The full study design and methods have been previously published.[15,16] In brief, initial enrollment from 1992 to 1996 included 39,876 American women health care professionals who were at least 45 years old and had no history of cardiovascular disease, cancer, or other major illnesses.

Baseline clinical information from participants was collected at enrollment and up to approximately 5 years after randomization in the 60-month questionnaire. Before randomization into the trial, approximately 71% of participants provided a blood sample that was assayed for total cholesterol and HbA1c. For the purposes of these analyses, our longitudinal cohort began at the receipt of this questionnaire. Women were followed from receipt of the 60-month questionnaire until incident stroke or TIA, end of study, loss to follow-up, or death, whichever occurred first. Women who reported a stroke or TIA before receipt of the 60-month questionnaire or who were missing data in any component of the BCS were excluded from these analyses.

Standard Protocol Approvals, Registrations, and Patient Consents

The WHS was approved by the Institutional Review Board at Brigham and Women's Hospital, and all participants provided written informed consent. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (eTable 1).

Exposure Assessment: WHS-Based BCS

The BCS was developed as a comprehensive and quantitative score to empower people with actionable steps to take care of their brain and reduce the incidence of stroke, dementia, and late-life depression.[17] The BCS consists of 12 modifiable risk factors, including physical components (blood pressure, blood sugar, cholesterol levels, and body mass index), lifestyle components (alcohol intake, diet, smoking, physical activity, and sleep), and social-emotional components (social relationships, stress, and meaning in life). The BCS ranges from 0 to 21 points, with a higher BCS indicating better brain health. Based on previous studies,[13] a five-point increase in BCS signifies a substantial yet achievable improvement in brain health; for example, a five-point increase can be attained by smoking cessation and reduction in stress. The BCS has previously been validated in the UK Biobank, showing that a higher baseline BCS was associated with a lower incidence of stroke.[13]

In this study, the BCS was adapted to the data available from the trial's baseline questionnaire and the 60-month questionnaire. The WHS adaptation of the BCS model is presented in detail in Figure 1. For each component, the minimum possible score was 0 and the maximum possible scores ranged from 1 to 3. For the clinical and lifestyle components, the scores were calculated using the same criteria from the original BCS following established, evidence-based ranges. The hypertension score was calculated using self-reported

Figure 1 Brain Care Score in the Women's Health Study

Components	Criteria/description	Categories	Score
Blood pressure	Measured SBP and DBP	BP ≥140/90 mmHg	0
		BP ≥120–139/80–89 mmHg	2
		BP <120/80 mmHg	3
Blood sugar	HbA1c%	HbA1c equal to or greater than 6.5%	0
		HbA1c between 5.7% and <6.5%	1
		HbA1c <5.7%	2
Cholesterol	Total cholesterol	Equal to or greater than 190 mg/dL	0
		Less than 190 mg/dL	1
Body mass index	Body mass index	BMI >= 30 kg/m^2	0
		BMI <=18.5, or 25<= BMI <30	1
		18.5 <= BMI <25	2
Diet	Dietary recommendations: a) 4.5 servings of fruits and vegetables/day; b) 2 servings of lean protein; c) ≥3 servings of whole grains/day; d) <1,500 mg of sodium/day; e) <36 oz of sugar sweet beverages/week	Typical weekly diet does not include at least two of the recommendations	0
		Typical weekly diet includes ≥2 of the recommendations	1
		Typical weekly diet includes ≥3 of the recommendations	2
Alcohol	Alcoholic drinks per week	4 Or more drinks per week	0
		>1 And <4 drinks per week	1
		0–1 Drink per week	2
Smoking	Smoker at 60 months	Yes	0
		No	3
Aerobic activities	≥150 Minutes/week of moderate or vigorous physical activity	No	0
		Yes	1
Stress	During the past 4 weeks, a) Have felt calm and peaceful? Or b) Have you been a very nervous person?	Spent calm/peaceful **little of time/none of time** or very nervous **all the time/most of time**	0
		Spent calm/peaceful or very nervous **good bit of time/some of time**	1
		Spent calm/peaceful **all the time/most of time** or very nervous **little of time/none of time**	2
Social relationships	Is there anyone you feel close to, who you can confide in?	No	0
		Yes	1
Meaning in life	In the past 4 weeks, a)Felt so down nothing could cheer you up?	Yes to a or b, or no to c	0
	In the past 4 weeks, b) Felt so downhearted and blue?		
	In the past 4 weeks, c) Have you been a happy person?	Yes to c or no to a or b	1
		Total Brain Care Score	**20**

blood pressure values and assigned based on the original BCS criteria; however, for participants who were not properly categorized, the systolic blood pressure cutoffs were used to assign the score. For the social-emotional components of the BCS, stress, social relationships, and meaning in life were calculated using survey responses further explained in eTable 2. A comparison of the social-emotional components of the BCS and the WHS-adapted questions is provided in eTable 3. The WHS adaptation of the BCS did not incorporate a sleep component, as this domain was not assessed in the WHS.

The total BCS was obtained as the sum of the score's components for each participant with complete data. The maximum possible BCS was 20, being interpreted as the best possible attainable score, given that higher total BCS meant better risk factor control.

Outcome Ascertainment

The WHS commenced in 1992, at a time when brain MRI was not widely available or routinely used. Consequently, imaging data were not available for the complete cohort to confirm CVE diagnosis. Participants were asked to self-report incident stroke and transient ischemic attacks during annual follow-ups. Women who reported events were asked for permission to review medical records, and an endpoints committee confirmed or disconfirmed the self-reported events. A nonfatal stroke was defined as a focal neurologic deficit of sudden or rapid onset and vascular mechanism that lasted >24 hours. A TIA was defined as a focal neurologic deficit of sudden rapid onset and vascular mechanism that resolved within 24 hours. To confirm fatal stroke events, all available sources, including death certificates and hospital records, were used to find evidence of a cerebrovascular mechanism.

Covariates

Demographics, medical history, and SDOH were obtained from study enrollment through the 60-month questionnaire. Medical history variables included history of myocardial infarction, intermittent claudication, liver disease, diabetes, cancer, or atrial fibrillation (all yes/no); family history of myocardial infarction in parent younger than 60 years (yes/no); postmenopausal status (premenopausal/postmenopausal/unclear); migraine headaches (yes/no); perceived memory changes (no change/improved/worse); and use of hormone replacement therapy (HRT) (never/past/current).

The SDOH included race (White/non-White), educational attainment, and income. Educational attainment captured the highest level of completed education with the following categories: licensed practical nurse/licensed vocational nurse (<2 years of nursing education), 2-year associate degree/registered nurse (RN), nurse diploma program (3-years-RN), bachelor's degree in nursing, master's degree, and doctoral degree. Income was assessed as total household income in the past year in the following categories: <$20,000;

$20,000–$29,999; $30,000–$39,999; $40,000–$49,999; $50,000–$99,999; and >100,000 USD. For this analysis, the reference categories were <2 years of nursing education and income <$20,000, respectively.

Statistical Analysis

Descriptive statistics were calculated for baseline demographic characteristics, medical history, and SDOH among all participants included in the analysis.

Logistic regression was performed to calculate the odds ratio and 95% CI to assess the association between baseline BCS and SDOH including race, educational attainment, and income level. For this analysis, the BCS was dichotomized by the median into 2 groups: below and equal to or above the median BCS.

Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% CIs examining the association between baseline total BCS and incident total CVE, only stroke, and only TIA. Model 1 was adjusted for potential clinical confounders including age, history of myocardial infarction, intermittent claudication, liver disease, diabetes, cancer, or atrial fibrillation; postmenopausal status; migraine headaches; and use of HRT. Model 2 accounted for SDOH (race, education, and income), in addition to the covariates included in model 1. Total BCS was modeled as a continuous variable, to assess the impact of both one-point and five-point increases in the score on total incident CVE. To further evaluate whether the association between BCS and CVE varied by age, participants were stratified by the median age (57.9 years) and unadjusted hazard ratio with 95% CI was calculated. An interaction term between BCS and age group was included in the Cox proportional hazard model to test whether the BCS varied significantly by age group. In secondary analysis, the BCS was dichotomized at the median with those below the median score serving as the reference group. Multicollinearity was assessed in the multivariable models using a variance inflation factor (VIF) threshold of 5.0.[18]

Participants with missing data on SDOH and other covariates were excluded from the analysis. A 2-tailed p value of <0.05 was deemed statistically significant. Analyses were completed in R 4.4.1.

Data Availability

The data in this study are not publicly available because of restricted access; however, further information about the data set can be made available from the corresponding author on request.

Results

Study Population

Of the total 39,876 participants in the WHS, 11,938 were ineligible because of no baseline blood or cholesterol values, 237 were ineligible because of history of stroke or TIA, and 4,957 were ineligible because of incomplete data to calculate the BCS and SDOH. A total of 1,473 participants did not return the questionnaire at 60 months and were excluded from the study. In total, 21,271 women were included in the analysis (Figure 2). The baseline demographic characteristics, medical history, and SDOH of eligible participants are presented in Table 1. The median age was 57.9 years (interquartile range [IQR] 53.9–63.8), and most participants were postmenopausal (80.9%) and prescribed HRT (62.6%). Most of the cohort identified as White (95.7%) and reported an annual income between $50,000 and 99,999 USD (42.3%) and 3-years-RN level of education (32.0%). The median total BCS at baseline was 15 (IQR 13–16).

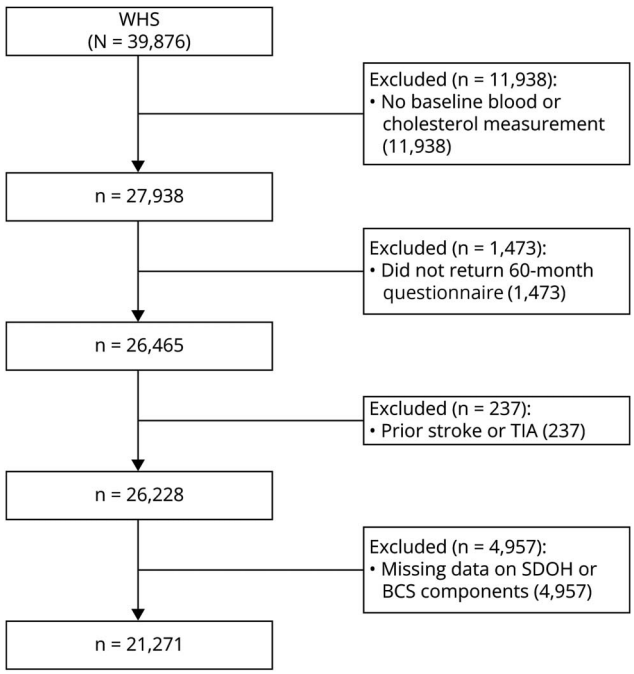
Cross-Sectional Associations Between BCS and SDOH

As given in Table 2, those who were non-White were more likely to have a BCS below the median than those who were White. Compared with those with annual household income <$20,000 USD, those with higher income were more likely to have BCS above the median. Compared with those with <2 years of nursing education, those with higher educational attainment were more likely to have BCS above the median.

Predictive Validity of the Score

Over a median 22.4 years of follow-up, 1,294 incident CVE cases (6.1%) were observed (718 stroke cases and 576 TIA cases). A one-point higher baseline BCS was associated with

Figure 2 Flow Diagram



BCS = Brain Care Score; N = number of participants; SDOH = social determinants of health; WHS = Women's Health Study.

Table 1 Baseline Characteristics of the Study Sample (N = 21,271)

Demographic characteristics	N	%
Median age (IQR)	57.9	53.9–63.8
Race/ethnicity		
Non-White, Hispanic[a]	911	4.3
White, non-Hispanic	20,360	95.7
Annual household income		
<20,000 USD	982	4.6
20,000–<30,000 USD	1,996	9.4
30,000–<40,000 USD	2,927	13.8
40,000–<50,000 USD	3,500	16.5
50,000–<100,000 USD	9,002	42.3
Equal or >100,000 USD	2,864	13.5
Education		
<2 years of nursing education	2,473	11.6
2 years of nursing education	2,339	11.0
3 years of nursing education	6,816	32.0
Bachelor's degree	5,144	24.2
Master's degree	3,305	15.5
Doctorate, MD	1,194	5.6
Median Brain Care Score at baseline (IQR)	15	13–16
History of migraine headaches	3,859	18.1
Family history of myocardial infarction in parent younger than 60 y at baseline[b]	3,003	14.1
History of migraine headaches during the past year[b]	2,690	12.6
History of diabetes	961	4.5
History of cancer	687	3.2
History of atrial fibrillation	543	2.6
History of liver disease	150	0.7
History of intermittent claudication	104	0.5
History of myocardial infarction	68	0.3
Postmenopausal status at baseline		
Premenopausal	1,503	7.1
Postmenopausal	17,204	80.9
Unclear	2,564	12.0
Memory changes[b]		
No change	16,820	79.1
Improved	267	1.3
Worse	4,175	19.6
Use of hormone replacement therapy		
Never	5,156	24.2

Continued

Table 1 Baseline Characteristics of the Study Sample (N = 21,271) *(continued)*

Demographic characteristics	N	%
Past	2,811	13.2
Current	13,304	62.6

Abbreviations: IQR = interquartile range, which represents 25th and 75th percentiles; USD = United States dollar.
[a] Non-White, Hispanic includes Hispanics (n = 198), African American (n = 354), Asian/Pacific Islander (n = 273), American Indian/Alaskan (n = 49), and other/unknown (n = 37).
[b] Percentage of missing observations (family history of myocardial infarction in parent younger than 60 y = 1.50; migraine headaches during the past year = 0.16; memory changes = 0.04).

9% decreased risk of incident CVE after adjusting for age, postmenopausal status, HRT, and comorbidities (myocardial infarction, intermittent claudication, liver disease, diabetes, cancer, atrial fibrillation, migraine headaches) (HR 0.91, 95% CI 0.89–0.93). This association remained significant after accounting for SDOH (HR 0.91, 95% CI 0.89–0.94) (Figure 3). A 37% decrease in the risk of incident CVE was observed for every five-point increase in the baseline BCS, after adjusting for age, postmenopausal status, HRT, and comorbidities (myocardial infarction, intermittent claudication, liver disease, diabetes, cancer, atrial fibrillation, migraine headaches) (HR 0.63, 95% CI 0.56–0.71) (eTable 4). This association remained significant after adjusting for SDOH (HR 0.64, 95% CI 0.57–0.72) (eTable 4). In the unadjusted model, analysis stratified by median age indicated that among participants younger than 57.9 years, every five-point increase in the baseline BCS was associated with a 55% decreased risk of incident CVE (HR 0.45, 95% CI 0.37–0.55), compared with 28% decreased risk of incident CVE (HR 0.72, 95% CI 0.62–0.83) among participants aged 57.9 and older (eTable 5), and similar to analysis stratified by age quartiles (eTable 6). The interaction term between age and BCS was significant (p value = 0.0003), indicating that the association between BCS and CVE varies based on baseline age. Similar results were obtained for incident stroke (p value = 0.026) and incident TIA (p value = 0.008).

Table 2 Association Between SDOH and Baseline Brain Care Score ≥15

Race	OR	(95% CI)
White, non-Hispanic	1.00 (reference)	
Non-White, Hispanic[a]	0.97	0.84–1.11
Annual household income		
<20,000 USD	1.00 (reference)	
20,000–<30,000 USD	1.08	0.93–1.26
30,000–<40,000 USD	1.14	0.98–1.32
40,000–<50,000 USD	1.21	1.04–1.40
50,000–<100,000 USD	1.39	1.21–1.60
Equal or >100,000 USD	1.82	1.56–2.12
Education		
<2 years of nursing education	1.00 (reference)	
2 years of nursing education	1.24	1.10–1.39
3 years of nursing education	1.36	1.23–1.49
Bachelor's degree	1.70	1.53–1.88
Master's degree	1.89	1.69–2.11
Doctorate, MD	1.86	1.60–2.18

Abbreviations: BCS = Brain Care Score; OR = odds ratio; SE = standard error; SDOH = social determinants of health.
Frequencies in the categories of the dependent variable median BCS: BCS <15 (N = 8,825; 41.49%) and BCS ≥15 (N = 12,446; 58.51%).
The sample size was 21,271.
[a] Non-White, Hispanic includes Hispanics (n = 198), African American (n = 354), Asian/Pacific Islander (n = 273), American Indian/Alaskan (n = 49), and other/unknown (n = 37).

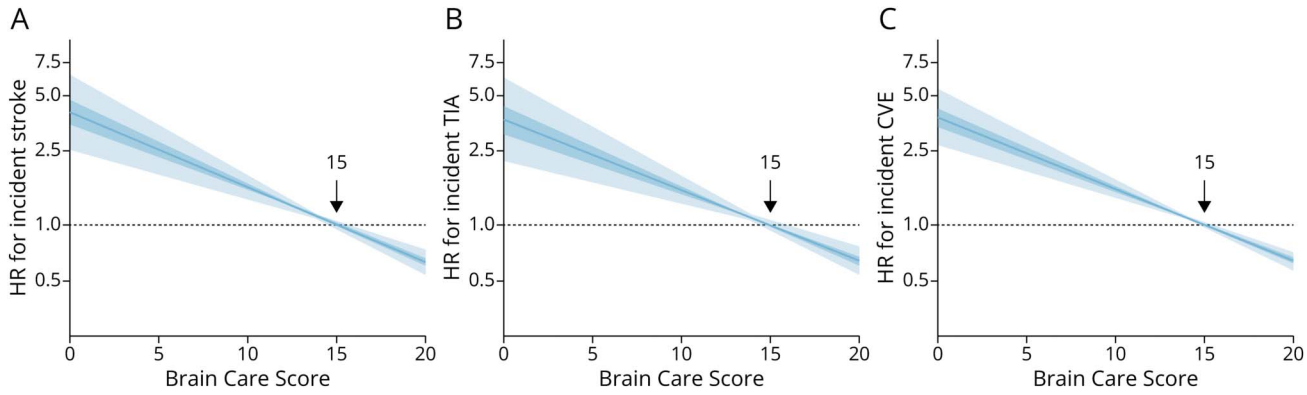
When BCS was treated as a dichotomous variable, a 28% decreased risk of incident CVE was observed among those with a score equal to or above the median BCS (i.e., BCS ≥ 15), compared with those with a score below the median BCS after adjusting for confounders including SDOH (Table 3). Comparable results were observed for only incident stroke or only incident TIA (Table 3). The VIF for all the multivariable models was <3.0.

Discussion

In this prospective cohort study of middle-aged women enrolled in the WHS, we found that a higher BCS at baseline was associated with decreased risk of incident CVE over time, supporting the predictive validity of a quantitative score that combines clinical, lifestyle, and socio-emotional factors that affect brain care.[19-30] These results are consistent with previous findings in the UK Biobank, which found that a higher BCS at baseline was associated with lower risk of incident stroke among nearly 398,990 UK participants after adjusting for age.[13] This study adds evidence by using a cohort with longer follow-up time and accounting for various confounders, including the influence of SDOH in an American population.

Several studies have shown that adverse social determinants are associated with worse health outcomes, including stroke.[31] In a recently published observational study,[9] adverse SDOH were associated with increased incidence of stroke. Our

Figure 3 Association of the BCS With Incident Stroke, TIA, and CVE in the WHS Cohort



The thick line represents the mean relative hazard curve for over the range of the Brain Care Score on a logarithmic scale; the shaded areas correspond to the 95% CIs. The risk curves were adjusted for age, race, education, income, postmenopausal status, hormone replacement therapy, and comorbidities (myocardial infarction, intermittent claudication, liver disease, diabetes, cancer, atrial fibrillation, migraine headaches). BCS = Brain Care Score; CVE = cerebrovascular event; TIA = transient ischemic attack; WHS = Women's Health Study.

analysis included race, income, and education level to assess SDOH and showed that higher income and higher educational attainment increased the odds of a higher BCS, demonstrating that SDOH are associated with overall brain care. Although we did observe associations between BCS and SDOH, controlling for SDOH did not attenuate the protective effect of a higher BCS later in life against incident CVE. This suggests that BCS is independently associated with CVE in this population.

Strengths of this study include its prospective, longitudinal design with ample follow-up time in a large study population, detailed information on a variety of modifiable risk factors, and confirmation of CVE events through medical record review. Another notable strength is the incorporation of social-emotional components, including stress, social relationships, and meaning in life, which provides a more comprehensive assessment of brain health. Limitations of our study include predominantly White and middle-aged women who work in health care, reflecting the entry criteria that required participants to be aged 45 or older, and working in health care in the 1990s. Given that certain racial and ethnic minority groups were underrepresented in the health care workforce at that time,[32] our findings may not be generalizable to a more diverse cohort.

Table 3 Associations Between Brain Care Score at Baseline and Incident Cerebrovascular Events (N = 21,271)

	HR (95% CI)		
	All cerebrovascular events[a]	**Stroke**	**TIA**
Total incident events (%)	1,294 (6.1)	764 (3.6)	606 (2.9)
Total Brain Care Score (continuous)			
Unadjusted	0.90 (0.88–0.92)	0.89 (0.87–0.92)	0.91 (0.88–0.94)
Model 1	0.91 (0.89–0.93)	0.91 (0.88–0.94)	0.91 (0.88–0.95)
Model 2	0.91 (0.89–0.94)	0.91 (0.88–0.94)	0.92 (0.88–0.95)
Below the median Brain Care Score (N = 8,825)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Equal to or above the median Brain Care Score (N = 12,446)			
Unadjusted	0.67 (0.60–0.74)	0.65 (0.56–0.75)	0.68 (0.58–0.80)
Model 1	0.71 (0.63–0.79)	0.70 (0.61–0.81)	0.71 (0.60–0.83)
Model 2	0.72 (0.64–0.80)	0.71 (0.62–0.83)	0.71 (0.60–0.84)

Abbreviations: CVE = cerebrovascular event; HR = hazard ratio.
Model 1 adjusted for age, postmenopausal status, hormone replacement therapy, and comorbidities (myocardial infarction, intermittent claudication, liver disease, diabetes, cancer, atrial fibrillation, migraine headaches).
Model 2 adjusted for Model 1 covariates + social determinants of health (race, income, education).
[a] The total incident events for CVE do not equal the sum of stroke and TIA events because 76 cases had both stroke and a TIA. These individuals are included in both stroke and TIA categories but are only accounted for once in the overall CVE category.

Compared with a previous publication of the UK BioBank cohort (median BCS 12),[13] we observed a higher median BCS in our study (median BCS 15). This difference could partially be explained by the composition of health care professionals in the WHS cohort and can potentially introduce bias because participants could have better access to health care and more health-related knowledge that can influence the BCSs. Thus, further studies will need to validate these results in more diverse populations, representative of the US population. Our study also relied on the traditional definitions of stroke and TIA at the time of the study, which were focused on the duration of signs and symptoms.[33,34] The updated tissue-based definitions were not retrospectively applied to our cohort to avoid misclassification, leading to limited applicability of our findings to current diagnostic practices.

In addition, we lack data on sleep patterns, a known component of brain health and risk factor of CVE.[29,35] Moreover, future iterations of the BCS are required to balance the contribution of individual components to the overall score, reflecting differential risk contributions that can potentially improve the predictive validity of the BCS. Finally, owing to the observational nature of the study design, causality cannot be inferred by these results and future studies are needed to evaluate the effect of longitudinal changes in the BCS on incident CVE.

In conclusion, this study demonstrates that a higher baseline BCS is associated with a decreased risk of incident CVE, stroke, and TIA later in life. Future studies should assess the impact of longitudinal changes in the BCS in incident CVE in more diverse populations.

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Author Contributions

D. Choksi: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. L. Gutiérrez-Martínez: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. P.M. Rist: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J.E. Buring: drafting/revision of the manuscript for content, including medical writing for content. J.R. Senff: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Marini: drafting/revision of the manuscript for content, including medical writing for content. C. Kourkoulis: drafting/revision of the manuscript for content, including medical writing for content. Z. Chemali: drafting/revision of the manuscript for content, including medical writing for content. A. Newhouse: drafting/revision of the manuscript for content, including medical writing for content. M.B. Westover: drafting/revision of the manuscript for content, including medical writing for content. R.E. Tanzi: drafting/revision of the manuscript for content, including medical writing for content. G. Fricchione: drafting/revision of the manuscript for content, including medical writing for content. S. Singh: drafting/revision of the manuscript for content, including medical writing for content. J. Rosand: drafting/revision of the manuscript for content, including medical writing for content. C.D. Anderson: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. N. Yechoor: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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