Stroke
Journal of the American Heart Association

Defining Optimal Brain Health in Adults: A Presidential Advisory From the American Heart Association/American Stroke Association

Philip B. Gorelick, Karen L. Furie, Costantino Iadecola, Eric E. Smith, Salina P. Waddy, Donald M. Lloyd-Jones, Hee-Joon Bae, Mary Ann Bauman, Martin Dichgans, Pamela W. Duncan, Meighan Girgus, Virginia J. Howard, Ronald M. Lazar, Sudha Seshadri, Fernando D. Testai, Stephen van Gaal, Kristine Yaffe, Hank Wasiak and Charlotte Zerna

Stroke. published online September 7, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

Systematic Review: Supplement to Defining Brain Health

Objective: To systematically search the literature to identify potentially modifiable risk factors for age-related cognitive decline and incident cognitive impairment in the general population. The results of the searches are intended to aid the writing committee for "Defining Optimal Brain Health", by complementing the targeted searches and expert knowledge of the committee members.

Background: We used the outline of "Defining Optimal Brain Health" (March 28, 2017 version) as the source document to plan the search methods. Because cognitive ability is (arguably) the most important function of a healthy brain, we devised search methods to identify risk factors for cognitive impairment or decline. To provide reasonable limits on the scope of the searches, we considered but ultimately rejected searches for other brain health outcomes such as cognitive-related activities of daily living, patient/participant reported outcomes of cognitive-related quality of life, and mental health outcomes such as mood disorders.

Methods:

Overview: For this review, we operationalized the concept of "brain health" as preserving cognitive function and the absence of cognitive disorders (all-cause mild cognitive impairment or synonyms, or dementia). To improve the quality of returned articles, we only included longitudinal studies reporting incident or progressive cognitive impairment, excluding cross-sectional studies. Longitudinal studies are expected to be less vulnerable to the possibility of reverse causality.

We sought information on a broad range of exposures, including the risk factors related to the American Heart Associations "Life's Simple 7"[1] as well as potentially modifiable exposures (defined below in Selection Criteria).

Selection Criteria: We included cohort studies that examined the relationships between potentially modifiable risk factors and either incident cognitive disorders (such as dementia or mild cognitive impairment) or longitudinal measures of cognitive decline (Table 1, Selection Criteria). We excluded exposures that we deemed non-modifiable, biologically implausible, intermediate physiological markers of other processes, highly vulnerable confounding, or for which there was randomized controlled trial (RCT) evidence that the modifying the exposure was either ineffective or produced harm (Table 2). We included prior systematic reviews.

[1] http://www.heart.org/HEARTORG/Conditions/My-Life-Check---Lifes-Simple-7_UCM_471453_Article.jsp#.WVJHN4jyvic

Table 1. Selection Criteria

Inclusion criteria	• Describes relationship between a potentially modifiable exposure and an outcome as defined below.
	  • Exposure: Potentially modifiable exposure, as defined in Table 2.
	  • Outcome: Change over time on neuropsychological testing or cognitive screening test (*e.g.* Folstein MiniMental State Exam), or incident dementia or mild cognitive impairment (including similar constructs as defined by the study authors, including cognitively impaired not dementia).
	• Design: Either cohort study or systematic review of other relevant studies. Exposure must have been measured prior to the outcome, with longitudinal follow-up of at least one year.
	• Population-based or community-based sampling.
	• Published in the English language.

Exclusion criteria	• Study sample is not a population-based or community-based study, *e.g.* sampling from a hospital or a clinic. • Disease-based study sample with neurological or psychiatric disorder. • Cross-sectional study design. • Fewer than 100 participants. • Outcomes in pediatric populations (<18). (Note: pediatric/in utero exposures allowed, if cognition/cognitive disorders or decline were assessed in adult life). • Study not in human subjects. • Non-English language. • Publication date prior to January 1, 1980.

Table 1. Classification of Included vs. Excluded Exposure Categories

Relevant and Included	Considered Not Relevant, and Not Included			
Potentially modifiable	**Not modifiable or not easily modifiable**	**Likely confounded or biased**	**Intermediate physiological markers unlikely to be causally related**	**Modifiable but RCT evidence fails to support effect on cognition**
Cholesterol	Age	Specific antihypertensive choices (e.g. angiotensin receptor blocker, calcium channel blockers)	Carotid intima-media thickness	Estrogen
Hypertension/blood pressure	Sex	Other prescription medications proposed to have off-target benefits or harms: proton pump inhibitors	Subclinical atherosclerosis	Hormone replacement therapy
History of stroke	Markers of inflammation (e.g. C-reactive protein, interleukin-6)		Heart rate	
Diabetes	Apolipoprotein E genotpye		Frailty	
Kidney disease	Other genetic polymorphisms		Walking speed	
Chronic obstructive pulmonary disease	Heart rate variability		Anemia	
Heart failure	Pulse pressure		Red cell membrane fluidity	
Coronary artery disease	Evidence of past infectious burden (e.g. herpes simplex virus)		Bone mineral density	
Tooth loss, periodontitis				
Sleep-disordered breathing, sleep duration				
Hearing loss				
Vision loss				
Physical activity				
Exercise				
Depression				
Anxiety				
Smoking				
Alcohol use				
Recreational drug use				
Education				
Social participation				

Cognitive activities	
Personality traits	
Built environment	
Occupation	
Dietary choices	
Mediterranean diet	
Caffeine	
Vitamin intake	
Vitamin and mineral levels	
Omega-3 fatty acids, micronutrients	
Homocysteine	
Thyroid hormone levels	
Insulin levels or resistance	
Body mass index, weight, waist-to-hip ratio	
Lead, aluminum	
Pesticides	
Air pollution	
Electromagnetic radiation	
Benzodiazepine use	
Anticholinergic drug use	

Search
Potentially relevant studies were identified using a Medline search conducted in the Ovid environment on April 1, 2017 (search strategy included as Appendix 1). The search strategy was intended to sensitively capture studies of the epidemiology of specific neurodegenerative disorders as well as of unspecified cognitive impairment using a broad array of inclusionary MeSH headings. Exclusionary MeSH headings were specified for specific disorders unrelated to neurodegenerative diseases (e.g. demyelinating diseases) and for reliably coded study characteristics (e.g. animal subjects).

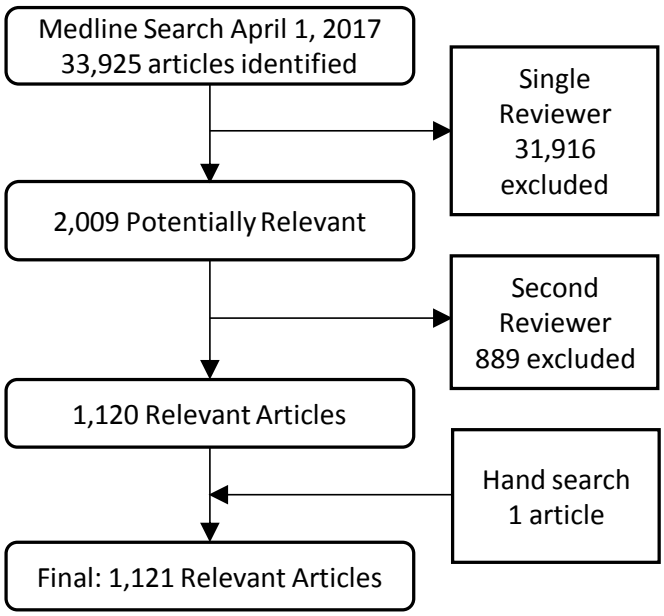
Review
Search results were transferred to Covidence (Veritas Health Innovation Ltd, Melbourne, Australia) for team review. Each study title and abstract was screened for relevance by one of three authors (CZ, SVG, ES).

Potentially relevant studies were moved forward to a second review stage where they were subsequently assessed by a second reviewer, and a final determination of eligibility was made. Discrepancies on eligibility were resolved by consensus.

A single reviewer sorted studies according to whether they assessed any of Life's Simple 7 as an exposure, assessed other exposures, or were systematic reviews. For an article to be considered relevant for a specific exposure category, the abstract must have noted that the exposure was studied as an independent variable of interest. Exposures described as covariates only were not included.

Results

The literature search identified 33,925 articles. After initial review by a single reviewer, intended to value sensitivity (i.e. inclusion of as many potentially relevant articles as possible), 2,009 articles remained. After 2nd review and consensus, 1,121 articles were deemed relevant (Figure). The 1,121 eligible studies, sorted by exposure category, were provided to Writing Committee members.



Appendix 1. Search strategy

1. exp Alzheimer Disease/
2. exp Dementia, Vascular/
3. Dementia/
4. exp Lewy Body Disease/
5. mild cognitive.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6. MCI.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. exp Risk Factors/
8. exp Epidemiology/
9. exp Cohort Studies/
10. 1 or 2 or 3 or 4 or 6
11. 7 or 8 or 9
12. 10 and 11
13. exp Cognitive Dysfunction/
14. Cognition Disorders/
15. exp Neuropsychological Tests/
16. exp Executive Function/
17. memory disorders/ or amnesia/
18. 13 or 14 or 15 or 16 or 17
19. 18 and 11
20. exp Alzheimer Disease/dh, ep, et, pc [Diet Therapy, Epidemiology, Etiology, Prevention & Control]
21. exp Lewy Body Disease/ep, et, pc [Epidemiology, Etiology, Prevention & Control]
22. exp Dementia, Vascular/dh, ep, et, pc [Diet Therapy, Epidemiology, Etiology, Prevention & Control]
23. Dementia/dh, ep, et, pc [Diet Therapy, Epidemiology, Etiology, Prevention & Control]
24. Cognition Disorders/dh, ep, et, pc [Diet Therapy, Epidemiology, Etiology, Prevention & Control]
25. Cognitive Dysfunction/dh, ep, et, pc [Diet Therapy, Epidemiology, Etiology, Prevention & Control]
26. Memory Disorders/dh, ep, et, pc [Diet Therapy, Epidemiology, Etiology, Prevention & Control]
27. Amnesia/dh, ep, et, pc [Diet Therapy, Epidemiology, Etiology, Prevention & Control]
28. 24 or 25 or 26 or 27
29. exp Pathology/
30. Animals/
31. exp Adult/
32. 29 or 30
33. 20 or 21 or 22 or 23
34. 12 or 33

35. 34 and 32
36. 34 not 35
37. 36 and 31
38. 19 or 28
39. 38 and 32
40. 38 not 39
41. 40 or 37
42. exp Child/
43. mental disorders/ or exp "bipolar and related disorders"/ or exp "disruptive, impulse control, and conduct disorders"/ or exp dissociative disorders/ or exp elimination disorders/ or exp "feeding and eating disorders"/ or exp neurodevelopmental disorders/ or exp neurotic disorders/ or exp paraphilic disorders/ or exp personality disorders/ or exp "schizophrenia spectrum and other psychotic disorders"/ or exp sexual dysfunctions, psychological/ or exp somatoform disorders/ or exp "trauma and stressor related disorders"/
44. exp "autoimmune diseases of the nervous system"/ or exp autonomic nervous system diseases/ or exp chronobiology disorders/ or exp cranial nerve diseases/ or exp demyelinating diseases/ or exp nervous system malformations/ or exp nervous system neoplasms/ or exp neurocutaneous syndromes/ or exp neuromuscular diseases/ or exp neurotoxicity syndromes/ or exp restless legs syndrome/ or exp trauma, nervous system/
45. 42 or 43 or 44
46. 41 and 45
47. 41 not 46
48. limit 47 to (abstracts and english language)