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REVIEW

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Current perspectives on prevention of vascular cognitive impairment and promotion of vascular brain health

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ABSTRACT

Introduction: The true global burden of vascular cognitive impairment (VCI) is unknown. Reducing risk factors for stroke and cardiovascular disease would inevitably curtail VCI.

Areas Covered: The authors review current diagnosis, epidemiology, and risk factors for VCI. VCI increases in older age and by inheritance of known genetic traits. They emphasize modifiable risk factors identified by the 2020 Lancet Dementia Commission. The most profound risks for VCI also include lower education, cardiometabolic factors, and compromised cognitive reserve. Finally, they discuss pharmacological and non-pharmacological interventions.

Expert Opinion: By virtue of the high frequencies of stroke and cardiovascular disease the global prevalence of VCI is expectedly higher than prevalent neurodegenerative disorders causing dementia. Since ~ 90% of the global burden of stroke can be attributed to modifiable risk factors, a formidable opportunity arises to reduce the burden of not only stroke but VCI outcomes including progression from mild to the major in form of vascular dementia. Strict control of vascular risk factors and secondary prevention of cerebrovascular disease via pharmacological interventions will impact on burden of VCI. Non-pharmacological measures by adopting healthy diets and encouraging physical and cognitive activities and urging multidomain approaches are important for prevention of VCI and preservation of vascular brain health.

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KEYWORDS
Ageing; depression; diabetes; hypertension; small vessel disease; stroke; vascular cognitive impairment; vascular dementia

1. Introduction

Cardiovascular disease alters brain perfusion leading to strokes and other cerebrovascular events. These overt changes are associated with various dementias as well as depressive illness [1–4]. Intracranial lesions described by cerebrovascular disease (CVD) are responsible for the second most common form of age-related dementia, namely vascular dementia (VaD). However, invariably in tandem with brain aging covert or sub-clinical changes are also evident. They include white matter disease, cerebral atrophy, silent lacunar infarcts, microinfarcts, microbleeds, arteriolosclerosis, and intracranial atherosclerosis, which are widely regarded as surrogates of underlying intracranial or cerebral small vessel disease (SVD). These cerebral lesions may accrue over time to impact on cognition, physical strength or ability, and cerebral reserve [5–8].

Older age is the strongest risk factor for VaD or SVD-related dementia. The genome harbors another risk that constitutes monogenic or polygenic characteristics. However, modifiable risk factors for VaD or SVD including hypertension, diabetes mellitus (DM), dyslipidaemia, obesity, and metabolic syndrome can be reduced or prevented in reality to improve brain perfusion and substantially delay or curtail cognitive impairment and dementia. Prevention of cognitive impairment and dementia would require control of cardiovascular or cerebrovascular risks involving multi-faceted strategies at the individual, community, and population levels, perhaps more so in low- and middle-income countries (LMICs). Degree of risk may be further influenced by inherent factors such as sex and ethnicity. Thus, targeting prevention of stroke for example in high-risk ethnicities across the life course would be beneficial to reduce the burden of vascular cognitive impairment (VCI) [9]. The key to prevention is, however, early detection of the type of risk and of apparent clinically silent disease, which often (~80%) progresses to frank dementia.

2. Scope of review

Our article incorporates clinical and pathological definitions of VCI, an estimation of the burden, accounts of the main modifiable risk factors and strategies for both non-pharmacological and pharmacological approaches to reduce or prevent VCI and promote vascular brain health. The narrative text is essentially compiled from papers published from original research performed by the authors as well as data derived from research papers in PubMed and Web of Science. We searched for all online narrative and systematic reviews on VCI, stroke epidemiology, and vascular disease risk and protective factors. We used the following combination of terms: Vascular cognitive

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Article highlights

- The worldwide prevalence of VCI is not known but is estimated to be high, particularly in the Global South.
- Vascular risk factors including hypertension, type 2 diabetes and dyslipidaemia evident in midlife are key modifiable factors.
- Current meta-analyses overall reveal control of the key vascular disease risks provide small to moderate benefits in reducing incident dementia but are not wholly detrimental.
- Prevention via control of risk factors, protective factors including adherence to diet and greater physical activity are key to reducing burden of VCI.
- All measures and drives at the individual and population levels to reduce stroke injury and protect vascular brain health would reduce the burden of VCI.

impairment or vascular dementia and review and hypertension or diabetes or dyslipidaemia or obesity, or metabolic syndrome or diet or physical activity or tobacco or multidomain. We were also mindful to include comments on the 12 risk factors identified by the 2020 Lancet Dementia Commission. These, in order of most modifiable to the least perhaps at the individual level, are lower education, excessive alcohol, smoking, physical inactivity, hypertension, diabetes, obesity, depression, traumatic brain injury, hearing loss, social isolation, and air pollution. Similarly, to search for references on pharmacological treatments we used vascular cognitive impairment and various classes of individual drugs, e.g. aspirin, statins, etc. We also performed a search of systematic reviews and meta-analyses on vascular risk factors, inflammation, and dementia.

3. Current view of vascular cognitive impairment

VCI comprises all causes of cerebral vascular disease in relation to cognitive dysfunction. VCI involves degrees of impaired cognition in a continuum that will depend on the type and extent of vascular brain injury [5,10,11]. Previously, vascular cognitive disorder [12] was described and for all practical purposes is another interchangeable label with the more popular VCI that also incorporates a continuum comprising cognitive disorders of vascular etiology with diverse clinical manifestations associated with varied pathologies. In the most recently developed DSM-5 criteria incorporate the categories of mild and major vascular cognitive disorders [13]. Major vascular neurocognitive disorder classification aligns with VaD, or frank dementia explained by largely cerebral vascular disease. This fits better with clinical practice, and more adapted to neurodegenerative cognitive disorders for which amnestic memory impairment is not superior but encompasses substantial pathologies in the frontal lobe [14]. Large vessel disease is more often related to lateralized sensorimotor changes and aphasia whereas SVD is akin to more subtle signs, including extrapyramidal signs and gait disturbances (see below). Dementia resulting from large vessel obstruction or disease, also categorized as multi-infarct dementia, in preference to 'cerebral atherosclerosis.' It is caused by multiple infarcts and prominent in the neocortex (cortical VaD) and can be so in the gray-white borderzone. Cerebral SVD may entail degrees of pathological changes including hypertensive strategic infarcts leading to subcortical ischemic VaD. Dementia associated with strategic infarcts is diagnosed in patients who have lesion volume below the threshold for dementia but in whom ischemic injury is in regions e.g. thalamus, critical for normal cognitive function. Strategically located infarcts may also be large involving the deep gray matter including the basal ganglia and thalamus), white matter or the limbic system. However, it is recognized that overlap between the subtypes is common. For example, microinfarcts may affect cognition in both large vessel disease and SVD. VaD often comprises a combination of cortical and subcortical lesions, thereby referred to as cortico-subcortical VaD. It is rare for vascular lesions to be localized exclusively within the cortex.

To attain consensus on the diagnosis of VCI (Figure 1), the vascular impairment of cognition classification consensus studies (VICCCS-1 and VICCCS-2) established key expressions in the understanding and language of cognitive impairment and dementia resulting from CVD [15,16]. Practical guidelines for the diagnosis of VCI were formulated via a Delphi type of iterative protocol. Given the various degrees of cognitive dysfunction could occur with varied lesions and location, VICCCS-1 study proposed the use of 'Mild' and 'Major' subdivisions of the severity of impairment, aligning with the recent nomenclature in DSM-5. VICCCS diagnosis guidelines specify deficits in at least 1 domain, with clinically significant cognitive deficits of sufficient severity e.g. moderate to severe, and severe deficits in daily living activities differentiating Mild and Major forms of VCI [16]. It was then concluded it would be premature to further sub-classify Mild VCI but the Major forms of VCI, constituting frank dementia or VaD should be categorized into 4 main subtypes including post-stroke dementia (PSD), subcortical ischemic vascular dementia, multi-infarct (cortical) dementia and various mixed dementias, subclassed according to additional types of neurodegenerative pathologies. Thus, in practice, all the categories of VaD subtypes based upon current clinical and neuroimaging evidence and defined by the origin of vascular disease, arterial territory or size of the vessels involved, and lesion location are described under VCI. In considering this, it is of note that the DSM-5 and VICCCS criteria [17] are comparable but the previous vascular behavioral and cognitive disorders (VASCOG) society criteria [14] have greater sensitivity but modest concurrent and better predictive validity than the NINDS-AIREN criteria for VaD [18].

Subcortical ischemic VaD or dementia resulting from mostly SVD has been of much recent interest globally [19–21] for two main reasons: 1) it results from the single most common cause of stroke injury and 2) survivors of lacunar strokes often survive long and at greater risk of cognitive impairment. Thus, cerebral SVD is probably the most common cause of cognitive impairment and dementia [22]. Clinical features incorporate motor and executive slowing, forgetfulness, and dysarthria. A short-stepped gait is also common and can mimic that of Parkinsonism. These may be caused by disruption of pathways running from the prefrontal cortex to the basal ganglia and of thalamocortical pathways. The main vascular pathology relates to sclerotic changes or loss of medial vascular smooth cells in intracranial arteries and arterioles,

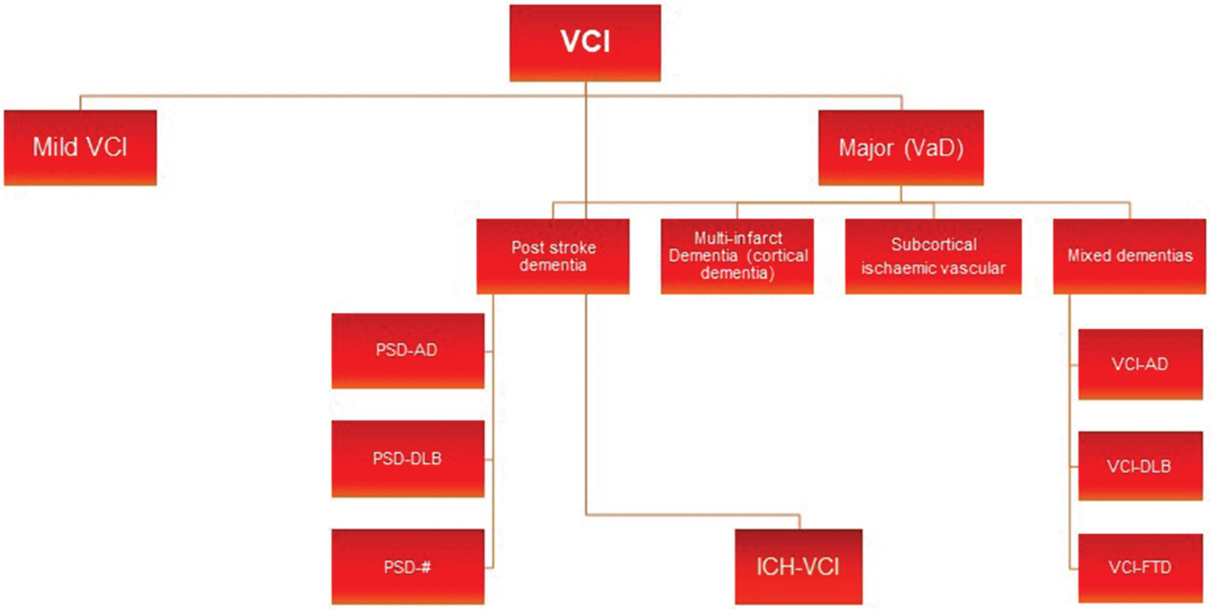

Figure 1. Classification of VCI according to level of impairment into mild VCI and major VCI (VaD). Major VCI (VaD or frank dementia of vascular origin) is classified into four main subtypes as depicted. The estimated 6-month temporal basis for cognitive decline after stroke differentiates PSD from other forms of major VCI (VaD). We propose that ICH-VCI is included since cerebral hemorrhages cause hemorrhagic dementia, which is more common in Asia and Africa than in Europe and the U.S. A. Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; ICH, intracerebral hemorrhage; PSD, post stroke dementia. PSD-# denotes other possible combinations when comorbid neuropathology is present in mixed dementias. Figure adapted from [15] with permission of John Wiley & sons.

most often evident in the basal ganglia. Evidence from pathological studies suggests there are two main presentations in subcortical ischemic VaD: 1) presence of multiple lacunar infarcts affecting subcortical gray matter and 2) diffuse or widespread rarefaction of the white matter.

Cognitive impairment or dementia following stroke or PSD [23] is recognized to be relatively common in older age [24,25], ranging from a prevalence of 7.4% in population-based studies of first-ever stroke to 41% (30–53) in hospital-based studies of recurrent stroke. However, a most recent analysis of 5-year data from the Oxford Vascular Study [26] found that either transient ischemic attack or stroke-related dementia at 1 year was 34% in patients with severe or major stroke, 8% in those with minor stroke, and 5% in those with transient ischemic attack. In comparison, systematic analysis involving 44 studies worldwide [27] indicated at 1 year the prevalence of PSD as 18% and if pre-stroke dementia cases were included it was 20%. Most dementia occurred in the first year after major stroke, whereas onset was more gradual after minor stroke. PSD may develop within three months or after a stabilization period of a year or longer after stroke injury [26,28–30]. Multiple lesions over time and the characteristics and complications of the stroke were found to be most strongly associated with PSD. Thus, PSD has a complex etiology with varying combinations of large lesions and SVD as well as non-vascular pathology. However, it is also important to recognize that depression may confound VCI diagnosis particularly relating to white matter hyperintensities (WMHs) with the oft-debated presence of 'vascular depression' [31,32]. Previous studies have shown that the depressive syndrome is not the primary disease but can be considered as one of the clinical manifestations in the wide symptom spectrum of VCI [33]. Mixed pathology is particularly common in the oldest old [34] and the overlap of these may synergize risk of cognitive impairment [5,35,36]. There should be sufficient evidence of clinical deterioration or progression [37]. The most common form of mixed dementia comprises significant vascular lesions and Alzheimer type of pathology. Mixed dementia cases with coexisting vascular changes, including cerebral amyloid angiopathy and Lewy body pathology or other neurodegenerative inclusions appear less frequent.

4. Epidemiology of VCI

Given that the worldwide prevalence of stroke-related cerebrovascular diseases and cardiovascular disorders are higher than any common neurodegenerative disorder, it is expected that there will proportionally be high burden of cognitive impairment due to vascular causes. Stroke patients may develop cognitive dysfunction in the form of mild cognitive impairment, possibly some involving amnestic memory deficits [38]. However, there are no large prospective population-based longitudinal studies to determine the true prevalence of VCI [20]. Global frequency of VCI may be estimated reliably from the current cases of stroke. The recent report from the global burden of disease (GBD) collaborators showed that in 2019 worldwide there were 12·2 million incident cases of all strokes [39] whereas 7.6 million cases of these comprised ischemic stroke [40]. This analysis reported 101 million prevalent cases of stroke [39]. Annual total numbers of all strokes increased substantially from 1990 to 2019 although they remained stable in many high-income countries and there were reductions in age-standardized rates, particularly among elderly who were over 70 years of age. The incidence of ischemic strokes increased by 88% from 1990 to 2019 [40]. Interestingly, the most rapidly growing risk factor for stroke between 1990 and 2019 was body-mass index of > 30 (Table 1). Previous meta-analyses [25–27] showed that on average 20–30% of stroke survivors of the first stroke and recurrent strokes develop dementia. Thus taking these numbers and computing against the 12.2 incident cases of all strokes in 2019, a conservative estimate calculates to 2.44 million, who will have developed VCI or VaD. This number compares with recent GBD data on four common causes of dementias including Down's Syndrome, Parkinson's disease, traumatic brain injury and stroke [41]. The analysis estimated 3.7 million stroke-related dementia cases occurred globally and for every region, stroke accounted for the largest number of dementia cases compared to the other causes. Given that there might be a number of mild VCI cases occurring after stroke, these numbers are likely gross underestimates. The GBD data showed that worldwide in 2019 there were 7.2 million dementia cases including those resulting from stroke. Taken together, the global prevalence of VCI in 2019 could be approximately 4 million and that number is likely to be much higher in 2023. Irrespective, since nearly 90% of the global burden of stroke can be attributed to modifiable risk factors, a formidable opportunity arises to reduce the burden of not only stroke but VCI outcomes.

Cardiovascular diseases also remain the leading cause of disease burden in the world. In 2019, prevalent cases of total cardiovascular disease were estimated to be 523 million, increased by nearly 100% since 1990 [42]. These estimates also suggest that at least 1 in 5 individuals with cardiovascular disease had a stroke. In addition, meta-analysis of data from 28 million individuals suggests that the global prevalence varies from 13% to 31% according to the definitions incorporated in high blood glucose, hypertension, waist-to-hip ratio, and high-density lipoprotein-cholesterol values [43]. The prevalence was significantly higher in the Eastern Mediterranean Region and the Americas and increased per level of country income. This suggests frequencies of VCI may vary widely in some global regions. The disparities and their drivers call for diversity, equity and inclusion in global VCI research and in the allocation of resources for research, prevention, treatment and rehabilitation by allocating resources where the burden is large. In addition, recent studies have revealed sex-differences in some cognitive domains and functional status of those diagnosed with post-stroke VCI [44] or mild VCI [45]. In the latter study [45], men performing worse in some cognitive domains was also reflected by differences in intracortical and cortico-spinal excitability to multimodal transcranial magnetic stimulation. These findings have prognostic and diagnostic implications as well as strategies for neuromodulation.

The ongoing calculations do not consider that many individuals will have covert lesions including WMHs, which occur at high frequencies in older age and denote presence of cerebral SVD. In addition to WMHs, silent infarcts mostly subcortical lesions were shown to increase the risk of all cause dementia including Alzheimer's disease (AD) in the earlier longitudinal Rotterdam study [10]. Evidence from the US Atherosclerosis Risk in Communities study showed that subclinical cerebrovascular disease may be up to ten times more common than clinically evident stroke in the general population [46]. Similarly, in the multicentre European Leukoariosis and Disability study (LADIS) the presence of WMHs was shown to independently predict functional decline [47] and contribute to vascular cognitive disorders and physical instability [48].

WM attenuation or WMHs may progress to precipitate mild VCI and dementia. Recent meta-analysis of longitudinal studies [49] suggests that mean WMH increases by 1.74 ml over time of 2–4 years but there are wide ranging changes. Various factors and mechanisms could be associated with regression of volume in asymptomatic stroke and neurocognitive disorders. There is also a significant association between WMHs, both deep WMHs and periventricular WMHs and post-stroke depression during the chronic post-stroke phase [50]. Periventricular lesions were more strongly related to post-stroke depression in each period after stroke than deep WMHs.

Carotid artery disease is a risk for ipsilateral strokes especially in patients with 70–99% stenosis compared to those with 50–69% stenosis [51] but high degrees of stenosis may affect cognition in the absence of strokes. In the Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis-2 or CREST-2 trial patients showed lower levels of baseline cognition particularly memory impairment compared to a population-based cohort, controlled for demographic as well as cardiovascular risk factors [52]. Irrespective these estimates are just the 'tip of the iceberg' and likely gross underestimates. They importantly implicate the urgent implementation of cost-effective primary prevention strategies to reduce stroke and CVD globally and hence prevent VCI.

5. Pathophysiology and inflammation in VCI

Several mechanisms including genetic, biological, and behavioral are likely involved in the link between risk factors causing vascular diseases and cognitive impairment or dementia or depressive illness. Ageing per se causes irreversible structural changes in the brain vasculature. Brain perfusion may not only be influenced by intracranial atherosclerotic disease but also arteriolosclerosis which increases exponentially with age [53,54]. In addition, blood supply via the carotid and vertebral arteries may be affected by degrees of age-related atherosclerotic disease and arterial stiffness within the cardiovascular system and a variety of heart conditions such as atrial fibrillation. Ageing also impacts on autonomic regulation, neurovascular uncoupling, and blood-brain barrier (BBB) functions, which will all dictate the ultimate dynamics of brain blood flow and local perfusion during different periods to initiate stroke injury and VCI [54]. It is not unlikely that venous diseases in form of varicose veins, venous insufficiency and deep vein thrombosis as well as cerebral venous collagenosis invariably play a part in vascular cognitive impairment [55]. Some evidence also suggests that age-related venous pathology is associated with WMHs [56]. Thus, age-related changes in brain blood vessels may be attributed to several structural and pathological alterations including cerebral atrophy, white matter attenuation, endothelial or blood-brain barrier (BBB)

Table 1. Unmodifiable and modifiable risk factors for VCI*.

Factor	2020 Lancet Dementia Commission Risk Factors	Global versus US Population Attributable Fractions†	Definition or Status	Outcomes or features leading to VCI	Pathophysiology and Vascular Mechanisms
Age (SD)	-	-	>50 years	Accumulative non-symptomatic changes; CI doubles every 5 years particularly in women >90 years	Age-related atherosclerosis and arteriolosclerosis
Sex	-	-	Male or female	Risk in males > females up to 85 years	Unclear
Family history	-	-	Self- reported CVD or stroke	Heritability of stroke, greater risk for WMHs	Inheritance patterns in vasculature
Genetic Factors	-	-	*APOE ε4* allele;*NOTCH3* mutations	Greater progression to disability, dementia or death	Mutations/alleles cause loss of VSMC and increase in ECM
Education	Low education	19%; 6%	>7 years globally; >12 years in HICs	Low education is strong risk for all cause dementias globally	-
Brain Health	Traumatic brain injury	9%; 12%	Head injury with loss of consciousness	Increased risk of all cause dementia	Focal ICH, SAH, microbleeds
Cardiovascular Health	-	6%;7%	Ischemic/ICH; lacunar strokes	Disability, depression, CI, dementia	Cortical and lacunar infarcts, SVD pathology
Blood Pressure¶	Midlife hypertension	5%; 20%	≥140/90 mm Hg;	Risk for strokes	Hypertensive encephalopathy, ICH, arteriolosclerosis
Blood Sugar††	Diabetes	3%; 13%	fasting plasma glucose >5.6 mmol/L; HbA1c 6.5%;	Risk for SVD	SVD type changes
Blood Lipids	-	-	Total cholesterol ≥5.2 mmol/L; high triglycerides	Risk for atherosclerosis and stroke	Atheroma in small intracranial arteries
Blood Homocysteine	-	-	Homocysteine >14.0 mmol/L	Risk for stroke and VCI	SVD type of pathology
Cardiac Health	-		HD: Any cardiac problem including AF, CHD, IHD and MI‡	Atrial Fibrillation or flutter based on ECG data risk for embolism	Small and large infarcts related to thromboembolism
Peripheral Circulation	-	-	PAD described by decreased lower extremity arterial perfusion; systemic atherosclerosis	Risk of undiagnosed CI	Unclear
Obesity	Waist-to-Hip ratio	2%; 21%	BMI ≥30	Higher levels of leptin and resistin but not adiponectin associated with decreased risk of dementia	SVD type of pathology
Hearing	Hearing Loss	22%; 9%	Age-related hearing loss in tonal and non-tonal languages; >25 dB threshold	Association between hearing loss and cognitive impairment and dementia	-
Mental Health	Depression	11%; 6%	Late-life clinical depressive illness; PH! Score ≥ 10	Moderate-severe depression increases risk for all cause dementia	Diffuse WM changes
Physical Activity	Physical inactivity	10%; 20%	Low moderate to vigorous activity,<150 min per week	Increased risk for CVD and T2DM	PA increases microvasculature
Diet	-		Healthy diet (leafy vegetables, high fiber); Medi diet	Foods with high saturated fat content risk for CI	Antioxidants reduce inflammation in vessels
Tobacco use	Smoking	14%; 5%	Current or former smoker	Elevated risk of stroke	Arteriosclerotic changes in peripheral vessels
Alcohol intake	Excessive alcohol use	2%; .7%	>21 units per week; loss of consciousness	Risk for hypertension, HD and stroke, and all cause dementia	Alcohol encephalopathy; WM changes
Social Activity	Low social contact	4%; 7%	Loneliness; lack of networks	High social engagement and frequent social contact are significantly associated with a lower risk of dementia,	-
Air Quality	Air pollution	6%; 2%	Fine particulate matter of 2.5 ($PM_{2.5}$) microns or less	$PM_{2.5}$ is a risk for all cause dementia	Arteriosclerotic changes and damage to cerebral endothelium

Data were derived from several sources including the global burden of disease, INTERSTROKE and PURE studies assessing incidence estimates and risk factors in HIC and LMICs [19,39,184–200]. †Unweighted PAFs derived from the Relative Risks and references [41,190,201] ¶ Data from 186 countries indicated global PAF of hypertension for dementia was 15.8% [202].

Abbreviations: APOE, apolipoprotein E; BMI, body mass index; CI, cognitive impairment; CVD, cardiovascular disease; CHD, coronary heart disease; dB, deci Bells; ECG, electrocardiogram; ICH, intracerebral hemorrhage; INTERSTROKE, International case-control study in stroke; HD, heart disease; IHD, ischemic heart disease; Medi, Mediterranean; N/A, not available; OR, odds ratio; PA, physical activity; PAF, population attributable fraction; PM, particulate matter; PURE, Prospective Urban Rural Epidemiologic; SIREN, Stroke Investigative Research and Educational Network; SVD, small vessel disease; T2DM, Type 2 diabetes mellitus; VCI vascular cognitive impairment; WM, white matter.

damage, oxidative stress, covert accumulation of neurodegenerative proteins such as amyloid and hyperphosphorylated tau and failure of intramural periarterial drainage (IPAD) inducing hypoperfusion or hypoxic events in the brain [57].

Moreover, complex physiological interactions between markers of metabolic syndrome (e.g. hypertension) and arteries occur to produce arteriolar inflammation that impacts on perfusion [58]. Brain inflammation is now considered as an early event and an important contributor in the progression of VCI. For example, systemic levels of the proinflammatory cytokine interleukin-1β have been reported to be increased in VCI. Experimental studies suggest that the inflammasome signaling pathways mediated by the NLR-pyrin domain containing 3 (NLRP3) and absent in melanoma 2 (AIM2) inflammasomes regulate interleukin-1β production. Furthermore, recent meta-analysis showed that three inflammatory markers interleukin-6 (IL-6), C-reactive protein, tumor necrosis factor-α were found to be higher in the blood and CSF samples from VaD patients and high IL-6 and tumor necrosis factor-α levels were also associated with increased risk of incident VaD [59]. These findings pave the way for future disease-modifying treatments to reduce inflammation induced damage and cognitive deficits observed in VCI.

6. Common risk factors for VCI

Various factors comprising inflexible and modifiable risks may alter cognitive status during the life course (Table 1). The association between vascular disease and cognitive dysfunction is compounded by hormonal, inflammatory, dietary and lifestyle factors such as physical inactivity. In addition, cognitively impaired subjects may be prone to unhealthy habits including ingestion of more processed foods, tobacco use and alcohol abuse resulting in obesity and insulin resistance. The combined potentially modifiable risk for dementia globally, estimated by the Lancet Commission for 12 risk factors was estimated to be 40% compared to 41% for the US population. While comparisons of unweighted population attributable fractions for dementia appear to be highly variable for some risk factors (Table 1), there is great potential to reduce the burden of dementia and therefore VCI globally.

The strongest risk factor for VCI is older age. Several genetic traits have also been associated with VCI, but the two of the common genes are *APOE* and *NOTCH3* (Table 1). We have previously reported on the association of *APOE* alleles *ε4* (OR = 1.85) and *ε2* (OR = 0.67) in VCI [60]. This is consistent with our previous study in elderly stroke survivors with early cognitive impairment, where the presence of an *APOE ε4* allele was associated with greater progression of cognitive decline [61]. With respect to *NOTCH3* while over 280 distinct gene mutations are causal in typical CADASIL. However, large exome analysis has indicated that the frequency of archetypal cysteine altering *NOTCH3* mutations are remarkably 100-fold higher than expected and cause SVD disease phenotype with less severe typical CADASIL symptoms [62]. In a recent UK Biobank study [63], *NOTCH3* mutation carriers were found to have 5-fold greater risk of VaD, adding to the global burden of SVD and risk of VCI. Other genes of interest were the high-temperature requirement A serine peptidase 1 (*HTRA1*) carriers, who have two-fold increased risk of all-cause dementia and *Collagen 4 (COL4) A1/2* carriers with nearly 4-fold risk of intracerebral hemorrhage [63]. The Biobank data emphasize that cardiovascular risk is associated with increased risk of stroke in *NOTCH3* and *HTRA1* variant carriers; control of cardiovascular risk factors could still improve disease prognosis in individuals with monogenic cerebral SVD variants. There is no doubt that a variety of mitochondrial mutations involving mitochondrial dysfunction modify risk and promote early onset of VCI [64]. Genetic factors, therefore, add to the risk for dementia beyond the identified 40% attributed to modifiable factors (Figure 2). This 40% attribution was also estimated in another important prospective real-world study which looked at modifiable risk factors including low education, obesity, hypertension, diabetes, depression, smoking, physical inactivity, hearing loss, loneliness, heart disease, stroke, head injury, and delirium and inflexible traits such as the *APOE ε4* allele [65].

Projected estimates indicate that by 2025, 3 of every 4 persons will be living with high blood pressure and may incur co-morbidities such as diabetes, high body-mass index or obesity and individual features of metabolic syndrome risks including high fasting plasma glucose, high total cholesterol and low glomerular filtration rate [66,67]. Current evidence also shows cumulative vascular disease risk factors worsen neurocognitive deficits [68] and promote depression [32] as well as severe frailty [69,70]. These realizations are a major alarm call for appraisal of vascular brain and mental health, work capacity and socioeconomic development particularly in the peoples of Africa, Asia and Latin America [71].

In addition to modifiable risk factors for VCI, cognitive reserve, both biological and cognitive aspects, is an important factor in the resilience of the brain to stroke or other injury [72]. This may be modulated by levels of education and type of occupation. Findings from a recent meta-analysis showed that besides the risk of stroke in less educated individuals, childhood socioeconomic background and intelligence are also associated with albeit modest risk of stroke and by extension VCI [73].

6.1. *High blood pressure and variability*

By 2025, it is estimated that the global prevalence of hypertension, diagnosed as blood pressure ≥ 140/90 mm Hg, will increase by 30%. Remarkably, on average 1 in 3 adults is hypertensive or will develop hypertension not only in high-income but also in low- and middle-income countries [74]. Long-term blood pressure variability also plays a major role in determining the outcome of stroke and is associated with cardiovascular and mortality suggesting serious implications for VCI [75]. However, improvements in the detection, treatment, and strict control of hypertension vary substantially across countries, with some middle-income nations now outperforming most high-income countries. Reducing the global burden of hypertension prevalence through primary prevention and enhancing its treatment and control is still attainable globally in all settings [76,77]

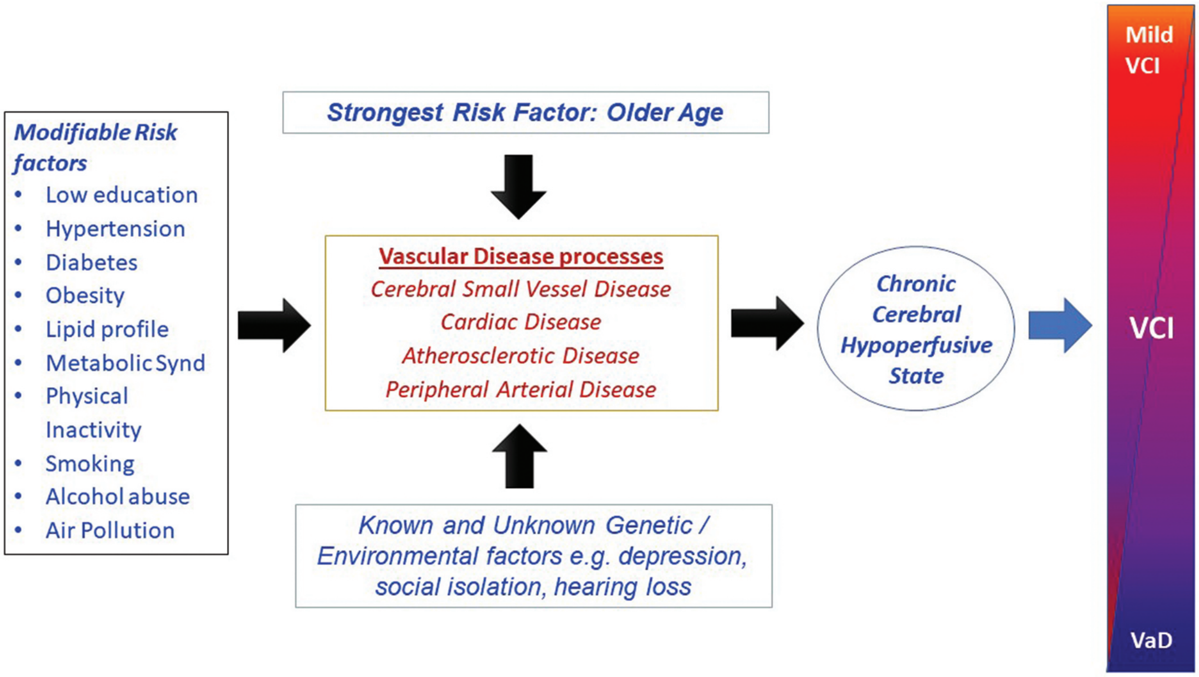
Modifiable Risk factors
Low education
Hypertension
Diabetes
Obesity
Lipid profile
Metabolic Synd
Physical Inactivity
Smoking
Alcohol abuse
Air Pollution
Strongest Risk Factor: Older Age
Vascular Disease processes
Cerebral Small Vessel Disease
Cardiac Disease
Atherosclerotic Disease
Peripheral Arterial Disease
Known and Unknown Genetic / Environmental factors e.g. depression, social isolation, hearing loss
Chronic Cerebral Hypoperfusive State
Mild VCI
VCI
VaD

Figure 2. Scheme illustrates how various risk factors may influence the cerebral as well as systemic vasculature at distinct levels to induce chronic brain or cerebral hypoperfusion and result in variable degrees of cognitive impairment over time. Several genetic and environmental factors may modify the intensity of vascular damage.

Hypertension is the most common risk factor and the most modifiable for VCI. Several studies over the past 25 years have collectively shown that sustained hypertension is a major vascular risk factor for cognitive dysfunction [78]. Hypertension particularly in midlife is associated with later-life cognitive impairment and the development of dementia [78]. Young-to-midlife higher blood pressure exposure is further associated with midlife cognitive impairment. The duration of hypertension during the life-time course may also impact on cognition differently. The association between hypertension and cognitive outcomes in very late-life is complex and less consistent but it seems hypotension is of greater importance in the oldest old [78]. Thus, distinct patterns of blood pressure changes over the whole life-course appear important predictors of late-life cognitive impairment. The cognitive deficits associated with hypertension include several domains including impairment of planning, reasoning and executive dysfunction. Older age and increased body weight are consistent predictors of hypertension, given that prevalence estimates of hypertension were substantially higher in the elderly, compared with younger adults, and in overweight/obese persons, compared with normal weight persons. Like dementia prevalence, lower educational status was also found to be largely associated with a higher prevalence of hypertension.

Previous inconsistent findings on certain effects of raised blood pressure on cognition during the life course have raised the concerns that there are other factors beyond determining the mean blood pressure [79]. This could be important for VCI prevention and early intervention. In a recent meta-analysis, that included 20 studies for the primary outcome, both a higher mean level of blood pressure as well as a higher degree of blood pressure variability were associated with cognitive impairment [80]. Thus, high blood pressure variability may be a predictor for the risk of VCI meaning that the relative contribution of variability in blood pressure appears to be more notable than the mean blood pressure. Variability might be a novel blood pressure-derived parameter to be considered in hypertension management as a future target to prevent VCI. In another meta-analysis of longitudinal studies [81], 13 studies reported visit-to-visit systolic blood pressure variability significantly increased risk of cognitive impairment and dementia. Both visit-to-visit and day-to-day diastolic blood pressure variability also increased risk of dementia and cognitive decline. While the biological mechanisms involved in how variability increases risk are not known it is plausible that even slight fluctuations in flow may exaggerate the dynamics of perfusion and exchange across the BBB as well as affect the glymphatic pathway [57]. However, these studies collectively suggest that long-term blood pressure variability is an independent risk factor for cognitive impairment or dementia. Therefore, an intervention plan for reducing blood pressure variability could be an important target for prevention of VCI.

Hypertension is associated with greater WMHs volumes and progression of white matter changes [82,83], which are known to cause cognitive decline. These observations suggest that high blood pressure promotes white matter damage. In addition, diffusion-tensor MR has indicated that there are more microstructural changes within the white matter in hypertensives than in normotensives. Consistent with this the CARDIA cohort study showed that higher systolic blood pressure from young adulthood to midlife was associated with greater changes in fluidity of normal appearing white matter in middle aged adults [84]. Thus, integrity of the white matter and therefore brain connectivity is an important substrate of hypertension and cardiovascular disease [85] related brain injury and potential VCI. Consistent with this is a recent post-mortem study [86], which showed that use of antihypertensives in life by older individuals was associated with a reduction in white matter perivascular dilation and rarefaction and edema.

Still hypertension probably remains the most modifiable among causes of cardiovascular and cerebral vascular diseases leading to VCI (Table 1). Hypertension can be reduced by 10–15% if controlled via safe medication and modification of behaviors [87]. While none of the recent trials have incorporated VCI as the primary cognitive outcome, current meta-analyses of randomized controlled trials suggest lowering blood pressure provides at best modest or no benefits on declining cognitive function (Table 2). However, several randomized controlled trials have shown marginally beneficial or neutral results in relation to blood pressure treatment or lowering and cognitive outcomes (Table 2). While cognition was not worsened, none of the blood pressure medications (e.g. candersartan, telmisartan, atenolol, ramipril) or combination of two agents showed consistent effects in blood pressure lowering on cognition [78]. Irrespective, majority of the meta-analyses (90%) show a clear association between blood pressure reduction and lower risk of incident dementia or stabilization of cognitive decline (Table 2).

Of increased interest is that as conveyed by the SPRINT MIND trials, beneficial effects were apparent not only on cognition but other markers of VCI (e.g. brain volume, WMHs), depending on whether the target treatment included intensive systolic blood pressure (<120 mm Hg) or standard treatment (<140 mm Hg). Upon secondary analysis of data from a SPRINT trial [119], intensive systolic blood pressure control in 80-year-olds resulted in lower risk of major cardiovascular events, mild cognitive impairment and death, with no between-group differences in the rate of injurious falls. However, the benefits did not extend to older adults with lower baseline cognitive function [119]. Encouraging results were also apparent in the most recent SPRINT study on intensive blood pressure control in mild cognitive impairment patients [120]. These results not only suggest that intensive treatment decreased risk for amnestic and multi-domain subtypes of mild cognitive impairment but highlight the relevance of using cognitive impairment as a primary outcome measure in individuals in prodromal stages of dementia or who progress to frank dementia. Taken together, these meta-analyses suggest there is a measure of benefit in slowing cognitive decline. In terms of classes of antihypertensives, angiotensin-2 receptor blockers (ARBs) seem better than other agents although diuretics were also effective in a limited way (Table 2). However, a number of variables seem to govern these trials including the type of eligibility criteria including patients with high enough cardiovascular risk, aim to preserve cognition or slow impairment, adequate sample size, follow-up time, and utilization of relevant neuropsychological tests for primary outcomes of cognitive impairment or dementia [78].

6.2. Diabetes mellitus and glucose-lowering strategy

Diabetes mellitus (DM) or T2DM is a considerable risk for VCI largely because it is involved in SVD [121]. It increases risk of VaD by 2.5 fold and of AD by 1.5 fold [122]. Recent analysis of the UK Biobank records [123] indicated that T2DM was associated with marked cognitive deficits, particularly in executive functioning and processing speed, which are key cognitive domains of VCI. Alarmingly, in U.S.A. approximately one-third of the adult population has prediabetes or diabetes [124]. Conversely, about one-half of persons aged 60 years and older, who are most at risk for cognitive impairment may have prediabetes or diabetes. The UK Biobank data also suggest there is marked acceleration of normal brain aging in individuals with long standing T2DM. Imaging records suggest gray matter atrophy occurs, particularly in subcortical regions involved in fronto-subcortical circuits, at a ~ 26% faster rate in diabetics compared to those aging normally whereas disease duration was associated with increased neurodegeneration [123].

The prevalence of T2DM tends to occur most often with hypertension, particularly in certain ethnic groups. For example, hypertension and T2DM frequencies were almost two times and five times higher in the Boston Hispanic community adults than in Alzheimer's Disease Neuroimaging Initiative (ADNI) non-Hispanic White participants. Diffusion-tensor MRI showed more white matter damage and smaller hippocampal volumes and larger brain aging deviations consistent with lower executive function and global cognitive scores in individuals with both hypertension and T2DM [125] Consistent with these findings, a large RCT reported that intensive blood pressure control (systolic BP target <120 mm Hg versus <140 mm Hg) may reduce death and cardiovascular events among patients with T2DM receiving standard glycemic treatment and without cognitive impairment [126].

Irrespective, it is clear that comorbidities promote greater brain structural disruptions and probably more cognitive domains than one risk such as hypertension alone. However, there is conflicting evidence from clinical trials of T2DM interventions evaluating the effects of greater glucose control on cognitive decline. Lifestyle interventions in people with diabetes and prediabetes do not seem to be related to better cognitive outcomes either. Collectively, these findings argue for targeting multiple domains or deploying polypill approaches to prevention of VCI. It is not entirely clear how diabetes causes SVD but there is increasing interest in use of glucose-lowering strategies [127]. Hyperglycaemia may inflict direct effects on brain tissue, or it is likely that there is deleterious accumulation of glycated protein conjugates and oxidants in blood vessel walls of smaller arteries causing reduced pulsatility and vascular tone to cause hypoperfusion. In addition, there may be effects of one or more diabetes-linked comorbidities including hypertension, dyslipidaemia and hyperinsulinemia. Among glucose-lowering agents, metformin was associated with better cognitive function, particularly executive tasks whereas injectable insulin was largely ineffective in improving or stabilizing cognitive decline (Table 2). Metformin is considered a first-line anti-diabetic medication

Table 2. Pharmacological approaches to control VRFs and prevent VCI progression.

Vascular Disease Risk Factor control	Class of Agents:	Specific used in Trials††	All-cause-dementia or VaD outcomes: meta-analyses*	Key References
Hypertension	Angiotensin-2 receptor blockers (ARBs):	Candesartan, Telmesartan, Irbesartan, Losartan, Valsartan, Olmesartan	• Meta-analyses (90%) indicate antihypertensives generally reduce risk of incident dementia or improve certain cognitive domains	[78,88–100]
	ACE Inhibitors: Inhibition of vasoconstrictor angiotensin II	Enalapril, Lisinopril, Perindopril, Ramipril	• Cognition or CBF not worsened but may even protect it. Single agents (e.g. candersartan, telmisartan, ramapril, atenolol) versus combination of two not shown consistent effects on BP lowering on cognition	
	Calcium Channel Blockers:	Amlodipine, Felodipine, Nifedipine, Diltiazem, Verapamil	• ARBs overall more effective compared to other classes	
	Beta Blockers	Atenolol, Bisoprolol	• Diuretics of benefit or reduced risk of incident dementia	
	Diuretics:	Indapamide, Bendroflumethiazide	• Certainty of overall evidence low due to sample sizes, design of trials, risk of bias in trials and statistical heterogeneity	
Coagulation	Nonsteroidal anti-inflammatory drugs (NSAID)	Aspirin: 75 mg	• No clear evidence to support the use of low-dose aspirin • Risk of bleeds with aspiring but no evidence of harm of other NSAIDs, no need to trial low-dose aspirin for dementia prevention • Other NSAIDs of any class (celecoxib, rofecoxib or naproxen) for the prevention of dementia	[101–103]
	Anti-coagulants: warfarin		• While warfarin is useful in reducing stroke-like events and embolism subsequent to AF, oral anticoagulants are better in slowing cognitive decline.	[104]
	Anti-platelet agents: clopidogrel		• Patients at high risk of VCI may benefit from addition of long-term clopidogrel monotherapy • Dual therapy more effective than monotherapy in reducing recurrent stroke or TIA risks of VCI	[104,105]
Diabetes/ glucose-lowering drugs	Metformin		• Metformin therapy likely reduces risk of cognitive decline in patients with 2TDM • Majority (>60%) of studies reported reduced risk of CI and dementia (by 23–26%) but two (12%) suggested increased dementia risk with metformin use • Studies addressing biases in general concluded lack of effect of metformin on dementia risk • Dual therapy with metformin (Met) and (DPP-4i) but not sulfonylureas (SU) were associated with reduced incidence of all-cause dementia and VaD. • Dual therapy with TZD lowered risk of all-cause dementia, VaD	[106–109]
	Glucagon-like peptide-1 (GLP-1) analogues and receptor agonists		• Five studies suggest GLP-1 receptor agonists use was associated with reduction in risk of all-cause dementia by ~ 33% • GLP-1 analogues exert no significant effects on general cognitive functioning but may be beneficial for patients <65 years with T2DM and those without history of cardio-cerebrovascular diseases	[110–112]
	DPP-4 inhibitors Dipeptidyl Peptidase IV (DPP 4) Inhibitors – gliptins: saxagliptin, vildagliptin, linagliptin, and sitagliptin		DPP-4 inhibitors use was associated with decreased risk of all-cause dementia and VaD (by ~ 40%). Previous studies found not enough irrefutable evidence to support positive effects of incretins (dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors/DPP-4I) and GLP-1receptor agonists on cognition	[111,113]
	Sodium glucose co-transporter-2 (SGLT2) inhibitors,		Findings from 3 studies suggest SGLT2 inhibitor users had a lower risk of all-cause dementia. SGLT2 inhibitors versus DPP-4 inhibitors were associated with lower risk of dementia over mean follow-up of 2.80 years. Dapagliflozin >empagliflozin but canagliflozin no association	[111,114]
Lipid-modifying agents†	Statins		• Most recent meta-analyses showed CHD, PAD, and CAD were all associated with stroke and CI and dementia • Several studies (one RCT and 55 cohorts) suggest post-stroke statin use decreased risk of CI • Indication bias and design limitations may have been a factor in several studies where evidence showed no effects	[115,116]
Other 'vascular' agents	NO donors: isosorbide mononitrate	Increase NO signaling	• LACI-2 trial in lacunar strokes suggested increased cerebrovascular reactivity	[117]
	PDE 5 Inhibitor: dipyridamole		• Used in combination with aspirin short-term, effects on thrombosis but not CI	[104]

(Continued)

Table 2. (Continued).

Vascular Disease Risk Factor control	Class of Agents:	Specific used in Trials††	All-cause-dementia or VaD outcomes: meta-analyses*	Key References
	PDE 3 inhibitor: cilostazol		• Cilostazol use was associated with decreased risk of incident dementia • Cilostazol use was also found to have a dose-dependent association with reduced rate of incident dementia • LACI-2 trial showed reductions in recurrent stroke, dependence, and CI after lacunar stroke	[117,118]

*Analyses specifically evaluating AD not included [162,203–205]. †Beneficial effects of fenofibrate are unclear. ††A network meta-analysis on cholinesterase inhibitors for VaD and VCI indicated moderate- to high-certainty evidence that donepezil 5 mg, donepezil 10 mg, and galantamine have a slight beneficial effect on cognition in people with VCI, although the size of the change is unlikely to be clinically important [206].

Abbreviations: ACE, angiotensin converting enzyme; CAD, carotid artery disease; CBF, cerebral blood flow; CHD, coronary heart disease; CI, cognitive impairment; GLP-1 glucagon-like peptide-1; LACI-2, Lacunar Intervention Trial-2; N/A, not available; NO, nitric oxide; PAD, peripheral arterial disease; PDE, phosphodiesterase; RCT, randomized control trials; VaD, vascular dementia; VCI, vascular cognitive impairment.

for T2DM. It has several effects including promoting neurogenesis, reduce oxidative stress, enhance spatial memory deficits and more probably acts as an antidepressant [128]. Adding thiazolidinedione, or dipeptidyl peptidase IV (DPP-4) instead of sulphonylureas as a second-line anti-diabetic treatment may be considered for delaying or preventing impairment although recommended clinical guidelines point at further investigation. Additionally, thiazolidinedione users relative to non-users on dual oral therapy were significantly associated with lower risk of various types of dementia [106]. Pooled results from large registries also suggest that glucagon-like pepetide-1 (GLP-1) receptor agonists provide another option to reduce VCI burden [110]. All cause dementia rate was lower in T2DM patients taking GLP-1 receptor agonists by 11–33% (Table 2).

Newer glucose lowering drugs were associated with a decreased risk of all-cause dementia in people with T2DM. However, the observational nature and significant heterogeneity between studies, necessitates that the results should be interpreted with caution. Further research is warranted to confirm our findings [111]. Sodium glucose co-transporter-2 (SGLT2) inhibitors showed an association with lower dementia risk in older people with T2DM. Randomized controlled trials are warranted [114].

6.3. *Dyslipidaemia and obesity*

The imbalance of lipids, particularly triglycerides and LDL-cholesterol in the blood, has been of much interest both in the context of stroke and dementia incidence [129]. Recent meta-analysis involving records of some 1.2 million subjects strongly suggests midlife hypercholesterolemia is associated with increased incidence of MCI as well as all cause dementia. Furthermore, each 1 mmol/L increase in low-density lipoprotein was associated with an 8% increase in incidence of all-cause dementia [130] Similarly, a longitudinal cohort study reported that elevated triglycerides as well as total cholesterol were associated with greater 20-year decline in executive function, attention and processing speed, all features of VCI. Higher total cholesterol and triglycerides were further associated with greater decline in memory [131]. Thus, in keeping with risk of stroke, dyslipidaemia even as component of the metabolic syndrome is invariably associated with higher risk of VCI.

Obesity defined as body mass index of greater than 30 is associated with decreased blood supply to the brain likely causing rarefaction of the white matter [132,133]. Obesity induces sustained release of the adipocyte-secreted proteins and a repertoire of inflammatory cytokines, which explain the association between obesity and increased risk of dementia. In chronic phase these changes may alter neuronal function and induce cerebral atrophy [134,135].

6.4. *Other risks both acquired and environmental*

Several other risk factors may directly or indirectly be implicated in the causation of VCI by enhancing covert changes or even overt vascular disease (Table 1). The well known among these with a clear vascular basis include hyperhomocysteinaemia and heart disease that may influence cognitive function. It is widely known that excessive alcohol and tobacco use increase vascular damage and therefore can affects cognitive function by compromised brain perfusion. Peripheral arterial disease is also regarded as a risk for cognitive impairment.

While there is not much information on hearing loss and VCI, there is now good evidence that depressive illness is strongly associated with cardiovascular disease as well as dementia. People with cardiovascular disease are at higher risk for dementia but also mental disorders including depression [1]. Major depressive disorder is associated with the progression of a range of vascular disease comorbidities and mortality [2]. In fact, there is a bidirectional relationship between depression and stroke risk. Depression increases the risk of stroke, there is high prevalence of depression post-stroke, and this appears to worsen post-stroke, outcomes possibly promoted by inflammatory mechanisms. In addition, the ‘vascular depression’ hypothesis is characterized by executive dysfunction and memory impairment and SVD in the frontal lobe [31], which is challenging to treat clinically, and where cognitive impairment does not full resolve with effective depression treatment, resulting in a high-risk state for progression. These observations, however, collectively suggest reducing risk for vascular disease and treating depression will impact on VCI. Among the least investigated risk factors associated with stroke incidence, air pollution is gaining prominence as an important risk to vascular brain health. Accumulating evidence suggests that exposure to several air pollutants containing particulate matter is associated with reduced white matter volumes and integrity [136,137]. Short-term and long-term particulate matter (e.g. at $PM_{2.5}$) may also cause vascular damage and lead to neurodegeneration [138].

Remarkably, there is increased risk of VCI compared with Alzheimer type of dementia in countries yet to undergo demographic transition [139]. This is because of the links between stroke and cerebrovascular diseases due to several infectious diseases including HIV [140]. In addition, adverse childhood experiences in LMICs including both psychosocial such as neglect and abuse but also displacement, and early malnutrition are recognized to be associated with increased cardiovascular risk in later life [141,142]. Moreover, there is an association between mental health conditions such as post-traumatic stress disorder and increased cardiovascular risk [143]. This may be due to more risky lifestyles but also long-term inflammation [140]. The mechanism is not well understood, but it's important to explore as a psychotherapy and addressing post-traumatic stress disorder may be protective against later CVD.

7. View on pharmacological interventions

Prevention of VCI may also be implemented by pharmacological management of blood pressure, T2DM, dyslipidaemia, and antiplatelet therapy for secondary prevention of stroke and relevant long-term outcomes. Interventions for specific causes of stroke including anticoagulation could also benefit patients at risk of VCI (Table 2). The recent European Stroke Organisation guidelines [144] suggest treatments for long-term risk of recurrent ischemic stroke should involve lowering blood pressure lowering to < 130/80 mmHg, use of statins (HMGCoA-reductase inhibitors) and reducing low density lipoprotein level to <1.8 mmol/l (70 mg/dl) as well as avoiding dual antiplatelet therapy with aspirin and clopidogrel after first 90 days, rule out direct oral anticoagulant drugs for embolic stroke of undetermined source and consider pioglitazone for T2DM or insulin resistance upon careful consideration of possible risks. However, encouragingly most current meta-analyses involving several thousands of patients have indicated mostly favorable effects of pharmacological agents on stabilizing, reducing or delaying VCI (Table 2).

8. Protective factors

To keep age-related vascular disease at bay and maintain cognitive function and vascular brain health a number of protective factors could prevent or substantially delay VCI. These include adopting healthy diets and, increasing physical and cognitive activities even in older age and promoting multidomain approaches globally in all settings at the population level are priority (Table 3).

8.1. Dietary measures and food ingredients

Over the past 20 years various efforts have been made to promote healthy eating habits in midlife and late-life (Table 3). There are several studies showing limited benefits of the Medi, DASH and MIND diets and from consumption of berries, leafy green vegetables, fresh food ingredients and nuts. Foods with high fiber content are also advocated but evidence for beneficial effects from consumption of these in large quantities is derived from experimental studies. Among Indigenous Africans, consumption of plant-based diets including green leafy vegetables has demonstrated dose-dependent protection against occurrence of stroke, hypertension giving some protection against post-stroke VCI [164,165]. These are largely thought to impact on oxidative and nitrosative stresses, mitophagy processes and inflammation. Thus diets rich in antioxidants, vitamins B, D and K can contribute to better vascular brain health [166]. The invention of the Mediterranean (medi) diet has been major advancement. Adherence to the medi diet indicates a positive trajectory with excellent potential benefits for mental and cognitive health among Southern Italian elderly [167]. Indeed, its implementation as an intervention as well as prevention has overall been perceived as a positive step forward although the benefits have not always been substantial. In recent years, the DASH and MIND diets have been invented particularly to reduce risk of AD [168] and related disorders (Table 3) and therefore have promise for VCI. Moreover, studies have also suggested intake of total saturated fatty acids intake appeared to be inversely associated with cognitive impairment and that specific subtypes of fatty acids including short- and middle-chain saturated fatty acids are more beneficial [169].

The benefits of coffee consumption have also been of interest in the context of dietary lifestyles. For example, moderate daily mocha coffee drinking was associated with higher cognitive and mood status among individuals at risk of mild VCI and age-related depression [170,171]. Other approaches have been to target the gut microbiome [172]. The production status of equol, a metabolite of soy isoflavone, is dependent on the gut microbiome, and equol-producing status was found to be associated with delayed burden of WMH some 6–9 years later, suggesting that the gut microbiome plays a key role in the development of SVD via the gut-brain axis. Overall, these measures have produced moderately positive results in either stabilizing or reducing cognitive decline but certainly show no harmful effects.

8.2.1. Physical Activity

Current meta-analyses suggest there are some effects on prevention of cognitive decline and dementia (Table 3). Just over 50% of all the studies show beneficial effects of exercise on cognition. Multiple activity component protocols involving aerobic exercise or integrity training seem to be more beneficial. For example, isometric exercise training improves vascular integrity and elicits blood pressure reductions in hypertensives greater than those seen with dynamic aerobic and resistance exercises. Such training may stimulate reactive hyperemia to trigger a cascade of vascular, neurotrophic and

Table 3. Lifestyle and non-pharmacological approaches to prevent VCI.

Risk Control Factor	Specific features	Action(s); Treatment Indication	VCI outcome: Overall results	References
Diet	Mediterranean (Medi) diet	Antioxidants, anti-inflammatory properties	• Adherence to Medi diet associated with better cognitive scores in 9 of 12 cross-sectional studies, 17 of 25 longitudinal studies, and 1 of 3 trials. • Few other nutritional interventions were found to convincingly improve cognition of individuals with MCI • Intake of 'tropical fruits-oats' dietary patterns protect against dementia incidence among older Malaysian Asians • More quality trials in MCI and VCI populations required to assess reduction in progression to dementia • Diet adherence advocated for both dementia and VCI	[145–147];
	MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay)		• Greater adherence to MIND diet was associated with better cognitive scores in 1 cross-sectional study and 2 of 3 longitudinal studies • In a meta-analysis of 11 cohort studies highest tertile of MIND diet score associated with lower risk of dementia • Overall, MIND diet associated with lower risk of incident dementia in middle-aged and older adults, but more quality trials needed for VCI	[145; 148]
	DASH (Dietary Approaches to Stop Hypertension)		• High adherence to DASH diet associated with better cognitive function in 1 cross-sectional study, 2 of 5 longitudinal studies, and 1 trial • Collectively, adherence to Medi, DASH, or MIND diets slow cognitive decline and with strongest association for MIND diet	[145]
	Vitamins		• B Complex vitamins, particularly folic acid, has positive effects on delaying risk of cognitive decline • Ascorbic acid and high dose vitamin E, given separately, beneficial for cognitive performance • Vitamin D supplementation trials inconclusive	[149]
	Berries		• Berry-based supplements and foods show beneficial effects on resting brain perfusion • Benefits also on cognitive domains involved in VCI including memory performance, executive functioning, processing speed and attention	[150]
	Citicoline	Food supplement (cytidine and choline)	• Citicoline is safe and tolerated agent with evidenced neuroprotective properties • Large clinical trials are needed to confirm its benefits	[151]
	Carotenoids		• Carotenoid intervention associated with better cognitive outcomes (Hedge's $g = 0.14$) • No evidence of heterogeneity among the studies • Further confirmatory studies are needed	[152]
Physical Activity (PA)/ Exercise	Single and multiple regimes		• Decreased risk of all-cause dementia (20%), and VaD (30%), even in longer follow-ups (≥20 years) for all-cause dementia • Neither baseline age, follow-up length nor study quality moderated associations • PA as a modifiable protective lifestyle factor for VCI even after reducing the effects of reverse causation • Multicomponent exercise beneficial effects on global cognition, especially executive function, flexibility, agility, mobility, muscle strength, gait speed and ADLs. • Some evidence for HIFT benefits on general cognition in older adults with CI • Two articles showed improvement in cognitive function but there is heterogeneity of intervention protocols, measurement time points, and control group activities, mixed results • Cognitive function improved in 2 studies, deteriorated in 3 studies, and remained stable in 11 studies. • In another review 9 out 16 studies showed greater improvement in cognition	[153; 154] [155] [156] [157]
	Multidomain exercise training		• Dose response study suggests every 500 kcal or 10 MET-h increase/week, ~10% in risk of any dementia • Analyses of 8 studies suggested multicomponent PA affects global cognition on MCI or dementia only when aerobic exercise is included	[158; 159]
Multidomain strategy			• After 2-year follow, FINGER trial showed effects on overall cognition including executive function and processing speed, and body mass index, dietary habits, and physical activity • Other multidomain non-pharmacological interventions seem to have small to medium improvements on global cognition in older MCI subjects, but it is not clear which specific cognitive domains are affected • It is expected that the J-MINT PRIME Tamba will support results from the FINGER trial	[160; 161]; [162; 163]

Other strategies in prevention of VCI such as cognitive therapy and rehabilitation have been used but it is too early to convey if there are definite beneficial effects.

Abbreviations: ADLs, activities of daily living; FINGER, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; HIFT, high intensity fitness training; J-MINT PRIME, Study to Prevent Cognitive Impairment and Disability Japan-Multimodal Intervention Trial for Prevention of Dementia PRIME Tamba; MCI, mild cognitive impairment; Medi, Mediterranean; MET, metabolic equivalent of task; VCI, vascular cognitive impairment.

neuro-endocrine events leading to improvement in cognitive function [173]. Similarly, regimes that promote cardiorespiratory fitness and increase cerebral vascular function incorporating cerebral vasoreactivity and cerebral pulsatility are more likely to impact on cognitive function even with increasing age-related arterial stiffness [174]. Consistent with experimental studies, the beneficial effects of enriched environment and intense physical activity not only reduce WM abnormalities but also recurrent stroke lesions [175,176]. However, more research is needed in human trials with greater optimization in methods of assessment, types of training to test, physiological limitations of the participants and outcome measures (Table 3). The presence of vascular pathology in the brain of would-be participants in such trials would also be factor in how they might benefit or improve. In a unique pathological study [177], cystic infarcts and microinfarcts, but not pathological markers of dementia were associated with physical performance levels five years prior to death. These observations suggest degrees of physical function in the years prior to death are affected by vascular brain pathologies, which include substrates of VCI such as WMHs, microbleeds and microinfarcts. Thus, an evident implication from these studies is that irrespective of the robust findings it is imperative to do all possible to reduce vascular disease risk and promote vascular protection.

9. Multidomain approaches

Multi-domain rather than single domain approaches is likely to be beneficial in prevention (Table 3). Interventions need to ensure factors such as frailty or co-morbid conditions, current medications and potential lifestyles could impede interpretation of the outcomes. Muti-domain trials that particularly target cardiovascular risk reduction or vascular prevention [178] would benefit not only VCI but all cause dementias. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial involving 60–77 year-olds and with high Cardiovascular Risk Factors, Aging and Dementia Risk scores showed a positive change in global cognition with effects on executive function and remarkably in processing speed [160]. Other large multidomain trials (FINGER, MAPT, and PreDIVA) have shown that a multidomain lifestyle intervention can benefit cognition in elderly people with an elevated risk of dementia (Table 3). Overall, results from these three trials suggest that targeting of preventive interventions to at-risk individuals is an effective strategy. There is further promise from more ongoing multidomain trials such as Medex-UK [179] with feasible protocols and strong encouragement to adherence. The Japan-Multimodal Intervention Trial for Prevention of Dementia PRIME Tamba (J-MINT PRIME Tamba) randomized clinical trials involving participants aged 65–85 years living in a rural Japan is also expected to deliver beneficial effects on those at risk of VCI and dementia [162].

Other non-pharmacological approaches may include the use of transcranial magnetic stimulation, as a noninvasive tool to evaluate in vivo cortical excitability and relate to the pathophysiological process and VCI progression. It can enable responders to benefit from specific pharmacological or other agents in the attempt to restore neural plasticity [180,181].

10. Expert opinion

VCI represents a huge burden in the older population. The true prevalence or incidence of VCI is not known but it is certainly more common than any of the dementias by virtue of the prevalence of both stroke and cardiovascular disease. The high global burden of VCI estimated to be greater than 4 million in 2019 compared to 7.2 million cases of dementia reported by the GBD collaborators predict proportionally high rates of morbidity, cognitive and behavioral disorders and mortality. While major VCI or VaD is recognized as the second most common cause of dementia worldwide, the prevalence of mild VCI which involving executive dysfunction different from memory deficits is grossly underestimated. Thus, we need better prevalence and incident data on VCI to more confidently address strategies for prevention and protection. VCI can also be different in LMICs. It is clear that both strategies for primary and secondary stroke prevention strategies will impact on VCI. The key modifiable risk factors for vascular disease include hypertension, T2DM, dyslipidaemia, obesity and metabolic syndrome. These factors clearly increased risk of stroke and impair vascular brain health. Indeed, there is now stroke epidemiological and experimental evidence suggesting that lifestyle factors and dietary habits influence cerebrovascular regulation and impact on VCI [182,183]. Hypertension is the most common modifiable risk factor for VCI, but emerging data suggest that blood pressure variability may be even more important. Recent meta-analyses on use of specific pharmacological approaches to control vascular risk suggest there are definite albeit small to moderate benefits in either preservation or improvement of cognitive function. This especially in those studies where there is good adherence to treatment. However, better designed randomized clinical trials to particularly assess efficacy of medications are needed. Universally standardized eligibility criteria, adequate sample size and length of follow-up time are key factors in obtaining more reliable data. In terms of eligibility for example the selection of patients with high enough cardiovascular risk should be considered [78]. The selection of primary outcomes would also be important. For VCI, trials should ensure either mild VCI or severe VCI (VaD) criteria is fulfilled. Mild VCI target is reasonable as it is defined to include impairment in at least one cognitive domain and mild to no impairment in activities of daily living or instrumental activities of daily living. This would be independent of any motor or sensory sequelae of the vascular event [16].

Other risk factors delineated by the 2020 Lancet Dementia Commission that negatively impact on vascular function and promote cognitive decline include lifestyle habits of smoking, alcohol use and physical inactivity. Non-pharmacological approaches including cessation of smoking even later in life and sustaining physical and cognitive activities and encouraging multidomain approaches are good for the prevention of stroke and cognitive decline. Thus, future trials should always consider multi-domain intervention rather than a single area of intervention. Current data suggest that physical exercise to a moderate level is beneficial. However, more vigorous or extreme training does not necessarily add to the benefit. Protocols encouraging cardiorespiratory fitness and enhance cerebral vascular function including cerebral vasoreactivity and pulse will have greater impact on cognitive function. Diet is an important player in maintaining vascular brain health. Several studies show reasonable benefits of the Medi, DASH and MIND diets and regular or even daily consumption of particularly berries, leafy green vegetables, nuts and high fiber are advocated for sustaining low blood pressure, better gut microbiome environment, reducing stroke risk and protection against other risks.

Exposure to degrees of air pollution no doubt enhances VCI and more vigorous control at the individual level in homes or within communities would promote better vascular functioning and cerebral perfusion. However, clear mechanistic studies are needed to fully understand how particulate matter affects vascular function. There is now a remarkable understanding on the association of cardiovascular disease and mental health, depression and behavioral disorders in both causal directions. In controlling cardiovascular risk there would be a dual advantage in reducing the burden of mental illness as well as VCI. There are still several other factors which may potentially affect VCI. These are not specifically addressed in this review. For example, factors such as stress, general wellness, sleep (or sleep apnea), poverty or satisfactory occupation could have implications for vascular brain health. However, all measures and policy changes that address control of vascular disease risk at the individual, community and population levels have the potential to protect vascular brain health and reduce the burden of VCI.

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Declaration of interest

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