Vascular cognitive impairment and dementia: An early career researcher perspective

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Abstract

The field of vascular contributions to cognitive impairment and dementia (VCID) is evolving rapidly. Research in VCID encompasses topics aiming to understand, prevent, and treat the detrimental effects of vascular disease burden in the human brain. In this perspective piece, early career researchers in the field provide an overview of VCID, discuss past and present efforts, and highlight priorities for future research. We emphasize the following critical points as the field progresses: a) consolidate existing neuroimaging and fluid biomarkers, and establish their utility for pharmacological and non-pharmacological interventions; b) develop new biomarkers, and new non-clinical models that better recapitulate vascular pathologies; c) amplify access to emerging biomarker and imaging techniques; d) validate findings from previous investigations in diverse populations, including those at higher risk of cognitive impairment (e.g., Black, Hispanic, and Indigenous populations); and e) conduct randomized controlled trials within diverse populations with well-characterized vascular pathologies emphasizing clinically meaningful outcomes.

1 Introduction

The study of vascular contributions to cognitive impairment and dementia (VCID) encompasses a broad range of research areas that aim to understand, prevent, and treat the detrimental effects of vascular disease burden on human brain structure, cognition, and overall function [1,2]. Neuropathological studies continue to demonstrate that dementia is often the result of multiple etiologies, with mixed vascular, amyloid-beta (Aβ), and tau pathology observed in more than two-thirds of cases [3,4]. By contrast, pure forms of vascular dementia are rare, accounting for only ~10% of dementia cases [5]. Therefore, research on VCID is particularly challenging and requires a comprehensive understanding of the underlying pathophysiology [6].

With the goal of discussing key priorities for future research on VCID, the International Society to Advance Alzheimer's Research and Treatment (ISTAART) Vascular Cognitive Disorders Professional Interest Area (PIA) held an online discussion panel of early career researchers (ECRs) in October 2020, with 177 attendees from 19 countries. Panelist expertise ranged from basic and translational science to epidemiology, prevention, and clinical care. In this perspective piece, we review the following key concepts discussed: a) the clinical definition of VCID; b) past and present efforts towards prevention and treatment; and c) perspectives and priorities for future research.

2 A brief overview of vascular contributions to cognitive impairment and dementia

In this section, we discuss the key elements of VCID, including terminology, diagnostic criteria, underlying neuropathology and potential for therapeutical and/or preventive strategies. A conceptual model of these elements is presented in **Figure 1**.

2.1 Terminology and clinical definition

Historically, research and clinical diagnoses of vascular cognitive impairment have focused on vascular dementia (VaD), large vessel disease, and stroke. Further characterization led to

the recognition of other significant contributors to vascular mild cognitive impairment (MCI) and dementia [1,2,7]. These include cerebral small vessel disease (cSVD), systemic vascular disease, and cerebrovascular pathologies such as cerebral amyloid angiopathy (CAA) concomitant with Alzheimer's disease (AD) and/or Lewy body pathologies [1,2,7]. More recently, the term "vascular contributions to cognitive impairment and dementia" (VCID) has been employed as it better captures the spectrum of associated pathologies [2,8]. However, use of the term "VCID" is not yet widespread among the more than 21,000 publications related to vascular disease and cognitive impairment (see **Figure 2** for publications through 2020).

Various diagnostic criteria have been proposed for independent categories which fall under the VCID umbrella, but integrated, overarching criteria covering all VCID have been difficult to develop and apply (historical evolution of various diagnostic criteria are reviewed in [6] and [8]). Two key features are required for VCID diagnosis: a) the presence of cerebrovascular disease or cerebral hypoperfusion, and b) impairment on neuropsychological assessment in at least one cognitive domain (based on the American Heart Association / American Stroke Association Scientific Statement [8] and the Vascular Impairment of Cognition Classification Consensus Study [7]). A causal link between these two criteria is used to distinguish between "probable" VCID where a causal link can be established, or "possible" VCID where a causal link cannot be established with certainty [6–8].

2.2 Neuropathology and neuroimaging

The most prevalent pathology underlying VCID is cSVD, which itself comprises several pathologies that affect the brain's small arteries, arterioles, veins, venules, and capillaries, the integrity of which are crucial to maintain adequate cerebral blood flow (CBF). Other VCID-related vascular pathologies include the venous deposition of collagen and subsequent vessel wall thickening (venous collagenosis), lipohyalinosis, and CAA [9,10]. The consequences of

cSVD are heterogenous in their manifestations; parenchymal lesions associated with cSVD vasculopathy include small focal infarcts (lacunes and microinfarcts), diffuse white matter (WM) lesions, microbleeds (also known as microhemorrhages), intracerebral hemorrhage, and subarachnoid hemorrhage [11].

Neuroimaging is heavily relied upon to assess the extent, location, and type of vascular lesion present, and to allow differential diagnosis. Individuals with VCID typically present evidence of prior strokes and diffuse white matter lesions, the variability in size and distribution of which may reflect differences in etiology and pathological severity. T1-weighted MRI is used to visualize atrophy, whereas T2-weighted MRI aids in the visualization of lacunar infarcts and WM hyperintensities (WMH). WMH are diffuse areas of hyperintense signal (also seen on fluid-attenuated inversion recovery [FLAIR] sequences) that occur in WM regions undergoing demyelination and subsequent axonal degeneration [12,13]. Although not required for the diagnosis, WMH are often interpreted clinically as a surrogate for cSVD contributing to VCID pathophysiology (reviewed in [10]). T2*-weighted MRI and susceptibility-weighted imaging (SWI) are used to identify hemosiderin deposits indicative of microbleeds and other forms of hemorrhage. Therefore, the different neuroimaging techniques are useful because they can discriminate the different pathophysiological mechanisms underlying the VCID syndrome in individual persons."

2.3 Epidemiology and risk factors

Estimates for prevalence and incidence of VCID are incomplete and have been variable depending on what is included in the definition. Factors contributing to this include historical diagnostic fragmentation, whether milder forms of cognitive impairment are included in addition to dementia, uncertain diagnostic categorization due to mixed cerebrovascular and neurodegenerative pathologies, whether neuroimaging characterization is available, and the recent introduction of the term VCID [2,8,11]. Occurrence of VCID varies by sex, age,

race/ethnicity, individual vascular and cardiometabolic risk factors, and comorbid conditions [14].

Inherited and modifiable factors traditionally associated with neurotoxicity, microglial activation, compromised neural repair mechanisms, thromboembolic phenomena, and blood-brain barrier (BBB) dysfunction, all increase dementia risk [15]. Cross-sectional studies have shown that the *APOE*-ε4 allele, midlife obesity, a family history of cardiovascular disease, and the number of cerebrovascular risk factors present are strongly associated with earlier dementia onset in selected populations [16]. Risk of post-stroke dementia is also high, especially when individuals present with additional vascular and cardiometabolic risk factors [17]. In both familial and sporadic forms of AD, prior history of stroke has also been associated with increased dementia risk [18]. Prospective studies have shown that later onset of AD and lifetime alcohol use are associated with faster cognitive and functional decline [19], and sex differences are also observed [20].

2.4 Genetics & RNA-seq

Genome-Wide Association Studies (GWAS) of VCID constitute a growing area of research, with new genetic underpinnings being linked to stroke [21,22] and cSVD [23]. Furthermore, many of the genes identified in GWAS for AD have been linked to vascular dysfunction (e.g., *APOE*, *PICALM*, *CLU*, *PSEN1*, *PSEN2*, *APP*, *MEOX2*, and *COL4A1*) [24–26]. Monogenic forms of cSVD (leading to cognitive impairment in some individuals), such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), are relatively rare [27]. Major efforts are underway to discover and understand genetic contributions to AD and VCID; nominated targets and other genes can be explored through the Agora database (https://agora.ampadportal.org/genes).

Genomic effects of cognitive reserve, cerebral perfusion, and hormonal changes interact to influence neurodegeneration in late life [19,20] (see the **Box** for specific effects of *APOE*).

Nevertheless, validation in larger and diverse populations is needed. Future long-term prospective studies that utilize GWAS data are needed to assess the risk of cognitive and functional decline in VCID in all populations.

3 Past and present studies of prevention and treatment

3.1 Non-clinical studies in animal models

Considering VCID is inherently heterogenous, animal models can aid in determining which treatments prove efficacious for specific VCID-associated pathologies. Drugs targeting vascular and metabolic factors, such as statins [28], anti-platelet medications [29], and anti-hypertensives [30] have proven efficacious in models of chronic hypertension and chronic cerebral hypoperfusion (CCH), improving CBF and cognition, reducing inflammation, and protecting against neuronal damage (reviewed in [31]). Anti-inflammatory drugs, such as minocycline, which has been shown in multiple models of CCH to attenuate microglial activation, improve memory function, enhance CBF, and preserve WM integrity [32–36]. Immunosuppressants, including cyclosporin A [37] and free radical scavengers [38], have also shown promise in CCH models. Medications that augment acetylcholine signaling have proven effective across models [39,40].

Estrogen and other sex hormones have demonstrated neuroprotective properties and play a role in vascular function and pathology (reviewed in [41,42]). While hormone therapy has been studied extensively in stroke models (reviewed in [43]), few studies have investigated hormonal effects in other VCID-relevant animal models. Estradiol is protective in models of CCH; however, these studies included only males [44,45]. Rodent studies treating females with estrogen are necessary, and should include models of menopause (e.g. ovariectomy, 4-vinylcyclohexene) to provide evidence on the safety and efficacy of hormone replacement therapy for preventing and/or treating VCID in all populations, including post-menopausal women [46].

The heterogenous nature of VCID requires that common comorbidities and clinically relevant risk factors such as sex, biological and endocrine aging, and vascular and metabolic risk factors, be commonly integrated in translational studies. Moreover, our ability to translate non-clinical data to the clinic can likely be improved by conducting studies in non-human primates or larger domesticated species, which share key attributes with humans, including lifespan, CBF, vascular architecture, immune function, and relative abundance of WM [47–49]. Finally, candidate therapies should be tested in animal models of multi-etiology dementias, particularly models with combined vascular and AD pathology [50].

3.2 Pharmacological prevention and treatment strategies in humans

There are no approved drugs specifically for VCID. In some countries current therapeutic management includes off-label use of cholinesterase inhibitors (particularly for those with multiple cortical infarcts and hippocampal atrophy) and of memantine (mainly for those with subcortical cSVD) [51]. Additionally, management of cerebrovascular risk factors continues to be part of the patient care strategy [2], though underlying neurobiological mechanisms are not yet fully understood. Furthermore, midlife arterial hypertension causes memory decline, vascular cognitive impairment [52] and earlier onset of sporadic AD, particularly in combination with other cerebrovascular risk factors [16]. Blood pressure lowering has been shown to reduce risk of cognitive impairment in SPRINT-MIND [53,54] and other cohorts [55,56], with further evidence showing that intensive blood pressure management also reduces accrual of WMH when compared to standard blood pressure management.

There are conflicting results regarding the effects of distinct anti-hypertensive classes over incidence or course of cognitive decline [55–57]. Molecular mechanisms have been studied more often concerning the effects of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers over cognitive decline [58,59]. A recent study of 193 patients with AD found evidence that angiotensin-converting enzyme inhibitors slowed

cognitive (but not functional) decline in one year by way of central or peripheral mechanisms that do not depend upon their anti-hypertensive properties, particularly for *APOE*-ε4 non-carriers who also carried specific *ACE* genotypes of rs1800764 or rs4291 [58]. Additionally, another study of 1689 patients with AD who used angiotensin II type 1 receptor blockers (*n*=578) or angiotensin-converting enzyme inhibitors (*n*=1111) found that, among *APOE*-ε4 non-carriers, use of angiotensin II type 1 receptor blockers was associated with greater preservation of memory and attention, effects that were particularly notable when compared to angiotensin-converting enzyme inhibitors with lower brain penetration [59]. These findings support the importance of pharmacogenetic studies in VCID.

Thiazolidinediones such as pioglitazone and rosiglitazone are agonists of the nuclear peroxisome proliferator-activated receptor γ (PPAR γ). They improve insulin sensitivity, and in animal models demonstrated enhanced Aβ clearance and reduced β-secretase activity [60]. One small study demonstrated that pioglitazone conferred cognitive and functional benefits to patients with mild AD and diabetes *mellitus* [61], while a phase III trial with *APOE*-ε4 carrier stratification showed no benefits of rosiglitazone [62].

3.3 Non-pharmacological treatment and prevention strategies in humans

In general, few studies have focused specifically on benefits of lifestyle modification for individuals with VCID or on VCID-related outcomes. Evidence from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study, an RCT testing a multidomain intervention, suggests that administering diet, exercise, cognitive training, and vascular risk monitoring could maintain or improve cognitive function in older adults thought to be at increased risk of cognitive decline or dementia [63]. While promising, replication of these results is necessary in larger and more diverse populations; this is currently being undertaken by the World-Wide FINGERS network (www.alz.org/wwfingers) which comprises over 30 interventional studies around the world [64,65]. Among these

studies, the US POINTER Study (NCT03688126) has an entire ancillary study dedicated to neurovascular function.

Differences in educational attainment are consistently associated with variations in cognitive and brain reserve. For instance, it is known that age-related reductions in hippocampal volume are less pronounced among more highly educated individuals [66]. A few studies have shown significant effects of cognitive reserve over the expression of VCID: education and managerial or professional occupations buffer individuals against cognitive impairment caused by stroke and promote rapid cognitive recovery early after stroke [67]; higher education preserves cognitive function in individuals with similar degrees of subcortical hyperintensity burden [68]; and education impacts processing speed in patients with CADASIL who have mild and moderate (but not severe) degrees of neuroimaging-confirmed brain pathology, reflecting faster cognitive decline once cognitive reserve is depleted [69]. However, one meta-analysis showed that formal education had a small to medium effect on vascular cognitive impairment after stroke in young patients, while the effect of education on post-stroke executive dysfunction was mediated by age, and below-average performance in the attention domain was more frequent for patients with lower levels of education [70]. Future prospective studies are expected to address whether strategies to enhance cognitive reserve can help patients cope with more extensive vascular neurodegenerative mechanisms.

Several studies have focused specifically on exercise as a single intervention. One randomized controlled trial (RCT) reported that aerobic exercise improves global cognition in older adults with mild subcortical ischemic vascular cognitive impairment [71] Results relating to neuroimaging outcomes are mixed. The results of a small ultra-high field MRI sub-study of a 24-month physical activity intervention RCT suggested that physical activity may be capable of beneficially altering small vessel morphology [72], while another suggested resistance training may also be protective by demonstrating reduced WMH volume progression in community-dwelling women [73]. Conversely, a 24-month physical activity

trial in individuals with high cardiovascular disease risk burden failed to demonstrate significant reductions in WMH progression or hippocampal atrophy [74], coinciding with evidence from the FINGER trial which also showed no effects on WMH or other brain structural outcomes [75]. Another ongoing RCT [76] exploring the effects of resistance exercise on cognition and WMH progression in older adults with cSVD will provide further clarification. Additional exercise trials such as Exercise in Adults with Mild Memory Problems (EXERT; NCT02814526) and Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE) [77], although not specifically targeting VCID, will include relevant neuroimaging data and blood-based biomarkers that will aid in further understanding the impact of exercise on outcomes of interest.

4 Perspectives and priorities for future research

4.1 Inclusion, diversity, and justice in dementia research

In order to prevent and treat VCID in all groups of people, research must include diverse study participants, evaluate diverse disease determinants, including social and policy determinants, and carry out rigorous scientific study. As researchers in health equity, social determinants of health, aging, and AD and related dementias have recently pointed out [78,79], inequitable representation in research is a barrier to both scientific accuracy and the human subjects research ethics principle of justice laid out in the Belmont report [80]. Much of the world's population with dementia (~60%) live in low- and middle-income countries (LMICs) [81], yet, most VCID studies have been carried out in high-income countries. Similarly, little is known about VCID in Indigenous and minoritized populations around the world, populations living in rural areas, by race/ethnicity, and by gender/sex. Furthermore, both neuroimaging and aging studies are known to suffer from selection and survival biases which limit the scope and accuracy of our VCID knowledge [82].

Understanding VCID in all populations will have significant impact considering that some bear a greater burden of or are at greater risk of cognitive impairment (e.g., Black/African Americans, American Indian/Alaska Natives, Latinx compared to Asian Americans or non-Hispanic white Americans [83,84]), some have more vascular risk factors and comorbidities (e.g., Latinx, Black/African Americans, American Indians [84–86]), some have unique exposures or differing social and structural circumstances that increase risk or impact care (e.g., sex-specific exposures such as preeclampsia and menopause [87,88]; discrimination and racism [84]; social stigma, and fewer potential caregivers among sexual and gender minorities [89]). Studying diverse groups can also give unique insights into protective factors.

Finding the best interventions for all people with VCID can therefore be enhanced by jointly applying the science of inclusion and population neuroscience. The science of inclusion (which has also been called the science of recruitment and retention) develops systematic approaches to achieve equitable representation in research [79]. Population neuroscience, which integrates epidemiology and neuroscience methods [79,90], provides a framework to further address existing research limitations in that it offers ways to harness population heterogeneity, incorporate neuroimaging and molecular markers, pool and coordinate data across studies and countries, and carefully and quantitatively address internal and external validity [91]. For example, this approach has found that mid- and late-life vascular risk factors increase risk of poor late-life brain health [17,92] and that simple physical activity, such as walking, is a protective factor [93]. A population neuroscience framework has been applied to dementia and cSVD, and can be applied to VCID more broadly [91,94]. Together, the science of inclusion and population neuroscience can improve the diversity of study samples and the quality of the conclusions drawn from VCID research.

Recommendations for future research on this topic:

1) Apply systematic approaches learned from the science of inclusion to carry out studies of VCID in diverse study samples and locations and to achieve equitable representation in research.
2) Apply epidemiologic methods to neuroscience research under a population neuroscience framework to enhance rigor of VCID study designs and analyses.

4.2 Exploring the genetic signature of VCID and improving non-clinical models

As bioinformatics and sequencing technologies have advanced, studies have aimed to measure genetic changes at the cellular level by performing single cell (sc-) or single nuclei (sn-) RNA sequencing. However, the dense basement membrane enveloping blood vessels makes it challenging to isolate single brain vascular cells (e.g., myocytes, pericytes, endothelial cells) or their nuclei. In a recent study that sequenced more than 75,000 brain cells from control or AD patients, only 0.2% were pericytes and 0.2% were endothelial cells, both of which were excluded from the differential analyses due to their limited abundance [95]. A new method has been developed to successfully isolate nuclei from human brain vascular cells from control and AD hippocampus and cortex [96]. The study identified that, unlike the mouse brain, the human brain has 2 types of pericytes defined as matrix- or transporter-type pericytes [96]. The authors determined that 30 of the top 45 AD GWAS genes are expressed in the human brain vasculature. Future research will be needed to elucidate the location and functions of matrix-type pericytes that are reduced in AD and to further characterize vascular genetic changes throughout the brain in VCID [96].

Experimental models (e.g., hypoperfusion, pericyte-deficient, *APOE*-ε4, Aβ- or tau-overexpressing, and aged) emulate various aspects of VCID, including reduced CBF, BBB leakage, pericyte dysfunction, WM damage, fibrin deposits, BBB transporter expression changes, and cognitive impairment [97]. The Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease (MODEL AD, https://www.model-ad.org/) and the UK

Dementia Research Institute (https://ukdri.ac.uk/) are working to develop next generation animal models to recapitulate pathophysiological features of AD including vascular dysfunction. The aforementioned study employing snRNA sequencing of vascular cells from control and AD human brains may inform the development of new transgenic and translational models, while the incorporation of relevant cardiovascular risk factors into existing animal models would enhance their translational value [1,96]. Human induced pluripotent stem cell models of the BBB and neurovascular unit are also promising new translational approaches, assuming they can recreate physiological conditions (e.g., capillary diameter, actual CBF, glycocalyx changes, flexible basement membrane matrix, and proper incorporation of all neurovascular unit cell types).

Pericytes are contractile cells capable of reducing capillary red blood cell flow [98]. Pericyte-deficient mice have disrupted neurovascular coupling resulting in reduced oxygen supply to the brain, metabolic stress, neurodegeneration [99], and WM degeneration [100]. One recent study implicated stalled capillaries (blocked by neutrophils) contributing to CBF reduction and likely short-term memory deficits [101]. Understanding the interplay between classic AD pathology (e.g., Aβ and tau) and CBF through capillaries is both timely and important [52,102,103]. A recent study showed that Aβ oligomers induce pericyte contraction and capillary constriction, which likely contribute to CBF reductions, vascular inflammation, and cognitive impairment [104].

Recommendations for future research on this topic:

1) Elucidate the location and functions of matrix-type pericytes that are reduced in AD.
2) Further characterize vascular genetic changes throughout the brain in VCID.
3) Develop and rigorously validate new models that fully mirror the pathophysiological range of VCID.

4) Explore new VCID models to determine whether pericyte dysfunction and loss, oxidative stress, BBB breakdown, or increased chronic vascular inflammation could lead to stalled capillaries using state-of-the-art methodologies such as intravital multiphoton microscopy (**Figure 3D** and **E**).

4.3 Efforts in biomarker identification and clinical diagnoses

Our ability to effectively identify and intervene for high-risk individuals hinges on validated biomarkers. Multiple fluid and neuroimaging markers are used in VCID research, but the development of standardized pre-analytic and analytic processes, harmonization of measures across multi-center studies, proof of measurement reliability, and biological validation against clinically relevant outcomes has been difficult. The MarkVCID consortium is working to address this barrier and is presently testing 11 candidate fluid and neuroimaging biomarkers (see the **Table**). We refer readers to the MarkVCID study design papers [105,106] and biomarker protocols (https://markvcid.partners.org/consortium-protocols-resources) for a full description. Another multinational effort to harmonize MRI measures of cSVD is the HARmoNizing Brain Imaging MEthodS for VaScular Contributions to Neurodegeneration (HARNESS) initiative [107]; imaging protocols may be found at their website (https://harness-neuroimaging.org/).

Furthermore, VCID-related biomarkers of interest to us as ECRs in this field include: cerebrospinal fluid soluble platelet-derived growth factor receptor-β (sPDGFRβ) as a marker of brain capillary and BBB damage [108], ultra-high field (7T) MRI susceptibility-weighted imaging of small veins and time-of-flight imaging of small arteries, cerebrospinal fluid flow imaging, and myelin water fraction via myelin water imaging (several of these techniques are shown in **Figure 3**). Overall, most existing neuroimaging measures of cSVD (reviewed in [13]) measure tissue damage thought to be due to cSVD but are unable to directly measure damage to the vessels themselves. Genetic factors may also be important prognostic

biomarkers for VCID. For example, although this may vary by race/ethnicity, *APOE*-ε4 increases risk of dementia both additively and synergistically with other vascular and cardiometabolic risk factors and may modify relationships of other biomarkers (such as sPDGFRβ) with cognitive decline [17,19,20,109,110]. Additional genetic variants involved in cerebrovascular metabolism may be better candidate markers of specific neuropsychiatric features rather than clinical diagnosis [94,111,112].

In addition to neuroimaging and fluid-based biomarkers, neurocognitive testing is critical to VCID research as clinical diagnosis relies heavily on it. However, cross-study collaborations and comparisons have been hampered by differing neurocognitive batteries. Efforts to harmonize neurocognitive assessments are crucial for progress in the field [113].

Recommendations for future research on this topic:

1) Further explore existing biomarkers and generate novel biomarkers of VCID.
2) Apply novel structural and functional neuroimaging techniques and fluid biomarkers to measure more direct vessel damage.
3) Effectively integrate neuroimaging and fluid biomarkers for diagnostic confirmation at enrollment and differential diagnoses with other dementia syndromes.
4) Develop and harmonize neurocognitive assessments to better address VCID.

4.4 Critical aspects of future randomized controlled trials

Understanding disease etiology will allow for identification of ideal targets for RCTs in the context of primary and secondary prevention [6]. Employing neuroimaging techniques as a diagnostic marker to confirm presence of cerebrovascular disease at enrollment is critical. As well, neuroimaging to assess the efficacy of various interventions for VCID is appealing, especially when techniques continue to be optimized (see **Figure 3**). Nonetheless, it is crucial to identify markers that are consistently sensitive to intervention effects, since evidence indicates that commonly used markers, such as WMH progression, may respond differently

to pharmacological [114] and non-pharmacological interventions [73,75], and may not directly correlate with changes in cognition [115]. Thus, understanding the sensitivity of other VCID neuroimaging markers, such as lacunar infarcts, microbleeds, enlargement of perivascular spaces, loss of microstructural tissue integrity, and secondary neurodegeneration will aid in designing future clinical trials [115]. Moreover, employment of novel neuroimaging techniques that correlate well with clinical outcomes, such as diffusion tensor imaging and myelin water imaging [116], will increase the clinical utility. Addressing these issues will allow for a mechanistic understanding of how, and to what degree, preventive or therapeutic interventions lead to clinical improvement [117]. In addition, it is essential that clinical trials include genetic association data (particularly regarding *APOE*-ε4 carrier status) and analyses by sex/gender, and race/ethnicity [20].

Further, with the increasing emphasis on lifestyle RCTs, having a clear and efficient pipeline to move promising interventions from pilot studies to well-powered RCTs could accelerate progress in the field. This is needed to overcome several limitations from previous investigations. For instance, many studies evaluate the effects of lifestyle interventions on dementia, without specifying subtype. Others include small sample sizes, short follow-ups, and modest effect sizes on primary outcome measures; therefore, replication of their findings in larger samples is critical. Moreover, few studies consider gender/sex as important variables despite evidence suggesting the efficacy of these interventions may vary based on these factors [118]. Multicomponent intervention, such as that implemented in the FINGER study, may be more successful in mitigating disease burden than either intervention alone (e.g., exercise, cognitive training, diet, vascular risk monitoring) [51]; however, it remains to be determined whether multicomponent interventions can be feasibly implemented in real-world settings. Notably, interventions targeting factors beyond exercise, cognitive training, and diet are warranted. For instance, improving sleep quality is feasible and could be beneficial [119] given the potential impact of poor sleep on cerebrovascular health [120].

Lastly, in July 2021, the FDA gave accelerated approval for aducanumab as the first amyloid-reducing drug for AD [121]. While the efficacy of aducanumab and other anti-amyloid mAbs is beyond the scope of this paper, its approval has widespread implications. Aside from potential benefits of anti-amyloid immunotherapy, one of the noted side effects in some individuals is the subsequent occurrence of amyloid-related imaging abnormalities (ARIA) in the form of vasogenic edema or hemorrhage [122–124]. ARIA has long been identified as an adverse event in AD trials of anti-amyloid candidate drugs and could be problematic for patients with cSVD and CAA [122]. Except for *APOE*-ε4 carrier status and history of CAA, little is known about what predisposes individuals to ARIA [122]. Thus, the use of anti-amyloid drugs in individuals with cardiometabolic risk factors and comorbid vascular conditions will need to be monitored in future trials, considering these individuals are already at higher risk of cSVD [125]. Especially for CAA, immune response in ARIA appears to be targeted against vascular amyloid, indicating that study of vascular-amyloid-immune interactions may be critical for translating these therapies safely.

Recommendations for future research on this topic:

1) Validate and incorporate neuroimaging and fluid-based biomarker outcomes to enable clearer understanding of effects of interventions in individuals along the VCID spectrum.
2) Establish minimal clinically important difference (i.e., the smallest change in outcome that a patient deems important) of primary outcomes in VCID sub-classes.
3) Explore feasibility of multidomain lifestyle interventions in real-world settings and assess long-term benefits of such interventions.
4) Test the safety and efficacy of new therapies in diverse populations with measures that are inclusive of cardiometabolic risk factors and comorbid vascular conditions [125].

5 Conclusions

In this perspective piece, we provide an overview of VCID, discuss current limitations in the field and highlight important areas of future research. Our recommendations should be interpreted as relevant research opportunities to advance the field in directions that span basic and clinical science. We acknowledge the need for support to ensure these recommendations can be realized. To that end, we call upon funders to support professional organizations and research institutions to train ECRs to do this work.

Author contribution

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Conflict of interest

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Box. Interactions of *APOE*-ε4 carrier status with neurological features in specific populations with VCID

- Greater risk of dementia [16,111]
- Variable age at dementia onset in selected populations [16,111]
- Cognitive activity and vascular health may reduce the risk of dementia also in *APOE*-ε4 carriers [17,126]
- Education and lifetime sanitary conditions have protective effects against risk of AD particularly for *APOE*-ε4 carriers [19]
- Modulation of frequency of most behavioral symptoms particularly in AD [111,112]
- Higher predisposition of *APOE*-ε4 carriers to blood-brain barrier dysfunction and subsequent cognitive decline [110]
- Predisposition to amyloid-related imaging abnormalities (ARIA) [122]
- Rises in blood pressure may compensate for endothelial dysfunction and improve cerebral perfusion rates in *APOE*-ε4 carriers with AD [57]
- *APOE*-ε4 carriers with AD exhibit decreased participation in physical activities [109]
- Higher body mass index seems to be protective in late life across *APOE* haplotypes [20]
- Longitudinal benefits of a worsening lipid profile to *APOE*-ε4 non-carriers with AD as a result of enhanced lipid availability for protection of neuronal membranes [127]
- Modulation of effects of cerebrovascular metabolism modulators [58,59,128]
- Pleiotropic effects and interactions with other genes, thus affecting clinical response to angiotensin-converting enzyme inhibitors [58] and statins [128]

Table. MarkVCID candidate neuroimaging and fluid biomarkers for vascular cognitive impairment and dementia.

Candidate biomarkers	
Neuroimaging	A risk score for arteriolosclerosis based on multimodal MRI and demographic characteristics (ARTS)
	Cerebrovascular reactivity
	White matter hyperintensities volume
	White matter hyperintensities progression/regression
	Peak skeletonized mean diffusivity
	Mean white matter free water fraction
	Optical coherence tomography angiography retinal vessel skeleton density
Fluid	Plasma endothelial signaling – vascular endothelial growth factor (VEGF-D), placental growth factor (PlGF), and basic fibroblast growth factor (bFGF)
	Plasma exosome endothelial inflammation – C3b and Bb (activated complement factors)
	Plasma neurofilament light (NfL)
	Cerebrospinal fluid PlGF

Figure 1. A conceptual model for VCID.

Note: This conceptual model highlights direct and indirect mechanisms in the causative chain of events yielding brain injury, ultimately leading to vascular cognitive impairment and dementia.

Figure 2. VCID publication trends over time based on a July 13, 2021, PubMed search through December 31, 2020.

Note: (A) Number of publications per year based on a full search using the following terms: (("vascular contributions to cognitive impairment and dementia") OR ((vascular) AND ((cognitive impairment) OR (dementia)))) OR ((vascular) AND (mild cognitive impairment)). (B) Number of publications per year based on searching specifically for "(“vascular contributions to cognitive impairment and dementia”) OR (VCID)”.

Figure 3. Emerging neuroimaging techniques in human and animal models.

Note: (A) Myelin water fraction maps used to image in vivo myelin content in the human brain. Warmer regions indicate greater degree of myelination. In comparison are maps from two individuals with varying degrees of white matter lesion burden, courtesy of Dr. Teresa Liu-Ambrose (The University of British Columbia). (B) Time-of-flight angiography used to visualize small arteries that appear as thin thread-like areas of flow-related contrast in the human brain. (C) Susceptibility-weighted image used to visualize small veins in the human brain. (B) and (C) were adapted from Jorgensen, Shaaban and colleagues [94] and replicated with permission. Images were acquired without the use of any contrast agents at 7T using the Tic Tac Toe Radiofrequency Coil System (http://rf-research-facility.engineering.pitt.edu/). Images were provided by Dr. Tamer Ibrahim (University of Pittsburgh). (D) 3D reconstruction of a wild-type mouse using three-photon microscopy, the blood vessels are

labeled with a 2.5% FITC-dextran (red). Selected z-stacks labeled with 2.5% FITC-dextran (blood vessels; red) and third-harmonic generation (THG) (myelinated axons; blue) labeled at 200 μm (upper panel) and the white matter at 800 μm (lower panel). Scale bar, 50 μm. (E) Vascular and pericyte architecture can be visualized in vivo in the mouse brain through a cranial window by multiphoton microscopy using Texas Red-Dextran, 70 kDa (white) and NeuroTrace 500/525 (Fuchsia), respectively. Dextran is not taken up by red blood cells (RBCs) allowing visualization and quantification of RBC flow when imaging speeds are 100 fps or greater.