Current Epidemiology Reports (2019) 6:347–363
https://doi.org/10.1007/s40471-019-00210-8

CARDIOVASCULAR DISEASE (R FORAKER, SECTION EDITOR)

Association of Cardiovascular Health and Cognition

Ambar Kulshreshtha[1] · Jannat Saini[2] · Taylor German[3] · Alvaro Alonso[4]

Published online: 27 July 2019

Abstract

Purpose of Review More than a third of dementia cases are potentially attributable to modifiable risk factors. The objective of this review is to summarize the evidence linking overall cardiovascular health (CVH) profile and modifiable cardiovascular disease risk factors (CVDRF) with cognition.

Recent Findings We conducted online searches for all relevant literature describing the relationship between CVDRF, overall CVH profile, and dementia. Studies have shown a positive association with the presence of clinical or subclinical CVD and accelerated cognitive decline. Individual CVH factors such as hypertension, diabetes, smoking, physical activity, and diet are independently associated with cognition. The association is, however, less clear for dyslipidemia and obesity. The mechanisms that define these associations are complex and mainly derived from vascular and cellular pathways affecting amyloid beta burden and brain volume.

Summary This review summarizes salient literature that highlight the role of a favorable CVH profile and optimum CVDRF levels, particularly in midlife to prevent decline in cognitive function.

Keywords Cardiovascular diseases · Cognition · Cardiovascular health · Dementia · Risk factors · Epidemiology

Introduction

Dementia is a clinical syndrome characterized by progressive impairment in cognitive ability and capacity for independent living. An estimated 35.6 million people lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2020 and 115.4 million in 2050 [1••]. Dementia and cardiovascular diseases (CVD) have an increasing incidence and prevalence in the elderly population, causing a decline in quality of life, and are the leading causes of death. A growing literature implicates CVD as a risk factor for dementia. Studies of both clinical and subclinical CVD have consistently reported associations with impaired cognitive function [2, 3•]. In addition, a number of studies suggest that CVD risk factors (CVDRF) such as hypertension, diabetes, obesity, and smoking are independently associated with the development of dementia [4•]. Primary prevention that has a focus on improving CVDRF control could have an important impact on the future prevalence and incidence of dementia. Prior studies have shown that even small shifts in risk factor levels at the population level can explain up to two-thirds to three-fourths of the dramatic reductions in CVD mortality rates [5–7]. This population-level strategy can similarly be applied for reducing dementia rates. In a modeling study, it was estimated that a modest 10% reduction in risk exposure levels could reduce the prevalence of Alzheimer's dementia by up to 1.1 million cases worldwide [8•]. Greater absolute reductions in dementia would come through public health measures that involve a modest lowering of risk factors among the larger proportion of the population with risk factors near or slightly above the mean [9•]. Further understanding the role of CVDRF in cognitive decline could have an important role in developing effective preventive strategies for dementia and improving quality of life in aging populations [10].

This article is part of the Topical Collection on *Cardiovascular Disease*

✉ Ambar Kulshreshtha
akulshr@emory.edu

[1] Department of Family and Preventive Medicine, Emory University School of Medicine, 4500 North Shallowford Rd., Suite 134, Atlanta, GA 30338, USA

[2] Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

[3] Department of Behavioral Sciences and Health Education, Rollins School of Public Health, Emory University, Atlanta, GA, USA

[4] Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

Prevention at the population level works best when programs to mitigate the risk factors are widely available throughout the whole population. In 2010, the American Heart Association adopted better cardiovascular health (CVH) as a population strategy to prevent heart disease and stroke epidemics by encouraging system approaches to help individuals identify and adopt healthier life choices [11••]. The construct of CVH is defined as a metric with the simultaneous presence of seven favorable health behaviors and factors (abstinence from smoking within the last year, ideal body mass index, physical activity at goal, consumption of a Mediterranean dietary pattern, untreated total cholesterol < 200 mg/dL, untreated blood pressure < 120/< 80 mm Hg, and absence of diabetes mellitus) [12•]. Each of the health behaviors and health factors have been consistently associated with CVD-free survival, quality of life, compression of morbidity, healthy aging, overall longevity, and reduction in healthcare costs [13]. Several recent studies have reinforced the relevance of this metric in reduction of CVD rates [14•, 15•].Given the close links between CVD and dementia pathophysiology, early identification and modification of common risk factors could have a major impact on reducing these epidemics, particularly among the elderly population. This article will review the current evidence linking CVD, CVDRF that are part of the CVH metric, and cognition. Even though there are many types of dementias, our review will focus on prevention of the two most common, Alzheimer's dementia and vascular dementia.

Cardiovascular Disease and Cognitive Decline: Overlapping Pathophysiology

Several studies have highlighted the association of CVD in middle age with dementia in later life regardless, of race and gender [16–19]. Cognitive syndromes such as Alzheimer's disease-type dementia and mild cognitive impairment (MCI) share several pathophysiological pathways with CVD, such as inflammation, increased oxidative stress, and changes to nitric oxide bioavailability [4•, 20]. The relationship between CVD and cognition suggests a primary role of metabolic and vascular damage in the etiology of dementia. Another postulated mechanism is that cognitive impairment could be due to changes in brain perfusion caused by CVD [21]. The association between the presence of CVD or CVDRF and late-life cognitive impairment has also been attributed to vascular changes and amyloid deposition [21]. A recent longitudinal study of community-dwelling adults strongly linked greater chronological age, symptoms of CVD, and processing speed decline to elevated white matter lesion burden [22]. Cerebral white matter lesions, which are prevalent in a majority of older adults, are thus also associated with both cognitive decline and CVD. Subclinical CVD has also been associated with poorer cognitive function. While associations in cross-sectional and prospective studies have been reported between prevalent CVD and cognition, there have also been some reports of important non-associations [16, 23]. These conflicting reports could be due to differences in the severity and definition of the disease, cognitive assessments utilized, duration of follow up, and sample size. Recent literature in the area of CVD and cognition is summarized in Table 1.

Association of Cardiovascular Health Factors and Behaviors with Cognition

More than one in three US adults have at least one CVDRF and the prevalence of these factors increases with age. Several of these CVDRF are modifiable and part of the CVH metric [36•]. Growing evidence indicates that CVDRF interfere with normal cognitive functioning and could be directly related to the pathogenesis of dementia via overlapping vascular and cellular mechanisms [37]. The CVDRF result in subtle structural changes in the brain at first, accelerating decline in cognitive abilities and eventually causing dementia [2]. Morphological changes to brain structures seem to occur with the presence of even a single untreated risk factor, causing cognitive impairment and dementia [2]. In a study of MCI patients, 60% of them developed dementia and subgroups with CVDRF had a higher conversion rate to Alzheimer's dementia [38]. Estimates suggest that up to a third of Alzheimer's cases are potentially attributed to CVDRF and, thus, could be prevented [39]. All known CVDRF continue to be the focus of studies to further identify modifiable risk factors of dementia. Below, we review individual health factors and behaviors that are part of the CVH metric and their relationship with cognitive function.

Hypertension

Blood pressure (BP) is the most studied CVDRF in cognition literature [40••]. Hypertension is an established risk factor for stroke and silent infarcts and is associated with both vascular and Alzheimer's dementia [41]. Sustained exposure to high pressure flow has multiple neuropathological effects including cerebrovascular atherosclerosis, vascular remodeling, hypoperfusion, and increased frequency of white matter lesions in the brain [42•, 43]. Reduced brain perfusion leads to ischemic lesions, lacunar, cortical infarcts [44••, 45]. Some studies have also shown that hypertension can be directly involved in amyloid beta deposits and neurofibrillary tangle formation [46, 47]. This can adversely affect cognitive function particularly relating to memory, attention, and executive function [48, 49•]. The Honolulu-Asia Aging study reported that elevated levels of BP are associated with lower gray matter volumes in the hippocampus and lateral temporal lobe [49•]. Studies in the elderly have similarly shown that higher systolic BP is

Table 1 Summary of recent relevant studies of association between clinical or subclinical cardiovascular disease (CVD) and cognition

Authors/year	Study design/ sample size	Location	Cognitive test	Main findings
Roberts et al./2010 Mayo Clinic Study of Aging [24•]	Cross-sectional $N = 1969$	Olmsted County, MN	Clinical Dementia Rating Scale Cognition; neurological evaluation, neuropsychological testing using nine cognitive tests to assess performance in four cognitive domains: memory (Wechsler, 1987; Ivnik et al., 1992), executive function (Reitan, 1958; Wechsler, 1987), language (Kaplan et al., 1982; Lucas et al., 1998), and visuospatial skills (Wechsler, 1987). Data for each participant reviewed by expert panel including physicians, neuropsychologists, and the nurses. Diagnosis of normal cognition, MCI, or dementia was reached by consensus.	CHD significantly associated with non- amnestic MCI (na-MCI), but not significantly associated with amnestic MCI (a-MCI) ApoE ε4 carrier status significantly associated with a-MCI but not na-MCI
Arntzen et al./2011 Tromsø study [25]	Cross-sectional, longitudinal $N = 5033$	Tromsø, Norway	Cognitive function; verbal memory test, digit-symbol coding test, tapping test Cognitive impairment; lowest quintile on cognitive test scores	No consistent association between total cholesterol (TC), high density lipoprotein (HDL)-cholesterol, CHD/BMI and cognition tests diabetes mellitus (DM), smoking, hypertension associated with lower cognitive test results
Kaffashian et al./2011 Whitehall II study [26]	Longitudinal cohort study $N = 3486$ men, 1341 women	England, UK	Cognitive function; tests of reasoning (AH 4-I), memory, phonemic and semantic fluency, and vocabulary (Mill- Hill), assessed three times (1997–1999, 2002–2004, 2007–2009) over 10 years	In cross-sectional age-adjusted models, 10% point increments in cardiovascular risk associated with poor performance in all cognitive domains in both men and women (all P values < 0.001) In models adjusted for age, ethnicity, marital status, and education, 10% higher cardiovascular risk was associated with greater overall 10-year cognitive decline in men, reasoning in particular (− 0.47; 95% CI − 0.81, − 0.11).
Kaffashian et al./2013 [27•]	Longitudinal cohort study $N = 4153$ men, 1657 women	England, UK	Cognitive tests; reasoning, memory, verbal fluency, and vocabulary assessed three times over ten years. Longitudinal associations between Framingham Stroke Risk Profile (FSRP) and its components tested using mixed	Higher stroke risk associated with faster decline in verbal fluency, vocabulary and global cognition No association for memory and reasoning

Table 1 (continued)

Authors/year	Study design/ sample size	Location	Cognitive test	Main findings
			effects models and rates of cognitive change over 10 years estimated	
Haring et al./2013 Women's Health Initiative Memory study (WHIMS) [19]	Prospective cohort study $N = 6455$	Multicenter US (39 clinical centers)	MCI or probable dementia (PD) via modified mini-mental state examination (3 MS) score, neurocognitive, and neuropsychiatric examinations (Consortium to Establish a Registry for Alzheimer's Disease (CERAD), DSM-IV)	Women with CVD tended to be at increased risk for cognitive decline compared to those free of CVD (HR, 1.29; 95% CI:1.00,1.67) - MI or other vascular disease at highest risk - AP moderately associated with cognitive decline - no significant relationships found for Afib or Heart Failure (HF)
Reis et al./2013 Coronary Artery Risk Development in Young Adults Study (CARDIA) [28•]	Longitudinal community based- study $N = 2932$	Multicenter 4 US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California)	Digit Symbol Substitution Test (DSST), modified Stroop test, Rey Auditory Verbal Learning Test (RAVLT) completed at year 25	Greater number of ideal cardiovascular metrics in young adulthood and middle age independently associated with better cognitive function in midlife (p for trend < 0.01, for all) Each additional ideal metric associated with 1.32 more symbols on the DSST (95% CI = 0.93–1.71), 0.77-point lower interference score on the Stroop test (95% CI = 21.03 to 20.45), 0.12 more words on the RAVLT (95% CI = 0.04 to 0.20) Participants who had > 5 ideal metrics at a greater number of the 3 examinations over the 25-year period showed better performance on each cognitive test in middle age (p for trend <0.01, for all).
Weinstein et al./2016 [29]	Randomized control trial N = 1232, $n = 536$	Multicenter Israel (8 central hospitals)	C-reactive protein (CRP) levels measured in subgroup with chronic CVD Cognitive performance; assessment of performance globally and in memory, executive function, visuospatial and attention domains—Neurotrax computerized cognitive battery—Benton visual retention test, brief visuospatial memory test, Tova, Stroop, subsets of WAIS-III (Wechsler Adult Intelligence Scale, 3rd Ed.), levels of difficulty adjusted upon performance, designed for the elderly Neurotrax software calculated raw	CRP at top tertile associated with poorer performance overall and on executive function and attention tests vs. rest CRP levels positively related to greater decline in executive function

Table 1 (continued)

Authors/year	Study design/ sample size	Location	Cognitive test	Main findings
			composite scores for each cognitive domain: memory, executive function, visual spatial processing, attention. A composite score was computed as a weighted average of all summary scores from each domain. Scores were normalized according to age- and education-specific normative data and scaled to an IQ-style scale with mean of 100 and SD of 15.	
Bleckwenn et al./2017 [30]	Prospective longitudinal cohort study $N = 3327$, $n = 118$ (AD or mixed dementia diagnosis)	Multicenter Germany (138 practices, 6 cities)	Cognitive performance; MMSE, Clinical Dementia Rating Scale Sum of Boxes (CDR-SoB) (cognitive-functional ability), SIDAM-ADL (activities of daily living) Dementia diagnosed by DSM-IV and SIDAM AD diagnosis made by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRD)	Presence of CHD significantly accelerated cognitive decline by about 66% (MMSE) and significantly reduced cognitive functional ability by about 83% (CDR-SoB) Showed deleterious effect on cognitive decline after Alzheimer's Disease (AD) diagnosis
Mahinrad et al./2017 Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) [23]	Randomized controlled trial $N = 5804$, $n = 4233$	Ireland, Scotland, the Netherlands	Global cognitive function; MMSE (<24 excluded) 4 tests to assess different domains of cognitive function—Stroop interference test (selective attention) –Letter-digit coding test (general cognitive speed) –Picture-word learning test (Immediate and delayed memory) – delayed recall test for Picture-Word Learning test – participants asked to repeat the test after 20 min. Different versions of cognitive tests at each visit used to avoid learning effect	At baseline, left ventricular hypertrophy (LVH) not associated with worse cognitive function. During follow-up, participants with higher levels of LVH had steeper decline in cognitive function including in selective attention ($p = 0.009$), processing speed ($p = 0.010$), immediate memory ($p < 0.001$), and delayed memory ($p = 0.002$). Associations were independent of cardiovascular risk factors, co-morbidities, and medications.
González et al./2017 Atherosclerosis Risk in Communities Cohort Study (ARIC) [31••]	Prospective epidemiologic study $N = 15{,}792$, $n = 13{,}270$	Four US communities (Forsyth County, NC; Jackson, MS (African Americans only); selected suburbs of Minneapolis, MN; and Washington County, MD.)	Cognitive measures at each visits—Delayed Word recall (DWR), Digit Symbol Substitution (DSS) test from the Wechsler Adult Intelligence Scale– Revised, and phonemic Word Fluency (WF) Z-scores for each test created at each testing occasion by scaling to their mean and standard deviation (SD) at baseline (1990–1992). Average of these three test-specific z scores was used to create a global longitudinal	Higher midlife (American Heart Association's Life's Simple 7) scores and individual metrics, (particularly blood pressure and glucose) associated with better midlife cognition and reduced 20-year decline. Midlife CVH 20-year neuroprotection more pronounced among whites than blacks.

Table 1 (continued)

Authors/year	Study design/ sample size	Location	Cognitive test	Main findings
			composite (global z) score, which was scaled to its baseline SD	
Gonzales et al./2017 [32]	Prospective cohort study	Chicago, IL, USA	Cognitive domains were calculated by averaging z-scores within each construct tested: - Learning (LRN): immediate recall from the California Verbal Learning Test-II (CVLT-II) Trials 1–5 and the Wechsler Memory Scales-III (WMS- III) Logical Memory-I and Visual Reproduction-I – Memory - (MEM): CVLT-II long delay free recall (32), WMS-III Logical Memory-II and Visual Reproduction-II - Executive Function (EF): Trail Making Test (TMT) part B time to completion (reversed), Delis-Kaplan executive function system category switching total, Stroop Interference score, Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Span Backwards raw score, Self-Ordered Pointing Task total errors (reversed)- Attention and Information Processing (AIP): TMT Part A time to completion (reversed), Stroop Color and Word raw scores, WAIS-III Digit-Symbol Coding raw score	Higher blood pressure associated with poorer learning ($B = -0.19$; $p = 0.019$), memory ($B = -0.22$; $p = 0.005$), and executive functioning performance ($B = -0.14$; $p = 0.031$), lower cortical thickness within the right lateral occipital lobe. Elevated glucose dysregulation associated with poorer attention/information processing performance ($B = -0.21$; $p = 0.006$) and lower fractional anisotropy in the right inferior and bilateral superior longitudinal fasciculi. Cholesterol was associated with higher cortical thickness within left caudal middle frontal cortex. Metabolic dysfunction was positively associated with right superior parietal lobe, left inferior parietal lobe and left precuneus cortical thickness.
An et al./2018 [17]	Longitudinal secondary analysis of community based prospective cohort study $N = 1996$	Beijing, China	Cognitive function; MMSE, participants categorized by score	Compared with MMSE scores of 28–30, participants with scores <18 independently associated with all-cause mortality and CVD mortality (HR, 4.52; 95% CI, 2.80–7.30, $P < 0.001$) Each 5-point decrease in MMSE score associated with a 34% increased risk of all- cause mortality and a 56% increased risk of CVD mortality This relationship remained statistically significant after using the competing risk model to consider non-CVD death as a competing risk event
Leng et al./2018 Women's Health Initiative Memory study (WHIMS) [33•]	Ancillary study to WHI-HT (women's health initiative trials of hormone therapy)—2	Multicenter US	Global cognitive functioning; Modified Mini-Mental State (3MS) exam Participants scoring below preestablished cut-points scheduled for a more extensive	For every 5-point lower baseline 3MS score, risk was 12% greater for incident CVD, 37% for HF, 35% for CVD death, 24% for all-cause mortality

Table 1 (continued)

Authors/year	Study design/ sample size	Location	Cognitive test	Main findings
	parallel, randomized, double blinded, placebo controlled trials Secondary analysis $N = 5596$ women		neurocognitive assessment and neuropsychiatric exam to determine presence/absence of probable dementia/MCI	No significant relationships found for CHD, angina, stroke/TIA, or coronary revascularization When change in 3MS added as a time- varying covariate in the fully- adjusted models——for each 1-point/year greater decline in 3MS, risk was 4% greater for incident CVD, 10% for CHD, 9% for Stroke/TIA, 17% for CVD death, 13% for all-cause mortality
Samieri et al./2018 Three-City (3C) Study [34••]	Population-based cohort study $N = 6626$	(Bordeaux, Dijon, ellier)	Cognitive decline; composite scores of global cognition and memory: - Global cognitive score computed as mean of z scores of 4 cognitive tests assessing (1) global cognition (using MMSE)(2) verbal semantic fluency (Isaacs' Set Test) (3) working memory and attention (Benton Visual Retention Test) (4) executive functioning (Trail Making Test Part A) -Memory tests combined in a composite memory score calculated as the mean of z scores of the Benton Visual Retention Test and a subset of the MMSE.	Increased numbers of optimal cardiovascular health metrics and a higher cardiovascular health score were associated with a lower risk of dementia and lower rates of cognitive decline
Kontari et al./2019 English Longitudinal Study of Aging (ELSA) [35]	Prospective cohort study $N = 4859$	England	Dementia incidence; identification of newly diagnosed dementia based on participant/ informant reported physician-diagnosed dementia or AD and incidence of dementia determined with 16-item Informant Questionnaire on Cognition Decline in the Elderly (IQCODE) (scores performance on cognitive, executive and daily functions compared with previous 10 years)	No evidence found for association of overall cardiometabolic abnormalities with incident dementia; however hyperglycemia, hypertension and abdominal obesity with depressive symptoms had an unadjusted association with incident dementia, and low-HDL cholesterol with depressive symptoms had an adjusted association with incident dementia (HR = 0.18; 95% CI, 0.04–0.75).

associated with higher rates of cognitive decline [50•]. Higher diastolic BP by itself is also associated with poor cognition and could impact executive function [51•]. Further evidence of the BP-cognition relationship is illustrated with the Atherosclerotic Risk in Communities cohort (*N*~11,000), which showed the relationship between CVDRF (particularly hypertension and diabetes) and decline in cognitive functioning in an older population [52••]. On the other hand, a reduction of blood pressure has a protective effect on cognition [53]. For example, patients who received anti-hypertensive treatment had lower rates of neuritic plaques and neurofibrillary tangles than controls [54].

Despite the strong BP-cognition data, there has been some controversy about the target Systolic BP for preventing cognitive decline [55••, 56]. The Systolic-Hypertension in Europe study reported that BP-lowering therapy reduced the risk of dementia by 55% [57]. In the Systolic Blood Pressure Intervention Trial - Memory and Cognition in Decreased Hypertension (SPRINT MIND), intensive lowering of BP to a goal of <120mm Hg reduced the risk of MCI and dementia risk [58••].This is the first randomized clinical trial demonstrating that an intervention can reduce the incidence of MCI/dementia, highlighting the significance of BP as a risk factor for cognitive decline.

Some observational studies have also found an association of low BP with cognitive impairment and that hypertension could be a protective response to cerebral hypoperfusion [59•]. Possible reasons for these conflicting findings could be use of varying cognitive instruments in different studies and heterogeneity in the impact of hypertension on specific cognitive domains. Further research into the effects of hypertension, particularly in midlife, could point to interventions for prevention of MCI and later dementia.

Diabetes

Diabetes is positively associated with a decline in cognitive function, including MCI, and dementia [60, 61, 62•, 63]. In a pooled analysis of 14 studies, individuals with type 2 diabetes were at 60% greater risk for developing dementia [64]. In a prospective study, an increase in the number of metabolic syndrome components, particularly diabetes, was associated with a 23% age-adjusted increase in the risk of dementia [65•]. Diabetes has an impact on overall brain volume and cognition particularly on measures of attention and working memory [66]. Chronic exposure to hyperglycemia results in improper cellular utilization of glucose, impacting most organs in the body, and is particularly damaging to the central nervous system [67]. There is often a convergence of physiological factors that result in comorbidity, such as increased oxidative stress in individuals having comorbid diabetes mellitus (DM) and Alzheimer's disease or the commonality of infarcts and atrophy in the brains of individuals with diabetes mellitus [68].

Results from several studies have shown that among people who have DM, those with longer disease duration and higher levels of glycosylated hemoglobin A1C have faster rates of cognitive decline and decreased cognitive function [60].

Studies that also explored the pathogenesis at the cellular level have concluded that physiological links between DM and Alzheimer's disease exist, often resulting in the exacerbation of one another [63, 69]. On the other hand, autopsy studies have pointed that DM is associated mostly with non-Alzheimer's type dementia pathology [70•]. Thus, the exact mechanisms and temporality informing this relationship between DM and cognitive functioning are still not fully understood [67, 71]. In the elderly population, DM has been linked with MCI and those with DM have greater baseline deficits in domains of memory and language [72•, 73]. Even in young adults, higher intra-individual fasting glucose variability was associated with worse processing speed, memory, and language fluency [74•]. Despite the growing evidence of diabetes and risk of cognitive impairment, there is no clear evidence that treating diabetes with intensive control is beneficial for cognitive outcomes. Action to Control Cardiovascular Risk in Diabetes - Memory in Diabetes Study (ACCORD MIND) is the first randomized trial in older persons with DM to test the effect of intensive compared with standard glycemic treatment strategies on multiple cognitive domains. The study failed to show a long-term benefit in cognitive outcomes (except brain volume) with intensive glycemic, BP, or lipid intervention [75••, 76•]. Cognitive dysfunction also influences the ability of patients to follow complex chronic disease management, affecting medication adherence and increasing DM complications such as hypoglycemia [77]. Due to the high prevalence of DM in the US population, future studies must be done to understand the impact of DM interventions on cognition.

Dyslipidemia

Dyslipidemia is also a highly prevalent condition in the US and is a widely recognized CVDRF. Proteins required for cholesterol distribution such as low-density lipoprotein (LDL) receptor and LDL receptor-related protein 1 (LRP1), may play a role in amyloid β homeostasis [78]. The APOE gene, a strong genetic risk factor for sporadic Alzheimer's disease, is also involved in cholesterol transport [79]. Studies have shown that higher levels of LDL, very low-density lipoprotein, and triglycerides are associated with poorer performance in attention, working memory, category fluency, and delayed recall [80]. Other prospective studies have shown that midlife dyslipidemia is associated with vascular dementia and Alzheimer's disease [81•, 82•, 83]. Animal studies have also shown that dietary cholesterol can accelerate amyloid β deposition in the brain and that it may indirectly promote production of neurofibrillary tangles [84]. Some epidemiological studies have, however, shown no association

between dyslipidemia and dementia risk [85•, 86]. For example, in the Framingham heart study, cholesterol levels were not associated with the risk of Alzheimer's dementia [87•]. In a systematic review, cholesterol levels in midlife but not later in life were associated with dementia [88•]. Despite observational studies suggesting that statins could be protective for dementia, several randomized clinical trials involving treatment of dyslipidemia with statins have shown no clear beneficial effect on cognition [89, 90•]. The role of cholesterol in cognitive decline and as a cause of dementia is thus unclear. More well-designed and larger studies are needed to further clarify the link between dyslipidemia and cognition.

Smoking

Tobacco use is one of many modifiable lifestyle factors associated with several negative health outcomes [91]. This behavioral risk factor has been associated with increased risks of accelerated cognitive decline, incidence of MCI, and Alzheimer's disease [92, 93]. A meta-analysis has shown that current smokers, relative to non-smokers, have a 79% increased risk of Alzheimer's dementia [94•]. Smoking is associated with increased oxidative stress, low-grade inflammation which leads to more white matter lesions, cerebral hypoperfusion, and accelerated cerebral atrophy, ultimately resulting in cognitive decline [95]. The mechanisms and degree of association are not completely understood and often debated [96]. Many studies that have not been successful in assessing the relationship between smoking and cognition are studies that included individuals over the age of 60 [97•]. The finding that smokers have been shown to have lower rates of cognitive impairment than non-smokers, could be attributable to survival bias. That is, older participants are generally more likely to experience issues with cognition and are less likely to be smokers because smokers have a decreased likelihood of surviving into old age [98].

Most of the recent literature shows that there is a dose-response association—those who smoke—and for a lengthy time period, have declining cognitive abilities compared with those who never smoked. To fully understand the relationship between smoking and cognitive abilities, several studies have been conducted to include younger (under the age of 60) populations [97•]. A cross-sectional study assessed midlife changes in cognitive abilities of 3035 individuals until they reached the age of 53 [97•]. Individuals in this cohort who smoked more than 20 cigarettes per day experienced significantly lower scores in domains of cognitive flexibility and psychomotor speeds. Because smoking tobacco has been previously identified as a strong risk factor for vascular disease, and vascular disease is often associated with dementia and other cognitive diseases, this potential mechanism continues to draw interest from researchers [99•].

Diet

Studies have shown positive effects of dietary patterns such as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), and antiinflammatory diets on cognitive health [100]. These dietary patterns generally emphasize plant-based, rich in poly-unsaturated fatty acids and lower consumption of processed foods. The most well-known is the MIND, which has been associated with a reduced risk of memory complaints and dementia [101•]. The MIND diet has ten brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). The Mediterranean part of the MIND diet has been associated with increased total brain volume, total grey matter volume, total white matter volume, and mean cortical thickness [102••]. Morris et al. compared the Mediterranean, DASH, and MIND diets and the onset of Alzheimer's disease and found all diets slowed the rate of Alzheimer's disease onset over the course of an average of 4.5 years, but the MIND diet most effectively reduced this rate [103]. On the other hand a "western diet" pattern of red meat and sausages has been associated with a smaller left hippocampal volume [104].

Many of these healthy diets for cognition contain high levels of nutrients such as vitamin C, flavonoids, tyrosine, and unsaturated lipids like omega-3 polyunsaturated fatty acids (n-3 PUFA) that have been positively associated with cognition by promoting hippocampal neurogenesis, cognitive function and plasticity during aging via the gut-brain axis [102••]. More recently, the Maine-Syracuse Longitudinal Study found an association between sugar-sweetened soft drink consumption in DM patients and decreased cognitive function but found no significant decrease with artificially sweetened beverages [105]. Research has moved to understanding the effect of whole diets rather than specific nutrients and supplements as they may interact in unclear ways [106•]. More randomized trials and longitudinal studies will help explain further the association of different diets with cognition.

Physical Activity

Aerobic and non-aerobic, acute and long-term physical activities are among the lifestyle factors that are positively correlated with connectivity of different parts of the brain [107–109]. Increasing physical activity is known to have favorable implications on cognitive abilities and functionality for all individuals, including children, healthy mid-aged adults, and older adults [108, 110•]. Exercise and physical activity has also been associated

with cognitive improvement for individuals with MCI [111]. The domains of cognitive improvement associated with physical activities include attention, processing speed, and working memory [112, 113•].

Though brain atrophy is often considered the norm among aging populations, preservation of brain functionality while aging is more likely for those who have maintained a consistent physically active lifestyle. However, several studies have shown that even acute physical activity and exercises have positive short-term alterations on cognition [114]. In a randomized controlled trial evaluating differing intensities of physical activity and cognitive response, those who performed moderately intense exercise had higher scores on the cognition tests than those who did not exercise [115]. In another study, individuals' cognitive performance improved after cycling, however, more fit individuals had longer cognitive improvement post-workout [114]. In another RCT, individuals with 378 MCI who participated in aerobic exercises showed more improvement in their cognitive assessment compared with those who participated in a health education seminar [111]. Though the neurophysiological mechanisms of acute and long-term physical activities' relationship with brain health and cognition have been researched, the degree and moderators of these mechanisms should be further explored [116]. Currently, most individuals in US are not meeting the scientifically recommended levels of physical activity. Therefore, public health measures are needed to motivate individuals to improve their levels of physical activity, and thus their neural efficiency and brain health.

Obesity

A higher body mass index (BMI) negatively affects brain structure and cognition [117]. Obesity is independently associated with reduced gray matter volumes and poor performance in measures of executive function that may subsequently affect cognition [118]. Obesity is also related to several other health conditions such as DM and hypertension and could exert a negative effect on cognition. Although studies demonstrate an association between obesity and cognitive decline, there remains inconsistency in the findings, likely from differences in methodology, type of cognitive measures used, and whether important covariates such as other CVDRF were considered. In the Cardiovascular Health Study, participants with high BMI in midlife had a significantly higher risk of dementia, but obesity in later life was protective against dementia [119•]. These findings suggest that a low BMI in elderly life is related to cognitive decline likely from frailty and poor nutrition [120•]. Thus, the association of obesity and

Table 2 Cardiovascular health (CVH) factors and association with cognition

CVH metric	Levels	Definition	Association with cognition
Total cholesterol	Ideal	< 200 mg/dL, without lipid lowering medication	++, mostly mid- life, unclear benefit of treatment
	Intermediate	200–239 mg/dL or treated to < 200 mg/dL	
	Poor	≥ 240 mg/dL	
Blood pressure	Ideal	< 120/< 80 mmHg, without antihypertensive medication	+++, mostly mid- life, treatment likely beneficial
	Intermediate	SBP 120–139 or DBP 80–89 mmHg or treated with antihypertensive to < 120/< 80 mmHg	
	Poor	SBP ≥ 140 or DBP ≥ 90 mmHg	
Blood glucose	Ideal	< 100 mg/dL, without antidiabetes medication	++, mostly with non-Alzheimer's pathology
	Intermediate	100–125 mg/dL or treated with antidiabetes to < 100 mg/dL	
	Poor	≥ 126 mg/dL	
Physical activity	Ideal	4 or more times per week of intense physical activity	+++, dose- response, null studies likely affected by reverse causation
	Intermediate	1–3 times per week of intense physical activity	
	Poor	No physical activity	
Healthy diet	Ideal	4–5 components of Mediterranean diet	++, complexity of nutritional assessments
	Intermediate	2–3 components of Mediterranean diet	
	Poor	0–1 components of Mediterranean diet	
Smoking	Ideal	Never or quit > 12 months	++, dose- response, survival bias possible in negative studies
	Intermediate	Former, quit ≤ 12 months	
	Poor	Current	
Body mass index	Ideal	< 25 kg/m^2	+, non-linear, age-dependent
	Intermediate	25–29.99 kg/m^2	
	Poor	≥30 kg/m^2	

cognition appears to be age-dependent and likely non-linear. More studies are needed to understand optimal weight and biological mechanisms such as the role of circulating leptins [121•].

Association of Composite Measures of CVDRF and Cognition

Several CVDRF are independently associated with cognitive decline as discussed above (Table 2). Studies have also investigated the combined effect of these risk factors on cognition. A favorable CVH profile has ample evidence to prevent CVD but could have secondary benefits for protection against cognitive decline and dementia [122, 123•]. Prior studies that have examined composite measures of CVDRF such as the Framingham risk score have found higher risk scores to be associated with worse cognitive function, markers of cognitive aging such as smaller brain volume, and a predictor of progression of MCI to Alzheimer's [124••, 125•]. The Cardiovascular Risk factors, Aging, and Incidence of Dementia (CAIDE) risk score which was specifically developed to assess dementia risk, shares many of the same CVDRF as the other composite scores [126••]. The CVH profile particularly emphasizes modifiable CVDRF. It has been used in the Framingham Heart Study Offspring cohort where ideal levels of the metric had significant association with stroke, vascular dementia, frontal brain atrophy, and cognitive decline on tasks measuring visual memory and reasoning [127•]. This is the first study to demonstrate an association between ideal CVH and incident dementia. The Maine-Syracuse Longitudinal study also showed that a better CVH profile (particularly ideal levels of smoking, diet, and physical activity) was associated with superior neuropsychological performance across multiple cognitive domains such as visual-spatial memory, working memory, executive function, and a global composite score [128].

The association of overall CVH profile and cognition has been replicated in several ongoing cohort studies. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS), ideal levels of CVH were associated with lower incident neurocognitive impairment in both Blacks and Whites regardless of US region [129•]. The Hispanic Community Health Study (HCHS/SOL) extended this finding to a population of Hispanic/Latino adults [130] and also showed that the benefits appear to be consistent across multiple domains of neurocognitive health, including episodic learning and memory, verbal fluency, and psychomotor speed. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, a favorable CVH profile was similarly associated with better neurocognitive function in midlife [28•]. Similarly, in the ARIC study, higher midlife CVH scores were associated with better midlife cognition and reduced 20-year cognitive decline [31••]. In the Northern Manhattan Study, the number of ideal CVH factors was associated with less decline in the domains of processing speed, but had a weaker association with executive function and episodic memory [131•]. More recent data from a large population-based study has shown that a favorable CVH profile at a younger age is associated with lower risk of dementia in older ages [132]. Even in the more elderly population, CVH was clearly associated with incident dementia [34••]. However, some studies have provided inconsistent results with incident dementia likely from the complexity of the interactions and measurements of various CVDRF that are part of the CVH metric [133•]. Despite this, data on overall CVH and cognition remains robust.

Conclusions

The remarkable heterogeneity of Alzheimer's disease and other forms of dementia, lack of curative treatments, and high cost of managing the disease burden, highlight the urgent need for scaling up preventive measures [134•]. The relationship of CVD and dementia is complex but accumulating evidence implicates an important role of CVDRF in the pathogenesis of cognitive decline. Timely detection and control of CVDRF in primary care can thus have a significant public health impact in the control of both CVD and dementia epidemics. In this context, the AHA concept of ideal CVH could be critical for promoting not just heart health but brain health as well. The focus of CVH is on modifiable health factors and behaviors; increasing education and improving motivation in different population subgroups can decrease the risk of cognitive decline later in life. Studies discussed in this review highlight that incorporating cardioprotective strategies particularly in early and midlife can improve patient's CVH profile long-term and help safeguard cognitive health. Further understanding the role of CVH and cognitive decline could have an important role in developing effective population strategies and addressing health disparities in aging populations. Few such measures include further taxation on tobacco products, education about salt reduction, emphasis on MIND diet, and more opportunities for young and old to increase physical activity. The CVH-cognition link also highlights the need for effective multimodal interventions that can target multiple pathophysiological pathways at the same time. More research is required in identifying common and disparate relationships of CVDRF and cognition, understanding genetics and biological pathways, which would in turn lead to targeted interventions in reducing cognitive decline in aging populations.

Compliance With Ethical Standards

Conflict of Interest Ambar Kulshreshtha was supported by grant from the Alzheimer's Association, AACSFD-17- 533468. Alvaro Alonso was

supported by NIH grant U01HL096902 and American Heart Association grant 16EIA26410001. Jannat Saini and Taylor German each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013;9(1):63–75 e2. https://doi.org/10.1016/j.jalz.2012.11.007 **A large systematic review and meta-analysis regarding the global prevalence of dementia (recent).**

2. Leritz EC, McGlinchey RE, Kellison I, Rudolph JL, Milberg WP. Cardiovascular disease risk factors and cognition in the elderly. Curr Cardiovasc Risk Rep. 2011;5(5):407–12. https://doi.org/10.1007/s12170-011-0189-x.

3.• Stampfer MJ. Cardiovascular disease and Alzheimer's disease: common links. J Intern Med. 2006;260(3):211–23. https://doi.org/10.1111/j.1365-2796.2006.01687.x **Common links between cardiovascular disease and Alzheimer's published in a journal with high impact factor.**

4.• Santos CY, Snyder PJ, Wu WC, Zhang M, Echeverria A, Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: a review and synthesis. Alzheimers Dement (Amst). 2017;7:69–87. https://doi.org/10.1016/j.dadm.2017.01.005 **Review of pathophysiologic relationship between Alzheimer's and cerebrovascular disease listing cardiovascular risks.**

5. Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. Eur Heart J. 2009;30(9):1046–56. https://doi.org/10.1093/eurheartj/ehn554.

6. Bennett K, Kabir Z, Unal B, Shelley E, Critchley J, Perry I, et al. Explaining the recent decrease in coronary heart disease mortality rates in Ireland, 1985-2000. J Epidemiol Community Health. 2006;60(4):322–7. https://doi.org/10.1136/jech.2005.038638.

7. Capewell S, Ford ES, Croft JB, Critchley JA, Greenlund KJ, Labarthe DR. Cardiovascular risk factor trends and potential for reducing coronary heart disease mortality in the United States of America. Bull World Health Organ. 2010;88(2):120–30. https://doi.org/10.2471/BLT.08.057885.

8.• Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011;10(9):819–28. https://doi.org/10.1016/S1474-4422(11)70072-2 **Study in a high impact factor respected journal stating the effect of reducing risk factors on Alzheimer's prevalence.**

9.• Rose G. Sick individuals and sick populations. Int J Epidemiol. 2001;30(3):427–32 discussion 33–4. **Discussion published in a respected journal**.

10. Crous-Bou M, Minguillon C, Gramunt N, Molinuevo JL. Alzheimer's disease prevention: from risk factors to early intervention. Alzheimers Res Ther. 2017;9(1):71. https://doi.org/10.1186/s13195-017-0297-z.

11.•• Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010;121(4):586–613. https://doi.org/10.1161/CIRCULATIONAHA.109.192703 **American Heart Association Impact Goal through 2020 and the future regarding cardiovascular disease reduction and health promotion.**

12.• Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146–603. https://doi.org/10.1161/CIR.0000000000000485 **Recently published statistics on stroke from American Heart Association.**

13. Willcox BJ, He Q, Chen R, Yano K, Masaki KH, Grove JS, et al. Midlife risk factors and healthy survival in men. JAMA. 2006;296(19):2343–50. https://doi.org/10.1001/jama.296.19.2343.

14.• Folsom AR, Yatsuya H, Nettleton JA, Lutsey PL, Cushman M, Rosamond WD, et al. Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence. J Am Coll Cardiol. 2011;57(16):1690–6. https://doi.org/10.1016/j.jacc.2010.11.041 **Prevalence of ideal cardiovascular health, going by the American Heart Association definition.**

15.• Yang Q, Cogswell ME, Flanders WD, Hong Y, Zhang Z, Loustalot F, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. JAMA. 2012;307(12):1273–83. https://doi.org/10.1001/jama.2012.339 **Publication listing trends in cardiovascular health metrics and associations with all-cause and CVD mortality.**

16. Schievink SHJ, van Boxtel MPJ, Deckers K, van Oostenbrugge RJ, Verhey FRJ, Kohler S. Cognitive changes in prevalent and incident cardiovascular disease: a 12-year follow-up in the Maastricht Aging Study (MAAS). Eur Heart J. 2017. https://doi.org/10.1093/eurheartj/ehx365.

17. An J, Li H, Tang Z, Zheng D, Guo J, Liu Y, et al. Cognitive impairment and risk of all-cause and cardiovascular disease mortality over 20-year follow-up: results from the BLSA. J Am Heart Assoc. 2018;7(15):e008252. https://doi.org/10.1161/JAHA.117.008252.

18. Angermann CE, Frey A, Ertl G. Cognition matters in cardiovascular disease and heart failure. Eur Heart J. 2012;33(14):1721–3. https://doi.org/10.1093/eurheartj/ehs128.

19. Haring B, Leng X, Robinson J, Johnson KC, Jackson RD, Beyth R, et al. Cardiovascular disease and cognitive decline in postmenopausal women: results from the Women's Health Initiative Memory Study. J Am Heart Assoc. 2013;2(6):e000369. https://doi.org/10.1161/JAHA.113.000369.

20. Stephan BCM, Harrison SL, Keage HAD, Babateen A, Robinson L, Siervo M. Cardiovascular disease, the nitric oxide pathway and risk of cognitive impairment and dementia. Curr Cardiol Rep. 2017;19(9):87. https://doi.org/10.1007/s11886-017-0898-y.

21. Duschek S, Schandry R. Reduced brain perfusion and cognitive performance due to constitutional hypotension. Clin Auton Res. 2007;17(2):69–76. https://doi.org/10.1007/s10286-006-0379-7.

22. Aichele S, Rabbitt P, Ghisletta P. Cardiovascular symptoms and longitudinal declines in processing speed differentially predict cerebral white matter lesions in older adults. Arch Gerontol Geriatr. 2018;78:139–49. https://doi.org/10.1016/j.archger.2018.06.010.

23. Mahinrad S, Vriend AE, Jukema JW, van Heemst D, Sattar N, Blauw GJ, et al. Left ventricular hypertrophy and cognitive decline in old age. J Alzheimers Dis. 2017;58(1):275–83. https://doi.org/10.3233/JAD-161150.

24.• Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, et al. Prevalence of mild cognitive impairment is higher in men. The Mayo Clinic Study of Aging. Neurology. 2010;75(10):889–97. https://doi.org/10.1212/WNL.0b013e3181f11d85 **sex-based differences of mild cognitive impairment prevalence.**

25. Arntzen KA, Schirmer H, Wilsgaard T, Mathiesen EB. Impact of cardiovascular risk factors on cognitive function: the Tromso study. Eur J Neurol. 2011;18(5):737–43. https://doi.org/10.1111/j.1468-1331.2010.03263.x.

26. Kaffashian S, Dugravot A, Nabi H, Batty GD, Brunner E, Kivimaki M, et al. Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. Eur Heart J. 2011;32(18):2326–32. https://doi.org/10.1093/eurheartj/ehr133.

27.• Kaffashian S, Dugravot A, Brunner EJ, Sabia S, Ankri J, Kivimaki M, et al. Midlife stroke risk and cognitive decline: a 10-year follow-up of the Whitehall II cohort study. Alzheimers Dement. 2013;9(5):572–9. https://doi.org/10.1016/j.jalz.2012.07.001 **Ten-year follow up of landmark Whitehall II cohort trial.**

28.• Reis JP, Loria CM, Launer LJ, Sidney S, Liu K, Jacobs DR Jr, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. Ann Neurol. 2013;73(2):170–9. https://doi.org/10.1002/ana.23836 **Cardiovascular health in young adulthood and midlife cognitive functioning links.**

29. Weinstein G, Lutski M, Goldbourt U, Tanne D. C-reactive protein is related to future cognitive impairment and decline in elderly individuals with cardiovascular disease. Arch Gerontol Geriatr. 2017;69:31–7. https://doi.org/10.1016/j.archger.2016.11.002.

30. Bleckwenn M, Kleineidam L, Wagner M, Jessen F, Weyerer S, Werle J, et al. Impact of coronary heart disease on cognitive decline in Alzheimer's disease: a prospective longitudinal cohort study in primary care. Br J Gen Pract. 2017;67(655):e111–e7. https://doi.org/10.3399/bjgp16X688813.

31.•• Gonzalez HM, Tarraf W, Harrison K, Windham BG, Tingle J, Alonso A, et al. Midlife cardiovascular health and 20-year cognitive decline: atherosclerosis risk in communities study results. Alzheimers Dement. 2018;14(5):579–89. https://doi.org/10.1016/j.jalz.2017.11.002 **landmark trial**.

32. Gonzales MM, Ajilore O, Charlton RC, Cohen J, Yang S, Sieg E, et al. Divergent influences of cardiovascular disease risk factor domains on cognition and gray and white matter morphology. Psychosom Med. 2017;79(5):541–8. https://doi.org/10.1097/PSY.0000000000000448.

33.• Leng X, Espeland MA, Manson JE, Stefanick ML, Gower EW, Hayden KM, et al. Cognitive function and changes in cognitive function as predictors of incident cardiovascular disease: the Women's Health Initiative Memory Study. J Gerontol A Biol Sci Med Sci. 2018;73(6):779–85. https://doi.org/10.1093/gerona/glx138 **Landmark study results—predictors of incident cardiovascular disease in women.**

34.•• Samieri C, Perier MC, Gaye B, Proust-Lima C, Helmer C, Dartigues JF, et al. Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA. 2018;320(7):657–64. https://doi.org/10.1001/jama.2018.11499 **Recent study researching examining the association of cardiovascular health level in older age, with cognitive decline and dementia in a respected journal.**

35. Kontari P, Smith KJ. Risk of dementia associated with cardiometabolic abnormalities and depressive symptoms: a longitudinal cohort study using the English longitudinal study of ageing. Int J Geriatr Psychiatry. 2019;34(2):289–98. https://doi.org/10.1002/gps.5019.

36.• Nash DT, Fillit H. Cardiovascular disease risk factors and cognitive impairment. Am J Cardiol. 2006;97(8):1262–5. https://doi.org/10.1016/j.amjcard.2005.12.031 **Publication in respected journal noting cardiovascular disease risk factors and cognitive impairment.**

37. Justin BN, Turek M, Hakim AM. Heart disease as a risk factor for dementia. Clin Epidemiol. 2013;5:135–45. https://doi.org/10.2147/CLEP.S30621.

38. Ettorre E, Cerra E, Marigliano B, Vigliotta M, Vulcano A, Fossati C, et al. Role of cardiovascular risk factors (CRF) in the patients with mild cognitive impairment (MCI). Arch Gerontol Geriatr. 2012;54(2):330–2. https://doi.org/10.1016/j.archger.2011.04.025.

39. de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC Med. 2015;13:132. https://doi.org/10.1186/s12916-015-0377-5.

40.•• Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. Hypertension. 2016;68(6):e67–94. https://doi.org/10.1161/HYP.0000000000000053 **Recent statement from the American Heart Association on the impact of high blood pressure on cognitive function.**

41. Staessen JA, Richart T, Birkenhager WH. Less atherosclerosis and lower blood pressure for a meaningful life perspective with more brain. Hypertension. 2007;49(3):389–400. https://doi.org/10.1161/01.HYP.0000258151.00728.d8.

42.• Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM, et al. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke. 2003;34(5):1126–9. https://doi.org/10.1161/01.STR.0000068408.82115.D2 **Rotterdam Scan Study results on physiologic factors increasing stroke risk in general population.**

43. Nagai M, Hoshide S, Kario K. Hypertension and dementia. Am J Hypertens. 2010;23(2):116–24. https://doi.org/10.1038/ajh.2009.212.

44.•• Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhager WH, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet. 1997;350(9080):757–64 **Landmark randomized double-blinded trial in Europe comparing placebo and active treatment for older patients with isolated systolic hypertension.**

45. Ciobica A, Padurariu M, Bild W, Stefanescu C. Cardiovascular risk factors as potential markers for mild cognitive impairment and Alzheimer's disease. Psychiatr Danub. 2011;23(4):340–6.

46. Bomboi G, Castello L, Cosentino F, Giubilei F, Orzi F, Volpe M. Alzheimer's disease and endothelial dysfunction. Neurol Sci. 2010;31(1):1–8. https://doi.org/10.1007/s10072-009-0151-6.

47. Lee BC, Mintun M, Buckner RL, Morris JC. Imaging of Alzheimer's disease. J Neuroimaging. 2003;13(3):199–214.

48. Vicario A, Martinez CD, Baretto D, Diaz Casale A, Nicolosi L. Hypertension and cognitive decline: impact on executive function. J Clin Hypertens (Greenwich). 2005;7(10):598–604.

49.• Shah NS, Vidal JS, Masaki K, Petrovitch H, Ross GW, Tilley C, et al. Midlife blood pressure, plasma beta-amyloid, and the risk for Alzheimer disease: the Honolulu Asia Aging Study. Hypertension. 2012;59(4):780–6. https://doi.org/10.1161/HYPERTENSIONAHA.111.178962 **Landmark trial on midlife hypertension and the risk for Alzheimer's disease.**

50.• Arvanitakis Z, Capuano AW, Lamar M, Shah RC, Barnes LL, Bennett DA, et al. Late-life blood pressure association with cerebrovascular and Alzheimer disease pathology. Neurology. 2018;91(6):e517–e25. https://doi.org/10.1212/WNL.0000000000005951 **Recent publication on late-life**

hypertension and link with cerebrovascular and Alzheimer's disease pathology.

51.• Tsivgoulis G, Alexandrov AV, Wadley VG, Unverzagt FW, Go RC, Moy CS, et al. Association of higher diastolic blood pressure levels with cognitive impairment. Neurology. 2009;73(8):589–95. https://doi.org/10.1212/WNL.0b013e3181b38969 **Research linking higher diastolic blood pressure levels with cognitive impairment.**

52.•• Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001;56(1):42–8 **Publication in journal with high impact factor listing risk factors for cardiovascular disease and cognitive decline in middle-aged adults.**

53. Fogari R, Mugellini A, Zoppi A, Lazzari P, Destro M, Rinaldi A, et al. Effect of telmisartan/hydrochlorothiazide vs lisinopril/hydrochlorothiazide combination on ambulatory blood pressure and cognitive function in elderly hypertensive patients. J Hum Hypertens. 2006;20(3):177–85. https://doi.org/10.1038/sj.jhh.1001964.

54. Hoffman LB, Schmeidler J, Lesser GT, Beeri MS, Purohit DP, Grossman HT, et al. Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons. Neurology. 2009;72(20):1720–6. https://doi.org/10.1212/01.wnl.0000345881.82856.d5.

55.•• Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358(18):1887–98. https://doi.org/10.1056/NEJMoa0801369 **Respected journal stating treatment of high blood pressure in older adults.**

56. Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, et al. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension. 2010;56(2):196–202. https://doi.org/10.1161/HYPERTENSIONAHA.109.146035.

57. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the systolic hypertension in Europe (Syst-Eur) study. Arch Intern Med. 2002;162(18):2046–52.

58.•• Group SMIftSR, Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, et al. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. JAMA. 2019;321(6):553–61. https://doi.org/10.1001/jama.2018.21442 **Landmark trial researching the effect of intensive versus standard blood pressure levels on dementia.**

59.• Mossello E, Pieraccioli M, Nesti N, Bulgaresi M, Lorenzi C, Caleri V, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015;175(4):578–85. https://doi.org/10.1001/jamainternmed.2014.8164 **Trial looking at the effects of low blood pressure in elderly patients with cognitive impairment, treated with blood pressure lowering drugs.**

60. Mayeda ER, Whitmer RA, Yaffe K. Diabetes and cognition. Clin Geriatr Med. 2015;31(1):101–15, **ix**. https://doi.org/10.1016/j.cger.2014.08.021.

61. Zhou H, Yang J, Xie P, Dong Y, You Y, Liu J. Cerebral microbleeds, cognitive impairment, and MRI in patients with diabetes mellitus. Clin Chim Acta. 2017;470:14–9. https://doi.org/10.1016/j.cca.2017.04.019.

62.• Biessels GJ, Strachan MW, Visseren FL, Kappelle LJ, Whitmer RA. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol. 2014;2(3):246–55. https://doi.org/10.1016/S2213-8587(13)70088-3 **Recent research linking dementia and cognitive decline in patients with type 2 diabetes and prediabetes.**

63. Stranahan AM. Models and mechanisms for hippocampal dysfunction in obesity and diabetes. Neuroscience. 2015;309:125–39. https://doi.org/10.1016/j.neuroscience.2015.04.045.

64. Chatterjee S, Peters SA, Woodward M, Mejia Arango S, Batty GD, Beckett N, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care. 2016;39(2):300–7. https://doi.org/10.2337/dc15-1588.

65.• Yaffe K, Weston AL, Blackwell T, Krueger KA. The metabolic syndrome and development of cognitive impairment among older women. Arch Neurol. 2009;66(3):324–8. https://doi.org/10.1001/archneurol.2008.566 **Women's health—researching cognitive impairment and metabolic syndrome in older adult women.**

66. Christman AL, Vannorsdall TD, Pearlson GD, Hill-Briggs F, Schretlen DJ. Cranial volume, mild cognitive deficits, and functional limitations associated with diabetes in a community sample. Arch Clin Neuropsychol. 2010;25(1):49–59. https://doi.org/10.1093/arclin/acp091.

67. Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. Biochim Biophys Acta. 2014;1842(9):1693–706. https://doi.org/10.1016/j.bbadis.2014.06.010.

68. Reijmer YD, Brundel M, de Bresser J, Kappelle LJ, Leemans A, Biessels GJ, et al. Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: a diffusion tensor imaging study. Diabetes Care. 2013;36(1):137–44. https://doi.org/10.2337/dc12-0493.

69. Silzer T, Barber R, Sun J, Pathak G, Johnson L, O'Bryant S, et al. Circulating mitochondrial DNA: new indices of type 2 diabetes-related cognitive impairment in Mexican Americans. PLoS One. 2019;14(3):e0213527. https://doi.org/10.1371/journal.pone.0213527.

70.• Abner EL, Nelson PT, Kryscio RJ, Schmitt FA, Fardo DW, Woltjer RL, et al. Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. Alzheimers Dement. 2016;12(8):882–9. https://doi.org/10.1016/j.jalz.2015.12.006 **Respected journal research into the association of diabetes with cerebrovascular disease and dementia finds no link with Alzheimer's disease neuropathology.**

71. Ho N, Sommers MS, Lucki I. Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. Neurosci Biobehav Rev. 2013;37(8):1346–62. https://doi.org/10.1016/j.neubiorev.2013.03.010.

72.• Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, Baertlein L, et al. Association of diabetes with amnestic and nonamnestic mild cognitive impairment. Alzheimers Dement. 2014;10(1):18–26. https://doi.org/10.1016/j.jalz.2013.01.001 **Respected journal looking at the association of diabetes with mild cognitive impairment.**

73. Palta P, Carlson MC, Crum RM, Colantuoni E, Sharrett AR, Yasar S, et al. Diabetes and cognitive decline in older adults: the Ginkgo Evaluation of Memory study. J Gerontol A Biol Sci Med Sci. 2017;73(1):123–30. https://doi.org/10.1093/gerona/glx076.

74.• Bancks MP, Carnethon MR, Jacobs DR Jr, Launer LJ, Reis JP, Schreiner PJ, et al. Fasting glucose variability in young adulthood and cognitive function in middle age: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Diabetes Care. 2018;41(12):2579–85. https://doi.org/10.2337/dc18-1287 **Landmark study on fasting glucose variability in young adulthood and its impact on cognitive function in the middle age.**

75.•• Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. Lancet Neurol. 2011;10(11):969–77. https://doi.org/10.1016/S1474-4422(11)

70188-0 **Landmark trial looking at the effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes mellitus.**

76.• Murray AM, Hsu FC, Williamson JD, Bryan RN, Gerstein HC, Sullivan MD, et al. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. Diabetologia. 2017;60(1):69–80. https://doi.org/10.1007/s00125-016-4118-x **Landmark trial—extended results.**

77. Simo R, Ciudin A, Simo-Servat O, Hernandez C. Cognitive impairment and dementia: a new emerging complication of type 2 diabetes-the diabetologist's perspective. Acta Diabetol. 2017;54(5):417–24. https://doi.org/10.1007/s00592-017-0970-5.

78. Wood WG, Li L, Muller WE, Eckert GP. Cholesterol as a causative factor in Alzheimer's disease: a debatable hypothesis. J Neurochem. 2014;129(4):559–72. https://doi.org/10.1111/jnc.12637.

79. Puglielli L, Tanzi RE, Kovacs DM. Alzheimer's disease: the cholesterol connection. Nat Neurosci. 2003;6(4):345–51. https://doi.org/10.1038/nn0403-345.

80. Takeda JRT, Matos TM, de Souza-Talarico JN. Cardiovascular risk factors and cognitive performance in aging. Dement Neuropsychol. 2017;11(4):442–8. https://doi.org/10.1590/1980-57642016dn11-040015.

81.• Evans RM, Emsley CL, Gao S, Sahota A, Hall KS, Farlow MR, et al. Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. Neurology. 2000;54(1):240–2 **Population-based study in African Americans looking at the cardiovascular risk factors of Alzheimer's disease.**

82.• Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology. 2001;56(12):1683–9 **Population-based study researching midlife vascular risk factors affecting late-life mild cognitive impairment (respected journal).**

83. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord. 2009;28(1):75–80. https://doi.org/10.1159/000231980.

84. Refolo LM, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, Tint GS, et al. Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiol Dis. 2000;7(4):321–31. https://doi.org/10.1006/nbdi.2000.0304.

85.• Mielke MM, Zandi PP, Shao H, Waern M, Ostling S, Guo X, et al. The 32-year relationship between cholesterol and dementia from midlife to late life. Neurology. 2010;75(21):1888–95. https://doi.org/10.1212/WNL.0b013e3181feb2bf **Trial looking at the relationship of cholesterol and dementia from midlife to late life.**

86. Chakrabarti S, Khemka VK, Banerjee A, Chatterjee G, Ganguly A, Biswas A. Metabolic risk factors of sporadic Alzheimer's disease: implications in the pathology, pathogenesis and treatment. Aging Dis. 2015;6(4):282–99. https://doi.org/10.14336/AD.2014.002.

87.• Tan ZS, Seshadri S, Beiser A, Wilson PW, Kiel DP, Tocco M, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. Arch Intern Med. 2003;163(9):1053–7. https://doi.org/10.1001/archinte.163.9.1053 **Part of a landmark trial.**

88.• Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry. 2008;16(5):343–54. https://doi.org/10.1097/JGP.0b013e31816b72d4 **Respected journal, systematic review.**

89. Menezes AR, Lavie CJ, Milani RV, O'Keefe J. The effects of statins on prevention of stroke and dementia: a review. J Cardiopulm Rehabil Prev. 2012;32(5):240–9. https://doi.org/10.1097/HCR.0b013e31825d2a03.

90.• Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD. Use of statins and incidence of dementia and cognitive impairment without dementia in a cohort study. Neurology. 2008;71(5):344–50. https://doi.org/10.1212/01.wnl.0000319647.15752.7b **Cohort study examining statin use and incidence of dementia and cognitive impairment without dementia.**

91. Clare L, Wu YT, Teale JC, MacLeod C, Matthews F, Brayne C, et al. Potentially modifiable lifestyle factors, cognitive reserve, and cognitive function in later life: a cross-sectional study. PLoS Med. 2017;14(3):e1002259. https://doi.org/10.1371/journal.pmed.1002259.

92. Barnes DE, Haight TJ, Mehta KM, Carlson MC, Kuller LH, Tager IB. Secondhand smoke, vascular disease, and dementia incidence: findings from the cardiovascular health cognition study. Am J Epidemiol. 2010;171(3):292–302. https://doi.org/10.1093/aje/kwp376.

93. Elbejjani M, Auer R, Jacobs DR Jr, Haight T, Davatzikos C, Goff DC Jr, et al. Cigarette smoking and gray matter brain volumes in middle age adults: the CARDIA brain MRI sub-study. Transl Psychiatry. 2019;9(1):78. https://doi.org/10.1038/s41398-019-0401-1.

94.• Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. Am J Epidemiol. 2007;166(4):367–78. https://doi.org/10.1093/aje/kwm116 **Meta-analysis in respected journal examining smoking as a risk factor for dementia and cognitive decline.**

95. Almeida OP, Garrido GJ, Lautenschlager NT, Hulse GK, Jamrozik K, Flicker L. Smoking is associated with reduced cortical regional gray matter density in brain regions associated with incipient Alzheimer disease. Am J Geriatr Psychiatry. 2008;16(1):92–8. https://doi.org/10.1097/JGP.0b013e318157cad2.

96. Tsai HJ, Chang FK. Associations of exercise, nutritional status, and smoking with cognitive decline among older adults in Taiwan: results of a longitudinal population-based study. Arch Gerontol Geriatr. 2019;82:133–8. https://doi.org/10.1016/j.archger.2018.12.008.

97.• Richards M, Jarvis MJ, Thompson N, Wadsworth ME. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. Am J Public Health. 2003;93(6):994–8 **Prospective birth cohort study researching cigarette smoking and midlife cognitive decline.**

98. Momtaz YA, Ibrahim R, Hamid TA, Chai ST. Smoking and cognitive impairment among older persons in Malaysia. Am J Alzheimers Dis Other Dement. 2015;30(4):405–11. https://doi.org/10.1177/1533317514552318.

99.• Wingbermuhle R, Wen KX, Wolters FJ, Ikram MA, Bos D. Smoking, APOE genotype, and cognitive decline: the Rotterdam Study. J Alzheimers Dis. 2017;57(4):1191–5. https://doi.org/10.3233/JAD-170063 **Landmark study looking at cardiovascular risk factors for cognitive decline.**

100. Chen X, Maguire B, Brodaty H, O'Leary F. Dietary patterns and cognitive health in older adults: a systematic review. J Alzheimers Dis. 2019;67(2):583–619. https://doi.org/10.3233/JAD-180468.

101.• Adjibade M, Assmann KE, Julia C, Galan P, Hercberg S, Kesse-Guyot E. Prospective association between adherence to the MIND diet and subjective memory complaints in the French NutriNet-Sante cohort. J Neurol. 2019;266(4):942–52. https://doi.org/10.1007/s00415-019-09218-y **French prospective cohort study examining association between MIND diet adherence and memory complaints.**

102.•• Solfrizzi V, Custodero C, Lozupone M, Imbimbo BP, Valiani V, Agosti P, et al. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life

cognitive disorders: a systematic review. J Alzheimers Dis. 2017;59(3):815–49. https://doi.org/10.3233/JAD-170248 **Systematic review of the impact of nutrition on Alzheimer's disease and late-life cognitive disorders.**

103. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA, et al. MIND diet slows cognitive decline with aging. Alzheimers Dement. 2015;11(9):1015–22. https://doi.org/10.1016/j.jalz.2015.04.011.
104. Jacka FN, Cherbuin N, Anstey KJ, Sachdev P, Butterworth P. Western diet is associated with a smaller hippocampus: a longitudinal investigation. BMC Med. 2015;13:215. https://doi.org/10.1186/s12916-015-0461-x.
105. Crichton GE, Elias MF, Torres RV. Sugar-sweetened soft drinks are associated with poorer cognitive function in individuals with type 2 diabetes: the Maine-Syracuse Longitudinal Study. Br J Nutr. 2016;115(8):1397–405. https://doi.org/10.1017/S0007114516000325.
106.• Frisardi V, Panza F, Seripa D, Imbimbo BP, Vendemiale G, Pilotto A, et al. Nutraceutical properties of Mediterranean diet and cognitive decline: possible underlying mechanisms. J Alzheimers Dis. 2010;22(3):715–40. https://doi.org/10.3233/JAD-2010-100942 **Publication reviewing possible underlying mechanisms linking diet and cognitive decline.**
107. Boraxbekk CJ, Salami A, Wahlin A, Nyberg L. Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network-a multimodal approach. Neuroimage. 2016;131:133–41. https://doi.org/10.1016/j.neuroimage.2015.12.010.
108. Tomporowski PD, Davis CL, Miller PH, Naglieri JA. Exercise and children's intelligence, cognition, and academic achievement. Educ Psychol Rev. 2008;20(2):111–31. https://doi.org/10.1007/s10648-007-9057-0.
109. Erickson KIHC, Kramer AF. Physical activity, brain, and cognition. Curr Opin Behav Sci. 2015;4:27–32. https://doi.org/10.1016/j.cobeha.2015.01.005.
110.• Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. Neuroimage. 2016;131:81–90. https://doi.org/10.1016/j.neuroimage.2015.09.071 **Systematic review, fitness and activity links with cognition and aging.**
111. Song D, Yu DSF. Effects of a moderate-intensity aerobic exercise programme on the cognitive function and quality of life of community-dwelling elderly people with mild cognitive impairment: a randomised controlled trial. Int J Nurs Stud. 2019;93:97–105. https://doi.org/10.1016/j.ijnurstu.2019.02.019.
112. Hsieh SS, Chang YK, Hung TM, Fang CL. The effects of acute resistance exercise on young and older males' working memory. Psychol Sport Exerc. 2016;22:286–93.
113.• Brunt A, Albines D, Hopkins-Rosseel D. The effectiveness of exercise on cognitive performance in individuals with known vascular disease: a systematic review. J Clin Med. 2019;8(3):E294. https://doi.org/10.3390/jcm8030294 **Systematic review of effectiveness of exercise on cognitive performance in people with vascular disease.**
114. Chang YK, Chi L, Etnier JL, Wang CC, Chu CH, Zhou C. Effect of acute aerobic exercise on cognitive performance: role of cardiovascular fitness. Psychol Sport Exerc. 2014;15:464–70.
115. Loprinzi PD, Kane CJ. Exercise and cognitive function: a randomized controlled trial examining acute exercise and free-living physical activity and sedentary effects. Mayo Clin Proc. 2015;90(4):450–60. https://doi.org/10.1016/j.mayocp.2014.12.023.
116. Booth JN, Leary SD, Joinson C, Ness AR, Tomporowski PD, Boyle JM, et al. Associations between objectively measured physical activity and academic attainment in adolescents from a UK cohort. Br J Sports Med. 2014;48(3):265–70. https://doi.org/10.1136/bjsports-2013-092334.
117. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes Rev. 2008;9(3):204–18. https://doi.org/10.1111/j.1467-789X.2008.00473.x.
118. Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. Hum Brain Mapp. 2010;31(7):1052–64. https://doi.org/10.1002/hbm.20916.
119.• Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol. 2009;66(3):336–42. https://doi.org/10.1001/archneurol.2008.582 **Cardiovascular health study examining midlife and late life obesity links with dementia risk.**
120.• Curtis JP, Selter JG, Wang Y, Rathore SS, Jovin IS, Jadbabaie F, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med. 2005;165(1):55–61. https://doi.org/10.1001/archinte.165.1.55 **Publication researching body mass index and outcomes in patients with heart failure.**
121.• Lieb W, Beiser AS, Vasan RS, Tan ZS, Au R, Harris TB, et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA. 2009;302(23):2565–72. https://doi.org/10.1001/jama.2009.1836 **Respected journal, physiological associations of cardiovascular disease markers with Alzheimer's disease and MRI measures of brain aging.**
122. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: a population-based perspective. Alzheimers Dement. 2015;11(6):718–26. https://doi.org/10.1016/j.jalz.2015.05.016.
123.• Daviglus ML, Plassman BL, Pirzada A, Bell CC, Bowen PE, Burke JR, et al. Risk factors and preventive interventions for Alzheimer disease: state of the science. Arch Neurol. 2011;68(9):1185–90. https://doi.org/10.1001/archneurol.2011.100 **Risk factors and interventions to prevent Alzheimer's disease.**
124.•• Seshadri S, Wolf PA, Beiser A, Elias MF, Au R, Kase CS, et al. Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. Neurology. 2004;63(9):1591–9 **Landmark trial, respected journal.**
125.• Harrison SL, Ding J, Tang EY, Siervo M, Robinson L, Jagger C, et al. Cardiovascular disease risk models and longitudinal changes in cognition: a systematic review. PLoS One. 2014;9(12):e114431. https://doi.org/10.1371/journal.pone.0114431 **Systematic review of cardiovascular disease risk models and cognitive changes.**
126.•• Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol. 2006;5(9):735–41. https://doi.org/10.1016/S1474-4422(06)70537-3 **Longitudinal study looking at dementia risk prediction in 20 years in midlife.**
127.• Pase MP, Beiser A, Enserro D, Xanthakis V, Aparicio H, Satizabal CL, et al. Association of ideal cardiovascular health with vascular brain injury and incident dementia. Stroke. 2016;47(5):1201–6. https://doi.org/10.1161/STROKEAHA.115.012608 **Respected journal researching association of ideal cardiovascular health with brain injury and dementia.**
128. Crichton GE, Elias MF, Davey A, Alkerwi A. Cardiovascular health and cognitive function: the Maine-Syracuse Longitudinal Study. PLoS One. 2014;9(3):e89317. https://doi.org/10.1371/journal.pone.0089317.

129.• Thacker EL, Gillett SR, Wadley VG, Unverzagt FW, Judd SE, McClure LA, et al. The American Heart Association life's simple 7 and incident cognitive impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) study. J Am Heart Assoc. 2014;3(3):e000635. https://doi.org/10.1161/JAHA.113.000635 **Landmark study, respected journal.**

130. Gonzalez HM, Tarraf W, Gouskova N, Rodriguez CJ, Rundek T, Grober E, et al. Life's simple 7's cardiovascular health metrics are associated with Hispanic/Latino neurocognitive function: HCHS/SOL results. J Alzheimers Dis. 2016;53(3):955–65. https://doi.org/10.3233/JAD-151125.

131.• Gardener H, Wright CB, Dong C, Cheung K, DeRosa J, Nannery M, et al. Ideal cardiovascular health and cognitive aging in the Northern Manhattan Study. J Am Heart Assoc. 2016;5(3):e002731. https://doi.org/10.1161/JAHA.115.002731 **Respected journal, researching links between ideal cardiovascular health and cognitive aging.**

132. Vu TT, Zhao L, Liu L, Schiman C, Lloyd-Jones DM, Daviglus ML, et al. Favorable cardiovascular health at young and middle ages and dementia in older age-the CHA study. J Am Heart Assoc. 2019;8(1):e009730. https://doi.org/10.1161/JAHA.118.009730.

133.• Hessler JB, Ander KH, Bronner M, Etgen T, Forstl H, Poppert H, et al. Predicting dementia in primary care patients with a cardiovascular health metric: a prospective population-based study. BMC Neurol. 2016;16:116. https://doi.org/10.1186/s12883-016-0646-8 **Prospective study looking at the prediction of dementia in primary care patients using cardiovascular health metrics.**

134.• Larson EB, Yaffe K, Langa KM. New insights into the dementia epidemic. N Engl J Med. 2013;369(24):2275–7. https://doi.org/10.1056/NEJMp1311405 **Respected journal looking into new trends in dementia.**