Revised diagnostic criteria for Vascular Cognitive Impairment and Dementia: the VASCOG-2-WSO criteria

The VASCOG-2-WSO Criteria Consortium

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Abstract

Importance: Several sets of diagnostic criteria have been proposed for vascular cognitive impairment and dementia (VCID). The International Society for Vascular Behavioural and Cognitive Disorders (VASCOG) working group published comprehensive operationalized criteria in 2014. Considering subsequent advances in the field, an international expert group was established in 2023 to revise these criteria. VASCOG criteria and other published diagnostic guidelines, aided by literature review of recent developments in VCID, were used as reference points for an online Delphi survey (minimum three rounds, ≥ 75% threshold for agreement) aimed at achieving consensus on diagnosis of VCID, including operationalization of criteria and guidance on potential biomarkers. Seventy international experts from diverse regions were invited to participate.

Observations: Three survey rounds included 49-54 participants that agreed on VASCOG-2 diagnostic criteria for *preclinical*, *mild* and *major/dementia levels of vascular cognitive impairment* (under the overarching term *VCID*). Research guidelines, including the use of novel neuroimaging and fluid biomarkers, were also agreed upon. The World Stroke Organisation (WSO) endorsed the criteria, hence named VASCOG-2-WSO.

Conclusions and Relevance: The VASCOG-2-WSO criteria update the VASCOG criteria for the diagnosis of VCID, providing operationalization and additional guidance on potential neuroimaging and fluid biomarkers. VASCOG-2-WSO should provide an international standard for VCID diagnosis, facilitating diagnostic consistency among clinicians and researchers.

Introduction

Vascular dementia (VaD) is the second most common form of dementia, accounting for 15-20% of cases [1-3] and cerebrovascular disease (CeVD) may contribute to cognitive and functional decline in up to 75% of all persons with dementia [4]. Despite its importance and the promise of prevention, the advancement of research and clinical practice in this field has been limited. One major obstacle is the absence of universally recognized and clearly operationalizable diagnostic criteria, reducing the validity and interpretability of clinical outcomes and research findings.

The introduction of the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) vascular dementia criteria [5] in 1993 was an important step toward standardisation. This allowed major investigations on the natural history and therapeutics to be undertaken. Thereafter, multiple attempts have been made to enhance these criteria. For instance, the expert consensus criteria developed by the American Heart Association and American Stroke Association (AHA-ASA) in 2011 [1], the Vascular Behavioural and Cognitive Disorders (VASCOG) criteria [6] (hereafter, *VASCOG-1* criteria) in 2014 that co-evolved with the DSM-5 criteria released in 2013 [7,8], the Vascular Impairment of Cognition Classification Consensus Study (VICCCS-2) criteria of 2018, derived via a Delphi consensus process [9,10], and the International Classification of Diseases, 11th revision (ICD-11) criteria proposed in 2019[11].

A study in 2019[12] showed that the VASCOG-1 criteria had greater sensitivity and better predictive validity than the older criteria for vascular cognitive impairment and dementia (VCID), but were comparable to the DSM-5 and VICCCS criteria. VASCOG-1 has advantages over other criteria, such as more detailed operationalization (e.g., suggested thresholds for cognitive impairment, severity of neuroimaging abnormalities, etc.). Despite the subsequent release of VICCCS-2 and ICD-11 criteria, there remains an ongoing lack of consensus on the overarching terminology of the cognitive decline, differing guidelines for clinical and cognitive assessments, and lack of accounting for major advances in neuroimaging and biomarkers. First, concerning terminology, the construct of VaD was broadened to the spectrum of vascular cognitive impairment (VCI) [13] that included individuals at increased risk of dementia as well as those with mild cognitive impairment (MCI) or dementia. Other terms proposed were vascular cognitive disorder [6,14], VCID [1], vascular neurocognitive disorder (DSM-5)[7], and dementia due to CeVD[11]. This lack of consensus on terminology has prevented consistency in definitions and diagnostic criteria.

Second, guidelines for assessment vary across the different criteria. The VICCCS-2 and AHA-ASA criteria do not require concern of a person, informant or clinician regarding decline of cognitive functioning for diagnosis, while VASCOG-1 and DSM-5 criteria require this in alignment with the criteria for Alzheimer's disease (AD) [15]. Most criteria specify executive function, attention, memory, language and visuospatial function as the cognitive domains of interest and most likely to be affected by cerebrovascular lesions[16]. The VICCCS-2 criteria, on the other hand, indicate processing speed, learning, and neuropsychiatric symptoms[17] as optional domains. Similarly, specificity of symptoms listed as supportive evidence in VASCOG-1 criteria, including early urinary frequency, gait disturbance, and personality and mood changes, may be limited.

Third, there have been major advances in neuroimaging and the development of other biomarkers for some types of dementia, and this needs to be revisited in the context of VCID. Consensus neuroimaging standards for small vessel disease (SVD) have been published (e.g., [16,17]), and their incorporation in any criteria set is arguably important. There have also been advances in the genetics of VCID which may help guide a phenotype of relatively 'pure' VCID [18].

Fourth, the status of VCID subtypes, with terms such as post-stroke dementia (PSD), subcortical ischemic vascular dementia (SIVaD) and multi-infarct dementia (MID) still being commonly used by clinicians, requires clarification within the nosology of VCID.

This study therefore aimed to reach international consensus on the diagnosis of VCID, via a revision of the VASCOG-1 criteria, in an iterative survey using a Delphi approach.

Methods

Participants

Survey participants were invited if they were internationally recognised clinicians and/or researchers in the field of cognitive decline and dementia with a focus on VCID These could be medical specialists (including geriatricians, neurologists, psychiatrists and rehabilitation physicians) or non-medical clinician experts (e.g., neuropsychologist, nurse, social worker, occupational therapist). Experts who had previously participated in the VASCOG-1, VICCCS-2 and AHA-ASA criteria were initially contacted, and snowball sampling was used to

192 expand this group. The aim was to have broad representation from all geographical regions including South
193 and East Asia, North and South America, Africa, Europe, and Oceania.

194 Three hundred and ten individuals were initially screened for invitation, of whom 143 were short-listed. Of
195 these, 70 responded indicating their interest in participation (nine declined, the remainder did not respond).
196 The World Stroke Organisation (WSO) was approached to provide input into the process and two members of
197 WSO with expertise in vascular dementia participated. The study was approved by the University of New
198 South Wales Human Research and Ethics Committee. Participants gave written informed consent.

199

200 **Data collection**

201 A modified Delphi method [19] was used, involving an iterative, multi-staged series of structured online
202 questionnaires with anonymised feedback from participants, and progressive refinement of questions across
203 stages to reach consensus for the updated diagnostic criteria. Only the independent coordinator (A.C.B who
204 did not participate in the survey) had access to identification details of the participants. The Guidance on
205 Conducting and REporting of Delphi Studies (CREDES) recommendations were followed [20]. Figure 1
206 illustrates the procedure.

207 *Figure 1 about here*

208 **Development of the survey**

209 Literature reviews on topics related to the criteria were conducted by the core team (ACB, PSS, NAK, JJ, SH,
210 RK, RJC and DS), which informed the first structured questionnaire. In brief, this entailed consulting all
211 previous diagnostic criteria for VCID, and major reviews on neuropsychological, neuroimaging and biomarker
212 developments in VCID since VASCOG-1.

213 Consensus was sought on:

214 - Each individual element of the existing VASCOG criteria;
215 - The standardisation of definitions, terminology and scope of the criteria;
216 - Further operationalization of the criteria, and;
217 - Potential additions to the criteria including novel neuroimaging, fluid, or retinal biomarkers.

218 A full summary of the topics addressed in each round is provided (eTable 1 in the Supplement).

Survey and consensus procedure: Consensus on any statement was defined as agreement or disagreement of ≥75% and non-consensus as <75% through multiple iterative rounds. Percent agreement is the most common measure of agreement used in Delphi studies, and 75% is the median value used [21] and was considered high enough to ensure the quality and reliability of the consensus outcomes. Statements that reached consensus were removed from subsequent rounds, while non-consensus statements were reworded incorporating participant feedback and reintroduced in subsequent rounds. Figure 1 illustrates the procedure.

Overall, three rounds of online surveys were administered, approximately one every two months. In response to feedback, an in-person participants' meeting was held on September 16th, 2023 at the International Society of Vascular Behavioural and Cognitive Disorders (VasCog) 2023 conference in Gothenburg, Sweden, to discuss the Round 1 results. VasCog encompasses clinician and researchers experts in cognitive disorders arising from cerebrovascular pathological changes. An additional meeting was held on October 25th, 2023 by videoconference for those who could not attend VasCog 2023 to discuss contentious Round 1 results and guide preparation of questions for Round 2. No questionnaire data was collected during these meetings, preserving the anonymity of the process.

Observations

Primary outcomes

Of the 70 participants invited, 54 (77% of invited) contributed to round 1, 51 to round 2 (94% of round 1) and 49 to round 3 (97% of round 2). Characteristics of the Delphi participants from Round 1 are shown in eTable 2. In brief, the majority (89%) of participants are medically trained and six (11%) are neuropsychologists; among the medically trained, most (77%) are neurologists, psychiatrists, geriatricians or epidemiologists. Most reported their primary workplace setting as a university, university clinic, hospital, memory clinic or stroke unit or some combination. Most reported having both clinical and research experience with VCID and having expertise demonstrated by relevant peer-reviewed research publications. The majority (78%) were from Europe, North America, or Australia with five (9%) from Asia, two (4%) from Brazil and 1 (2%) from the Caribbean.

Table 1 about here

Definition of the vascular cognitive construct

In round 1, the naming of the overarching vascular cognitive construct that includes all forms of cognitive deficits from mild to major/dementia resulted in a split between the most popular options *vascular cognitive disorder* (30% agree) and *vascular cognitive impairment* (26%), with other options being *vascular neurocognitive disorder (*18%) and *vascular cognitive impairment and dementia* (16%). The question was reduced to two options in round 2, i.e., *vascular cognitive impairment* (61%) and *vascular cognitive disorder* (39%), but subsequent discussion in a conference suggested that this was an unsatisfactory outcome, and the options were brought to round 3. In the 3rd round, the proposal to name the construct *vascular cognitive impairment and dementia (VCID)*, with the term *vascular mild cognitive impairment (vaMCI)* for a mild level of severity of VCID, and the term *vascular dementia (VaD)* for a major or dementia-level of severity of VCID, reached consensus (84%) and VCID, vaMCI and VaD are therefore the default terms used hereafter.

Table 1 presents the diagnostic criteria for MCI and dementia reached by consensus. This is the first step in the diagnostic process, prior to establishing a vascular etiology. These criteria are little changed from VASCOG-1 besides minor rewording.

Table 1 about here

Table 2 displays the consensus cognitive domains assessed in VCID, for which the DSM-5 domains replace the VASCOG-1 domains (80% in round 2) with minor changes, i.e., changing the domain name *Complex Attention* to *Attention and Processing Speed* and subsuming *Praxis-gnosis-body schema* into *Perceptual-motor function*.

Table 2 about here

The criteria for establishing vascular etiology for MCI or dementia are presented in Table 3. For criterion A1, in a separate question, consensus was not reached on the choice of a specific timeframe (3mo, 6mo, other, or none) for the persistence of cognitive deficits following a stroke (3 months: 39% agreement, 6 months: 30%, round 2). Consequently, the “beyond 3 months” guidance was retained from VASCOG-1 as the most supported option.

Table 3 about here

Criterion B1 combines two criteria from VASCOG-1, i.e., former B1 “large vessel infarcts” and B2 “extensive or strategically placed single infarct” to simplify the criteria as former B1 was not supported (56%

disagreement). Otherwise, imaging criteria are marginally more lenient with respect to lacunes and white matter hyperintensities (see Table 3 for description). For criterion A2, only the supportive clinical features of personality and mood changes reached consensus, unlike gait disturbance and urinary frequency which were considered too non-specific to be included within the diagnostic criteria.

In the exclusion criteria, major depression was removed due to a lack of consensus on the original or reworded alternatives, and the agreement that there is considerable overlap between depression and VCID symptoms in later life. Mood disturbance, personality change, and apathy are included as supportive, but not essential, features for the diagnosis of VCID. The addition of biomarkers for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB) (guidance) reached consensus, but not for frontotemporal dementia (FTD) primarily due to lack of validated biomarkers. There was consensus against (≥ 75% disagreement, round 1) the use of additional novel neuroimaging markers, plasma and serum, and retinal biomarkers in either the clinical or research setting to assist in VCID diagnosis (see eResults 1 for the list of markers). Consensus was reached for using neuroimaging markers for the staging of cerebrovascular disease in a research setting (81%, round 1). Details of this will be explored in a future research framework.

Table 4 presents miscellaneous criteria. For a diagnosis of *probable* VCID, a clinical diagnosis should be supported by neuroimaging or the presence of a genetic disorder such as CADASIL, the latter being a new inclusion. Another notable addition is the inclusion of the preclinical/at-risk VCID category, indicated by neuroimaging evidence of CeVD, with or without clinical history of cerebrovascular events (CVEs) and/or vascular risk factors. This recognises the common occurrence of what has also been referred to by clinicians as covert CeVD [22].

Table 4 about here

Multiple causation was simplified into vascular with neurodegenerative and non-neurodegenerative additional pathologies with the more clinically salient etiology to be stated. In VASCOG-1 multiple causation was centred on AD. The subcortical/cortical-subcortical subtype from VASCOG did not reach consensus, nor did a suggested poststroke dementia or poststroke VCID subtype, while the hemorrhagic/ischemic subtype was maintained with an added mixed hemorrhagic-ischemic category.

See eTable 3 for a summary of the VASCOG-2-WSO diagnostic criteria for VCID, and eTable 4 for a comparison of VASCOG-2-WSO criteria to VICCCS-2, VASCOG-1, DSM-5 and AHA-ASA criteria.

Discussion

This paper provides consensus VASCOG-2-WSO diagnostic criteria for VCID. These criteria aim to update the VASCOG-1 criteria to address inconsistencies between extant criteria in terminology and assessment guidelines and align with advances in neuroimaging and biomarkers[6]. The overarching vascular concept was named *vascular cognitive impairment and dementia*, maintaining its subdivision into *vaMCI* and *VaD*. The primary updates include refinement of the VASCOG neuroimaging and clinical criteria and subtyping, the addition of AD and other neurodegenerative disease biomarkers in criteria for alternative or additional etiologies, and the addition of a preclinical/at-risk category for risk reduction and preventive purposes. These updates will be of great value in reflecting the substantial advancement of knowledge since VASCOG-1, addressing limitations of the previous criteria, and thereby facilitate ongoing clinical and research developments.

The VASCOG-2-WSO are highly operationalized, with needed, practical guidance on thresholds for cognitive and neuroimaging criteria. This is designed to assist with decision making in both clinical and research settings, while remaining sufficiently broad and flexible to facilitate clinical judgment. For example, criteria for white matter hyperintensities (WMH) include guidance on Fazekas score thresholds [23] in recognition that WMH are common and increase with age [24] and that visual scoring methods remain in use in the clinic. For other neuroimaging markers (i.e., infarcts, lacunes, and intracerebral hemorrhage) there is reference to strategic placement in recognition of the long-understood associations between lesion location and the risk of cognitive impairment (e.g., thalamus and basal ganglia) with recent lesion-mapping studies enhancing our understanding (e.g., [25-27]).

VASCOG-2-WSO, like the VASCOG-1 criteria, recognise that the neuropsychological domains of *attention and processing speed* (within *complex attention* in VASCOG) and *executive function* are affected early in the disease process and are helpful in identifying SVD-related impairment in the early stages [28]. The heterogeneity of the cognitive profile of VCID is also acknowledged, as multiple domains are commonly affected owing to the widespread nature of the cerebral pathology. This includes *learning and memory*, a feature commonly associated with AD. Memory impairment in early VCID, however, may present differently from early AD, with reduced efficiency and organisation of learning and retrieval in the former, and impaired consolidation and rapid forgetting in the latter (e.g., [29]). Tests such as a repeated supra-span word list, with

measures of learning over trials, free recall and recognition can help distinguish the nature of the learning and memory deficits in the two disorders. The VASCOG-2-WSO consensus cognitive domains are harmonised with the domains in the consensus VASCOG-2-NP neuropsychological battery and standards [30]. Other supportive aspects of the clinical criteria considered insufficiently specific (e.g., gait and/or urinary disturbance as supportive and major depression as exclusion criteria) were removed, which may improve diagnostic accuracy.

An important aspect of any dementia diagnosis is its level of certainty. The approach in the previous criteria sets for both VCID and AD has been to have two levels – probable and possible. In AD, the probable level is a clinical construct supported by molecular biomarkers and genetics [31]. Biomarkers are similarly important for probable VCID, but molecular biomarkers for VCID are currently lacking [32] and neuroimaging, in particular MRI, remains the mainstay. There are several neuroimaging biomarkers – large and small infarcts, WMH, lacunes, dilated perivascular spaces, macro- and micro-bleeds, cerebrovascular reactivity, diffusivity measures and blood-brain barrier integrity measures. The definitions of the SVD-related measures have been standardised in the STRIVE criteria [16,17]. Several challenges remain: not all of these markers (e.g., some WMH) are necessarily vascular in origin [33], with the description 'of presumed vascular origin' being used [17]; these lesions are commonly seen as incidental findings in 'cognitively healthy' older people [34] and in neurodegenerative diseases including AD[35], and the association between the severity of these markers and cognitive impairment is generally modest [36]. Further work in developing a biomarker profile for VCID is needed to place the diagnosis of probable VCID on a more secure footing. While there is accumulating evidence of monogenic vascular disorders that lead to VCID, these are very uncommon, with most cases being sporadic, albeit with genetic risk factors [37]. The monogenic disorders can, however, serve as models of a pure form of VCID [18].

The Delphi process of VASCOG-2-WSO attempted the subtyping of VCID. Previous subtyping of VCID, such as into PSD, SIVaD, and MID, were not supported by consensus, while ischemic/hemorrhagic subtype was maintained with an added mixed category. Instead of intensive subtyping, the focus of VASCOG-2-WSO criteria is on the evidence for vascular etiology *per se*, with evidence for stroke and non-stroke etiology included as separate criteria. While a lack of consensus on these specific terms likely reflects their current inadequacy, future attempts at subtyping should not be ruled out.

The VASCOG-2-WSO preclinical/at-risk VCID category is aimed at identifying non-symptomatic persons with high levels of CeVD, discovered incidentally via neuroimaging, and hence at risk of cognitive decline and stroke that could be targeted for monitoring, risk reduction and preventative interventions particularly in a research setting. While this is similar to the 'brain-at-risk' concept proposed several years ago [32], the recent interest in *covert CeVD* and the possibility of interventions to slow its progression is noteworthy [22].

VASCOG-2-WSO present novel features that may suggest VCID may not be the primary or sole pathology, using AD biomarkers such as cerebrospinal fluid Aβ and pTau levels and amyloid imaging using PET, as well as biomarkers for other pathologies such as Lewy body disease (Table 4). However, these novel features should be used cautiously as the presence of these features or biomarkers does not exclude the possibility of multiple brain pathologies being present, as is common in older people [4]. The criteria therefore encourage the identification of multiple pathologies and support an attempt to determine the most salient pathologies that possibly underlie cognitive impairment. This is important for identifying vascular pathologies amongst multiple pathologies in relation to the selection for current and future amyloid and other neurodegeneration focused therapies [38].

Strengths

Strengths of these criteria include their determination by Delphi consensus process that involved a broad international representation of experts with excellent engagement, with the process including one in-person meeting and a videoconference, and adherence to the CREDES recommendations [20]. The benchmark for all criteria, consensus at 75%, was high. The criteria were operationalized for use by both clinicians and researchers, including the determination of vascular etiology. This contrasts to most previous criteria that adopt more general guidelines. Hence the VASCOG-2-WSO criteria are arguably more useful for decision making, more amenable to validation against biological criteria for CVD such as neuropathology, and provide a clearer framework for ascertaining prognosis and guiding treatment (e.g.,[1,39,40]). They are consistent with DSM-5 criteria as well as the latest criteria for AD and DLB and their biomarkers, adopt the STRIVE-2 standards, and align with the harmonised VASCOG-2-NP neuropsychological assessment [30]. The combination of these features positions the VASCOG-2-WSO criteria well for future research and development.

Limitations

Like all exercises aiming to reach expert consensus, the criteria run the risk of prevalent biases that are only correctable with novel data. The criteria remain to be tested in the field and their validation is an important future goal to build upon previous efforts involving VASCOG-1 and other criteria [12]. Despite its adoption here it is recognised that terms such as *dementia* are potentially limited and not always preferred, and it should be interchangeable with alternative names such as *major cognitive impairment* or *major cognitive disorder*.

Future directions

The VASCOG-2-WSO should be validated against other extant criteria and in longitudinal studies for which neuropathological data are available. Their utility for participant selection in clinical trials needs to be determined. Their ease of application in the clinic and population level should be examined. The criteria may require some refinement for exclusive research use. However, real advances in diagnostic criteria will only come with better biomarkers, and this is an area of active research internationally, with novel neuroimaging, retinal and fluid biomarkers under investigation.

Conclusions

The VASCOG-2-WSO criteria update the VASCOG criteria for the diagnosis of VCID, providing operationalization and additional guidance on potential neuroimaging and fluid biomarkers. VASCOG-2-WSO should provide an international standard for VCID diagnosis, facilitating diagnostic consistency among clinicians and researchers.

Author contributions

Dr Bentvelzen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sachdev, Bentvelzen.

Acquisition, analysis, or interpretation of data: Acquisition and analysis: Bentvelzen. Interpretation: Bentvelzen, Sachdev, Kochan, Jiang, Hosoki, Koncz, Chander, Saks, Aben, Acosta, Andersen, Assal, Bae, Biessels, Blacker, Bordet, Briceno, Brodaty, Brodtmann, Caramelli, Castro-Costa, Chabriat, Chen, Clancy, Cysique, DeCarli, Ding, Duering, Engelhardt, Gauthier, Geranmayeh, Godefroy, Gorelick, Greenberg, Jelic,

Jokinen, Kalaria, Krishna, Lancaster, de Leeuw, Lim, Marseglia, Marta-Moreno, O'Brien, Pantoni, Pase, Pendlebury, Rosenberg, Sabayan, Salvadori, Samaras, Sebastian, Seshadri, Smith, Srikanth, Stokes, Sudo, Sveikata, Valenzuela, Wallin, Wardlaw, Xu.

Drafting of the manuscript: Bentvelzen, Sachdev, Kochan, Jiang, Hosoki, Koncz, Chander, Saks.

Critical revision of the manuscript for important intellectual content: Sachdev, Bentvelzen, Kochan, Jiang, Hosoki, Koncz, Chander, Saks, Aben, Acosta, Andersen, Assal, Bae, Biessels, Blacker, Bordet, Briceno, Brodaty, Brodtmann, Caramelli, Castro-Costa, Chabriat, Chen, Clancy, Cysique, DeCarli, Ding, Duering, Engelhardt, Gauthier, Geranmayeh, Godefroy, Gorelick, Greenberg, Jelic, Jokinen, Kalaria, Krishna, Lancaster, de Leeuw, Lim, Marseglia, Marta-Moreno, O'Brien, Pantoni, Pase, Pendlebury, Rosenberg, Sabayan, Salvadori, Samaras, Sebastian, Seshadri, Smith, Srikanth, Stokes, Sudo, Sveikata, Valenzuela, Wallin, Wardlaw, Xu.

Statistical analysis: Bentvelzen.

Obtained funding: Sachdev, Brodtmann, Samaras, Kochan, Srikanth, Pase.

Administrative, technical, or material support: Bentvelzen, Sachdev, Jiang, Hosoki, Koncz, Chander, Saks.

Study supervision: Sachdev, Bentvelzen, Kochan.

Conflict of interest disclosures

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Figure 1. Delphi consensus process used for defining the diagnostic criteria for VCID.

*Selection criteria: i) international experts in the neuropsychological assessment of VCID, recognised from the content of their international, peer-reviewed publications and/or referral by peers, ii) clinicians, researchers or both with experience in the diagnosis of cognitive decline and dementia in older adults and iii) medical specialists (including geriatricians, neurologists, psychiatrists and rehabilitation physicians) but non-medical clinician experts (e.g., neuropsychologist, nurse, social worker, occupational therapist) were also included if they satisfied criteria i) and ii).

^ See eTable 1 for details of main topics per round.

Table 1. Consensus diagnostic criteria for mild cognitive impairment and dementia

Mild cognitive impairment (both A and B are necessary)

(A)	Acquired decline from a documented or inferred previous level of performance in one or more cognitive domains as evidenced by the following:
a)	Concerns of the person, knowledgeable informant or a clinician of mild levels of decline from a previous level of cognitive functioning. *<u>Guidance:</u> Typically, the reports will involve greater difficulty in performing the tasks and greater effort, compensatory strategies, or accommodation may be required.*
b)	Evidence of modest deficits on objective cognitive assessment based on a validated measure of neurocognitive function (either formal neuropsychological testing or an equivalent clinical evaluation[a]) in ≥ 1 cognitive domains listed in Table 3. *<u>Guidance:</u> The test performance is typically in the range between 1 and 2 SDs below appropriate norms* (or between the third and 16th percentiles) and/or below an estimate of the person's premorbid cognitive functioning when a formal neuropsychological assessment is available, or an equivalent level as judged by the clinician including from appropriate score cut-offs and/or decline measured from cognitive screening tests.*
(B)	The cognitive deficits are not sufficient to interfere with independence (i.e., instrumental activities of daily living are preserved), but greater effort, compensatory strategies, or accommodation may be required to maintain independence.

Dementia (both A and B are necessary)

(A)	Evidence of substantial cognitive decline from a documented or inferred previous level of performance in one or more of the domains outlined above. Evidence for decline is based on (both a and b):
a)	Concerns of the person, a knowledgeable informant, or the clinician, of significant decline in specific abilities;
b)	Clear and significant deficits in objective assessment based on a validated objective measure of cognitive function (either formal neuropsychological testing or equivalent clinical evaluation[a]) in

	≥ 1 cognitive domain. *<u>Guidance:</u> Test performance typically falls ≥ 2 SDs below appropriate norms* (or below the third percentile) and/or below an estimate of the person's premorbid cognitive functioning when a formal neuropsychological assessment is available, or an equivalent level as judged by the clinician including from appropriate score cut-offs and/or decline measured from cognitive screening tests.*
(B)	The cognitive deficits, in isolation from physical deficits, are sufficient to interfere with independence (e.g., at a minimum requiring assistance with instrumental activities of daily living, e.g., performing tasks such as managing finances or medications)

496 * Appropriate norms should include, where possible, normative sample of similar age, sex, education, and
497 sociocultural background.

498 [a]The equivalent clinical evaluation should include objective and valid tests including cognitive screening tests
499 but can replace a formal neuropsychological assessment if the latter is not available, except in research
500 studies where a formal assessment is warranted.

501

Table 2. Consensus cognitive domains assessed in vascular cognitive impairment and dementia.

Cognitive domains	Sub-domains / description
1) Attention and processing speed	sustained attention, divided attention, selective attention, processing speed
2) Executive function	planning, decision-making, working memory, responding to feedback, inhibition, flexibility
3) Learning and memory	free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, implicit learning
4) Language	object naming, word finding, fluency, grammar and syntax, receptive language
5) Perceptual-motor function	visual perception, visuoconstructional reasoning, perceptual-motor coordination
6) Social cognition	recognition of emotions, theory of mind, insight

Table 3. Consensus evidence for predominantly vascular etiology of cognitive impairment. Both A and B are required. Features under (C) suggest multiple contributing etiologies (*Mixed or Multifactorial Cognitive Impairment and Dementia*) or an alternative etiology, in which case the likely predominant etiology should be recognised.

(A) One of the following two clinical features (A.1. or A.2.)	
1	The onset of the cognitive deficits is temporally related to ≥ 1 clinical strokes. *Guidance: Onset is abrupt and cognitive deficits persist beyond 3 mo after the stroke. Multiple strokes may be associated with a stepwise or fluctuating course.* The evidence of stroke is one of the following
	a) Documented history of a stroke, with cognitive decline temporally associated with the event
	b) Physical signs consistent with stroke in the absence of a history of stroke or if the history of stroke is unknown, and the signs are not due to another cause including another neurodegenerative disorder. *Guidance: Physical signs may include but are not limited to hemiparesis, lower facial weakness, Babinski sign, pronator drift, sensory deficit, visual field defect, pseudobulbar syndrome—supranuclear weakness of muscles of face, tongue and pharynx, spastic dysarthria, swallowing difficulties — and cerebellar signs e.g. limb ataxia.* *Covert neuroimaging evidence (e.g. brain infarct or hemorrhage) of cerebrovascular disease (see Part B) may be present in the absence of clinical history of stroke and should be taken into consideration, as for physical signs of stroke.*
2	In the absence of history of a stroke or transient ischemic attack, evidence for decline from subcortical ischemic pathology may be associated with a picture of gradual onset and slowly progressive course, typically predominant in some combination of attention and processing speed, and/or executive functioning, with additional domains potentially affected to a lesser extent. *Guidance: Memory impairment, where present, typically involves inefficient encoding and/or retrieval (versus consolidation and storage in AD).* *Guidance (supportive features): Personality and mood changes, particularly apathy, depressive symptoms and emotional lability, and gait-balance disorders are common in VCID.*

(B) Presence of significant neuroimaging MRI (preferable) or CT evidence of cerebrovascular disease (at least one of the following)	
	1) Multiple infarcts or a single extensive or strategically placed infarct, for example in the thalamus, may be sufficient for VaD.
	2) Multiple lacunes (≥ two) outside the brainstem; one lacune may be sufficient if strategically placed or in combination with extensive white matter hyperintensities.
	3) White matter hyperintensities, particularly if they are extensive and confluent. *<u>Guidance</u>: "Extensive and confluent" may correspond to a Fazekas score[25] of 2 or 3; or by region: periventricular Fazekas = 3 and/or deep Fazekas = 2 or 3.*
	4) Intracerebral hemorrhage; one may be sufficient if large and/or in a lobar location or otherwise strategically placed, or two or more intracerebral hemorrhages
	<u>Guidance (supportive features for cerebrovascular burden, not sufficient on their own without meeting neuroimaging criteria above):</u> *i) cerebral microbleeds and cortical superficial siderosis* *ii) abnormalities that meet the criteria of cerebral amyloid angiopathy (e.g., Boston criteria version 2.0 [41])* *<u>Guidance (all imaging evidence):</u> The STRIVE-2[18] definitions and guidelines of measurement of cerebrovascular lesions and changes should be adopted.*
(C) Features that May Suggest an Alternative Predominant Etiology or that Vascular Disease is Not the Sole Etiology	
1	*Clinical features*
	a) Insidious early onset of cognitive, perceptual and motor symptoms suggestive of Alzheimer's disease in the absence of corresponding focal vascular lesions (infarct or small vessel disease) on brain imaging or history of vascular events. *<u>Guidance:</u> Where available, supported by indicative biomarkers as outlined in 3a below.*
	b) Early and prominent movement disorder suggestive of Lewy body disease or other alpha-synucleinopathy or other non-vascular movement disorder *<u>Guidance:</u> Where available, supported by indicative biomarkers (as per [42] for dementia and [43] for MCI)* ***and outlined in 3b below.***
	c) Features strongly suggestive of another primary neurological disorder such as multiple sclerosis,

	encephalitis, toxic or metabolic disorder, etc. sufficient to explain the cognitive impairment.
2	*Neuroimaging*
	a) Absent or minimal cerebrovascular lesions on CT or MRI
3	*Biomarkers* a) The presence of any of the following biomarkers for Alzheimer's disease *may* provide supportive evidence for AD as an alternative cause of the cognitive syndrome, or that AD is present in addition to vascular disease.
	i) Cerebrospinal or plasma Aβ and pTau derived species such as Aβ42:40 ratio, pTau181, pTau 217 or other established biomarker[45,46] at levels consistent with brain amyloid pathology
	ii) Imaging brain amyloid levels (i.e., using PET) at accepted centiloid/SUVR thresholds
	iii) The presence of an autosomal mutation associated with AD, or being homozygous for APOE4 (apolipoprotein E ε4). #
	b) The presence of biomarkers of dementia with Lewy bodies[43,44], including dopamine transporter imaging and α-synuclein seed amplification assay in CSF[47]. #
	b) The presence of biomarkers for any other disease process known to be related to cognitive decline and judged to be implicated (e.g., pathogenetic variant of frontotemporal dementia[48], neuroimaging evidence of brain tumour or traumatic brain injury, etc.). #

Criteria 3aiii, 3b and 3c were not part of the consensus Delphi process, and were added during preparation of this paper as considered by the group to add important details concerning biomarkers for potential differential diagnoses.

511 **Table 4. Consensus criteria for VCID (vaMCI or VaD): Miscellaneous Aspects.**

Level of certainty	
1	*Probable (a or b are required)*
	a) Clinical criteria for VCID are supported by neuroimaging
	b) Both clinical and genetic evidence of cerebrovascular diseases. *<u>Guidance:</u> genetic disorders include but are not limited to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CADASIL; cerebral autosomal recessive arteriopathy with subcortical autosomal recessive leukoencephalopathy, CARASIL; hereditary endotheliopathy retinopathy nephropathy and stroke, HERNS; pontine autosomal dominant microangiopathy and leukoencephalopathy, PADMAL; retinal vasculopathy with cerebral leukodystrophy, RVCL; collagen type IV, α-1 (COL4A1)-related disorders.*
2.	*Possible.* Clinical criteria for VCID are met, but neuroimaging and/or genetic evidence is not available
Subtypes of VCID.	
	Hemorrhagic, ischemic or mixed hemorrhagic-ischemic
Multiple or mixed causation (Multifactorial or Mixed Cognitive Impairment or Dementia) State which etiology is clinically more salient: vascular or other	
1	VCID with one or more concomitant neurodegenerative disease(s) (e.g., AD, LBD) (a and b are required) (a) Meets criteria for VCID (except for *features that suggest an alternative etiology/etiologies)*) (b) Meets criteria for other neurodegenerative disease(s) (e.g., VCID (primary) with contribution from AD; or AD (primary) with contribution from VCID)
2	VCID with additional non-neurodegenerative pathology (e.g., VCID (primary) with contribution from traumatic brain injury, brain tumour, etc.)
3	VCID with contribution from depression

Associated behavioural or psychiatric symptoms: with apathy, depressive symptoms, emotional lability, psychotic symptoms, agitation, etc.	
Preclinical/at-risk VCID The purpose of this group would be to signal the importance of further study, primarily in a research setting, and for risk reduction and preventive medicine. The category would require the person to present with (a and b):	
	a) significant incidental neuroimaging evidence (MRI (preferred) or CT) of cerebrovascular disease that satisfies the VCID criteria for vascular etiology Criterion B; and
	b) does not satisfy criteria for mild or major cognitive impairment/dementia and the person, their informant or relevant clinician do not have concerns of cognitive change
	Guidance: this diagnosis is supported by the presence of substantial vascular risk factors for VCID.

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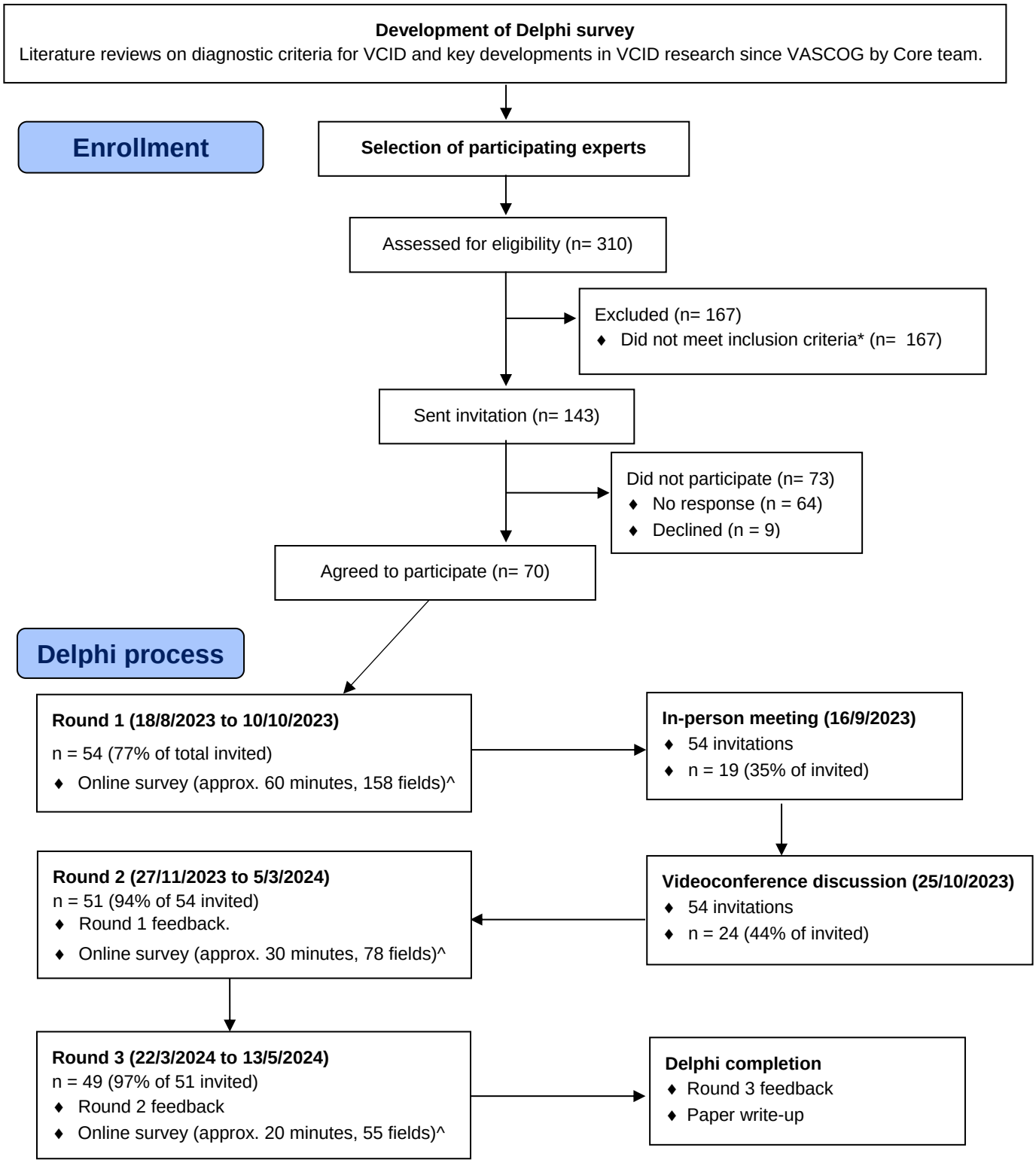
References

1. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke.* 2011;42(9):2672-2713.
2. Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology.* 2000;54(11 Suppl 5):S4-9.
3. Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. *Neurology.* 2000;54(2):447-451.
4. Boyle PA, Wang T, Yu L, et al. To what degree is late life cognitive decline driven by age-related neuropathologies? *Brain.* 2021;144(7):2166-2175.
5. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology.* 1993;43(2):250-260.
6. Sachdev P, Kalaria R, O'Brien J, et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. *Alzheimer Dis Assoc Disord.* 2014;28(3):206-218.
7. American Psychiatric Association D, Association AP. *Diagnostic and statistical manual of mental disorders: DSM-5.* Vol 5: American psychiatric association Washington, DC; 2013.
8. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nat Rev Neurol.* 2014;10(11):634-642.
9. Skrobot OA, Black SE, Chen C, et al. Progress toward standardized diagnosis of vascular cognitive impairment: Guidelines from the Vascular Impairment of Cognition Classification Consensus Study. *Alzheimers Dement.* 2018;14(3):280-292.
10. Skrobot OA, O'Brien J, Black S, et al. The Vascular Impairment of Cognition Classification Consensus Study. *Alzheimers Dement.* 2017;13(6):624-633.
11. WHO. *International Classification of Diseases, Eleventh Revision (ICD-11).* 2019/2021.
12. Sachdev PS, Lipnicki DM, Crawford JD, Brodaty H. The Vascular Behavioral and Cognitive Disorders criteria for vascular cognitive disorders: a validation study. *Eur J Neurol.* 2019;26(9):1161-1167.
13. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke.* 2006;37(9):2220-2241.
14. Roman GC, Sachdev P, Royall DR, et al. Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia. *J Neurol Sci.* 2004;226(1-2):81-87.
15. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):270-279.
16. Duering M, Biessels GJ, Brodtmann A, et al. Neuroimaging standards for research into small vessel disease-advances since 2013. *Lancet Neurol.* 2023;22(7):602-618.
17. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12(8):822-838.
18. Saks DG, Sachdev PS. Monogenic causes of cerebral small vessel disease- models for vascular cognitive impairment and dementia? *Current Opin Psychiatry.* 2025.
19. Graham B, Regehr G, Wright JG. Delphi as a method to establish consensus for diagnostic criteria. *J Clin Epidemiol.* 2003;56(12):1150-1156.
20. Junger S, Payne SA, Brine J, Radbruch L, Brearley SG. Guidance on Conducting and REporting DElphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliat Med.* 2017;31(8):684-706.

21. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol.* 2014;67(4):401-409.
22. Meinel TR, Wardlaw JM, Kent DM. Is Incidentally Discovered Covert Cerebrovascular Disease Ignorable? *JAMA Neurol.* 2024;81(5):437-438.
23. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am J Roentgenol.* 1987;149(2):351-356.
24. Debette S, Schilling S, Duperron MG, Larsson SC, Markus HS. Clinical Significance of Magnetic Resonance Imaging Markers of Vascular Brain Injury: A Systematic Review and Meta-analysis. *JAMA Neurol.* 2019;76(1):81-94.
25. Coenen M, Kuijf HJ, Huenges Wajer IMC, et al. Strategic white matter hyperintensity locations for cognitive impairment: A multicenter lesion-symptom mapping study in 3525 memory clinic patients. *Alzheimers Dement.* 2023;19(6):2420-2432.
26. Weaver NA, Kuijf HJ, Aben HP, et al. Strategic infarct locations for post-stroke cognitive impairment: a pooled analysis of individual patient data from 12 acute ischaemic stroke cohorts. *Lancet Neurol.* 2021;20(6):448-459.
27. Weaver NA, Mamdani MH, Lim JS, et al. Disentangling poststroke cognitive deficits and their neuroanatomical correlates through combined multivariable and multioutcome lesion-symptom mapping. *Hum Brain Mapp.* 2023;44(6):2266-2278.
28. Iadecola C, Duering M, Hachinski V, et al. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. *J Am Coll Cardiol.* 2019;73(25):3326-3344.
29. Lafosse JM, Reed BR, Mungas D, Sterling SB, Wahbeh H, Jagust WJ. Fluency and memory differences between ischemic vascular dementia and Alzheimer's disease. *Neuropsychology.* 1997;11(4):514-522.
30. Bentvelzen AC, Kochan NA, Saks D, et al. Consensus harmonised neuropsychological assessment and standards for Vascular Cognitive Impairment and Dementia: the VASCOG-2-NP Battery. *JAMA Neurol.* Submitted.
31. Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a Clinical-Biological Construct-An International Working Group Recommendation. *JAMA Neurol.* 2024;81(12):1304-1311.
32. Hosoki S, Hansra GK, Jayasena T, et al. Molecular biomarkers for vascular cognitive impairment and dementia. *Nat Rev Neurol.* 2023;19(12):737-753.
33. Dadar M, Mahmoud S, Zhernovaia M, Camicioli R, Maranzano J, Duchesne S. White matter hyperintensity distribution differences in aging and neurodegenerative disease cohorts. *Neuroimage Clin.* 2022;36:103204.
34. Das RR, Seshadri S, Beiser AS, et al. Prevalence and correlates of silent cerebral infarcts in the Framingham offspring study. *Stroke.* 2008;39(11):2929-2935.
35. van den Berg E, Geerlings MI, Biessels GJ, Nederkoorn PJ, Kloppenborg RP. White Matter Hyperintensities and Cognition in Mild Cognitive Impairment and Alzheimer's Disease: A Domain-Specific Meta-Analysis. *J Alzheimers Dis.* 2018;63(2):515-527.
36. Staals J, Booth T, Morris Z, et al. Total MRI load of cerebral small vessel disease and cognitive ability in older people. *Neurobiol Aging.* 2015;36(10):2806-2811.
37. Mega Vascular Cognitive I, Dementia c. A genome-wide association meta-analysis of all-cause and vascular dementia. *Alzheimers Dement.* 2024;20(9):5973-5995.
38. Greenberg SM, Aparicio HJ, Furie KL, et al. Vascular Neurology Considerations for Antiamyloid Immunotherapy: A Science Advisory From the American Heart Association. *Stroke.* 2025;56(1):e30-e38.
39. Smith EE, Barber P, Field TS, et al. Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD)5: Guidelines for management of vascular cognitive impairment. *Alzheimers Dement (N Y).* 2020;6(1):e12056.
40. Smith EE, Markus HS. New Treatment Approaches to Modify the Course of Cerebral Small Vessel Diseases. *Stroke.* 2020;51(1):38-46.
41. Charidimou A, Boulouis G, Frosch MP, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol.* 2022;21(8):714-725.

42. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology.* 2017;89(1):88-100.
43. McKeith IG, Ferman TJ, Thomas AJ, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. *Neurology.* 2020;94(17):743-755.


Development of Delphi survey
Literature reviews on diagnostic criteria for VCID and key developments in VCID research since VASCOG by Core team.
Enrollment
Selection of participating experts
Assessed for eligibility (n= 310)
Excluded (n= 167)
♦ Did not meet inclusion criteria* (n= 167)
Sent invitation (n= 143)
Did not participate (n= 73)
♦ No response (n = 64)
♦ Declined (n = 9)
Agreed to participate (n= 70)
Delphi process
Round 1 (18/8/2023 to 10/10/2023)
n = 54 (77% of total invited)
♦ Online survey (approx. 60 minutes, 158 fields)^
In-person meeting (16/9/2023)
♦ 54 invitations
♦ n = 19 (35% of invited)
Videoconference discussion (25/10/2023)
♦ 54 invitations
♦ n = 24 (44% of invited)
Round 2 (27/11/2023 to 5/3/2024)
n = 51 (94% of 54 invited)
♦ Round 1 feedback.
♦ Online survey (approx. 30 minutes, 78 fields)^
Round 3 (22/3/2024 to 13/5/2024)
n = 49 (97% of 51 invited)
♦ Round 2 feedback
♦ Online survey (approx. 20 minutes, 55 fields)^
Delphi completion
♦ Round 3 feedback
♦ Paper write-up