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What have observational studies taught us about brain health? An exploration of select cardiovascular risks and cognitive function

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ABSTRACT

Observational research studies serve as the cornerstone for gathering evidence on risk factors and contributors to cognitive decline and impairment. The evidence can then be combined with data from preclinical studies and randomized controlled trials to ultimately inform the development of effective interventions and the content of guidance statements. Observational cohort designs on modifiable risk factors and brain health can be particularly beneficial for studying questions that are unethical or impractical for a clinical trial setting, associations with dementia which may develop over decades, and underrepresented populations typically not included in clinical trials. This chapter will review the major observational, epidemiologic studies pertaining to the traditional vascular risk factors – hypertension, diabetes mellitus, hypercholesterolemia, smoking, and physical inactivity – and how they may impact brain health.

Introduction

An important way to develop a greater understanding of vulnerabilities to brain health [1] is to prospectively follow large epidemiologic cohorts exposed to vascular risks to determine the full range of structural and cognitive changes associated with these risks and which of the intermediate phenotypes results in expression of clinical disease. While optimal brain health is often defined as the absence of cognitive impairment, stroke, and other brain diseases [1,2], for the purposes of this chapter, we chose cognitive function as the primary focus of brain health given the crucial role it plays in defining brain health, but acknowledge that other brain-related functions such as activities of daily living (ADL), instrumental ADL, psychiatric parameters of health such as depression and mood, and others may be important functions allied with brain health. This chapter will review the major observational, epidemiologic studies pertaining to the traditional vascular risk factors – hypertension, diabetes mellitus, hypercholesterolemia, smoking, and physical inactivity – and how they may impact brain health. We chose to study these factors as generally there is a substantial scientific literature base for these risks. Furthermore, they are practicable as they are measurable, monitorable, and modifiable [3]. While other risk factors, such as alcohol consumption and obesity, may negatively affect brain health, there has been a smaller body of published work in large prospective cohorts in relation to these factors.

Although clinical trials are considered the gold standard for demonstrating causality, observational data provide valuable information not always obtainable from trials. For many risk factors negatively impacting brain health over decades, treatment or intervention trials may not be feasible. Additionally, certain risk factors (such as smoking) cannot be ethically studied in randomized trials, and thus observational data is necessary to understand the impact of these risks. Finally, clinical trials tend to recruit less representative populations than community-based observational studies. Therefore, while the data on disease progression in observational studies need to be interpreted cautiously, given the potential for confounding by indication, they provide key complementary information to those results from randomized clinical trials.

Methods

For each subsection of this article, a search was performed of the relevant English literature using an up-to-date search strategy of

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reference databases and appropriate search terms. In addition to identifying articles reporting important cognitive outcomes, we also reviewed the manuscripts of the primary findings of the study and the study design. Because of the heterogeneity of the studies spanning several decades, rigid inclusion/exclusion criteria could not generally be applied. We did not use a data abstraction tool.

The following databases were searched: The MEDLINE (via Ovid), Embase (via Elsevier), and Web of Science – Science Citation Index Expanded and Emerging Sources Citation Index (via Clarivate). The following search terms were utilized: 'cognitive impairment' OR 'cognitive decline' OR 'cognitive function' OR 'hypertension OR 'hyperlipidemia' OR 'diabetes' OR 'smoking' OR 'physical activity." Our formal search yielded the following number of abstracts by topic of interest (abstract number in parenthesis): hypertension (4605), diabetes mellitus (7812), hyperlipidemia (434), smoking (2164), and physical activity (7880). After review of the search results and elimination of duplicate abstracts or abstracts not in English language format, by topical area the following number of abstracts served as the basis for this review article (abstract number in parenthesis): hypertension (28), diabetes mellitus (20), hypercholesterolemia (9), smoking (19), and sedentary lifestyle (16). Cohort and case-control studies were selected that included at least 250 participants.

Hypertension

Hypertension is considered to be the most important modifiable traditional cardiovascular risk as it is a highly prevalent disease affecting an estimated 122 million people in the United States [4] and 1.3 billion individuals worldwide [5], and plays a major role as a risk for cerebrovascular disease, cognitive impairment, and dementia. Hypertension's influence on brain health has been recognized since 1947 [6], and gained considerable attention in 1964, after a seminal case-control study was published showing that air traffic controllers and pilots with hypertension performed with reduced psychomotor speed [6]. A large body of evidence from several observational studies in the subsequent decades has shown a strong association between hypertension and a range of adverse outcomes including cognitive decline (worsening of cognitive function over years to decades, greater than would be expected due to age alone), mild cognitive impairment (MCI) (reduced cognitive function that does not impact daily functioning), and dementia (impairments in cognition with adverse impacts on daily functioning). When we refer to dementia in the context of this paper, we mean the severe stage of cognitive and functional decline, which occurs on a continuum of severity ranging from at-risk to mild to moderate and to severe (dementia). While the term dementia is non-specific, as it does not reflect mechanism of brain injury, it is still frequently used in the literature in large epidemiological studies as a classification term for outcomes.

Observational studies, particularly longitudinal studies which have followed participants across their lifespan, also have established a relationship between elevated blood pressures, particularly in mid-life, and impairment of different domains of cognitive function, including abstract reasoning (executive function), mental processing speed, and memory [7]. While a large body of epidemiologic data has illustrated the importance of hypertension in the development of stroke [8], it should be noted that the influence of elevated blood pressure (BP) on cognitive function appears to be independent of stroke. Similar inverse associations have been observed in studies where participants with incident stroke are excluded from analyses on cognition [9–11], though fewer studies have completely excluded subclinical stroke or cerebral small vessel disease (i.e. lacunar infarcts, microbleeds, white matter disease burden, and enlarged perivascular spaces), key mediators of the impact of hypertension on cognitive outcomes. Hypertension is hypothesized to affect brain health through a number of mechanisms that include accelerated arteriosclerosis, impairment of cerebrovascular autoregulation, and micro or small vessel damage [12].

The relationship between baseline BP levels and cognitive function later in life may differ across age groups. Although there is not a clear age cutoff at which the relationship between BP and cognitive function later in life reverses, there seems to be a gradual shift with age from high BP being a risk factor for cognitive impairment to high BP potentially helping to preserve cognitive function in the oldest old, ostensibly through maintaining adequate perfusion pressure [13].

Early life hypertension

The CARDIA (Coronary Artery Risk Development in Young Adults) study is among the few studies that has examined the relationship between BP and cognitive function in early adulthood, and has shown that hypertension, even at an early age, may be harmful to cognition. In this study, subjects with mean baseline age of 25 years and a higher burden of systolic blood pressure (SBP) over 25 years had worse performance on several cognitive tests in midlife in verbal memory, processing speed, and executive function domains [14]. A cross-sectional study using the CARDIA year 25 MRI data found that early adulthood elevations in SBP and diastolic blood pressure (DBP) were associated with abnormal white matter volume, white matter fractional anisotropy, and gray matter cerebral blood flow [15]. Similarly, data from the Study of Healthy Aging in African Americans (STAR) and Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) studies, which were harmonized longitudinal cohorts of racially and ethnically diverse adults aged 50 years and older from the San Francisco Bay area and Sacramento Valley in California, showed that in early adulthood (ages 30–40 years) hypertension was associated with smaller overall cerebral, cerebral gray matter, hippocampal, frontal cortex, and parietal cortex volumes as well as larger lateral ventricle and third ventricles, and lower white matter fractional anisotropy in later life (i.e., 50 years and older) [16].

Mid-life hypertension

More substantial evidence supports a longitudinal association between mid-life BP and cognitive function in late life than that between early adulthood and late life. Several studies have demonstrated cognitive impairment in participants over the age of 70 when BP is elevated in the fourth and/or fifth decades of life. The Honolulu-Asia Aging Study [17,18] (HAAS) measured cognition in 3734 Japanese-American men (with a mean age of 78) whose BP had been measured twenty-five years earlier. In an adjusted model, for every 10 mmHg increase in SBP in midlife, there was a 9 % increase in risk for poor cognitive function in late-life. In the Maine-Syracuse Longitudinal Study, greater baseline BP (increases of 10 mm Hg) was associated with worse cognitive performance and a decline in visualization up to 20 years later in an African-American and Caucasian population [7]. In the Framingham Study, higher midlife SBP and DBP (i.e., increases of 10 mm Hg) in participants without stroke correlated with worse performance in global cognition, attention, and memory functions [9]. In the National Heart, Lung, and Blood Institute (NHLBI) Twin study, higher midlife SBP was associated with steeper 10-year cognitive decline as well [19]. Hypertension in midlife (45–64 years of age) in the Atherosclerosis Risk in Communities (ARIC) study was associated with steeper 20-year cognitive decline in processing speed, verbal fluency, and global cognitive function, without similar associations with late-life hypertension, which was not associated with cognitive decline over the preceding 20 years [20].

Even prehypertension, previously considered as a SBP $<$140 mmHg, has been reported as a risk factor for cognitive decline. Prehypertension in middle-aged women in the Women's Health and Aging Project was associated with reduced processing speed and verbal memory a decade later [21]. The ELSA-Brasil cohort, a longitudinal study with 7063 participants in Brazil, showed an inverse association of prehypertension (SBP between 121 and 139 mm Hg or DBP between 81 and 89 mm Hg) with verbal fluency, as well as an inverse association of hypertension

with memory [22].

In other observational studies of hypertension in mid-life, hypertension and higher BP values (particularly SBP ≥140 mm Hg) were associated with a greater risk of late-life dementia, Alzheimer's disease, and vascular dementia. In the HAAS Study, there was an interaction between elevated midlife BP (particularly DBP) and decrease in plasma amyloid-β (Aβ) and an increase risk of late-life dementia [23]. Elevated SBP, defined as >140 mmHg in midlife was associated with a 1.77-times higher risk of dementia between age 71–93 [24]. In the Framingham Offspring cohort, midlife (mean age 55 years) SBP ≥140 mm Hg was associated with a 1.6-fold higher risk of dementia over 18 years of follow-up [25]. In the ARIC study, both midlife hypertension and pre-hypertension conferred a similar risk for dementia, at about a 40 % higher risk than among normotensive individuals [10].

Studies using neuroimaging as a surrogate measure for cognitive function have also demonstrated an association between mid-life BP and cognitive impairment or dementia. In the NHLBI Twin Study, mid-life SBP was associated with not only more white matter hyperintensities in late life, but also reduced cerebral volumes [19]. Greater BP was also associated with atrophy of the amygdala and the hippocampus, regions implicated in Alzheimer's disease [19]. The UK Biobank study with approximately 10,000 mid- to late-life participants likewise showed that hypertension was associated with decreased frontal and temporal cortical volumes, as well as subcortical thalamic, putamen, pallidum, hippocampus, and amygdala volumes [26]. In France, the longitudinal Epidemiology of Vascular Ageing study's EVA MRI cohort, which included 845 subjects undergoing MRI to evaluate severity of white matter intensities over a 4-year follow-up period, reported that higher BP was associated with a higher risk of having severe white matter hyperintensities (OR 2.9 [1.6–5.3] for SBP > 160 or DBP >95), and that the frequency of severe white matter hyperintensities was significantly higher when elevated BP was present at both baseline and at 4-year follow-up, compared with 4-year follow-up only [27].

Observational studies have shown different findings in relation to BP parameter (e.g., SBP, DBP, mean arterial pressure [MAP], and pulse pressure [PP]) and cognitive domain affected. For example, and in relation to BP and white matter integrity, higher SBP [28], DBP [29], and MAP[30] have all been associated with increased white matter disease burden in late life. However, PP was not significantly associated with white matter hyperintensities in the UK Biobank cohort study [31] or with dementia in the Honolulu-Asia Aging Study [24], but was associated with cognitive decline among APOE4 carriers in the Framingham Offspring Study. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a prospective national cohort of 22,164 Black and White Americans ≥45 years enrolled in 2003–2007 and followed through September 2015, faster rates of decline in global cognition were associated with higher PP, but not MAP [32]. With increasing age, significantly faster declines in global cognition over 8 years were also associated with higher SBP and lower DBP [32]. Additionally, SBP-related cognitive declines were greater in Blacks and men [32].

Late-life hypertension (>69 years)

Findings of cross-sectional, population-based studies in the elderly on the relationship between BP and cognitive function have varied greatly and can be challenging to interpret. Many of the early analyses have small sample sizes, short duration of follow-up, and high attrition (i.e., loss to follow-up) rates, particularly among the most cognitively impaired. Some studies do not account for important potential confounders such as age, sex, educational attainment, race or ethnicity, or level of BP control. Some studies do not have measurements of BP and instead rely on a diagnosis of hypertension or administration of antihypertensive treatment as the predictor variable. The outcome measures vary as well, ranging from clinical diagnoses of dementia to highly sensitive measures of mild cognitive function. Addressing these inconsistencies necessitates a careful exploration of the relationships between age, BP and cognitive function while controlling for potential confounders that may impact the association.

The Iowa 65+ study found higher rates of cognitive impairment associated with elevated DBP [33], but in a community-based UK cohort, SBP correlated negatively with cognitive function, and DBP showed no significant overall correlation [34]. And, in a community-based Swedish cohort of 1736 people aged 75–101 years, SBP of 160–179 mmHg conferred a lower risk of cognitive impairment [35]. Other cross-sectional studies have reported little or no association [36]. These findings mirror the opposing associations between BP and cardiovascular mortality noted in observational studies of the elderly [37].

Prospective longitudinal studies serve as the best means for investigating a causal relationship between BP and cognitive impairment. Given the potentially long lag period between the onset of hypertension as well as cognitive decline, cross-sectional studies may fail to detect an association. The Baltimore Longitudinal Study, a prospective study of community-dwelling volunteers initiated by the National Institute on Aging in 1958 which examined both cross-sectional and longitudinal relationships of BP, was among the earliest studies to report that elderly persons may be particularly vulnerable to negative effects of high BP on select tests of executive function, confrontation naming, and perceptuomotor speed [38]. With respect to longitudinal change in cognitive function, this study found that among individuals in mid-life (i.e., age 60 years) at baseline, those with higher SBP performed more poorly than those with lower SBP across all sessions on a test of confrontation naming [38]. In contrast, among elderly persons age 80 at baseline, those with higher SBP demonstrated longitudinal decline on tests of nonverbal memory and confrontation naming [38], suggesting that elderly persons may be most susceptible to cognitive decline with higher SBP over time. In almost all instances, significant linear relations of BP to cognitive function were qualified by nonlinear associations. Previous longitudinal studies had not noted interactions between age, BP, and cognitive decline in cohorts of similar (although not identical) elderly populations [39,40]. However, in these studies, nonlinear effects were not always assessed, there were less follow-up visits, and different cognitive tests were used. Additionally, measurement of both BP and cognitive function on >2 testing occasions in the Baltimore Longitudinal Study may have significantly strengthened measurement reliability and ability to track longitudinal covariation between BP and cognitive outcome.

Other longitudinal studies also offer conflicting findings. In the Women's Health Initiative Memory Study (WHIMS), over a 4.5-year period in women aged 65 years and older, hypertension and high BP at baseline were not independently associated with mild cognitive impairment or probable dementia (as assessed by a Modified Mini-Mental State Examination [MMSE]) [41]. It is possible that the MMSE was not sensitive enough to detect subtle cognitive impairment in a short follow-up period and in a relatively cognitively healthy cohort. The Duke Established Populations for Epidemiologic Studies of the Elderly found a U-shaped association in systolic (not diastolic) BP, although this association was not observed in Blacks, [42] and a linear association was reported in the Women's Health and Aging Study II, where women aged between 76 and 80 years with SBP≥160 mmHg or with PP ≥84 mmHg over a 9-year period showed five times higher incidence of impairment on the Trail Making Test (TMT), a measure of executive function, when compared to their control groups [43].

Oldest old

Few longitudinal studies have been published on BP and cognition in the oldest old. The Rotterdam and Leiden-85 longitudinal studies demonstrated an inverse association between high SBP and DBP at older ages (65–74 years), but not in mid-life (55–64 years), and worse cognitive function after 11 years of follow-up [44]. In a

population-based Swedish cohort with subjects 80 years of age and older, higher SBP was associated with better cognitive function at both baseline and longitudinally [45]. Lower SBP was associated with cognitive decline and dementia [45]. Both cognitive decline and blood pressure lowering were inversely associated with time to death, and may therefore be considered as potential expressions of the frailty of the oldest old. Even when time to death was considered, the alterations of SBP, adjusted for age, gender, ApoE4, S-homocysteine, and clinical hypertension, maintained their association with alterations in MMSE scores [45].

The aggregated data from these few observational studies suggests that, in the oldest old, higher BP may confer benefit with respect to cognitive performance, potentially due to supporting adequate cerebral perfusion. Local regulation of cerebral blood flow tightly regulates cerebral perfusion over a wide range of BP [13]. With older age, basal cerebral blood flow decreases, possibly caused by impaired cerebral autoregulation through arteriolosclerosis or endothelial dysfunction [13]. In the oldest old, greater BP may thus be beneficial to increase cerebral perfusion and maximize cognitive function.

In summary, based on a large body of evidence from observational studies, hypertension is a major modifiable risk factor for cognitive impairment and dementia. A pattern of consistently raised BP during earlier adulthood to mid-life followed by low BP levels in later life appears to negatively influence cognition (Table 1). The cognitive domains most affected by hypertension include executive function, attention, and motor speed. To better understand the discrepancies across all age groups, including older adults, further research is needed to explore the methodological and biological factors that influence these outcomes as well as the relationship of hypertension with race/ethnicity, age, sex, and other brain health risk factors. Finally, there are several more recently studied blood pressure parameters, such as blood pressure variability[46] and cumulative systolic blood pressure [47], which may play a role in conferring brain injury and contribute to cognitive and functional impairments, and require further study.

Diabetes mellitus

A growing body of evidence from observational studies consistently supports the role of diabetes as a risk for adverse cognitive outcomes. Several cross-sectional studies have reported an inverse association between diabetes and cognitive performance in older adults [48]. Among 2374 women aged 70–78 years in the Nurses' Health Study, participants with type 2 diabetes performed worse than those without diabetes on tests measuring general cognitive function, immediate and delayed verbal recall, and verbal fluency. Overall, women with diabetes were twice as likely to have a low score on the tests of cognitive function as

Table 1
Key observational studies of blood pressure and cognitive decline and dementia.

Author, Year	Study Name	Location	Exposure Life Stage/ Follow-up Period	Sample	BP Parameters Tested	Cognitive Testing/Diagnosis	Findings
Studies of Cognitive Decline/Change of Cognitive Score							
Elias et al., 1993	Framingham Study	Framingham, MA	Mid-life/14 years	1702 Caucasians	SBP and DBP	Weschler Adult Intelligence Scale, Weschler Memory Scale, and Multilingual Aphasia Examination	Higher SBP and DBP correlated with worse performance
Launer et al., 1995	Honolulu-Asia Aging Study (HAAS)	Honolulu, Hawaii	Mid-life/25 years	3734 Japanese men	SBP and DBP	100-point Cognitive Abilities Screening Instrument (CASI)	Higher SBP was associated with worse cognitive performance
Swan et al., 1998	National Heart, Lung, and Blood Institute (NHLBI) Twin	California, New England, and Indianapolis, IN	Mid-life/10 years	392 Caucasian male veterans	SBP	Mini-Mental State Examination, Digit Symbol Substitution Test, Benton Visual Retention Test, and Verbal Fluency Test	Higher SBP was associated with greater decline in performance
Elias et al., 2004	Maine-Syracuse Longitudinal Study	Maine, New York	Early and Mid-life/20 years	529 African-Americans and Caucasians	SBP, DBP, MAP	Wechsler Adult Intelligence Scale	Higher SBP, DBP, and MAP were associated reduced performance in both younger and older groups
Yaffe et al., 2014	CARDIA (Coronary Artery Risk Development in Young Adults)	Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA	Early Life/ 25 years	3381 African-Americans and Caucasians	Cumulative SBP and DBP	Digit Symbol Substitution Test, Stroop Test, and Rey Auditory Verbal Learning Test	Higher cumulative SBP and DBP and fasting blood glucose were associated with worse cognition on all tests
Gottesman et al., 2014	Atherosclerosis Risk in Communities (ARIC)	Washington County, Maryland, Forsyth County, North Carolina, Minneapolis, Minnesota, and Jackson, Mississippi	Mid-life/up to 20 years	13,476 African-Americans and Caucasians	SBP and DBP	Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), Word Fluency test (WFT), and the ARIC Neurocognitive Study	Higher SBP was associated with steeper 10-year decline in performance, particularly on DSST
Wallace et al., 1985	Iowa 65+ study	Iowa	Late-life (over 65 years)/1 year	3673 participants	SBP and DBP	Free-recall memory test	Iowa 65+ study
Studies on Dementia							
McGrath et al., 2017	Framingham Offspring	Framingham, MA	Mid- to late-life/8 years	1440 Caucasians	SBP	DSM-IV	SBP was associated with risk of incident dementia
Gottesman et al., 2017	Atherosclerosis Risk in Communities (ARIC)	Washington County, Maryland, Forsyth County, North Carolina, Minneapolis, Minnesota, and Jackson, Mississippi	Mid-life/25 years	15,744 Caucasians and African-Americans	SBP and DBP	ICD-9 code	Both midlife SBP and prehypertension conferred a higher risk for dementia

those without diabetes [48]. Longer duration of diabetes and recent lack of diabetes treatment were associated with worse performance [48]. In a Finnish elderly community cohort, abnormal glucose tolerance was associated with impaired cognitive function among these subjects [49].

Firm conclusions regarding the magnitude and importance of the relationship between diabetes and cognitive dysfunction can be difficult to make, as investigations often are prone to methodological weaknesses, including small sample size, heterogeneous populations, different batteries of cognitive tests and cognitive outcomes, and failure to control for major confounding factors [50]. Two prospective community-based studies that were relatively free of the above limitations yielded discrepant results: the first one, the Framingham Study, found that a diagnosis of diabetes at any time before administration of the neuropsychological tests, i.e. within 28–30 years after the study was initiated, was associated with a higher risk of poor cognitive performance for logical memory-delayed recall, independent of hypertension [51]. Number of years in which the participants were diagnosed with diabetes also resulted in significantly greater odds of poor performance for three tests: logical memory-immediate recall, logical memory-delayed recall, and similarities [51]. But this association was not found in another community-based study, the Rancho Bernardo cohort [52]. Both studies relied, however, on a single time point evaluation of cognition at the end of follow-up, so it was not possible to control for the subjects' baseline cognitive function.

Thus far, few longitudinal studies have been able to analyze cognitive change over time. The Study of Osteoporotic Fractures, a large prospective study of almost 10,000 community-dwelling older women, showed that diabetes was associated with both poorer cognitive performance at baseline and faster decline over 3–6 years on two tests evaluating attention, independently of a series of confounders, including cardiovascular disease and hypertension [53]. The EVA Study cohort of healthy community-dwelling elderly subjects showed that when diabetic subjects were compared with subjects with normal blood glucose, they appeared to have more than a twofold greater probability of serious worsening on four of the eight proposed domain-specific tests: one memory test, one test of psychomotor speed, and two tests of attention. In the ARIC cohort study, a large biracial, multisite, longitudinal investigation of initially middle-aged individuals, the presence of diabetes at baseline was associated with greater decline in cognitive performance. The association of diabetes with cognitive decline persisted when analysis was restricted to the 47 to 57-year-old population [54,55]. Also, diabetes, poor glycemic control, and longer diabetes duration were associated with incident cognitive impairment; persons with well-controlled diabetes (HbA1c <7 %) did not have significantly higher risk of cognitive impairment compared with persons without diabetes [56]. In a longitudinal cohort study in Northern Manhattan with 918 participants, diabetes was associated with a higher risk of incident all-cause mild cognitive impairment. Diabetes remained associated with a higher risk of amnestic mild cognitive impairment even after adjustment for vascular risk factors, heart disease, and stroke [17].

Diabetes in mid-life has been also associated in several observational studies with a greater risk of late-life dementia, Alzheimer's disease, and/or vascular dementia. In the ARIC study, diabetes in midlife was associated with a 1.77-fold the risk of dementia (95 % CI 1.53, 2.04) over 25 years compared with participants without diabetes [57]. In the Whitehall II prospective cohort, a longitudinal cohort study with a median follow-up of 31.7 years, younger age at onset of diabetes was significantly associated with higher risk of subsequent dementia [58]. Data spanning 35 to 75 years for age of diabetes onset found that every 5-year earlier onset of diabetes occurrence was significantly associated with higher hazard of dementia [58]. In the Sydney Memory and Ageing Study, with community-dwelling older participants without dementia aged 70–90 years at baseline, diabetics treated with metformin had less cognitive decline and dementia than those not treated with metformin [59]. Incident dementia was significantly higher in diabetics who did not take metformin compared with diabetics who did (OR 5.29 [95 % CI 1.17–23.88]) [59].

These associations also have been observed for both prediabetes and changes in glucose metabolism/hyperinsulinemia. In the prospective, community-based Adult Changes in Thought (ACT) study which included 2581 randomly selected dementia-free participants in Washington State, higher glucose levels were associated with an increased risk of dementia in populations without and with diabetes [60].

Finally, diabetes mellitus has been associated with decreased whole brain volumes, particularly gray matter volume [54,55], as well as greater atrophy rates. Moreover, T2DM-related volumetric differences appear to increase with diabetes duration. Longitudinal case-control and population-based studies have shown brain volume loss in diabetics that is similar to or up to three times the atrophy rate of normal aging [61]. The loss of brain tissue is most clearly reflected by ventricular enlargement [62]. Longitudinally, diabetes is associated with faster white matter disease accumulation [17].

In summary, while the exact mechanisms are still unknown, several observational studies have clearly identified diabetes as a major risk factor for cognitive dysfunction (Table 2). Even prediabetes and changes in glucose metabolism clearly appear to be related to a greater risk of the development and progression of cognitive impairment. Findings from future research should identify critical windows of vulnerability during diabetes, possibly indicating optimal times for preventive interventions.

Hyperlipidemia

Although a linear relationship exists between serum cholesterol levels and coronary heart disease, the relationship between total serum cholesterol and brain health is more complex and less consistent. Like with other risk factors, variations in study designs, lengths of follow-up, cognitive outcomes, and the timing of onset of high cholesterol may influence study findings. Although findings are somewhat mixed, in general, risk of cognitive impairment and dementia risk is not clearly elevated in association with hypercholesterolemia.

In the 13,997 participants in the ARIC cohort study, elevated total cholesterol, low-density lipoprotein cholesterol, and triglycerides in midlife were associated with greater 20-year cognitive decline, but high-density lipoprotein cholesterol was not associated with cognitive performance [63].

Data from observational studies have suggested that high cholesterol levels in midlife may increase risk for subsequent dementia and Alzheimer's disease [64]; however, in late life, low cholesterol levels have been predictive of subsequent dementia [65] or no association has been observed. Nevertheless, results are conflicting as some studies have not found high midlife cholesterol level to predict later life dementia [66]. Among 184,367 Kaiser Permanente participants in Northern California, those with the highest levels of HDL had a 15 % higher rate of dementia and those with the lowest levels had a 7 % higher rate of dementia, compared to older adults in the middle range of cholesterol levels [67]. In the Prospective Population Study of Women initiated in Gothenburg, Sweden in 1968–1969 and consisting of 1462 women aged 38–60 years, mid-life cholesterol level was not associated with an increased risk of Alzheimer's disease [66].

Taken together, while the alteration in blood concentration of lipid profiles may precede the incidence of dementia and there may be a drop off in lipid concentration before the onset of cognitive impairment or dementia, their relationship remains a subject of ongoing research and debate. Future research may build on previous findings by examining the effect of mid-life interventions on the temporal behavior of lipids and subsequent lifetime risk of cognitive decline.

Smoking

Findings from observational cohorts on associations between smoking and brain health outcomes should be interpreted with caution as these analyses, like those with the other risk factors, need to account for

Table 2
Key observational studies on diabetes and cognitive decline and/or dementia.

Author, Year	Study Name	Location	Exposure Life Stage/ Follow-up Period	Sample	Diabetic Parameters for Diagnosis	Cognitive Testing/ Diagnosis	Findings
Grodstein et al., 2001	Nurses' Health Study	United States	Late-life (70–78 years of age)/4 years	2374 females	History of Type II diabetes based on questionnaire	Telephone Interview of Cognitive Status [TICS], immediate and delayed recall of the East Boston Memory Test, and verbal fluency	Participants with type 2 diabetes performed worse than those without diabetes. Diabetics were twice as likely to have a low score as those without diabetes. Longer duration of diabetes and recent lack of diabetes treatment were associated with worse performance
Elias et al., 1997	Framingham Heart Study	Framingham, MA	Mid-life/ 28–30 years	1811 Caucasians	Casual blood glucose levels, urinary sugar values, and a history of clinical diagnosis of diabetes	Eight subtests from the Wechsler Adult Intelligence Scale (WAIS), the Wechsler Memory Scale (WMS), and the Multilingual Aphasia Examination	History and duration of diabetes was a significant risk factor for poor performance
Rawlings et al., 2019	Atherosclerosis Risk in Communities (ARIC)	Washington County, Maryland, Forsyth County, North Carolina, Minneapolis, Minnesota, and Jackson, Mississippi	Mid- to late-life/5 years	5099 Caucasians and African-Americans	Self-report, medications, or HbA_{1c} $\geq$6.5 %	Mini-Mental State Examination, the Clinical Dementia Rating, the Functional Activities Questionnaire	History of diabetes, poor glycemic control in diabetics, and longer diabetes duration ($\geq$5 vs. <5 years were significantly associated with incident cognitive impairment. A J-shaped association between HbA_{1c} and incident dementia was noted. Glycated albumin and fructosamine were associated with incident dementia, independently of HbA_{1c}. HbA_{1c} and fructosamine were also associated with incident MCI.
Amidei et al., 2021	Whitehall II Prospective Cohort Study	United Kingdom	Mid- to late-life/31 years	10,095 Caucasians, South Asians, and Blacks	Fasting glucose	HES database, the Mental Health Services Data Set, and the Office for National Statistics Mortality Register for dementia diagnosis.	Younger age at onset of diabetes was significantly associated with higher risk of subsequent dementia

a number of methodologic issues. Early longitudinal studies have provided only global neuropsychological assessments, did not have the ability to detect early stages of cognitive decline [68,69] or provided only short-follow-up periods [69]. Because public health messages on smoking over the past thirty years have also led to changes in smoking behavior, studies should assess smoking behavior over time, and differentiate between long-term and current smoking status, recent ex-smokers, long-term ex-smokers, and never smokers. Additionally, studies need to account for significant loss to follow-up among smokers due to premature death and non-participation/dropout. Finally, those who stop smoking may be more likely to change other health behaviors.

Smoking has been associated with cognitive decline in at least three previous observational studies with at least two timepoints of cognitive testing first assessed in midlife, but not consistently so. Also the current evidence does not allow conclusions to be made about the association between smoking and specific cognitive domains. In the 1946 British National Birth Cohort study, smoking was associated with increased decline in memory, but not visual search [70]. In the Doetinchem Cohort Study [71], smokers had faster decline in memory but not processing speed. However, the ARIC MRI Study [72] did not find smoking to influence cognitive decline. Finally, the Whitehall II Study, a large prospective cohort study of 10,308 middle-aged (aged 35–55 years at baseline) British civil servants (phase 1; 1985–1988), suggested that smoking history was associated with a greater risk of memory loss (OR 1.37 (1.10–1.73) over 5 years in fully adjusted models, as well as decline in reasoning abilities, but not memory decline or decreased fluency. The Whitehall II results may have under-estimated a smoking-cognition effect as the authors noted premature death and lower participation among smokers.

Current evidence from observational studies is also conflicting about the association between smoking and cognitive impairment by sex. To account for bias in estimates due to selection from mortality or dropout over follow-up, a second analysis in the Whitehall II cohort that allowed for joint modeling of cognitive decline, time to dropout, and time to death was performed [73]. This analysis, using six assessments of smoking status over 25 years and three cognitive assessments over ten years, showed that, in men, smoking was associated with faster cognitive decline; analyses using pack-years of smoking suggested a dose-response relation [73]. Additionally, men who continued smoking over the follow-up experienced greater decline across all cognitive testing [73]. Finally, men who quit smoking in the 10 years preceding the first cognitive measure were still at risk of greater cognitive decline, especially in executive function [73]. Notably, this study did not show an association between smoking and cognitive decline in women, and the underlying reasons remain unclear. One possible explanation for the lack of association in the ARIC MRI Study described above as well is that the study population was predominantly female (62 % of the total population) [72]. Some studies have reported differences between men

and women in the association between smoking and cognitive decline [73,74], while others, such as the Doetinchem Cohort, report no differences [71]. One explanation for the sex difference observed in the Whitehall II study might be the greater quantity of tobacco smoked by men [74]. Indeed, the mean pack-years of smoking (36 vs 31; $P = .05$) as well as the number of cigarettes smoked (19 vs 16; $P = .007$) were higher in men than women [73]. It is also possible that smoking clusters with other risk factors differently in men and women, and it may be challenging to understand and account for these interactions.

With regard to ex-smokers, results on the association between smoking and cognition have also been mixed, but there is evidence that quitting smoking closer to middle age versus still smoking or quitting later in life may reduce the risk of cognitive decline or dementia. In the EURODEM study, ex and never smokers did not differ with regard to cognitive impairment [75]. Additionally, apart from a few [69,70,76], the majority of studies have investigated ex-smoking status without differentiating between "long-term" and "recent" ex-smokers [77,78]. In the 1946 British National Birth Cohort study [70], "long-term ex-smokers" had better memory and a slower decline in memory compared to "never smokers." In the Honolulu-Asia Aging Study, "long-term ex-smokers" did not have a lower risk of cognitive impairment than "never smokers" and "recent ex-smokers" had the same increased risk of impairment as "current smokers." [76] The Whitehall II Cohort results showed that long-term ex-smokers did not have greater cognitive decline than never smokers while male recent ex-smokers had on average greater decline in executive function than never smokers, suggesting that residual effects of smoking on cognition might wear off approximately a decade after smoking cessation [73].

Observational data supporting an association with current smoking status and dementia has been generally consistent (Table 3) [79]. The ARIC Study found that risk of dementia depended on time since smoking cessation [80]. Current cigarette smoking and recent cessation (<9 years) were associated with increased risk of all-cause dementia over 12 years in a dose-dependent manner: 33 % and 24 %. A meta-analysis of prospective studies has shown a powerful ~30 % increase in all-cause dementia risk in older adults associated with current smoking [81]. Other meta-analyses of longitudinal studies suggest a stronger association with probable Alzheimer's disease than for other dementias – a 40–80 % increase in risk [82,83]. Among 12 dementia risk factors across the life course described in the Lancet Commission dementia prevention, intervention and care analysis, smoking in later life (i.e., age > 65 years) had one of the highest population attributable risks at 5.2 % [83].

In summary, collective evidence from observational studies supports a robust association with current smoking and dementia. Because some evidence suggests that the effect of smoking on decline in memory is confined to the elderly or those over 75 years of age [84], future studies are needed to estimate the age at which smoking related decline in memory may become apparent. Additional future work should investigate if the risks for cognitive decline and dementia are sex-specific. Although there is consensus that smoking cessation is beneficial for brain health, there is a lack of evidence as to when cessation should occur to minimize dementia risk, though from a general health perspective, no history of smoking or the least amount of smoking exposure is preferrable. Finally, even secondhand smoke, particularly over a long time period, has been associated with poorer cognitive function, and further study is needed [85,86].

Physical inactivity

Physical activity has been associated with a lower risk of cardiovascular and nonvascular diseases as well as mortality [87]. The possibility that physical activity might favorably influence brain health is based upon the basic biological principle that cellular and molecular events in the brain are modifiable by the environment [88]. Potential mechanisms for such an effect include the reduction of inflammation and increasing trophic factor production and neurogenesis in addition to the reduction in cardiovascular disease [89,90].

Although methodologic limitations of the existing evidence base derived from observational studies preclude forming of definitive conclusions, a strong case can be made for a positive association between physical activity and preservation of cognitive function. Results from studies, however, have individually shown conflicting results. Some observational studies have demonstrated better cognitive outcomes in individuals with more leisure-time physical activity, especially in mid-life, including larger brain volumes, and less cognitive decline. In the Framingham Study, even light physical activity was shown to be advantageous for brain health, with more sedentary behavior associated with diminished cognitive performance [91]. Similar findings for sedentary behavior were noted in the Hispanic Community Health Study/Study of Latinos [86,92]. In the Nurses Health Study cohort (females aged 70–81) women in the highest quintile of physical activity were 20 % less likely to show cognitive decline over a decade later, compared with the lowest quintile [93]. In the Rush Memory and Aging Project, a longitudinal, community study in the elderly, in a linear mixed-effect model, the level of total daily physical activity was associated with the rate of global cognitive decline (estimate 0.033, SE 0.012, $p = .007$) [94]. These studies provide important data suggesting that physical activity may be protective of and forestall the development of cognitive impairment. A systematic review however by Aarsland et al. [95] noted that of five longitudinal studies conducted prior to 2010 assessing physical activity and cognitive decline, one found a significant association for both sexes [96], two found a significant relationship for females only [97,98], and one showed no association [99]. The picture has been mixed for dementia and physical activity as well. Several observational studies in mid-life have not found a statistically significant association [100], but others have [101,102] (in one study, this relationship was found only in men) [103].

The reasons for these discrepancies and subsequent need for caution in interpretation are many-fold. Prospective observational studies on cognition and physical activity are marred by methodologic heterogeneity with regard to follow-up length [104,105], follow-up rate, physical activity categories (household activities versus athletic), description, or

Table 3
Key observational studies on smoking and cognitive decline and/or dementia.

Author, Year	Study Name	Location	Exposure Life Stage/ Follow-up Period	Sample	Parameters	Cognitive Testing/ Diagnosis	Findings
Deal et al., 2019	Atherosclerosis Risk in Communities (ARIC)	Washington County, Maryland, Forsyth County, North Carolina, Minneapolis, Minnesota, and Jackson, Mississippi	Mid-life/12 years	13,002 Caucasians and African-Americans	Never, former, or current smoker	Delayed Word Recall, Word Fluency, and the Digit Symbol Substitution	Current cigarette smoking and recent cessation (<9 years) were associated with increased risk of all-cause dementia
Merchant et al., 1999	Community based Manhattan Study	Manhattan, NY	Mid- to late-life/2 years	2128 Caucasians, African-Americans, and Hispanics	Never, former, or current smoker	Clinical Dementia Rating score of 1.0 or higher	Relative risk of dementia was almost double among current smokers

intensity type (for instance, "leisure-type," high vs. low resistance, high, moderate, and low intensity, or number of hours of physical activity), physical activity measurement quality (most are self-reported rather than objective) [106], and quality of study design (i.e. neglecting to account for a non-linear relationship between physical activity and cognition or not controlling for confounders). The simplification of physical activity as a predictor variable may potentially mask more nuanced associations of physical activity with brain health. Moderate-intensity physical activity is the most reported dose [107, 108], yet there is a consistent lack of clarity across studies about how moderate-intensity is defined and measured. Some studies have only binary outcomes: cognitive impairment or decline or no cognitive impairment or decline and have examined only a few confounders [99, 109]. Finally, data from longitudinal studies examining both physical activity and cognition at multiple timepoints across a lifespan are scarce.

Despite individual discrepancies between studies, however, multiple earlier meta-analyses of longitudinal studies have lent support to moderate associations between physical activity, cognitive decline, and dementia [110-112]. One meta-analysis by Blondell et al. showed negative associations of physical activity with both cognitive decline and dementia, with overall effects of RR 0.65, 95 % CI 0.55–0.76 and RR 0.86, 95 % CI 0.76–0.97, respectively [112]. Another meta-analysis of 15 prospective studies investigating 30,331 nondemented subjects followed for a period of 1–12 years and 3003 incident cases of cognitive decline showed that physically active individuals at baseline have a significantly reduced risk of developing cognitive decline during follow-up. The cumulative analysis demonstrated a 38 % reduced risk of cognitive decline in subjects with high levels of physical exercise, compared to sedentary subjects [110]. Moreover, low-to-moderate levels of physical activity similarly resulted in a significantly reduced risk of deterioration of cognitive performance (35 %) [110]. A more recent meta-analysis of observational studies found only a weak (but persistent) association between physical activity and cognition [113]; however on a population health level, this mild association is significant for its potential to slow cognitive decline or the onset of dementia.

Cross-sectional observational studies have established an association of physical inactivity with brain aging on neuroimaging. Studies utilizing neuroimaging techniques have, for example, found physically active older persons to have greater brain volume than less active older individuals (2–2.5 % increase, per physical activity quintile) [114]. The Framingham and Framingham Offspring Study cohorts (aged 60 years or older) found a linear association between physical activity levels and total cerebral and hippocampal brain volume [115].

It is unclear from the current evidence base if specific cognitive domains are more vulnerable to lack of physical activity or sedentary lifestyle. Executive function has emerged as the most consistent cognitive domain affected [113,116], but many studies have prioritized the assessment of executive functions over that of other cognitive domains, and there is considerable variability in the type of testing used to evaluate cognitive domains. Additionally, many of the instruments used to assess executive functioning are traditional neuropsychological tools that were originally developed to support clinical diagnosis rather than to study individual variation in cognitive functioning. As such, their sensitivity to detect changes from exposure to a risk factor remains questionable. A recent meta-analysis evaluating physical activity and specific cognitive domains revealed weak associations for episodic memory and verbal fluency (pooled standardized regression coefficients between 0.02 and 0.05) [113].

In summary, physical activity may have a role in preserving brain health and in reducing the risk of cognitive decline and dementia (Table 4). Conclusions about the effects of physical inactivity across the lifespan are inherently limited because of the lack of high-quality data available across all age groups, but the preponderance of evidence from multiple observational studies suggests negative sequalae for brain health. Clearly more high-quality research is needed to determine effects across age groups, the optimal dose, and to examine whether the magnitude of the benefit of physical activity is greater at some ages (or in some populations) relative to others. Future research should use objective and standardized measures of physical activity, adjust for the full range of known, or likely, confounders, and have adequate follow-up length.

Conclusion

The heterogeneous and multi-dimensional nature of brain health requires the consideration of all components of health when predicting the risk of its decline and planning strategies for its preservation. Given the lack of a disease-modifying treatment or cure for cognitive impairment, decreasing the risk of cognitive decline or delaying the onset of dementia takes on additional importance. Even if effective treatments are developed, risk reduction of modifiable risk factors will likely remain a key strategy in reducing the number of individuals affected. There is a large body of evidence from observational studies to support the link between several modifiable risk factors – hypertension, diabetes, smoking, and physical inactivity – and a reduced risk for cognitive decline, and sufficient evidence to suggest that treatment or prevention of these risk factors may be associated with reduced risk of dementia. However, improvements in research methods are required, such as accurate, better validated, and more sensitive cognitive assessment measures at multiple time points across studies, and studies of longer duration. The effects of different combinations of these modifiable risk factors, that is, clusters and interactions of comorbidities, may have a greater cognitive impact, and this also remains to be further defined. Future well-designed observational studies should also take into account the intensity, duration, and timing of exposures to different risk factors because some exposures may be more significant, and thus interventions

Table 4
Key observational studies on physical inactivity and cognitive decline and/or dementia.

Author, Year	Study Name	Location	Exposure Life Stage/ Follow-up Period	Sample	Definition of Activity	Cognitive Testing/ Diagnosis	Findings
Wueve et al., 2004	Nurses Health Study cohort	United States	Late-stage/2 years	18,766 female nurses aged 70–81	Different activities reported by questionnaire in the past year were assigned metabolic equivalent values (MET)	Telephone Interview for Cognitive Status (TICS), East Boston Memory Test (EBMT), Digit Span Backwards Test	Long-term regular physical activity, including walking, was associated with significantly better performance and less decline in older women
Vasquez et al., 2017	Hispanic Community Health Study/ Study of Latinos	Miami, Fl, Bronx, NY, Chicago, IL, and San Diego, CA	Early to late-stage	7478 Latino Americans	Accelerometer assessed moderate-to-vigorous physical activity and sedentary behavior	Digit Symbol Substitution Test (DSST), Word Fluency Test, and Spanish English Verbal Learning Test	Sedentary behavior but not moderate-to-vigorous physical activity was associated with executive functioning in middle-aged and older Latino adults

more impactful, during key periods of life.

CRediT authorship contribution statement

Sara Hassani: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Philip B. Gorelick:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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