A Presidential Advisory From the American Heart Association/American Stroke Association

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Abstract—Cognitive function is an important component of aging and predicts quality of life, functional independence, and risk of institutionalization. Advances in our understanding of the role of cardiovascular risks have shown them to be closely associated with cognitive impairment and dementia. Because many cardiovascular risks are modifiable, it may be possible to maintain brain health and to prevent dementia in later life. The purpose of this American Heart Association (AHA)/American Stroke Association presidential advisory is to provide an initial definition of optimal brain health in adults and guidance on how to maintain brain health. We identify metrics to define optimal brain health in adults based on inclusion of factors that could be measured, monitored, and modified. From these practical considerations, we identified 7 metrics to define optimal brain health in adults that originated from AHA’s Life’s Simple 7: 4 ideal health behaviors (nonsmoking, physical activity at goal levels, healthy diet consistent with current guideline levels, and body mass index <25 kg/m²) and 3 ideal health factors (untreated blood pressure <120/80 mm Hg, untreated total cholesterol <200 mg/dL, and fasting blood glucose <100 mg/dL). In addition, in relation to maintenance of cognitive health, we recommend following previously published guidance from the AHA/American Stroke Association, Institute of Medicine, and Alzheimer’s Association that incorporates control of cardiovascular risks and suggest social engagement and other related strategies. We define optimal brain health but recognize that the truly ideal circumstance may be uncommon because there is a continuum of brain health as demonstrated by AHA’s Life’s Simple 7. Therefore, there is opportunity to improve brain health through primordial prevention and other interventions. Furthermore, although cardiovascular risks align well with brain health, we acknowledge that other factors differing from those related to cardiovascular health may drive cognitive health. Defining optimal brain health in adults and its maintenance is consistent with the AHA’s Strategic Impact Goal to improve cardiovascular health of all Americans by 20% and to reduce deaths resulting from cardiovascular disease and stroke by 20% by the year 2020. This work in defining optimal brain health in adults serves to provide the AHA/American Stroke Association with a foundation for a new strategic direction going forward in cardiovascular health promotion and disease prevention. (Stroke. 2017;48:e00-e00. DOI: 10.1161/STR.0000000000000148.)

Key Words: AHA Scientific Statements ■ aging ■ brain ■ cognitive dysfunction ■ prevention and control ■ risk factors ■ stroke

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Life expectancy is projected to continue to increase in developed countries in the Americas, Australasia, central and western Europe, and Asia-Pacific and is expected to be highest in South Korea, western European countries, and some emerging economies. Anticipated gains in longevity will occur in older age groups, particularly among women. By 2030, it is estimated there will be a >50% probability that women in some of the aforementioned regions will break the 90-year survival barrier. These gains may be explained by improvements in social status, education, and childhood and adolescent nutrition; expanded primary and secondary health care; a rapid scale-up of new medical technologies; and advances in public health and hygiene.

An increase in life expectancy creates an important public health challenge to plan for health and social services, housing, and pensions for the elderly and to care for those at risk for cognitive impairment and dementia. Another major challenge is that increased longevity is likely to be associated with an increase in the prevalence of cognitive impairment and dementia. It is estimated that there are 47 million people with dementia worldwide and that this will increase to 75 million in 2030 and 131 million by 2050. These public health projections suggest the need for the prevention of cognitive impairment and treatments to delay cognitive decline. Cardiovascular risks have been viewed as important targets for strategies to prevent or delay cognitive impairment. Thus, there is a linkage between brain health and cardiovascular health.

Cognitive function is an important feature of successful aging, affecting quality of life, functional independence, and risk of institutionalization. According to the US Centers for Disease Control and Prevention, a healthy brain is one that can perform all the mental processes that encompass cognition such as the ability to learn and judge, use language, and remember. The Centers for Disease Control and Prevention has concluded, however, that there is limited consumer information about cognitive health and maintenance of cognition, existent messaging is inadequate, and the perception of brain health varies by ethnic, cultural, and geographic group. In this American Heart Association/American Stroke Association (AHA/ASA) presidential advisory, we aim to expand knowledge in this area by defining optimal brain health in adults and suggesting ways to maintain it. Such information will provide the AHA/ASA with the foundation for a new strategic direction going forward in cardiovascular health promotion and disease prevention.

Methods

The writing committee was commissioned in November 2016 to review the literature on brain health and maintenance and to develop a definition of optimal brain health in adults. With guidance from the officers of the AHA and members of the AHA Stroke Council, a task force developed an outline for the establishment of a manuscript on optimal brain health in adults. The outline focused on 3 key topics: public health impact of cognitive impairment, definition of optimal brain health, and recommendations for maintenance of brain health. In December 2016, the writing committee members were selected by the chair and co-chairs of this writing group. Writing committee members were chosen on the basis of expert knowledge in the area and experience with guideline development. Discretion was taken to achieve a balance of early-career and later-career investigators, as well as a balance in relation to sex, race, and ethnicity. All writing committee members were required to declare conflicts of interest.

The first writing committee conference call was held in March 2017. During the call, the purpose and topics of the statement were discussed and finalized, and a literature strategy was established. Each of the major sections of the manuscript was assigned a lead, and the chair and co-chairs were responsible for drafting the introduction, methods, and concluding sections and editing all subsections of the manuscript. Relevant literature was identified through a systematic review complemented by hand searching of reference lists and expert knowledge of relevant articles focused primarily on topics relating to brain health and maintenance of brain health. Literature searches were conducted centrally. Full details of the search strategy are available in the Data Supplement (see Systematic Review: Supplement to Defining Brain Health). Section writing leads and members reviewed abstracts and titles for relevance and abstracted key information from the articles. Detailed evidence tables, however, were not required.

The statement was independently reviewed by the AHA Science Advisory and Coordinating Committee. The writing committee responded point by point to each comment made by the reviewers. Final approval of the manuscript was provided by the AHA Science Advisory and Coordinating Committee.

Public Health Impact of Cognitive Impairment, Dementia, Stroke, and Cardiovascular and Stroke Risks

Cognitive Impairment and Dementia

A healthy brain is essential for living a longer and fuller life. Brain health enables thought, planned action, and emotional connections that affect the daily lives and progress of individuals, families, and communities. Sustaining brain health over the course of a lifetime is important to allow one to maximize one’s overall ability and independence. Maintenance of brain health may also curtail the need for diversion of economic and healthcare resources for care and treatments that may have limited the allocation of resources to efforts aimed at maintaining and restoring one to a healthy brain state. Thus, the impact of maximizing and maintaining brain health has the potential to benefit individuals, family and friends, healthcare providers and systems, and society.

Poor brain health may eventually manifest as cognitive impairment or dementia via underlying disorders that include but are not limited to Alzheimer disease (AD), stroke and other causes of vascular cognitive impairment, brain trauma, and other neurodegenerative disorders. In 2010, it was estimated that the second largest number of people living with dementia resided in the United States (3.9 million people), with the largest number living in China (5.4 million people). Modifiable risks associated with poor cardiovascular health such as uncontrolled hypertension, diabetes mellitus, obesity, physical inactivity, smoking, and depression are associated with compromised brain health.

Worldwide, >7 million new dementia cases are diagnosed annually. By 2050, the prevalence of dementia is expected to...
increase by 116% in high-income countries and 264% in low-income countries. From self-report, it is estimated that 1 in 8 adults >60 years of age has memory loss and ≥35% of those report functional difficulties. In addition, an estimated 5.1 million individuals in the United States who are ≥65 years of age have AD, which in the United States is predicted to rise to 13.2 million by 2050.

Cognitive impairment and dementia exact a high economic cost. In the United States, AD and related dementias are among the most expensive diseases to treat, with direct care expenses being greater than those for cancer and equal to those for heart disease. In 2013, direct payments for health care, long-term care, and hospice care were $203 billion, and among chronic diseases, dementia is the largest single contributor to disability and to the need for longer-term care among older individuals. However, direct care costs of cognitive impairment represent only part of the total financial costs. In 2011, >15 million Americans spent an average of 21.9 h/wk caring for family members with dementia, and the estimated monetary cost may be as high as $215 billion annually. This does not take into account, however, stress and related factors placed on caregivers and other family members. The toll on caregivers’ emotional state, for example, is just as striking, with an increased risk of anxiety, depression, and poorer quality of life. Although some studies have shown a benefit of caregiving, up to 50% of caregivers have been shown to suffer from depression compared with 15% of noncaring individuals. Finally, dementia and cognitive impairment challenge the effective treatment of many concurrent illnesses, complicating consent and compliance.

**Impact of Stroke**

Stroke is especially common among those who are older, and it is estimated that 1 in 3 individuals will have a stroke, dementia, or both. Subclinical or silent stroke occurs at least 5 times as commonly as symptomatic stroke and may not be silent because subclinical events are associated with impairment of cognition and disturbances of mood and personality. Furthermore, macroscopic infarcts occur in about one third to one half of elderly individuals, and of all major cognitively impairing disorders, including AD, there is a vascular component in up to 80%. Thus, stroke and its antecedents play a pivotal role in the processes underlying cognitive impairment and dementia.

**Cardiovascular and Stroke Risks**

Cardiovascular and stroke risks are common in the United States and worldwide. In the United States, there are 75 million people (1 of every 3 adults) with hypertension, and 54% of those have uncontrolled blood pressure (BP). When race and ethnicity are taken into account, there are higher rates of hypertension in blacks, followed by US non-Hispanic whites and Mexican Americans. In addition, diabetes mellitus and obesity are increasing in frequency across the United States. In 2014, there were an estimated 22 million Americans living with diabetes mellitus, a 4-fold increase from the 5.5 million with diabetes mellitus in 1980 and nearly double the 12.1 million in 2000. Obesity rates are also high in the United States. Currently, 36.5% of US adults are categorized as being obese, with the prevalence of obesity being higher in women (38.3%) than men (34.3%) and highest in non-Hispanic blacks and Hispanics followed by non-Hispanic whites and non-Hispanic Asians. Among the 20 most populous countries, the highest level of age-standardized childhood obesity occurs in the United States.

Because hypertension, obesity, smoking, and diabetes mellitus contribute to cognitive impairment and dementia and there are interventions that successfully prevent or modify these risk factors, a strategy using AHA’s Life’s Simple 7 to decrease cardiovascular risk, stroke, and heart attack should also contribute to maintenance of brain health. Potential factors that may or may not favor optimal brain health and a causal chain of factors mediated by cardiovascular risks that lead to stroke, dementia, and cognitive dysfunction are depicted in Figure 1. Cardiovascular risks may mediate subclinical and clinical brain injury, the antecedents of cognitive impairment.

**Summary**

Cognitive impairment and dementia are common in the population, especially among older people, and exact a substantial economic and personal toll. As the population in the United States ages, cardiovascular risk factors such as obesity, hypertension, and diabetes mellitus are expected to continue to significantly increase in frequency. Subclinical vascular brain injury (eg, brain white matter hyperintensities, microinfarcts, cerebral microbleeds) and symptomatic stroke, antecedent risks, and associated factors are frequently observed and linked to cognitive impairment and dementia in both clinical and neuropathologic studies. Thus, risks for stroke and cardiovascular disease are well positioned to be targets of preventive strategies for cognitive impairment and dementia. In
addition, maintaining brain health is paramount because many public health sectors such as individual health care, healthcare finance, maintenance of employment, and family and community health may be affected.

**Optimal Brain Health**

**Basic Mechanisms and Milieu**

Optimal brain function depends on many energy-intensive activities ranging from synaptic activity and subsequent restoration of resting ionic gradients and chemical milieu to protein synthesis and axonal transport. With minimal or no energy reserves and the exquisite sensitivity of neurons and glia to chemical changes in the internal milieu, normal brain function is highly dependent on adequate delivery of energy substrates, mainly oxygen and glucose. These are delivered by cerebral blood flow, which, in turn, depends on cardiovascular and cerebrovascular health.

Vital cerebrovascular regulatory mechanisms ensure that the brain is adequately perfused. Neurovascular coupling ensures that focal increases in brain activity are associated with corresponding increases in blood flow to the activated areas. Cerebrovascular autoregulation maintains cerebral blood flow relatively independently of changes in arterial pressure to protect the brain from damage during fluctuations in cerebral perfusion, whereas cerebral endothelial cells regulate microvascular flow by releasing vasoactive agents such as nitric oxide and prostanooids. These fundamental properties of the cerebrovascular microcirculation depend on the coordinated interaction of neurons, astrocytes, vascular endothelial cells, smooth muscle cells, pericytes, perivascular cells, and the cerebrovascular matrix, which collectively constitute a functional ensemble called the neurovascular unit (NVU; Figure 2).

In addition to regulating cerebral perfusion, the NVU is responsible for the blood-brain barrier, which finely controls the molecular exchange between blood and brain and vice versa through an intricate system of transporters located on the endothelial cell membrane. Another important function of the NVU is to dispose of unwanted products of brain activity and metabolism, such as β-amyloid and tau to prevent their accumulation in the brain tissue. To this end, clearance pathways efficiently remove these potentially deleterious molecules through transport across the vessel wall (transvascular pathway), retrograde convective flow in the perivascular space or vessel wall (perivascular pathway), and paravascular pathways involving astrocytic end-feet (glymphatic system). The NVU is also involved in the immune surveillance of the brain processes and in producing growth factors that support the survival of brain cells and blood vessels. Therefore, the NVU is critical for maintaining the homeostasis of the cerebral microenvironment, which is essential for brain health (Figure 2).

Increasing evidence indicates that cumulative exposure to vascular risk factors throughout life, perhaps starting as early as in utero, and certainly from the fourth decade onward, affects the risk of common neurological diseases, such as stroke and dementia, as well as the burden of covert (or silent) brain lesions that may diminish optimal brain function, although not sufficiently to be recognized clinically until later in the course of disease. Vascular risk factors, for example, hypertension, diabetes mellitus, and dyslipidemia, have deleterious effects on the structure and function of cerebral blood vessels, leading to vascular remodeling and stiffness, impaired cerebral blood flow autoregulation, endothelial dysfunction, altered neurovascular coupling, and failure of clearance systems, resulting in neurovascular dysfunction and suboptimal brain health.

**Parallels Between Cardiovascular and Cerebrovascular Health and Brain Health**

Aging affects all organ systems through common underlying mechanisms, such as changes in the immune system, oxidative stress, and DNA damage and replication errors, as well as epigenetic changes and accumulation of abnormal proteins across multiple organ systems. Aging has profound effects on the structure and function of the cerebrovascular system, which may act in concert with vascular risk factors to further compromise brain health. Furthermore, age-related alterations in systemic organs, such as the liver, kidney, lung, and endocrine and immune systems, may also produce secondary deleterious effects on the brain. In turn, brain dysfunction and damage caused by age, age-related systemic diseases, and vascular risk factors may lead to deleterious effects on the cardiovascular system by altering neurohumoral mechanisms controlling the heart, blood vessels, and metabolism and promoting cardiac damage and hypertension. Therefore, the health of the brain is inextricably related to cardiovascular and cerebrovascular health, and interventions aimed at promoting cardiovascular health would be expected to promote brain health and vice versa.

**How Do We Define Optimal Brain Health?**

Most existing definitions of brain health emphasize an absence of overt vascular or neurodegenerative injury such as from stroke and AD. Some definitions additionally emphasize the absence of subclinical injury on brain imaging such as white matter hyperintensities, silent infarcts, microbleeds on brain magnetic resonance imaging (MRI), or cognitive function assessment values above the age- and education-dependent normative thresholds. More recently, molecular interrogation of brain parenchyma through cerebrospinal fluid studies and positron emission tomography imaging of amyloid and tau burden and of brain network connectivity patterns through functional and diffusion-weighted MRI has been added as a marker of subtle brain injury. There is a need for a broader perspective of the definition of brain health that does not depend on the mere absence of anatomic and physiological disease and encompasses the potential measurement, monitoring, and modification in individuals and in the population.

Optimal brain health can theoretically be defined as an optimal capacity to function adaptively in the environment. This could be assessed in terms of competencies across the domains of “thinking, moving, and feeling,” encompassing, for example, the abilities to pay attention, perceive, and recognize sensory input; to learn and remember; to communicate; to problem solve and make decisions; to have mobility; and to regulate emotional status. These domains are largely attributable to the functions of the brain (except for aspects
Defining Optimal Brain Health in Adults

Bodily functions such as sleep, continence, and appetite are also affected by the brain. These constructs can be readily understood by patients and their primary care providers and should be used as the equivalent of vital signs of the brain, that is, early warning indexes of brain health to be monitored and addressed at an at-risk stage for the brain.

Maintenance of Brain Health Requires Consideration of the Life Continuum

Many brain disorders manifest later in life but, in fact, are life-course illnesses. It has been shown that even during the period of brain development, subclinical injury can begin to accrue. Thus, the risk of stroke in the fifth and sixth decades of life depends not only on the BP at the time that risk is being assessed but also on BP patterns experienced in the preceding 1 or 2 decades. Although this advisory statement is focused on adults, to best prevent late-life disease, interventions focused on modifiable risk and protective factors may ideally need to be applied in young adulthood, possibly as far back as childhood. Optimal brain health may be defined at any life stage as average performance levels among all people at that age who are free of known brain or other organ system disease in terms of decline from previously documented levels of function or as adequacy to perform all activities that the individual wishes to undertake.

Pragmatic Criteria to Evaluate and Promote Optimal Brain Health Throughout the Life Span

Actionable criteria need to focus on age-appropriate sensitive measures and modifiable risk factors. Screening tests for brain health range from structured or semistructured questionnaires that score self-assessments or close family member assessments of daily function (Everyday Cognition, AD8, Informant Questionnaire on Cognitive Decline in the Elderly, Clinical Dementia Rating Scale, Lawton-Brody Instrumental Activities of Daily Living) to brief objective assessments of the abilities to attend, perceive, learn, remember, communicate, problem solve, and decide (Folstein Mini-Mental State Examination, Montreal Cognitive Assessment, Telephone Interview of Cognitive Status, Modified Mini-Mental State Examination, Clock
are also major contributors to vascular brain health. Finally, pathways.68,69 Obesity,71–73 dyslipidemia, 74–77 and high BP 78,79 through atherosclerosis, inflammation, and oxidative stress

age,66 as well as changes in cerebral blood flow and alterations in β-amyloid processing and deposition.67 Smoking has been implicated in the risk of cognitive decline68,89 and dementia70 through atherosclerosis, inflammation, and oxidative stress pathways.68,69 Obesity, 71–73 dyslipidemia,74–77 and high BP78,79 are also major contributors to vascular brain health. Finally, adherence to a Mediterranean or DASH (Dietary Approach to Stop Hypertension) diet80 has been associated with reduced cognitive decline, potentially and controversially a result of homocysteine reduction, and through antioxidant and anti-inflammatory pathways.81–83 Despite being well-established key risk factors of cognitive decline, AD, and other dementias, much less is known about how cardiovascular risk factor exposure affects brain health in midlife or earlier in the life course.

The specific critical periods of influence of some key cardiovascular risk factors such as high body mass index (BMI) and hypertension on cognitive decline remain uncertain. For example, studies have shown that there may be a U-shaped association between BMI and dementia such that individuals with either low or high BMI have the greatest risk.84 In addition, the timing of obesity (midlife versus late-life) and the type of obesity (overall versus central) may have different effects on cognitive outcomes in late life. Studies suggest that midlife and late-life central obesity increases the risk of cognitive impairment but that high late-life obesity (as assessed by BMI) may be protective.71–73 Further study is needed to clarify these risk relationships, which may be explained away, at least in part, by reverse causation.

Hypertension is another risk factor with an influence on cognition and dementia that may depend on age, severity, and cumulative time of exposure. Several population-based studies have found that midlife hypertension or high systolic BP is associated with cognitive dysfunction and decline85–88 and dementia.65,79 A J- or U-shaped association between systolic BP and cognitive decline has also been suggested in old age.79 Inconsistencies in these associations may reflect the timing of exposure measurement relative to the age of study subjects, reverse causation, potential survivor bias, and the possibility of either a cumulative effect or more specific window of opportunity for the exposure to exert a deleterious effect during the life course. The CARDIA study (Coronary Artery Risk Development in Young Adults), for example, showed that cumulative systolic and diastolic BPs and fasting glucose were consistently associated with worse cognition.89 The reader is referred to additional informative studies that detail the effect of various BP metrics in young adults on cognitive function in midlife.90–92

Prospective observational studies have generally found a positive association between physical activity and cognitive health outcomes. A meta-analysis of these studies concluded that physically active adults had a 35% lower risk of cognitive decline (relative risk, 0.65; 95% confidence interval, 0.55–0.76) compared with those who were physically inactive.93 In another recent systematic review, 21 of 24 prospective studies showed a positive association between physical activity and cognitive outcomes.94

A number of intervention studies have reported a benefit of physical activity and exercise on cognition. For example, in a randomized trial, older women assigned to aerobic exercise for 4 months had better performance on cognitive tasks than women randomized to strength and flexibility training or no exercise.95 Other interventional studies have often, but not always, found beneficial effects of aerobic exercise on cognition.96–99 Several
meta-analyses have reported modest positive effect sizes for the exercise-cognition relationship. Some studies have shown larger benefits on executive tasks than other cognitive domains.\textsuperscript{97,99,102,103}

Finally, 2 other factors merit mention. Atrial fibrillation is an important risk in that it is causally linked to stroke and subclinical stroke, is increased by certain cardiovascular risks, is associated with cognitive impairment, and is modifiable or preventable.\textsuperscript{104–108} In addition, a number of studies have suggested that various aspects of sleep (eg, short or long sleep duration, excessive daytime sleepiness, greater number of night awakenings) may be associated with poorer cognition or cognitive decline.\textsuperscript{107–111} Because the findings have been inconsistent, additional studies are needed to determine whether and which sleep characteristics are causal in relation to cognitive impairment.

**AHA’s Life’s Simple 7**

A recent study examined the association between overall cardiovascular health defined by AHA’s Life’s Simple 7 in early life to midlife and cognition in midlife. The authors investigated 7 components of cardiovascular health (BMI, diet, smoking status, physical activity, total cholesterol, BP, and fasting glucose) and reported that having a greater number of cardiovascular health metrics at ideal levels in early life was associated with better cognition in midlife.\textsuperscript{112} Furthermore, in another study, cumulative exposure to cardiovascular risk factors from early to middle adulthood, especially above recommended guideline levels, has been associated with worse cognition in midlife.\textsuperscript{89} In REGARDS (Reasons for Geographic and Racial Differences in Stroke), a US national study of 17,761 blacks and whites >45 years of age and followed up for an average of 4 years, those with intermediate or high cardiovascular health defined by AHA’s Life’s Simple 7 had a significantly lower incidence of cognitive impairment compared with those with low indexes of cardiovascular health.\textsuperscript{25}

**Other Factors**

Education and literacy are well-established predictors of later-life cognitive function.\textsuperscript{113–115} This protective effect may be mediated by higher socioeconomic conditions that influence health behaviors and lifestyle choices, as well as improved access to health care and quality health care.\textsuperscript{116} Higher socioeconomic conditions also provide more opportunities for cognitive enrichment through more complex occupational exposure. Aside from education level, quality of education in early life, which is known to vary greatly by geographic region,\textsuperscript{117,118} also contributes to cognitive outcomes later in life. Regional disparities in cognitive decline have been shown to be similar to regional disparities in stroke mortality; residents of the Stroke Belt in the southeastern United States had greater adjusted odds of incident cognitive impairment than non–Stroke Belt residents,\textsuperscript{119} suggesting shared risk factors for these 2 outcomes. Less is known about other geographic and environmental factors that may contribute to vascular health. Air pollution is the factor that has been studied the most, but the results have not been consistent. Thus, air pollution was not included as a metric for optimal brain health in this AHA statement.\textsuperscript{120–122}

**Rationale for Incorporation of the Ability to Monitor, Measure, and Modify as a Consideration for Defining Metrics of Brain Health and the Distinction Between Metrics and Outcomes**

To efficiently translate knowledge into action and to achieve the desired goal of optimal brain health, practitioners, individuals, and policy makers should be provided with metrics that are measurable, modifiable, and easily monitored. For instance, although age and genetic factors are among the substantial determinants of brain health, they are not modifiable and thus not well suited as metrics. To achieve the highest possible gain, metrics for optimal brain health should meet the following requirements: have a strong basis of evidence for affecting brain health; be measurable by simple methods that are broadly available and can be performed at reasonable cost; have a sufficient basis of evidence that modifying the metric will result in improved brain health; be applicable to all subsets of the population; and have face validity to ensure acceptance by relevant parties and can be acted on by individuals, practitioners, and policy makers. For instance, public health messages about a diet rich in fruits, vegetables, and fiber-rich whole grains is better suited for health communication, translation, and action by practitioners, policy makers, and individuals than details on specific nutrients, which may be difficult to communicate and monitor.

Criteria for metrics to achieve optimal brain health (eg, ability to monitor, measure, and modify) are to be distinguished from outcomes such as cognitive function, stroke, and dementia. The latter outcomes are strongly influenced by metrics that act as antecedents for optimal brain health and serve as ongoing indicators for brain health and the potential for maintenance of optimal brain health. Outcomes should meet the following criteria: be clearly attributable to brain health, have a documented impact on quality of life, and be measurable by simple methods. The primary outcome should be a robust measure consisting of items that are easy to assess (eg absence of both stroke and dementia). However, additional metrics to define secondary outcomes, including both clinical (eg, cognitive decline) and neuroimaging (eg, brain infarcts) outcomes, are needed.

**Metrics for Defining Optimal Brain Health: AHA’s Life’s Simple 7**

The health-related behaviors and health factors listed below have been chosen as metrics to define optimal brain health. These factors are derived from AHA’s Life’s Simple 7. Available evidence from study of AHA’s Life’s Simple 7 indicates that these factors play a role in the preservation of cognition and can be measured, modified, and monitored.\textsuperscript{25} These factors have been reviewed in the Risk Factors section above, and other study information on the factors is found elsewhere for nonsmoking status,\textsuperscript{4,123,124} physical activity,\textsuperscript{4,123,125} BMI <25 kg/m\textsuperscript{2},\textsuperscript{71} healthy diet consistent with current guidelines,\textsuperscript{4} untreated BP <120/<80 mmHg,\textsuperscript{4} untreated total cholesterol <200 mg/dL,\textsuperscript{5,86,134–142} and fasting blood glucose <100 mg/dL.\textsuperscript{4,123,124}

**Health-Related Behaviors**

1. Nonsmoking status
2. Physical activity at goal levels
3. BMI <25 kg/m²
4. Healthy diet consistent with current guidelines

Health-Related Factors
5. Untreated BP <120/<80 mm Hg
6. Untreated total cholesterol <200 mg/dL
7. Fasting blood glucose <100 mg/dL

Of note, the thresholds for definition of ideal levels of BP, glucose, and cholesterol are consistent with current guidelines and expert recommendations.

Other Factors
Besides AHA’s Life’s Simple 7, a number of additional factors have an established impact on brain health either by influencing stroke or dementia risk or by independent mechanisms. Examples include but are not limited to atrial fibrillation, which can be prevented or efficiently monitored and treated to prevent cardioembolism; low cardiac output, leading to hypoperfusion dementia; acute or chronic brain diseases distinct from stroke or neurodegeneration; and head injury, which can in part be influenced by behavior. Although the importance of these factors with respect to optimal brain health is acknowledged, AHA’s Life’s Simple 7 was chosen to be the backbone of the definition of the metrics because of their relevance on individual and population levels, life-course perspective, and fit with the ability to monitor, measure, and modify, and because they further affect other established risk factors for brain health, including atrial fibrillation.

The relationship between education or social engagement across the life span and brain health is complex. For instance, education may affect brain health by enhancing the capacity to compensate for the effects of brain pathology on brain function (eg, cognitive reserve). A potential benefit of interventions to enhance social or cognitive lifestyle has thus far not convincingly been demonstrated. Nevertheless, this remains an important area for further investigation. A more detailed appraisal of other factors beyond AHA’s Life’s Simple 7 will be the focus of future brain health publications.

Primary and Secondary Outcomes for Brain Health Monitoring

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Secondary outcomes</th>
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<tr>
<td>Stroke</td>
<td>Transient ischemic attack</td>
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<tr>
<td>Dementia</td>
<td>Subjective or mild cognitive impairment</td>
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Table 1. Primary and Secondary Outcomes for Brain Health Monitoring

Maintenance of Brain Health

Evidence for Maintenance of Brain Health

There is robust observational epidemiological evidence associating young adult and midlife vascular risk factors with later development of cognitive impairment. However, the randomized clinical trials (RCTs) investigating the effect of vascular risk factor modification on the prevention of cognitive decline have not shown consistent results (Table 2). Observational epidemiological study shows that individuals with hypertension treated to a BP <120/<80 mm Hg have less risk of stroke and cardiovascular events, but that risk is not as low as those the risk for those who have maintained untreated BP <120/<80 mm Hg. Thus, primordial prevention may be a powerful means to prevent key primary and secondary cardiovascular outcomes because once risk factors are present, one may not be able to optimally reduce stroke and cardiovascular disease risk.

There is some suggestion for clinical benefit from BP control or multidomain interventions, including vascular risk modification combined with lifestyle and behavioral interventions (Table 2). For example, in the placebo-controlled Syst-Eur study (Systolic Hypertension in Europe), a BP reduction of 8.3/3.8 mmHg was associated with a marginally significant drop in the risk of dementia of 50% at 2 years (P<0.05). However, several additional randomized trials failed to show a beneficial effect of BP reduction on cognition. Thus, while BP lowering has been shown to substantially reduce the risk of stroke, in individuals with elevation of BP, BP lowering in a clinical trial setting has not been shown conclusively to preserve cognitive function.

Data from longitudinal observational studies indicate that different cardiovascular and lifestyle-related factors such as diabetes mellitus, dyslipidemia, anthropometric measures, and smoking, among others, may influence the trajectory of cognitive health. Encouraging results have been observed in some, but not all, RCTs targeting some of these conditions. In the PREDIMED study (Prevención con Dieta Mediterránea), for example, participants randomized...
Table 2. Summary of Trial Data on Maintenance of Cognitive Function

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age at Inclusion (mean), y</th>
<th>Follow-Up, y</th>
<th>Intervention</th>
<th>Cognitive Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syst-Eur trial</td>
<td>2418</td>
<td>≥60 (69.9)</td>
<td>2</td>
<td>Nitrendipine±enalapril±hydrochlorothiazide to reduce systolic BP by at least 20 mm Hg to reach a value &lt;150 mm Hg</td>
<td>Dementia (DSM-III, Revised, criteria) and Mini-Mental State Examination</td>
<td>Active treatment was associated with a lower incidence of dementia by 50% (P=0.05)</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>22,629</td>
<td>≥55 (66)</td>
<td>4.6</td>
<td>Ramipril vs telmisartan vs a combination of both drugs</td>
<td>Mini-Mental State Examination</td>
<td>No effect of treatment on cognition</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>5231</td>
<td>≥55 (67)</td>
<td>…</td>
<td>Telmisartan vs placebo</td>
<td>Mini-Mental State Examination</td>
<td>No effect of treatment on cognition</td>
</tr>
<tr>
<td>HYVET</td>
<td>3336</td>
<td>≥80 (84)</td>
<td>2.2</td>
<td>Indapamide±perindopril vs placebo</td>
<td>Dementia (DSM-IV criteria) and Mini-Mental State Examination</td>
<td>No effect of treatment on dementia</td>
</tr>
<tr>
<td>SCOPE</td>
<td>4694</td>
<td>70–89 (76)</td>
<td>3.7</td>
<td>Candesartan vs placebo</td>
<td>Mini-Mental State Examination</td>
<td>No effect of treatment on cognition</td>
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<tr>
<td>PROFESS</td>
<td>20,332</td>
<td>≥55 (66)</td>
<td>2.4</td>
<td>2×2 Factorial allocation</td>
<td>Mini-Mental State Examination</td>
<td>No effect of treatment on cognition</td>
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<tr>
<td>PROGRESS</td>
<td>6105</td>
<td>No set age criteria (64)</td>
<td>3.9</td>
<td>Perindopril±indapamide vs placebo</td>
<td>Dementia (DSM-IV criteria) and Mini-Mental State Examination</td>
<td>Active treatment reduced cognitive decline by 19% (P=0.01) but had no effect on dementia</td>
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<tr>
<td>SHEP</td>
<td>4736</td>
<td>≥60 (72)</td>
<td>5</td>
<td>Chlorothalidone±atenolol vs placebo</td>
<td>Short-Comprehensive Assessment and Referral evaluation</td>
<td>No effect of treatment on cognition</td>
</tr>
<tr>
<td>ACCORD-MIND</td>
<td>2977</td>
<td>No set age criteria (62)</td>
<td>3.3</td>
<td>Diabetic patients randomized to systolic BP &lt;120 vs &lt;140 mm Hg and to fibrate vs placebo</td>
<td>Digit Symbol Substitution Test</td>
<td>No effect of intensive blood pressure and fibrate treatment on cognition</td>
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<tr>
<td>HOPE-3</td>
<td>1626</td>
<td>Cognition assessed in individuals ≥70 only (74)</td>
<td>5.6</td>
<td>2×2 Factorial allocation</td>
<td>Digit Symbol Substitution Test</td>
<td>No effect of treatment on cognition</td>
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<td>SPS3</td>
<td>2916</td>
<td>No set age criteria (63)</td>
<td>3</td>
<td>2×2 Factorial allocation</td>
<td>Cognitive Abilities Screening Instrument</td>
<td>No effect of treatment on cognition</td>
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<tr>
<td>preDNA</td>
<td>3526</td>
<td>70–78 (75)</td>
<td>6.7</td>
<td>Usual care vs multidomain intervention (smoking habits, diet, physical activity, weight, BP, diabetes mellitus, and dyslipidemia)</td>
<td>Dementia (DSM-IV criteria)</td>
<td>No effect on dementia</td>
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<tr>
<td>FINGER</td>
<td>2654</td>
<td>60–77 (69)</td>
<td>2</td>
<td>Usual care vs multidomain intervention (diet, physical exercise, cognitive training, and intensive vascular risk factor monitoring)</td>
<td>Neuropsychological test battery</td>
<td>Multidomain intervention reduced mean z score at 2 y from 0.20±0.02 to 0.16±0.01 (P=0.03)</td>
</tr>
<tr>
<td>MAPT</td>
<td>1680</td>
<td>≥60 (75)</td>
<td>3</td>
<td>Usual care vs multidomain intervention (cognitive training, diet, nutrition advice, and 3 preventive consultations±omega 3 polyunsaturated fatty acids)</td>
<td>Free and Cued Selective Reminding test, 10 Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test</td>
<td>No effect of treatment on cognition</td>
</tr>
</tbody>
</table>

(Continued)
to a Mediterranean diet had modestly better cognition at 4 years. In the FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability), participants randomized to a multidomain intervention, including coaching for vascular risk reduction, exercise, cognitive training, and adherence to a Mediterranean diet, had modestly better cognitive performance at 2 years, with improvements in executive functions and processing speed but not episodic memory. Studies are needed, especially in younger age groups, with the inclusion of sensitive indicators of trajectories of cognitive function and vascular function.

**Summary of Previous Guidance for Maintenance of Cognitive Vitality From the AHA/ASA and Other Organizations**

Although the RCT evidence to prevent cognitive decline and dementia is still incomplete and evolving, the observational epidemiological evidence for modifiable risk factors is substantial. This evidence has been previously reviewed by several national organizations, along with guidance on how to translate this information into strategies to improve brain health.

In 2011, the AHA/ASA released a scientific statement on vascular contributions to cognitive impairment and dementia, reviewing clinical considerations for diagnosis and management of symptomatic patients and prospects for the prevention of vascular cognitive impairment and AD. The statement did not recommend changes to the current management of cardiovascular risk factors to prevent dementia; however, it should be noted that the statement was released before the publication of the FINGER, LIFE (Life Interventions and Independence for Elders), and PREDIMED trials. The only Class I recommendation was, “In people at risk for vascular cognitive impairment, treatment of hypertension is recommended.” A more contemporary scientific statement found inconclusive evidence that BP control preserves cognition in the population of patients with vascular contributions to cognitive impairment and dementia, and thus inadequate statistical power, poor sustainability of intensive vascular care; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SPS3, Secondary Prevention of Small Subcortical Strokes Trial; Syst-Eur, Systolic Hypertension in Europe; and TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Age at Inclusion (mean), y</th>
<th>Follow-Up, y</th>
<th>Intervention</th>
<th>Cognitive Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREDIMED158</td>
<td>334</td>
<td>Men: 55–80</td>
<td>4.1</td>
<td>Mediterranean diet supplemented with extravirgin olive oil vs Mediterranean diet supplemented with mixed nuts versus control diet</td>
<td>Mini-Mental State Examination, Rey Auditory Verbal Learning Test, Animals Semantic Fluency, Digit Span Subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from the Wechsler Memory Scale, and the Color Trails Test</td>
<td>Improvement in cognition</td>
</tr>
<tr>
<td>LIFE159</td>
<td>1635</td>
<td>70–79 and 80–89</td>
<td>2</td>
<td>Moderate-intensity physical activity program vs educational workshops and upper-extremity stretching</td>
<td>Digit Symbol Coding, Wechsler Adult Intelligence Scale, and Hopkins Verbal Learning Test</td>
<td>Among sedentary adults, a moderate-intensity physical activity program vs a health education program did not improve global or domain-specific cognitive function</td>
</tr>
</tbody>
</table>

**Table 2. Continued**

| ACCORD-MIND indicates Action to Control Cardiovascular Risk in Diabetes; BP, blood pressure; DSM, Diagnostic and Statistical Manual of Mental Disorders; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; HOPE-3, Heart Outcomes Prevention Evaluation-3; HYVET, Hypertension in the Very Elderly Trial; LIFE, Life Interventions and Independence for Elders; MAPT, Multidomain Alzheimer Preventive Trial; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; PREDIMED, Prevención con Dieta Mediterránea; preDIVA, Prevention of Dementia by Intensive Vascular Care; PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; SPS3, Secondary Prevention of Small Subcortical Strokes Trial; Syst-Eur, Systolic Hypertension in Europe; and TRANSCEND, Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease. |
The Alzheimer’s Association has summarized previous systematic reviews and meta-analyses, consensus statements, and selected articles on modifiable risk factors for cognitive decline and dementia. The writing committee concluded that the evidence was sufficiently strong to support promotion of physical activity, management of vascular risk factors, healthy eating, and lifelong learning and cognitive training. The Alzheimer’s Association website lists “10 Ways to Love Your Brain,” consisting of advice to increase physical activity, pursue lifelong learning, cease smoking, manage cardiovascular risk, protect against brain injury, eat a healthy diet, get adequate sleep, take care of mental health, stay socially engaged, and partake in challenging mental activities.

In 2015, the Institute of Medicine commissioned a report on cognitive aging. For individuals and families, the report recommended being physically active, managing cardiovascular risk factors, discussing health conditions and medications that might influence cognition with a healthcare professional, being socially and intellectually engaged, getting adequate sleep, taking steps to avoid delirium if hospitalized, and carefully evaluating products advertised to improve cognition. For society, key recommendations included increasing research on preserving cognitive function, ensuring appropriate policies and guidelines for products that affect cognitive function, developing core competencies and curricula in cognitive aging distinct from dementia for health professionals, and expanding community services to meet the needs of older adults and their families with respect to cognitive health.

Recommendations for Maintenance of Optimal Brain Health

Considering the emerging evidence that now justifies a definition of optimal brain health, prudent actions are warranted to maintain optimal brain health throughout the life span. Thus, this statement endorses the recommendations from the Institute of Medicine and Alzheimer’s Association as means to maintain brain health. In addition, for primordial, primary, and recurrent stroke prevention and its relationship to brain health, we recommend following AHA/ASA guidance (see also Table 3).

Decades of efforts to reduce stroke and cardiovascular risks by the AHA/ASA and other health organizations and, more recently, to promote cardiovascular health are likely to have already contributed to the declining incidence of dementia. These efforts should be additionally leveraged for the promotion of optimal brain health. This should include not only prevention of stroke but also treatment of stroke to improve outcomes, including poststroke cognitive impairment.

Addressing cardiovascular and stroke risk is a large part of maintaining optimal brain health, but not the only part. Addressing the many factors that may promote cognitive reserve, including such factors as access to education, meaningful interpersonal and community social engagement, and access to mental health care, is also likely to be a useful strategy. Active engagement by not only healthcare practitioners but also policymakers at all levels of government is needed.

Table 3. Recommendations for Promotion and Maintenance of Optimal Brain Health

<table>
<thead>
<tr>
<th>Individual</th>
<th>Health systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check health status with AHA’s Life’s Simple 7 (<a href="http://www.heart.org">http://www.heart.org</a>)</td>
<td>Support patients by providing access to preventive care and lifestyle modification</td>
</tr>
<tr>
<td>Remain physically active</td>
<td>Support good-quality care for stroke and for primary prevention of cardiovascular disease</td>
</tr>
<tr>
<td>Eat a healthy diet; evidence suggests that a Mediterranean-style diet preserves cognitive function better than a low-fat diet</td>
<td>Disseminate knowledge of potentially modifiable risk factors for cognitive decline and dementia</td>
</tr>
<tr>
<td>Address vascular risk factors, if present, with a primary care practitioner</td>
<td>Provide tools and resources to maintain healthy lifestyles such as the AHA Healthy for Good program</td>
</tr>
<tr>
<td>Pursue cognitively stimulating and rewarding activities</td>
<td>Provide opportunities for stimulating cognitive, physical, and social activities</td>
</tr>
<tr>
<td>Address mental health concerns with a primary care practitioner or specialist as needed</td>
<td>Maintain a healthy environment, including neighborhoods that promote cognitive and physical activity</td>
</tr>
<tr>
<td>Healthcare practitioners</td>
<td>Fund research on risk factors for cognitive decline and dementia and how to intervene to reduce risk</td>
</tr>
</tbody>
</table>

AHA indicates American Heart Association; and ASA, American Stroke Association.

Maintaining optimal brain health requires actions by individuals, healthcare practitioners, public health organizations, policy makers, and the private sector. An overview of approaches to promoting optimal brain health is provided in Table 3 and categorized by target stakeholder.

Discussion

The main aim of this AHA/ASA advisory is to provide an initial definition of optimal brain health and guidance on how to maintain brain health. Our definition of optimal brain health emphasizes the importance of a favorable or ideal cardiovascular risk profile. Such a risk profile earlier in life is associated with compression of morbidity and mortality. This has been shown in a recent publication from the CHA (Chicago Heart Association Detection Project in Industry). CHA included a cohort of men and women employed in 1967 to 1973 who were 90% white, 44 years of age on average at baseline, and followed up for 40 years. Overall, those CHA cohort members...
who had a favorable health profile in midlife had prolonged survival by ≈4 years and postponed onset of all-cause and cardiovascular mortality of 7 years. In addition, all morbidities were reduced, compression of morbidity was observed both absolutely and relatively, and there were lower cumulative and annual healthcare costs during the Medicare-eligibility life span in older ages for those with favorable cardiovascular health profiles in midlife. Although cognition was not the primary focus of this publication, several other study results support the belief that favorable cardiovascular health earlier in life leads to maintenance of cognitive vitality.

Although healthy lifestyle, advances in overall medical care, and favorable socioeconomic profile might compress major morbidities of later life, they may be influenced by the age at which the subjects are studied and the time in life when preventive are administered, as suggested by the results of a Chinese longevity study of the oldest old. In this study, there was compression of activities of daily living disability, but life-span extension was associated with expansion of disability of physical and cognitive functioning because there were more frail elderly who survived health problems.

Modifiable cardiovascular risks are prevalent worldwide, may occur across the age continuum, and are associated with adverse consequences later in life. Furthermore, cardiovascular mortality, including ischemic heart disease and stroke, may vary substantially on the basis of geographic variation. Atherosclerosis, a manifestation of nonfavorable cardiovascular health, however, may not be inevitable. Recently, it has been shown that a forager-horticulturalist population, the South American Tsimane of Bolivia, who have few coronary artery disease risk factors, have the lowest reported levels of coronary artery disease of any population, suggesting the value of primordial prevention.

Furthermore, the development of vascular arterial stiffness, a measure of vascular aging, may not be inevitable. In the Framingham study, lower age, female sex, lower BMI, use of lipid-lowering drugs, and absence of diabetes mellitus in a cross-sectional study were associated with healthy vascular aging. In addition, for every 1-unit higher AHA’s Life’s Simple 7 score (ie, 1 more factor or behavior at ideal levels), there was a 1.5-fold age- and sex-adjusted odds of healthy vascular aging. This observational study provides support for prevention strategies focused on modifiable health factors and behaviors to prevent or delay vascular aging and risk of cardiovascular disease and possibly other health consequences associated with aging such as cognitive impairment. This approach may apply to elderly populations.

Prevention of cognitive impairment and dementia may be viewed as a lifelong process predicated on a number of antecedent factors, with cardiovascular risks playing an important role. The promotion of healthy living across the life span may allow one to avoid adverse health outcomes such as multimorbidity, including cognitive impairment and other health-related adverse outcomes or events. In addition, favorable cardiovascular health may be associated with lower healthcare expenditures and resource use.

In this advisory, AHA’s Life’s Simple 7 was chosen as the metric to define optimal brain health. AHA’s Life’s Simple 7 consists of 4 ideal health behaviors (physical activity at goal levels, healthy diet consistent with current guideline recommendations, nonsmoking, and BMI <25 kg/m²) and 3 ideal health factors (untreated total cholesterol <200 mg/dL, fasting blood glucose <100 mg/dL, and untreated BP <120/<80 mm Hg). These factors have been shown to improve the health trajectory. In addition, AHA’s Life’s Simple 7 has been linked to successful cognitive health and is an ideal starting point for defining optimal brain health because it is easy to measure, monitor, and modify. Additional study to test the influence of AHA’s Life’s Simple 7 on brain health among different racial and ethnic groups, men and women, and people from different age groups across the life continuum is needed.

Beyond the metrics to initially define optimal brain health, primary and secondary outcomes for brain health have been identified in this advisory. On the basis of practical considerations, 2 main primary outcomes, stroke and dementia, and 2 main secondary outcomes, transient ischemic attack and subjective or mild cognitive impairment, have been designated. Metrics of brain structure and function such as subclinical injury detected on brain imaging (eg, presence or volume of MRI-defined white matter hyperintensities, covert infarcts, microbleeds, and microscopic injury [quantifiable by diffusion tensor imaging]), molecular markers (eg, amyloid measured by positron emission tomography or cerebrospinal fluid analysis), and those of structural and functional connectivity, as assessed by diffusion tensor imaging and functional MRI, are important factors for future consideration as the definition of optimal brain health evolves.

Finally, the available RCT and observational epidemiological data were reviewed to provide guidance on the maintenance of cognitive health. Although the RCT evidence to prevent cognitive decline and dementia is incomplete but evolving, the observational epidemiological evidence for modifiable risk factors was judged to be substantially in favor of modifying key cardiovascular risks. Thus, application of the Institute of Medicine and Alzheimer’s Association guidance for the maintenance of cognitive vitality, which includes both cardiovascular risk factor modification and other strategies, and primordial, primary, and secondary stroke prevention recommendations from the AHA/ASA as they relate to brain health has been recommended.

The definition of optimal brain health and its maintenance chosen for this advisory has limitations. We acknowledge the complexity of defining optimal brain health for adults and that a broader definition of optimal brain health is possible when taking into account the various stages of the life continuum spanning from conception to old age and consequent environmental, lifestyle, and genetic exposures. For example, there is a limited but increasing body of knowledge on the importance of childhood exposures affecting cognition in later life. Furthermore, intrauterine and early-life exposures may play important roles in neurocognitive development, as may stress in early life. Therefore, we anticipate that future publications from the AHA/ASA brain health writing group will expand the definition of optimal brain health and incorporate factors of interest from, for example, earlier in life. In addition, there were inherent limitations of availability of variables of interest such as those based on demographic and race-ethnic composition of the available RCTs and observational epidemiological studies that were reviewed. Such limitations suggest the need for study.
of individuals representing groups disproportionately affected by cardiovascular health disparities and those from early stages of life such as childhood.

**Future Directions and the AHA Strategic Impact Goal**

The AHA/ASA has set a Strategic Impact Goal by the year 2020 to improve the cardiovascular health of Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%. The AHA/ASA is promoting cardiovascular health through application of Life’s Simple 7. As part of the effort to promote cardiovascular health, the AHA/ASA is adding brain health to its overall strategic initiatives. Brain health is an important component of successful aging and one in which cardiovascular risks seem to play a key role. The main purpose of this document is to serve as the first step in defining optimal brain health and how to maintain it. Future work will serve to refine the definition, metrics, and strategies to maintain cognitive vitality.

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**Disclosures**

**Writing Group Disclosures**

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<th>Writing Group Member</th>
<th>Employment</th>
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<th>Consultant/ Advisory Board</th>
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<td>University of California, San Francisco</td>
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<td>None</td>
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<td>None</td>
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives $10,000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $100,000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

*Modest.
†Significant.
‡Dr Lazar is now at the University of Alabama.

## References


Gorelick et al Defining Optimal Brain Health in Adults e19

M. A 2 year multidomain intervention of diet, exercise, cognitive train-
ing, and vascular risk monitoring versus control to prevent cognitive de-


158. Liu K, Colangelo LA, Davilis ML, Goff D, Fletcher M, Schreiner PJ, Sibley CT, Burke GL, Post WS, Michos ED, Lloyd-Jones DM. Can antihypertensive treatment restore the risk of cardiovascular dis-
ease to ideal levels? The Coronary Artery Risk Development in Young Adults (CARDIA) Study and the Multi-Ethnic Study of Atherosclerosis (MESA). J Am Heart Assoc. 2015;4:e002275.

159. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, John H. Summary of the evidence on modifiable risk factors for cognitive de-


165. Zeng Y, Feng Q, Hesketh T, Christensen K, Vauel JW. Survival, disabili-
 ties in activities of daily living, and physical and cognitive functioning among the oldest-old in China: a cohort study. Lancet. 2017;389:1619–

166. GBD 2015 Tobacco Collaborators. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a system-


169. Zeng Y, Feng Q, Hesketh T, Christensen K, Vauel JW. Survival, disabili-
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**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.

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\(^1\) [http://www.heart.org/HEARTORG/Conditions/My-Life-Check---Lifes-Simple-7_UCM_471453_Article.jsp#WVJHN4jyvic](http://www.heart.org/HEARTORG/Conditions/My-Life-Check---Lifes-Simple-7_UCM_471453_Article.jsp#WVJHN4jyvic)
Table 1. Selection Criteria

<p>| 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 (<em>e.g.</em> 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, <em>e.g.</em> 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 (&lt;18). (<em>Note: pediatric/in utero exposures allowed, if cognition/cognitive disorders or decline were assessed in adult life</em>). |
|                                         | • Study not in human subjects. |
|                                         | • Non-English language. |
|                                         | • Publication date prior to January 1, 1980. |</p>
<table>
<thead>
<tr>
<th>Relevant and Included</th>
<th>Potentially modifiable</th>
<th>Not modifiable or not easily modifiable</th>
<th>Likely confounded or biased</th>
<th>Intermediate physiological markers unlikely to be causally related</th>
<th>Modifiable but RCT evidence fails to support effect on cognition</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cholesterol</td>
<td>Age</td>
<td>Specific antihypertensive choices (e.g. angiotensin receptor blocker, calcium channel blockers)</td>
<td>Carotid intima-media thickness</td>
<td>Estrogen</td>
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<tr>
<td></td>
<td>Hypertension/blood pressure</td>
<td>Sex</td>
<td>Other prescription medications proposed to have off-target benefits or harms: proton pump inhibitors</td>
<td>Subclinical atherosclerosis</td>
<td>Hormone replacement therapy</td>
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<td></td>
<td>History of stroke</td>
<td>Markers of inflammation (e.g. C-reactive protein, interleukin-6)</td>
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<td>Heart rate</td>
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<td></td>
<td>Diabetes</td>
<td>Apolipoprotein E genotype</td>
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<td>Frailty</td>
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<td></td>
<td>Kidney disease</td>
<td>Other genetic polymorphisms</td>
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<td>Walking speed</td>
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<td>Chronic obstructive pulmonary disease</td>
<td>Heart rate variability</td>
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<td>Anemia</td>
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<td>Heart failure</td>
<td>Pulse pressure</td>
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<td>Red cell membrane fluidity</td>
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<td>Coronary artery disease</td>
<td>Evidence of past infectious burden (e.g. herpes simplex virus)</td>
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<td>Bone mineral density</td>
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<td>Tooth loss, periodontitis</td>
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<td>Sleep-disordered breathing, sleep duration</td>
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<td>Hearing loss</td>
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<td>Vision loss</td>
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<td>Physical activity</td>
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<td>Depression</td>
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<td>Smoking</td>
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<td>Alcohol use</td>
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<td>Recreational drug use</td>
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<td>Education</td>
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<td>Social participation</td>
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<td>Cognitive activities</td>
<td>Personality traits</td>
<td>Built environment</td>
<td>Occupation</td>
<td>Dietary choices</td>
<td>Mediterranean diet</td>
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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)