SUPPLEMENTAL MATERIAL

Association of Ideal Cardiovascular Health with Vascular Brain Injury and Incident Dementia

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Supplemental Methods

Supplemental Table Legend

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Assessment of stroke and dementia
Participants suspected of having a stroke were visited by a Framingham Heart Study stroke physician within 48 hours. Participants were also questioned about the occurrence of stroke and stroke symptoms during annual health status updates. A study diagnosis of stroke was determined by a committee comprised of at least 3 Framingham Heart Study investigators, including at least 2 neurologists. The committee made an informed decision after reviewing all medical records, imaging studies, and the assessment of the study neurologist who visited the participant.

For the surveillance of incident dementia, participants underwent routine cognitive screening at each examination cycle using the Mini-Mental State Examination (MMSE)[1] and complete neuropsychological testing at selected examination cycles. The MMSE was used to flag participants for dementia review if (i) performance fell below education-based cut-off scores at any exam,[2] (ii) a decline of >2 points was observed between consecutive exams or (iii) a decline of >4 points was observed from the participants highest obtained MMSE score. In addition, participants were screened for dementia in response to referrals or concern from the participant, their family, their doctor, or other health professional. Participants with suspected dementia or cognitive impairment underwent neuropsychological and neurological evaluation before referral to our dementia review committee. A diagnosis of dementia was made in accordance with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*.[3] Type of dementia was also recorded. A diagnosis of AD was based on the criteria of the *National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association for definite, probable, or possible AD*.[4] The presence of VaD was determined based on the *National Institute of Neurological Disorders, and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences* (NINDS-AIREN) criteria.[5] Diagnosis was made by a committee comprised of at least 1 neurologist and neuropsychologist. Participants with evidence of both clinical AD and VaD were classified as having both diseases.

Assessment of cognitive function
Visual Reproductions and Logical Memory are primarily tests of visual and verbal memory respectively, with higher scores reflecting a greater number of correct responses recalled after a delay. Similarities examines how well a subject can describe the common elements linking a pair of related items or how well they integrate the item pair under a single concept. The task involves verbal comprehension, categorization, and executive functions such as verbal reasoning and abstraction. Trail making A is primarily a test of processing speed, visual search, and motor control in which a participant draws a continuous line linking a set of numbered circles in sequential order. Trail making B involves linking ascending digits and letters in an alternating fashion (1-A, 2-B etc.). This test involves the complexities of trail making A plus demands on executive functions, including task switching, mental flexibility, and working memory. Both trail making tasks are scored as time to completion. Trained research assistants and neuropsychologists administered the tests and all neuropsychological tests are commonly used in research and have adequate reliability [6, 7]. In addition to examining the individual cognitive tasks, we created an overall cognitive score using principal component analysis, forcing a single component solution. Numerous task scores were first standardized before being summed together according to their weighting to the overall cognitive factor (please see Table S2 online). Analysis was performed on Exam 7 data (baseline), with weights and formulas carried over to the repeat cognitive assessment, for the purpose of calculating annualized change in global cognitive scores.

Supplemental Table I. Operationalization of the Ideal-Cardiovascular Health Score

Goal	Ideal Cardiovascular Health criteria
Current smoking status	Never smoked or quit >12 mo ago
Body mass index	<25 kg/m^2
Physical activity*	≥150 min/wk moderate intensity or ≥75 min/wk vigorous intensity or combination
Healthy diet†	> 2 of the following components: ≥ 4.5 cups/day fruits and vegetables, ≥ 2x3.5 oz servings/week of fish, ≥ 3x1 oz servings/day of fiber-rich whole grains, < 1500 mg/d of sodium, and < 36 oz/week of sugar sweet beverages.
Serum total cholesterol	Untreated and <200 mg/dL
Blood pressure	Untreated and <120/<80 mmHg
Fasting plasma glucose	Untreated and <100 mg/dL

Note: 1 point was awarded for each goal that was met with total scores ranging from 0-7.
*Physical activity was calculated using the following formula as per a pervious Framingham Heart Study publication[8]: 1*sleep hrs/day + 1.1*sedentary hrs/day + 1.5*slight activity hrs/day + 2.4*moderate activity hrs/day + 5*heavy activity hrs/day. The top quartile of this score was used to indicate ideal physical activity, which corresponds qualitatively to the definition used by the AHA[9].
†Diet scores were adapted from the AHA guidelines[9], consistent with a previous Framingham Heart Study publication[8].

Supplemental Table II. Creation of the global cognitive score

Cognitive Task	Natural Log-Transformations	Standardizing formula†	Component loading‡
Trails A	-log (Trails A)	(Trails A - 0.68) / 0.34	0.13
Trails B	-log (Trails B)	(Trails B + 0.22) / 0.45	0.18
Trails (B – A)	-log (2 + Trails (B -A))	(Trails (B – A) + 1.03) / 0.22	0.16
Logical Memory IR		(Logical Memory IR - 11.55) / 3.4	0.14
Logical Memory DR		(Logical Memory DR - 10.61) / 3.59	0.15
Visual Reproductions IR		(Visual Reproductions IR - 9.07) / 3.15	0.17
Visual Reproductions DR		(Visual Reproductions DR - 8.2) / 3.36	0.18
PAL DR		(PAL DR - 8.3) / 1.46	0.13
Hooper VOT	-log (31 - Hooper VOT)	(Hooper VOT + 1.65) / 0.52	0.14
Similarities		(Similarities - 16.77) /3.55	0.14

DR = delayed recall; IR = immediate recall; PAL = paired associate learning; VOT = visual organization test.
†Natural log transformed cognitive tasks were used to create the standardized variables, where applicable.
‡Global cognitive score calculated by summing the products of the standardizing formulas and the component loadings for each cognitive task.

Supplemental Table III. 14-point Ideal-Cardiovascular Health score and the 10-year risk of incident stroke and dementia

Event	Recent Ideal-CVH			Remote Ideal-CVH		
	n cases / subjects	**HR (95% CI)**	**P**	**n cases / subjects**	**HR (95% CI)**	**P**
Stroke	87/2631	0.89 (0.81, 0.99)	0.03	70/2139	0.87 (0.78, 0.97)	0.01
All-cause dementia	84/1364	0.97 (0.87, 1.08)	0.59	69/1131	0.88 (0.79, 0.99)	0.03
Alzheimer's disease	64/1364	1.00 (0.88, 1.14)	0.98	51/1131	0.90 (0.79, 1.03)	0.13
Vascular dementia	14/1364	0.72 (0.55, 0.96)	0.03	13/1131	0.77 (0.59, 0.01)	0.06

CI = Confidence Interval, CVH = Ideal-Cardiovascular Health, HR = Hazard Ratio. Results are adjusted for age, sex.

Supplemental Table IV. 14-point Ideal-Cardiovascular Health and annualized change in cognition and markers of brain atrophy

Measures	Recent Ideal-CVH		Remote Ideal-CVH	
	β±SE	P	β±SE	P
Cognitive decline				
Global decline	0.001±0.001	.19	0.003±0.001	.007
Visual reproductions delayed	0.01±0.01	.02	0.01±0.01	.02
Similarities	0.01±0.01	.10	0.02±0.01	<.001
Trails A	0.001±0.001	.61	-0.002±0.001	.13
Trails B	-0.004±0.002	.10	-0.004±0.003	.11
Logical Memory Delayed	-0.01±0.01	.16	-0.0003±0.007	.97
Brain atrophy and white matter injury				
Total brain volume	0.11±0.05	.02	0.15±0.05	.01
Frontal brain volume	0.25±0.06	<.001	0.12±0.07	.10
Lateral Ventricular Volume	0.01±0.01	.28	0.0001±0.01	.99
WMHV	0.001±0.004	.87	0.002±0.004	.68

CVH = Cardiovascular health; WMHV = White matter hyperintensity volume. Analyses are adjusted for age, sex, age squared, baseline (exam 7) scores on each respective measure and education (in the case of cognitive decline).

References

1. Folstein MF, Folstein SE, McHugh PR. 'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 1975;12:189-198
2. Bachman DL, Wolf PA, Linn R, Knoefel JE, Cobb J, Belanger A, et al. Prevalence of dementia and probable senile dementia of the alzheimer type in the framingham study. *Neurology*. 1992;42:115-119
3. American Psychatric Association. *Diagnostic and statistical manual of mental disorders 4th ed. Text revision*. Washington DC; American Psychatric Assocaition; 2000
4. McKhann G, Drachman D, Folstein M. Clinical diagnosis of alzheimer's disease: Report of the nincds-adrda work group under the auspices of department of health and human services task force on alzheimer's disease. *Neurology*. 1984;34:939-944
5. Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: Diagnostic criteria for research studies. Report of the ninds-airen international workshop. *Neurology*. 1993;43:250-260
6. Strauss E, Sherman EMS, Spreen O. *A compendium of neuropsychological tests: Administration, norms, and commentary*. Oxford, NY: Oxford Univesity Press; 2006.
7. Au R, Seshadri S, Wolf PA, Elias M, Elias P, Sullivan L, et al. New norms for a new generation: Cognitive performance in the framingham offspring cohort. *Exp Aging Res*. 2004;30:333-358
8. Xanthakis V, Enserro DM, Murabito JM, Polak JF, Wollert KC, Januzzi JL, et al. Ideal cardiovascular health: Associations with biomarkers and subclinical disease and impact on incidence of cardiovascular disease in the framingham offspring study. *Circulation*. 2014;130:1676-1683
9. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The american heart association’s strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586-613