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CONTEMPORARY REVIEW

Life's Essential 8: Essential for Brain and Cognitive Health

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ABSTRACT: Cognitive impairment and Alzheimer disease and related dementias are increasingly prevalent and carry significant morbidity. Growing evidence has highlighted the complex interactions between cardiovascular and brain health, implicating vascular dysfunction in the pathogenesis of many forms of cognitive impairment. The American Heart Association (AHA) and the American Stroke Association have outlined a comprehensive framework, known as Life's Essential 8, that includes 4 behavioral health factors (healthy dietary pattern, physical activity, avoidance of nicotine, and healthy sleep) and 4 health factors (cholesterol, blood glucose, blood pressure, body mass index) that collectively define optimum cardiovascular health. Modifiable risk factors account for an estimated 40% of worldwide dementia. Adherence to Life's Essential 8 principles may also help individuals mitigate the risk of cognitive impairment via improved cardiovascular health. However, a comprehensive understanding of the causal relationships between vascular and behavioral risk factors and Alzheimer disease and related dementias remains unclear and requires further study. This narrative review summarizes well-established data and highlights new data for how health and behavioral factors included in Life's Essential 8 also promote optimal brain and cognitive health.

Key Words: brain health ■ cardiovascular disease ■ cognition ■ dementia ■ Life's Essential 8

Cognitive impairment affects 1 in 5 individuals in the United States, and its prevalence is expected to increase substantially because of aging and increased life expectancy.[1] There are an estimated 22% of individuals over 65 years who have mild cognitive impairment (MCI), and an additional 10% to 15% of those will progress to clinical dementia within 1 year with 50% to 70% progressing within 5 to 7 years.[2,3] Between 2000 and 2018, deaths from HIV and heart disease decreased, while deaths from Alzheimer disease (AD) increased by 146% during the same period.[4] It is estimated that up to 40% of dementia cases are caused by modifiable risk factors.[5] Identifying strategies that individuals can adopt to optimize brain health and improve cognition is of increasing importance, as emphasized by the addition of a new goal focused on lifestyle modification in the national strategic plan.[6]

Cardiovascular disease (CVD), which includes cerebrovascular disease, and AD share many risk factors, with vascular dysfunction being a hallmark of CVD. Many studies have established a strong link between cardiovascular and cognitive health, and many of these CVD risk factors have been identified as modifiable risk factors for AD and AD related dementias (ADRD), summarized in the Lancet Commission report of 2020 on dementia.[5] Building on the American Heart Association's (AHA) previous statement identifying 7 modifiable factors for cardiovascular health (CVH), known as Life's Simple 7 (LS7), both the AHA

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Nonstandard Abbreviations and Acronyms

ADRD	Alzheimer disease and related dementias
DASH	Dietary Approach to Stop Hypertension
LE8	Life's Essential 8
LS7	Life's Simple 7
SDOH	social determinants of health

and American Stroke Association suggested that these principles could also apply to cognitive and brain health.[7] CVH as a concept provides the means for assessing current individual or population health status, and identifying opportunities for improving it today, with a positive context of health promotion and not just risk prevention. A large amount of literature supports this approach as a means for prevention of chronic diseases across the spectrum of primordial, primary, and secondary prevention strategies. In 2022, the AHA updated LS7 to Life's Essential 8 (LE8), incorporating healthy sleep into the recommendations and expanding the scoring of CVH to enhance detection of inter-individual differences and intra-individual changes in CVH.[8] The LE8 score (range 0–100, with higher indicating better CVH) demonstrates improved performance in quantifying CVH compared with the older LS7 score (range 0–14).[9]

The modifiable CVH metrics in LE8 include 4 behavioral factors (healthy dietary patterns, physical activity, avoidance of nicotine, and healthy sleep) and 4 health factors (blood glucose, non-HDL-cholesterol, blood pressure, and BMI). These factors define CVH and each has been independently linked to cardiovascular and brain outcomes, longevity, and numerous other health outcomes (Table).[8,9] The AHA/ACC has updated their 2024 Guideline for the Primary Prevention of Stroke to reflect the connection with LE8 and stroke prevention, saying that the most common treatable behaviors and conditions that increase stroke risk are based in LE8.[10] With a litany of recent studies and the addition of sleep to LS7, this narrative review consolidates well-established data and highlights new evidence associating each component in AHA's LE8 with brain and cognitive health.

Brain Health, Dementia, and Cardiovascular Disease: A Multifaceted Connection

The relationship between cardiovascular and brain health is an area of significant study, given the profound impact the cardiovascular system has on brain function (Figure 1). The vasculature is responsible for supplying the brain with oxygen and nutrients and helping clear the brain of toxins.[11] Diseases affecting the vasculature, such as atherosclerosis, can

Table. Summary

LE8 factors	Key points
Healthy Dietary Patterns	• Mediterranean and DASH diets are associated with reduced cognitive decline • Fruit and vegetable consumption has an inverse and dose dependent relationship with cognitive disorders in older adults
Physical Activity	• Physical activity is associated with less cognitive decline and neurodegeneration • Positive effects are seen across all age groups • Ideal duration of activity is unclear although largest marginal benefit is seen within the first minutes
Avoidance of Nicotine	• Chronic tobacco and nicotine use is a preventable risk factor for MCI and dementia, with an 80% increased risk for AD • Nicotine use is associated with cerebral atrophy, infarcts, and white matter hyperintensities • Vaping also negatively impacts cognition independent of nicotine or tobacco
Healthy Sleep	• Sleep duration has a U-shaped association with cognition, with 7–9 h of sleep achieving the best cognitive outcomes • Impaired cognition is only partially and temporarily reversed with stimulants • Quality of sleep is important, with sleep fragmentation and reduced rapid eye movement-sleep duration associated with ADRD
Cholesterol	• In midlife, higher LDL-C levels are quantitatively associated with ADRD • Among elderly patients, HDL cholesterol has a U-shaped association with cognition and dementia, with levels below 60mg/dl and above 80mg/dl being associated with worse outcomes • Long term statin use is associated with lower ADRD
Blood Glucose Control	• Type 2 diabetes is associated with ADRD • Metformin, GLP-1 agonists, SGLT-2 inhibitors, and DPP4 inhibitors are associated with lower risk for ADRD • Strict diabetes control (HbA1c <6%) does not have better cognitive outcomes than labile diabetes control (HbA1c 7.0–7.9%)
Blood Pressure Control	• There is a dose-dependent linear relationship between SBP and ADRD. • DBP shows similar but weaker trends. • Treatment with antihypertensives targeting SBP <120 is associated with ~20% lower rates of MCI compared with SBP <140
Weight	• Obesity is associated with increased risk for cognitive impairment • Intentional weight loss is associated with improved cognition among those who are overweight or obese

AD indicates Alzheimer disease; ADRD, Alzheimer disease and related dementias; DASH, Dietary approach to stop hypertension; DBP, diastolic blood pressure; DPP, Dipeptidyl peptidase; GLP, glucagon-like peptide; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LE8, Life's Essential 8; MCI, mild cognitive impairment; SBP, systolic blood pressure; and SGLT, sodium-glucose cotransporter.

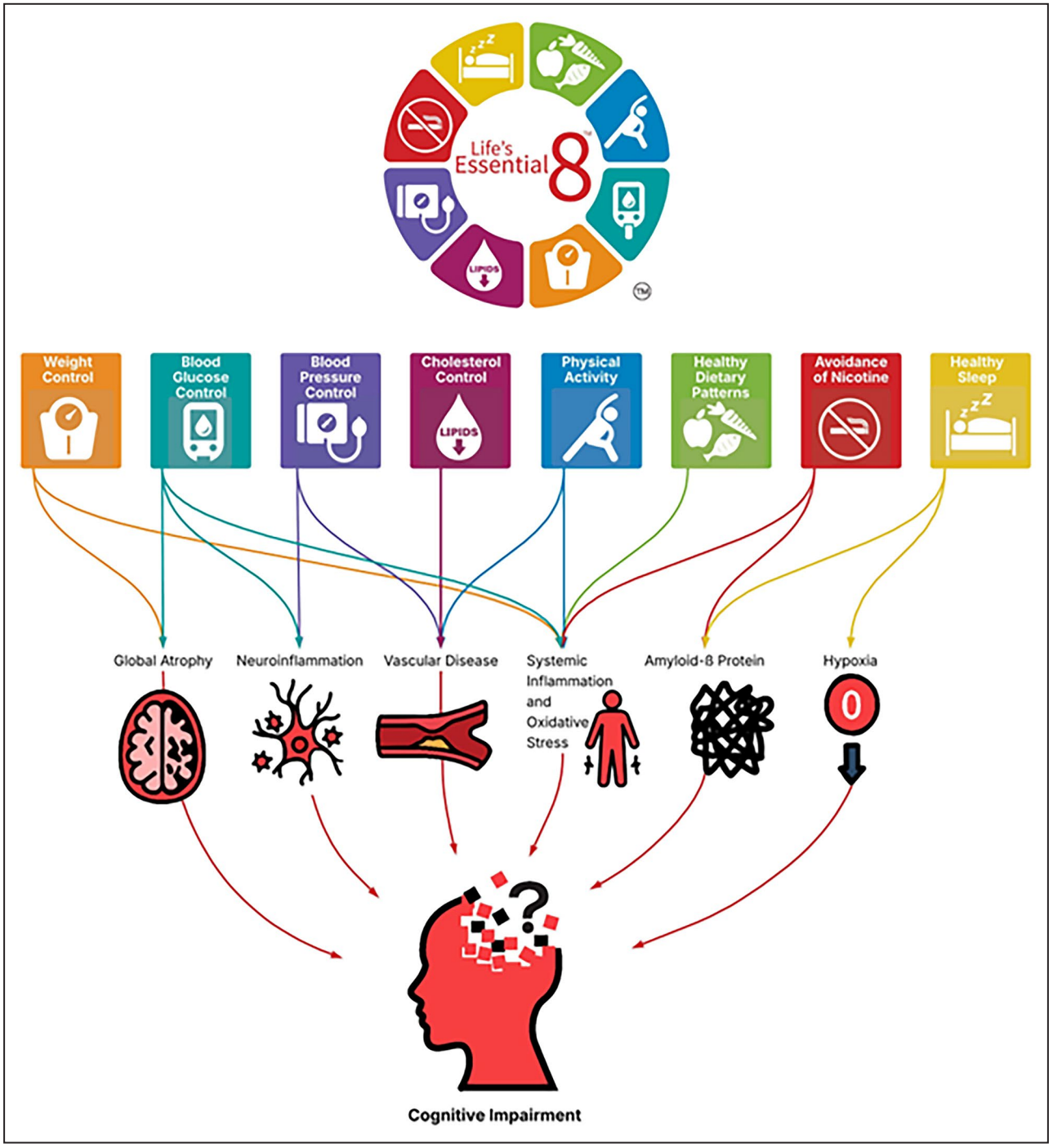

Figure 1. Visual representation of Life's Essential 8 health factors that contribute to cardiovascular and brain health.

compromise blood flow. If the vasculature becomes obstructed, regions of the brain may become ischemic, resulting in an ischemic stroke. Those who suffer from stroke are at a pronounced increased risk for impaired cognition or dementia with a strong dose effect with up to 70% experiencing altered cognition.[12] Other vascular diseases, such as hypertension, have been associated with cerebral small vessel disease found at autopsy in over half of the individuals over 65 years old.[13]

There are various types of dementia including AD, vascular dementia, frontotemporal dementia, Lewy body dementia, and mixed dementia (Figure 2).[14] Oftentimes, the diagnosis of AD is made clinically although they may have mixed-type dementia. Among Western countries, AD is the most prevalent form of dementia,

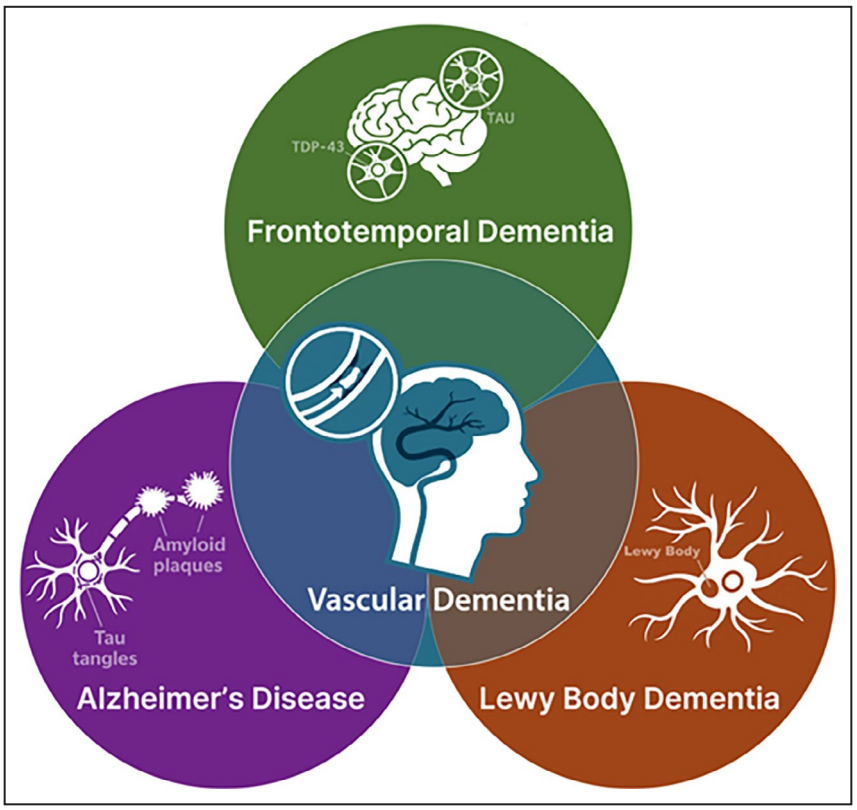

Figure 2. **The main types of dementia and how they overlap.**

accounting for 60% to 80% of all cases, followed by vascular dementia, which likely represents about 20% of cases.[4] AD is characterized by a progressive buildup of abnormal amyloid protein plaques, neurofibrillary tangles, and neurodegeneration and definitively diagnosed by post-mortem examination of the brain, complex neuro-imaging, and/or specialized biomarkers. Most cases of Alzheimer disease are clinically diagnosed, but the brain almost always harbors a mixture of pathologies, including a strong vascular component.[15] Vascular dementia primarily results from pathological changes in cerebral blood vessels presenting in various forms, depending on the location, extent of damage, and type of blood vessels affected.[13] Small blood vessels account for many of the ischemic and white matter changes.[13] There is growing recognition that there is significant pathological overlap between AD and vascular dementia. Studies demonstrated that between 50% and 84% of individuals exhibit changes indicative of both atherosclerotic disease and AD on neuro-pathological examination.[4,16] Further, these cerebrovascular changes often precede changes in cognitive performance.[17] It is important to recognize that MCI, AD, and vascular dementia share common risk factors as well as pathologic characteristics.

Multiple studies have linked risk factors for atherosclerotic CVD with structural brain changes and cognitive decline.[11,18] Additionally, impairments in vascular function tests that assess the health of blood vessels, such as flow mediated dilation and reactive hyperemia index, have been independently associated with cognitive impairment, even after adjusting for demographics and traditional CVD risk factors.[19,20] Many CVD risk factors are modifiable. Given the lack of currently affordable, highly effective and sustainable treatments for dementia, investigating these modifiable factors for cognitive decline is important and presents potential targets for dementia prevention.

LE8: BEHAVIORAL FACTORS

Healthy Dietary Patterns

Evidence supporting a connection between healthy dietary patterns and cognition relies largely on observational studies. These studies indicate that diets rich in green leafy vegetables, nuts, berries, and olive oil are associated with a lower risk of AD.[21,22] Large observational prospective trials and randomized controlled trials (RCT) have further shown that adherence to Mediterranean or DASH (Dietary Approach to Stop Hypertension) dietary patterns are associated with reduced cognitive decline, independent of CVD risk factors.[22,23] Further, an iteration of the DASH

diet called the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND diet) has been shown in RCTs to reduce the risk of cognitive decline in select populations.[24] There is also some evidence from prospective observational studies and 1 RCT suggesting that high-sodium dietary patterns are associated with poor cognition.[25] Epidemiological studies examining fruit and vegetable consumption and cognition indicate that inadequate intake is correlated with higher rates of cognitive decline.[26] A meta-analysis of 16 observational studies in over 64 000 patients, followed for an average of 9.8 years, demonstrated an inverse and linear dose–response relationship between fruits and vegetable intake and the prevalence of cognitive disorders in older adults, with most studies adjusting for demographics and some CVD risk factors.[27] These associations are believed to be related to neuroprotective anti-inflammatory and antioxidant processes.[26] However, diets high in saturated fats may trigger neuroinflammatory processes and can impair hippocampal-dependent memory.[28] Meta-analyses of randomized controlled dietary trials have yielded mixed results, possibly attributable to study heterogeneity and potential bias.[29]

The evidence linking vitamin or supplement consumption with cognition remains limited and inconclusive. Some animal and prospective observational studies suggest that either plasma vitamin C concentrations or vitamin E consumption may be protective against cognitive decline, potentially because of their antioxidant properties.[30,31] Vitamins B6, B9 (folate), and B12 are important in healthy brain function. While deficiencies in these vitamins have been linked to cognitive decline, the evidence for supplementation related to cognition in individuals with adequate levels is less clear.[32] There is also evidence that omega-3 fatty acids may enhance learning, memory, cognitive well-being, and brain-related blood flow.[33] Some studies demonstrate an association between vitamin D deficiency and AD, as well as cognitive impairment.[34] However, the efficacy of vitamin D supplementation in preventing and treating cognitive impairment and dementia is inconsistent.[35] Other supplements such as tyrosine or caffeine have been shown to improve cognitive performance among sleep-deprived young men.[36] Numerous other supplements have been studied, however, the evidence supporting their use is limited.

The DASH diet and Mediterranean eating pattern for Americans provide the optimal approach for cerebrovascular health.

Physical Activity

Lack of physical activity has been identified as one of the most important modifiable risk factors for cognitive decline and dementia.[37] This finding is supported by numerous animal and clinical studies including RCTs. One meta-analysis of 12 observational prospective studies reported that physically active adults had a 35% lower risk of cognitive decline compared with physically inactive adults.[38] Similarly, another meta-analysis of over 20 observational prospective studies following patients for an average of 4 years, demonstrated that physical activity has a population attributable risk of approximately 32% on incident AD.[39] Furthermore, RCTs have shown that participants assigned to various types of physical activity, such as aerobic exercise, tai chi, and resistance training, all exhibited beneficial impacts on cognition compared with the control groups.[40,41] These positive effects of physical activity have been observed across all age groups.[42] Furthermore, intervention has been shown to improve outcomes. In the RCT called LIFE (Lifestyle Interventions and Independence for Elders) study, sedentary older people who were randomized to physical activity intervention had a significantly lower risk of major mobility disability, persistent mobility disability, and the combined risk of major mobility disability or death.[43]

It remains unknown whether low levels of physical activity are sufficient to maintain brain health or whether optimal physical activity levels vary across each decade of life.[42,44] While some reports suggest that higher levels of physical exercise may yield more significant effects on cognition, the existing evidence for a dose–response relationship has not demonstrated a precise and robust association.[45,46] Moreover, the ideal duration of physical activity is unclear, with recent evidence indicating significant benefits at shorter durations.[47] However, as with CVH, the biggest marginal benefit of exercise on the brain is usually with the first minutes of activity.[48] There is benefit beyond that, but each additional minute has a slightly smaller marginal gain and asymptotes. Current guidelines recommend that adults should engage in 150 minutes of moderate-intensity aerobic activity per week or 75 minutes of vigorous-intensity aerobic activity a week.[49]

Physical activity may play a role in protecting the brain against the structural and functional effects of aging.[45] Physical activity appears to be protective against neurodegeneration, preserving both gray and white matter, as well as improving structural changes in the hippocampus.[45,50] Proposed mechanisms for the benefits of physical activity include reduction in inflammation, improved insulin sensitivity, and increased production of brain derived neurotrophic factor.[45] Animal and human studies further characterize the mechanisms behind exercise-induced cognitive benefits by showing increased neuroplasticity and neurotrophic factor production.[51] Studies also support the role of a neuronal synaptic regulator molecule, known as the brain-derived neurotrophic factor, as a mediator of the

benefit of physical activity on cognition.[50] However, a significant contributor may be from improvements in the cardiovascular system and its resultant molecular and cellular effects on the cerebrovascular system.[45,52]

Healthy amounts of physical activity have positive effects on brain structure and cognition across all age groups, with the highest marginal benefits seen in the first minutes.

Avoidance of Nicotine

The effect of tobacco use on cognition is multidimensional but firmly established. Tobacco use is a preventable risk factor for MCI and dementia, including AD.[37] While nicotine use may lead to an acute, transient increase in cognitive performance,[53] prolonged exposure to nicotine and tobacco use has detrimental effects on cognition.[54,55] Most longitudinal prospective studies analyzing the effect of smoking on cognition report a negative impact. For instance, a meta-analysis of 19 prospective studies with at least 1 year of follow-up demonstrated that current smokers had an almost 80% higher risk of incident AD and a 27% higher risk of any type of dementia compared with never smokers.[56] While acute abstinence and withdrawal from nicotine-containing products initially results in a transient reduction in cognitive performance,[57] continued abstinence from cigarette smoking has been associated with improvements in cognition.[55,58]

Before the development of clinical neurocognitive symptoms, consistent tobacco use is associated with structural brain changes, including cerebral atrophy, infarcts, and white matter hyperintensities.[59] Additionally, cigarette smoking exacerbates amyloid load and plaque density in animal models.[60] However, much of the cognitive decline observed in smokers is believed to be caused by vascular pathologies induced by oxidative stress, leading to higher rates of stroke and cerebral hemorrhage.[61] Exposure to nicotine and other addictive substances during adolescence negatively impacts brain development, particularly affecting the frontal cortical regions essential for executive and decision-making processes.[62]

Recent data on vaping nicotine products also suggest negative impacts on cognition.[63] These effects appear to be linked to toxic ingredients of the inhaled materials of vaping products and electronic cigarettes, independent of nicotine.[64] Of note, vaping-related data are observational, underscoring the need for more robust RCTs to better assess causality.

Optimal brain and cognitive health are achieved with total nicotine avoidance, in all forms.

Healthy Sleep

Healthy sleep is the newest addition to the AHA's LE8, yet its link with cognition and AD is well established. Beyond insufficient sleep, excessive sleep may also be detrimental to cognition, with sleep duration likely exhibiting an inverse-U shaped relationship. Extremes of sleep (<4 hours or >10 hours per night) are associated with greater rates of cognitive decline compared with those with 7 hours per night, based on large observational longitudinal studies spanning 4 to 8 years.[65] In this study, less than 4 hours of sleep was associated with a higher risk of incident dementia, while greater than 10 hours of sleep was associated with lower cognitive scores (Figure 3).[65] The LE8 scoring reflects this U-shaped relationship with CVH as well, with highest points for 7 to 9 hours on average, and lower points for >9 and <7 hours.[8]

In the short-term, continuous wakefulness impairs reaction time, psychomotor abilities, memory, and cognitive speed; these effects worsen as sleep deprivation is prolonged.[66] Several studies suggest that after 17 hours of sustained wakefulness, individuals exhibit psychomotor performance equivalent to a blood alcohol concentration of 0.05%, dropping to 0.10% after 24 hours of sustained wakefulness.[67] Interventions to reduce the negative effects of sleep have mostly revolved around promoting wakefulness. However, impaired cognition from sleep deprivation has only been partially and temporarily reversed with the use of stimulants.[68] Importantly, certain sleep-aiding medications have shown a reverse effect, increasing the association with cognitive impairment and dementia.[69]

Poor sleep quality and duration have been linked to alterations in brain structure through changes in cerebral gray matter and blood flow.[70] Numerous other findings in the brain have been reported. Even 1 night

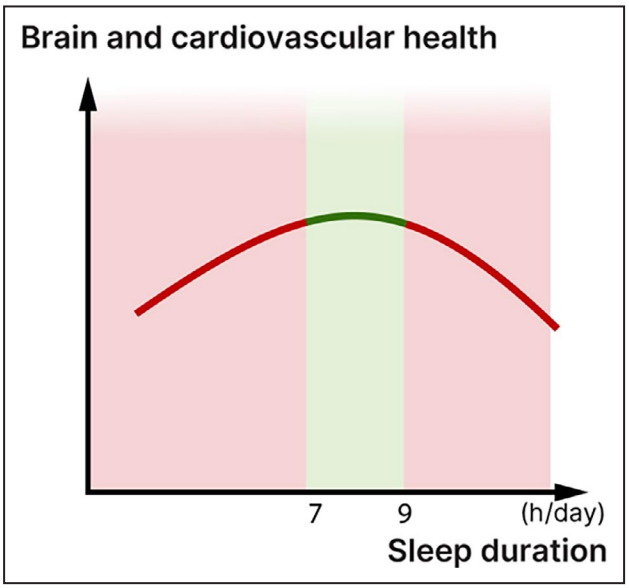

Figure 3. Sleep duration has a U-shaped association with cognition, with 7 to 9 hours of sleep achieving the best cognitive outcomes.

of sleep deprivation has been shown to significantly increase cerebrospinal fluid levels of beta-amyloid 42, cerebrospinal fluid tau protein, and other AD-related cerebrospinal fluid biomarkers.[71,72] Excessive sleeping is also associated with brain structural changes, such as reduced gray-matter volume in brain regions independently correlated with executive function, particularly in the prefrontal cortex.[70,73] Evidence has emerged indicating that the quality and architecture of sleep also contribute to cognitive impairment and AD.[73,74] Alongside poor subjective sleep quality, sleep fragmentation, reduction in rapid eye movement sleep duration, and latency between rapid eye movement cycles have been implicated.[74] Furthermore, sleep disorders and sleep-disordered breathing, especially obstructive sleep apnea, negatively affects cognition and neurodegeneration, largely attributable to increased blood-oxygen desaturation, apnea or hypopnea.[73] Treatment with continuous positive airway pressure improves executive functioning and is associated with slower progression and reduced incidence of both MCI and AD.[75]

The brain is affected both by sleep quality and sleep duration, which is ideally between 7 to 9 hours per night.

LE8 HEALTH FACTORS

Cholesterol

High cholesterol levels have a strong association with cognitive impairment, yet the nuances of this relationship across different age groups and the impact of lipid lowering pharmacotherapy on cognition are less clear. Several observational studies have demonstrated a link between higher plasma low-density lipoprotein (LDL) levels and MCI or AD, including their association with the formation of beta-amyloid plaques.[76,77] In a meta-analysis of observational studies involving individuals in midlife (ages 42.4–56.7) followed for a median of 21.2 years, each 1 mmol/L (38.8 mg/dL) higher LDL-cholesterol level was associated on average with an 8% higher risk of incident all-cause dementia and a 17% increase in incident risk for AD specifically at the time of follow up.[77] Additionally, higher levels of plasma LDL-cholesterol have also been particularly correlated with reduced simple recognition, inhibitory processing, contextual recognition, and spatial working memory in cross-sectional analyses.[78]

It is less clear if this effect is homogeneous across all age groups. Some prospective data suggest that among those over 70 years old, higher cholesterol levels are associated with a reduced risk of developing dementia, even when individuals on statins were excluded from the analysis.[79] However, this finding may be attributable to depletion of those susceptible at younger ages (ie, healthy survivor bias). Further, there may bee via reverse causation, as older people who are getting sicker often have declining LDL levels.[80]

The type of cholesterol also seems to influence the relationship with cognition, with higher levels of serum high-density lipoprotein (HDL) associated with improved cognition, compared with most studies demonstrating an inverse relationship with LDL.[81] For example, general cognitive performance was higher in those with HDL levels greater than 60 mg/dL among those over 60 years of age.[81] However, another study revealed that elevated HDL levels greater than 80 mg/dL were associated with a 27% higher risk for incident all-cause dementia compared with those with HDL between 40 and 60 mg/dL among those over 70 years of age.[82] For those with very high HDL, some of this is apolipoprotein (apo) C-III related, and some is likely also alcohol-related elevations in HDL.[83] The U-shaped relationship seen with HDL and cognition is also seen in coronary heart disease and all-cause and cardiovascular mortality.[84] This suggests a complex relationship between cholesterol and dementia risk that depends on various factors and possibly differs among different age groups. Genetic factors also play a role. Apo E-4 is one of the strongest risk factors for AD with a prevalence of about 14%, and carriers of apo E-4 tend to have the highest LDL and total blood cholesterol levels while apo E-2 carriers have the lowest.[85] Further, those with apo E-4 may have greater therapeutic efficacy and reduced cognitive decline from statin therapy compared to those without.[86]

The neurocognitive effects of lipid lowering medications remain unclear, although recent evidence suggests a neutral or beneficial role. While short-term studies (up to 1.5 years of follow up) have suggested a possible association between cognitive impairment and statin use in the statin clinical trials,[87] longer term studies[88] and meta analyses have contradicted this, even suggesting statin use carried a risk reduction of 18% of all-cause dementia and 27% risk reduction in AD.[89] The effect of statins on cognition may vary by age group, with 1 study showing a negative effect in younger patients and beneficial effect in older patients.[90] Most of the suggested mechanisms are related to improvements in vascular health.[91] Some studies have also hinted at a potential association between use of PCSK9 (proprotein convertase subtilisin/kexin type 9) protease inhibiting monoclonal antibodies and self-reported adverse cognitive events.[92] However, recent larger trials with longer follow-up have found no significant association between PCSK9 inhibitor use and neurocognitive events.[93] Data suggest that the relationship between lipid lowering therapies and cognition is independent of LDL levels,[94] and the use of other non-statin lipid lowering medications appears to be unrelated to cognition.[95]

The LE8 score focuses on reduction of non-HDL to capture the atherogenic and dysmetabolic aspects of lipids, and treatment with statins are safe and effective to support brain and cognitive health.

Blood Glucose

There is clear evidence that diabetes and poor glycemic control are linked to cognitive dysfunction and dementia, but these effects appear to be largely modifiable.[37] In a meta-analysis of several hundred studies, including both observational and RCTs, type 2 diabetes was associated with a 69% increased relative risk for the development of AD.[96] Cross-sectional and longitudinal studies have shown diabetes to be associated with impairment in various cognitive domains, including motor function, executive function, processing speed, language, attention, and multiple forms of memory.[97] Similar associations have been observed with type 1 diabetes in both longitudinal and cross-sectional analyses.[98] Impaired glycemic control at both high and low extremes is also linked to an elevated risk of cognitive dysfunction. For instance, 1 cross-sectional study found that an HbA1c greater than 7% was associated with worse cognitive performance compared to those with a glycated hemoglobin (HbA1c) <7%,[99] which was found to have a graded negative association with higher blood glucose levels when observed longitudinally.[100] This association with impaired cognition is also present at mildly elevated blood glucose levels in the prediabetes range,[101] as well as with hypoglycemia events in prospective observational studies.[100,102]

Several diabetes medications have shown potential in reducing the negative effects of diabetes and high blood glucose levels on cognition. A meta-analysis of cohort, cross-sectional, and RCTs suggests that treatment with metformin is associated with a lower incidence in both cognitive impairment and dementia compared with any control group not taking metformin, independent of diabetes control.[103] Additionally, there is evidence to suggest cognitive benefits with glucagon-like peptide-1 receptor agonists among patients with diabetes, even when adjusted for both weight loss and glycemic control.[104] Another meta-analysis evaluating the use of glucagon-like peptide-1 receptor agonists, sodium glucose co-transporter-2 inhibitors, and dipeptidyl peptidase-4 inhibitors in patients with diabetes showed a significantly lower risk of all-cause dementia in patients using any of these medications compared with those participants not on these medications.[105] Further, improvements in serum glucose levels, oral glucose tolerance testing, and HbA1c on follow up are associated with better results on cognitive testing, independent of diabetes medications.[106] However, there may be a threshold effect where this benefit occurs, as demonstrated by the randomized controlled trial, ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes), which showed that intensive control with an HbA1c <6.0% was not associated with improved cognition compared with an HbA1c of 7.0% to 7.9%, despite higher brain volumes in the intensive-therapy group.[107]

Hypotheses on how diabetes and impaired glucose control affect cognition appear to be complex, as diabetes is associated with structural, vascular, and functional changes in the central nervous system. Diabetes is also known to cause autonomic dysfunction and neuroinflammation, both implicated in the pathogenesis of how diabetes affects cognition.[108] Diabetes may affect brain structure through decreased thalamic gray matter density, global and localized cerebral atrophy, as well as white matter changes.[109] Impairments in insulin receptors among neuronal and dendritic processes have been found in patients with AD.[110] Further, impairment in insulin and insulin receptors via amyloid deposits may alter the energy reserves of neuronal mitochondria.[111]

It is recommended to manage diabetes and maintain blood glucose within a normal range to support brain health.

Blood Pressure

Hypertension is an important modifiable risk factor for cognitive impairment and dementia supported by strong evidence from prospective, observational, and RCTs.[37] Several studies have established a causal relationship between higher systolic blood pressure (SBP) and the incidence of cognitive impairment, vascular dementia, and AD.[112,113] This association appears to be dose-dependent, with the strongest effect observed with exposure during midlife compared with later in life, as demonstrated in longitudinal studies.[113,114] Elevated diastolic blood pressure (DBP) shows weaker but similar trends.[112] Moreover, elevations in both SBP and DBP in midlife have been linked to increased cerebral beta amyloid on pathologic examination.[115] There is also some evidence for a U-shaped relationship with both SBP and DBP with some studies indicating that low SBP and DBP may increase dementia risk, playing a larger role later in life.[113] However, this may be attributable to reverse causation in those with low cardiac output. Additionally, even blood pressure elevation and blood pressure variability within the elevated/pre-hypertensive range have cumulative effects on cognitive function, demonstrating that this effect does not just start at the current threshold for hypertension diagnosis.[116,117] Further, there may be a penalty for time spent at elevated blood pressure even for those who subsequently regain well controlled blood pressure with treatment.[118]

The impact of hypertension on cognition can be modified through better SBP control and antihypertensive medications. For instance, in the randomized

controlled trial SPRINT-MIND (Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension), individuals randomized to a SBP goal of <120 mm Hg showed ~20% lower incidence of MCI and fewer white matter lesions compared with those targeting an SBP goal of <140 mm Hg.[119] Similarly, a double-blinded placebo-controlled trial that began in 1988 called the Systolic Hypertension in Europe study, found that those treated for hypertension (SBP ranging from 160 to 219 mm Hg and DBP <95 mm Hg) had lower incident dementia compared with those given placebo.[120] In this trial, antihypertensive treatment of 1000 patients over 5 years was estimated to prevent 20 cases of dementia, while treatment with nitrendipine specifically reduced the incidence of dementia by 55%. Moreover, a large meta-analysis of RCTs and observational longitudinal studies found that antihypertensive medication was associated with a 21% reduction in dementia risk among those with hypertension.[113] However, treatment of hypertension needs to mitigate the risk of hypotension, which has also been associated with impaired cognition.[121]

Several proposed mechanisms explain this phenomenon linking hypertension with cognitive decline and dementia, primarily related to effects on the vasculature. One hypothesis suggests that elevated intravascular pressure compromises the structural and functional integrity of the cerebral microcirculation, impairing cerebral blood supply by promoting cerebral microvascular rarefaction, endothelial dysfunction, and neurovascular uncoupling.[122] In addition, high blood pressure disrupts the blood–brain barrier, leading to neuroinflammation and exacerbating amyloid pathologies.[123] Neuroradiological markers of hypertension-induced cerebral small vessel disease, such as white matter hyperintensities, lacunar infarcts, and microhemorrhages, are all associated with cognitive decline.[124] In addition to the intravascular pressure lowering effects, some antihypertensive drug classes have other mechanisms that may influence AD risk. For example, use of angiotensin receptor blockers (ARBs) in participants with MCI was associated with a decrease in cerebrospinal fluid (CSF) levels of both total tau (P=0.002) and p-tau (P=0.01) relative to those treated with non-ARB classes.[125] Moreover, the ARB candesartan had beneficial effects on cognition and AD biomarkers even in non-hypertensive individuals with MCI.[126]

There is a dose-dependent linear relationship between SBP and ADRD, and some antihypertensive treatment may reduce AD risk.

Weight

The relationship between obesity and cognitive health is complex yet supports obesity as a modifiable risk factor for dementia and cognitive decline. A meta-analysis of prospective, population-based studies including over 500 000 participants, followed up to 42 years, demonstrated that in middle-aged individuals, obesity increased the risk of cognitive impairment by 33% compared with those with a normal BMI. This finding was not significant among overweight individuals.[127] However the age range where this relationship prevails remains unclear. Some studies suggest that the link between BMI and increasing dementia risk is primarily observed in mid-life and may even exhibit an inverse association later in life.[128] Additionally, fluctuations in BMI in either direction have been associated with impaired cognition.[129]

Obesity is associated with reductions in various aspects of executive functioning, including inhibition, cognitive flexibility, decision-making, working memory, verbal fluency, and planning.[130] One potential pathway through which obesity may directly contribute to cognitive decline is obesity-induced systemic inflammation, with hypothalamic inflammation particularly implicated in remodeling and disruption of internal circuitry and connections to other regions of the brain.[131] Other potential pathways include metabolic consequences such as type 2 diabetes leading to cerebrovascular disease, resulting in reduced parenchymal volume, disruption of the gut microbiota, and insulin resistance.[132]

Interventions targeting obesity appear to be associated with cognitive improvements. A meta-analysis including seven RCTs demonstrated that intentional weight loss among both obese and overweight individuals is associated with improved cognition.[133] However, it remains unclear if there is a specific age or BMI range where intervention is more appropriate. Further research is needed to clarify these aspects and to better understand the effectiveness of interventions targeting obesity in preserving cognitive health.

Individuals who are obese are at an independently increased risk of developing impaired cognition.

Overall LE8 Score and Cognition

The composite 100-point LE8 score serves as a valuable objective tool for assessing CVH. In over 250 000 participants of the United Kingdom Biobank followed for over 10 years, higher LE8 scores were associated with lower risk of dementia.[134] Specifically, individuals in the least healthy quintile of LE8 score had a 50% higher risk of all-cause dementia and an 86% higher risk of vascular dementia compared with the healthiest quintile, independent of demographic and lifestyle factors. Moreover, individuals in the lowest quintile developed all-cause dementia approximately 2.45 years earlier than their healthier counterparts. The study indicated that an intervention capable of increasing the LE8 score in the lowest health quintile by 10-points could have prevented 6.8% of all-cause dementia cases. Similarly, a meta-analysis of observational longitudinal studies demonstrated that improved adherence to LS7 was

associated with improved cognition in older adults.[135] There appeared to be a dose–response and linear relationship between the LS7 score and dementia risk, with each 1-point increase in the score correlating with a 6% decrease in incident dementia. Notably, this effect seemed to be primarily mediated through physical activity, fasting plasma glucose, total cholesterol, and smoking, with no significant association observed for the components of diet, BMI, or blood pressure. There are some studies that further suggest utilization of a risk assessment tool can help patients improve their CVH,[136] and others are actively ongoing.[137] RCTs are needed to explore the potential benefits of incorporating LE8 into clinical practice and its impact on both cardiovascular and cognitive outcomes.

Social Determinants of Health and Stress

While not included in LE8, social determinants of health (SDOH) and stress are recognized as important contributors to CVD and impaired cognition.[138] The design of LE8 acknowledges the foundational context that SDOH provides for an individual or a population to achieve their best possible CVH. SDOH, such as poverty, access to health care, quality of health care, increased exposure to violence, systemic racism, and structural inequities, can negatively impact brain development and disproportionally affect minoritized groups with a pronounced dose response effect of multiple SDOH.[139] Racial and ethnic disparities in dementia risk and vascular risk factors are quite large and not improving with approximately 2x higher dementia prevalence for Black people and 1.5x for Hispanic people compared with their White counterparts.[140] Understanding the underlying mechanisms behind this phenomenon has been elusive. However, some suggest that SDOH factors masquerade as racial differences in cognition.[141] For instance, 1 study found that SDOH contributed to 51% of the differences in volume in some brain regions between White and Black children.[142] Reducing the disparities have the potential for major public health improvements.

Chronic psychological stress and emotional well-being have also been linked to both CVD[143] and impaired cognition, affecting individuals both with and without CVD.[144,145] Early life adversity and childhood trauma has been associated with psychiatric diseases like posttraumatic stress disorder, anxiety, depression, and substance abuse, all of which can have negative impacts on cognition.[146] Furthermore, acute mental stress has been shown to induce myocardial ischemia.[147] An evolving paradigm is that chronic and acute stress alter physiological and molecular pathways involved in emotional responses through effects on the neuroendocrine and autonomic nervous systems.[148] Hemodynamic alterations and vascular reactivity in responses to stress seem to correlate with CVD risk and impaired cognition, and have been associated with endothelial dysfunction.[149,150] Moreover, ischemia induced by mental stress and peripheral vasoconstriction during mental stress have been associated with poorer cognitive function.[151]

While few studies have demonstrated moderating effects of stress on cognition, some evidence suggests potential avenues for intervention. In 1 study among stable coronary artery disease (CAD) patients undergoing mental stress, those on beta blockers were 50% less likely to exhibit low stress/rest peripheral artery tonometry ratios, indicating a lower risk of having adverse outcomes.[150] Additionally, a cross-sectional analysis of military veterans demonstrated that those with higher psychological resilience scores had better cognitive function, although prospective studies are needed to confirm these findings.[152]

CONCLUSIONS

There is evidence indicating that each behavioral and health factor of CVH, as outlined in LE8, is intricately linked to cognitive and brain health. Optimizing these factors may lead to improvement in brain health. However, several important contextual caveats need consideration. First is that there is a crucial lack of racial and ethnic representation in most preventive and clinical trials evaluating ADRD, despite a greater risk and burden among some large, underrepresented groups.[153] For instance, in the clinical trials leading up to the 2021 approval for aducanumab, only 0.6% of participants identified as African American/Black, and 1.5% were Hispanic/Latino(a).[153] Another important consideration is the differences in cognitive impairment and ADRD among women compared with men. Women are at a higher risk of AD than men, with faster disease progression and greater amyloid and tau pathology, potentially influenced by hormonal changes post-menopause and genetic factors.[154] Men are more likely to have vascular contributions to dementia, while women's higher baseline verbal memory may delay detection despite brain changes.[155] Sociocultural factors, such as caregiving burdens and health care disparities, further amplify these differences, highlighting the need for sex-specific research and treatment strategies to improve outcomes.

Many studies using dementia as an endpoint often rely solely on a clinical diagnosis without biomarker confirmation. Clinical diagnoses of AD have a sensitivity ranging around 71–87% and specificity around 44–71%.[156] Consequently, conclusions drawn from association studies regarding CVH factors and AD may be misleading. Additionally, the lack of RCTs contributes to a limited evidence base and uncertainty about

causality, with potential for significant bias and unaccounted potential confounders.

Each of these LE8 factors affects both vascular and brain health. There is a significant vascular contribution to the development of cognitive impairment and AD, independently of cerebrovascular disease.[19,20] Vascular risk factors such as smoking, hypertension, diabetes, and hyperlipidemia significantly increase the likelihood of AD, possibly through a synergistic effect with vascular dysfunction being the shared mediator.[157] However, a comprehensive understanding of the causal relationship between vascular risk factors and AD remains unclear and requires additional study. These associations of LE8 with neurocognitive outcomes may serve as an indicator of high-risk population for appropriate treatment and do not necessarily imply that intervention will improve outcomes. Additional RCTs are needed to better identify the causality of LE8 health factors. In summary, this review underscores the importance of measuring, monitoring, and modifying behavioral and health factors as defined by LE8, which may reduce the risk for cognitive decline.

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