CLINICAL/SCIENTIFIC NOTE

Brain Care Score and Neuroimaging Markers of Brain Health in Asymptomatic Middle-Age Persons

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Abstract

Objectives

To investigate associations between health-related behaviors as measured using the Brain Care Score (BCS) and neuroimaging markers of white matter injury.

Methods

This prospective cohort study in the UK Biobank assessed the BCS, a novel tool designed to empower patients to address 12 dementia and stroke risk factors. The BCS ranges from 0 to 21, with higher scores suggesting better brain care. Outcomes included white matter hyperintensities (WMH) volume, fractional anisotropy (FA), and mean diffusivity (MD) obtained during 2 imaging assessments, as well as their progression between assessments, using multivariable linear regression adjusted for age and sex.

Results

We included 34,509 participants (average age 55 years, 53% female) with no stroke or dementia history. At first and repeat imaging assessments, every 5-point increase in baseline BCS was linked to significantly lower WMH volumes (25% 95% CI [23%–27%] first, 33% [27%–39%] repeat) and higher FA (18% [16%–20%] first, 22% [15%–28%] repeat), with a decrease in MD (9% [7%–11%] first, 10% [4%–16%] repeat). In addition, a higher baseline BCS was associated with a 10% [3%–17%] reduction in WMH progression and FA decline over time.

Discussion

This study extends the impact of the BCS to neuroimaging markers of clinically silent cerebrovascular disease. Our results suggest that improving one's BCS could be a valuable intervention to prevent early brain health decline.

Introduction

As the concept of brain health becomes increasingly known for its public health impact, early interventions to prevent devastating conditions such as stroke and dementia are sought for. The progressive decline in brain structure and function can be accurately monitored with select

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neuroimaging markers long before clinical manifestations. One of the most prominent markers are white matter hyperintensities (WMHs), which accumulate from silent cerebral small vessel disease.[1] Furthermore, changes in fractional anisotropy (FA) or mean diffusivity (MD) are measures of white matter architectural disorganization and, therefore, useful biomarkers of declining brain structure and function.[2] WMHs, FA, and MD have 2 important characteristics: first, their appearance and progression are determined by known risk factors, such as smoking[3] and hypertension[4]; and second, such imaging changes are known to precede the onset of stroke and dementia by many years, enabling continuous assessment of brain structural integrity.[5,6] Finally, evidence robustly justifies early interventions based on these markers.[2,5]

Cerebral small vessel disease progression is largely influenced by modifiable risk factors, with hypertension, diabetes, hyperlipidemia, and smoking identified as its main determinants.[4,7] Those risk factors are summarized in a novel tool, the 21-point Brain Care Score (BCS), validated for its predictive value for stroke, dementia, and late-life depression.[8,9] To evaluate the impact of risk factor modification on early brain health decline, as represented by improvement in one's BCS, the aim of this study was to evaluate the association of the total BCS with WMHs, FA, and MD profiles, as well as their evolution over time. We hypothesized that better brain care as captured by higher BCS values in middle-age persons who have not yet developed brain diseases would be associated with better neuroimaging profiles assessed by metrics of white matter injury and disintegrity.

Methods

UKB Study and Inclusion Criteria

The UKB study was a prospective cohort encompassing over 500,000 UK patients, aged 40–69 years, recruited from 22 centers (2006–2010), as previously described.[10] From 2014, a subset of these participants underwent brain MRIs,[11] with a median of 9.3 years [Q1–Q3: 7.8–10.4] after baseline. From 2018, a further subset underwent repeat MRIs, with a median interval of 825 days [Q1–Q3: 793–914] between both imaging assessments. In this study, we included participants who completed at least the first neuroimaging assessment and without a medical history of dementia or stroke before it.

The Brain Care Score

The BCS was constructed through the selection of modifiable risk factors that were endorsed by professional agencies worldwide. A subsequent scoring system was developed to give emphasis to more potent modifiable risk factors. Finally, qualitative data from patient interviews were utilized to address motivational aspects of the BCS. The BCS consists of 12 components, each aimed at 1 modifiable risk factor, using a scoring system ranging from 0 to 21.[12] For the purposes of this study, the BCS was tailored for application in the UKB data set, resulting in a modified 19-point scale[9] (Table 1).

Neuroimaging Outcomes

The research brain MRI procedure and specifications have been previously described.[11] We considered 3 markers of white matter injury: WMH volume, FA, and MD, where higher FA or lower MD indicates better white matter integrity. WMH volume was calculated using BIANCA,[11] with value natural-log transformed and normalized. FA and MD values were calculated in 48 different neuroanatomical regions using DTIFIT[13] and then averaged to generate aggregate measures for the entire brain.

Statistical Analysis

Following previous research,[9] we performed a complete case analysis of participants with full BCS data. In our primary analysis, we examined the association between 5-point increments in the BCS obtained as baseline and WMH volume, FA, and MD at the first imaging assessment using multivariable linear regression models adjusted for age and sex. Secondary analyses applied the same model to the repeat MRI data and explored total changes between the first and second MRIs, adjusting for age, sex, and time between assessments. Significance was set at $p < 0.017$ to minimize Type II error from multiple observations with the 3 markers.

Data Availability

The UK Biobank study was performed in line with the Declaration of Helsinki and approved by the Northwest Multi-Centre Research Ethics Committee (reference number 06/MRE08/65). All participants provided informed consent. The data used in this study can be accessed by contacting the UK Biobank (ukbiobank.ac.uk). This analysis was approved by the UK Biobank access committee as part of project 58743.

Results

The UKB study enrolled 502,408 participants, with 40,413 undergoing the first neuroimaging assessment. After excluding 5,552 participants (14%) for incomplete BCS data and 352 participants (0.9%) with prior stroke or dementia, 34,509 patients remained for the primary analysis (mean age 55 years, 53% female; Table 2).

A 5-point increase in baseline BCS was associated with better neuroimaging profiles: 25% lower WMH volume (beta: −0.25, 95% CI [−0.27 to −0.23], Figure, eTable 1), 18% higher FA (beta: 0.18 [0.16–0.20]), and 9% lower MD (beta: −0.09 [−0.11 to −0.07]) at the first imaging assessment.

A subset of 3,465 (10%) participants had a second MRI 825 days (median) later. Among them, a 5-point increase in baseline BCS was associated with 33% lower WMH volume (beta: −0.33 [−0.39 to −0.27]), 22% higher FA (beta: 0.22 [0.15–0.28]), and 10% lower MD (beta: −0.10 [−0.16 to −0.04]) at the follow-up imaging assessment.

Table 1 The Brain Care Score in the UK Biobank

Category	Criteria/description	Rank
Physical		
Blood pressure	Systolic *or* diastolic blood pressure of greater than 140/90 mm Hg	0
	Systolic *or* diastolic blood pressure 120–140/80–90 mm Hg, and systolic *and* diastolic blood pressure lower than 140/90 mm Hg	2
		3
Blood glucose	Hemoglobin A1c greater than 6.4%	0
	Hemoglobin A1c between 5.7% and 6.4%	1
	Hemoglobin A1c less than 5.7%	2
Cholesterol	Total cholesterol 190 mg/dL or higher	0
	Total cholesterol less than 190 mg/dL	1
Body mass index	Lower than 18.5 kg/m^2	1
	Between 18.5 and 25 kg/m^2	2
	Higher than 25 and lower than 30 kg/m^2	1
	Higher than or equal to 30 kg/m^2	0
Lifestyle		
Nutrition	Dietary habits • 4.5 or more servings of fruit and vegetables per day • A red meat score of 1 or 2 • 3 or more servings of bread slices or cereal bowls per day • Sometimes, rarely, or never add salt to a meal	
	Typical diet does not include at least 2 of the recommendations above	0
	Typical diet includes 2 of the recommendations above	1
	Typical diet includes 3 or more of the recommendations above	3
Alcohol consumption	Drinking ≥3 times/week	0
	Drinking 1–2 times/week or 1–3 times/month	1
	Drinking only on special occasions or never	2
Smoking	Current smoker	0
	Former or never smoker	2
Aerobic activities	At least 10 min of moderate or vigorous activity on fewer than 5 d/wk	0
	At least 10 min of moderate or vigorous activity on 5 or more days/wk	1
Sleep	Less than 7 h/d	0
	7 or more hours/d	1
Social emotional		
Stress	Self-perceived tension, fidgetiness, or restlessness several days, more than half the days, or nearly every day in the last 2 wk	0
	No self-perceived tension, fidgetiness, or restlessness in the last 2 wk	1
Social relationships	No friends or family members outside the household; no or almost no visits, or only once every few months	0
	Visits once a month, once a week, 2 to 4 times a week, or almost daily	1

The red meat score is based on beef, pork, and lamb/mutton consumption, in which an individual score was first assigned for each meat type ("Never" or "Less than once a week" with 0; "Once a week" or "2–4 times a week" with 1; and "5–6 times a week" or "Once or more daily" with 2); these were then summed, with a score of 1–2 dichotomized into 1 and less than 1 or more than 2 with a 0. Moderate activity includes physical activities such as carrying light loads or cycling; vigorous activity includes activities such as fast cycling, aerobics, or heavy lifting.

Table 2 Characteristics at Baseline of the Whole Cohort and Imaging Subgroups

	Whole cohort (N = 502,386)	Neuroimaging subgroup (n = 40,462)	Repeat neuroimaging subgroup (N = 4,602)
Sex			
Female	273,311 (54.4%)	21,452 (53.0%)	2,417 (52.5%)
Male	229,075 (45.6%)	19,010 (47.0%)	2,185 (47.5%)
Age			
Mean (SD)	56.5 (8.09)	55.0 (7.52)	52.8 (7.41)
Total Brain Care Score			
Median (Q1-Q3)	12 (10–15)	12 (10–14)	12 (11–14)
Missing	85,246 (17.0%)	5,651 (14.0%)	617 (13.4%)
Systolic blood pressure			
Mean (SD)	138 (18.7)	135 (17.7)	134 (17.2)
Missing	1,325 (0.3%)	19 (0.0%)	1 (0.0%)
Diastolic blood pressure			
Mean (SD)	82.3 (10.2)	81.4 (9.94)	81.1 (9.96)
Missing	1,323 (0.3%)	19 (0.0%)	1 (0.0%)
Glycated hemoglobin (HbA1C) in %			
Mean (SD)	5.46 (0.620)	5.35 (0.463)	5.31 (0.443)
Missing	35,992 (7.2%)	2,875 (7.1%)	341 (7.4%)
Cholesterol (mg/dL)			
Mean (SD)	220 (44.3)	222 (41.9)	221 (41.6)
Missing	32,905 (6.5%)	2,595 (6.4%)	298 (6.5%)
BMI			
Mean (SD)	27.4 (4.80)	26.5 (4.19)	26.4 (4.14)
Missing	3,104 (0.6%)	52 (0.1%)	10 (0.2%)
Fruit and vegetable servings per day			
Mean (SD)	2.71 (3.81)	2.65 (3.79)	2.56 (3.74)
Missing	894 (0.2%)	11 (0.0%)	1 (0.0%)
Bread and cereal servings per day			
Mean (SD)	2.28 (1.39)	2.32 (1.35)	2.30 (1.36)
Missing	4,666 (0.9%)	518 (1.3%)	67 (1.5%)
Red meat score			
Mean (SD)	0.952 (1.03)	0.902 (1.02)	0.903 (1.01)
Missing	6,998 (1.4%)	153 (0.4%)	14 (0.3%)
Salt added to food			
Always	24,424 (4.9%)	1,204 (3.0%)	142 (3.1%)
Usually	58,380 (11.6%)	4,171 (10.3%)	435 (9.5%)
Sometimes	140,588 (28.0%)	10,726 (26.5%)	1,237 (26.9%)
Never/rarely	277,869 (55.3%)	24,348 (60.2%)	2,787 (60.6%)
Missing	1,125 (0.2%)	13 (0.0%)	1 (0.0%)
Alcohol intake frequency			

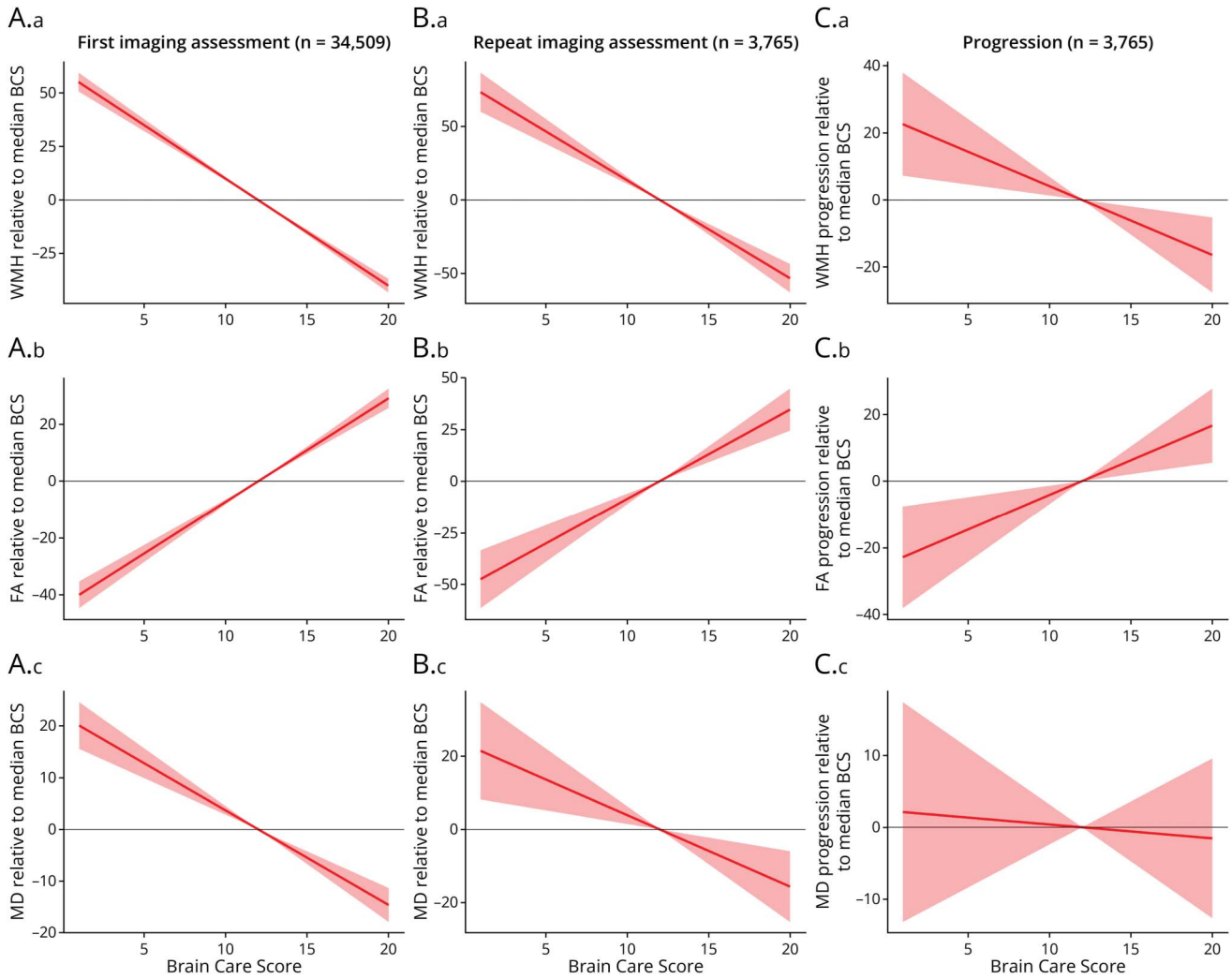
Continued

Table 2 Characteristics at Baseline of the Whole Cohort and Imaging Subgroups *(continued)*

	Whole cohort (N = 502,386)	Neuroimaging subgroup (n = 40,462)	Repeat neuroimaging subgroup (N = 4,602)
Daily or almost daily	101,750 (20.3%)	9,200 (22.7%)	943 (20.5%)
Three or 4 times a week	115,417 (23.0%)	11,341 (28.0%)	1,392 (30.2%)
Once or twice a week	129,262 (25.7%)	10,362 (25.6%)	1,223 (26.6%)
One to 3 times a month	55,838 (11.1%)	4,420 (10.9%)	502 (10.9%)
Special occasions only	57,993 (11.5%)	3,284 (8.1%)	340 (7.4%)
Never	406,26 (8.1%)	1836 (4.5%)	201 (4.4%)
Missing	1,500 (0.3%)	19 (0.0%)	1 (0.0%)
Smoking status			
Current	52,962 (10.5%)	2,484 (6.1%)	257 (5.6%)
Previous	173,016 (34.4%)	13,256 (32.8%)	1,443 (31.4%)
Never	273,460 (54.4%)	24,632 (60.9%)	2,896 (62.9%)
Missing	2,948 (0.6%)	90 (0.2%)	6 (0.1%)
Days per week with 10+ minutes of moderate activity			
Mean (SD)	3.37 (2.52)	3.37 (2.34)	3.38 (2.31)
Missing	878 (0.2%)	11 (0.0%)	1 (0.0%)
Days per week with 10+ minutes of vigorous activity			
Mean (SD)	1.67 (2.04)	1.82 (1.87)	1.93 (1.88)
Missing	878 (0.2%)	11 (0.0%)	1 (0.0%)
Hours of sleep per day			
Mean (SD)	7.10 (1.30)	7.15 (1.02)	7.13 (0.989)
Missing	887 (0.2%)	11 (0.0%)	1 (0.0%)
Number of days with tension, fidgetiness, or restlessness in the last 2 weeks			
Nearly every day	9,339 (1.9%)	473 (1.2%)	52 (1.1%)
Several days	105,428 (21.0%)	8,379 (20.7%)	967 (21.0%)
More than half the days	13,426 (2.7%)	712 (1.8%)	90 (2.0%)
Not at all	352,001 (70.1%)	29,922 (74.0%)	3,403 (73.9%)
Missing	22,192 (4.4%)	976 (2.4%)	90 (2.0%)
Frequency of friends or family visits		81.4 (9.94)	
Almost daily	57,756 (11.5%)	3,768 (9.3%)	415 (9.0%)
2–4 times a week	152,002 (30.3%)	11,817 (29.2%)	1,396 (30.3%)
About once a week	66,475 (13.2%)	15,092 (37.3%)	1733 (37.7%)
About once a month	176,370 (35.1%)	6,092 (15.1%)	662 (14.4%)
Once every few months or never	41,854 (8.3%)	3,066 (7.6%)	320 (7.0%)
Missing	7,929 (1.6%)	627 (1.5%)	76 (1.7%)

Blood sugar levels were measured as hemoglobin A1c (HbA1C). The red meat score is based on beef, pork, and lamb/mutton consumption, in which an individual score was first assigned for each meat type ("Never" or "Less than once a week" with 0; "Once a week" or "2–4 times a week" with 1; and "5–6 times a week" or "Once or more daily" with 2); these were then summed, with a score of 1–2 dichotomized into 1 and less than 1 or more than 2 with a 0. Moderate activity includes physical activities such as carrying light loads or cycling; vigorous activity includes activities such as fast cycling, aerobics, or heavy lifting. BMI stands for body mass index.

Figure Associations of Total BCS at Baseline With Neuroimaging Markers



(A and B) The thick line is the change in white matter hyperintensities volume (A.a and B.a), fractional anisotropy (A.b and B.b), or mean diffusivity (A.c and B.c) standard deviation units (z-score units) over the range of the Brain Care Score on a percentage axis; the shaded areas correspond to the 95% confidence intervals. The associations were adjusted for age and sex and plotted relative to the median Brain Care Score. (C) The thick line is the change in the evolution of white matter hyperintensities volume (C.a), average fractional anisotropy (C.b), or mean diffusivity (C.c) between the first and repeat imaging assessments over the range of the Brain Care Score on a percentage axis; the shaded areas correspond to the 95% CIs. The associations were adjusted for age, sex, and time between imaging assessments and plotted relative to the median Brain Care Score.

In the same subset, a 5-point increase in baseline BCS was associated with higher BCSs between imaging assessments, as represented by a 10% reduction in WMH volume progression (beta: −0.10 [−0.17 to −0.03]) and FA decline (beta: 0.10 [0.03,0.17]). No significant association was found between BCS increase and MD change over time (beta: −0.01 [−0.08 to 0.06]).

Discussion

In this study, we demonstrate the association between the BCS and neuroimaging markers of brain health in 34,000 middle-age persons without prior stroke or dementia. WMHs, FA, and MD showed significant improvements in participants with elevated BCSs. In addition, our study reveals that an increased BCS is associated with a preserved brain health over time, as evidenced by slower progression of these markers between the initial and repeat imaging assessments. Overall, these results suggest that the BCS targets risk factors that drive the pathophysiologic processes, leading to cerebrovascular disease and dementia.

The strengths and limitations of the BCS have been discussed in previous literature.[9] To summarize, the current version of the BCS should be regarded as a prototype, with systematic and regular optimization needed for the included components and weighing system through a (modified) Delphi process. There is no consensus on causality between some of the individual components of the BCS and dementia, stroke, or late-life depression incidence (e.g., because of reverse causality or measurement errors). Finally, components of the BCS should be culturally tailored to specific populations in future iterations

(e.g., the dietary component may be different for an American vs Japanese population). For this study, the major strength lies in the robust sample size derived from the comprehensive neuroimaging data of the UKB cohort, reducing the likelihood of false positive results. However, a limitation of this study is the demographic and age range constraints of the UKB, which includes patients aged 40–69 years at baseline, with a predominant representation of participants of European White descent. Furthermore, the participants with MRIs were healthier and had higher BCS on average. This limitation may affect generalizability of our findings to other age and ethnic groups, underscoring the need to validate our results in diverse populations to confirm their broader applicability.

In the context of the rising global incidence of brain diseases, prioritizing the modification of risk factors is critical.[14] Adopting a comprehensive health perspective,[12] the BCS suggests that lifestyle modifications mitigating the risk of stroke, dementia, and late-life depression may also reduce the progression of cerebral small vessel disease in middle-age patients without clinically evident neurologic disease. Given that the neuroimaging markers evaluated not only precede stroke and dementia but are also markers of cognitive and functional decline,[15] our findings advocate for the modification of risk factors—such as increasing physical activity, controlling blood pressure, and dietary adjustments—not only to lower the risk of clinical outcomes but also to maintain cerebral structure and function as we age.

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Appendix *(continued)*

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Appendix *(continued)*

Name	Location	Contribution
Aleksandra Pikula, MD	Department of Medicine (Neurology), University of Toronto; Krembil Brain Institute; The Jay and Sari Sonshine Centre for Stroke Prevention & Cerebrovascular Brain Health, University Health Network, Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Sarah Ibrahim, RN, PhD	Program for Health System and Technology Evaluation; Toronto General Hospital Research Institute; The Jay and Sari Sonshine Centre for Stroke Prevention & Cerebrovascular Brain Health, University Health Network; Centre for Advancing Collaborative Healthcare & Education (CACHE) and Institute of Health Policy, Management and Evaluation (IHPME), Dalla Lana School of Public Health, University of Toronto, Ontario, Canada	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Virginia J. Howard, PhD	Department of Epidemiology, School of Public Health, University of Alabama at Birmingham	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
George Howard, DrPH	Department of Biostatistics, School of Public Health, University of Alabama at Birmingham	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
H. Bart Brouwers, MD, PhD	Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Netherlands; Department of Medicine, Massachusetts General Hospital, Boston; Department of Neurosurgery, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Cornelia M. Van Duijn, PhD, FMedSci	Nuffield Department of Population Health, Big Data Institute, University of Oxford, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Gregory Fricchione, MD	Henry and Allison McCance Center for Brain Health; Benson-Henry Institute for Mind Body Medicine, Massachusetts General Hospital, Boston	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Rudolph E. Tanzi, PhD	Henry and Allison McCance Center for Brain Health, Massachusetts General Hospital, Boston	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Appendix *(continued)*

Name	Location	Contribution
Nirupama Yechoor, MD, MSc	Henry and Allison McCance Center for Brain Health; Department of Neurology, Massachusetts General Hospital, Boston; Broad Institute of MIT and Harvard, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Kevin N. Sheth, MD	Department of Neurology, Yale School of Medicine; Yale Center for Brain and Mind Health, New Haven, CT	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
Christopher D. Anderson, MD	Henry and Allison McCance Center for Brain Health; Department of Neurology, Massachusetts General Hospital, Boston; Broad Institute of MIT and Harvard, Cambridge; Department of Neurology, Brigham and Women's Hospital, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Jonathan Rosand, MD	Henry and Allison McCance Center for Brain Health; Department of Neurology, Massachusetts General Hospital, Boston; Broad Institute of MIT and Harvard, Cambridge, MA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Guido J. Falcone, MD	Department of Neurology, Yale School of Medicine; Yale Center for Brain and Mind Health, New Haven, CT	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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