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Diagnostic criteria for vascular cognitive disorders: a VASCOG statement

Perminder Sachdev, MD* **[Scientia Professor]**,
Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, Australia

Raj Kalaria, PhD, FRCP [Professor],
Cerebrovascular Pathology (Neuropathology), Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle-Upon-Tyne NE4 5PL, United Kingdom

John O'Brien, DM [Professor],
Old Age Psychiatry, Institute for Ageing and Health, Newcastle University, Campus for Ageing and Vitality, Newcastle NE4 5PL, UK

Ingmar Skoog, PhD [Professor],
Social Psychiatry and Epidemiology, Neuropsykiatri SU/M[illegible]lndal, Wallinsgatan 6, 431 41 M[illegible]lndal, Sweden

Suvarna Alladi, DM,
Department of Neurology, Nizam's Institute of Medical Sciences, Hyderabad, India

Sandra E Black, MD FRCP(C) [Brill Chair],
Neurology, University of Toronto, Sunnybrook Health Sciences Centre, Room A421- 2075 Bayview Avenue, Toronto, ON M4N 3M5

Deborah Blacker, MD, ScD [Associate Professor],
Psychiatry, Harvard Medical School, Boston Mass., USA

Dan Blazer, MD [JP Gibbons Professor],
Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina 27710, USA

Christopher Chen, FRCP [Director],
Memory Aging and Cognition Centre, National University Health System, Kent Ridge Road, Singapore 119228

*Corresponding Author: Prof Perminder Sachdev, School of Psychiatry, Faculty of Medicine, University of New South Wales, NPI, Euroa Centre, Prince of Wales Hospital, Barker Street, Randwick NSW 2031, Australia, Tel: +612 9382 3763, Fax: +612 9382 3774, p.sachdev@unsw.edu.au.

AUTHOR CONTRIBUTIONS

Perminder Sachdev initiated the project, summarized results of the discussions, wrote the first draft, and finalized the manuscript. Raj Kalaria, John O'Brien, Ingmar Skoog, Suvarna Alladi, Sandra Black, Deborah Blacker, Dan Blazer, Christopher Chen, Helena Chui, Mary Ganguli, Kurt Jellinger, Dilip Jeste, Florence Pasquier, Jane Paulsen, Niels Prins, Kenneth Rockwood, Gustavo Roman and Philip Scheltens reviewed the literature, made substantive contributions to the content, and provided comments on multiple drafts of the manuscript.

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Helena Chui, MD [McCarron Professor and Chair],
Department of Neurology, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

Mary Ganguli, MD [Professor],
Psychiatry, Neurology, and Epidemiology, University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, USA

Kurt Jellinger, MD [Director],
Institute of Clinical Neurobiology, Kenyongasse 18; A-1070 Vienna

Dilip V. Jeste, MD,
Estelle and Edgar Levi Chair in Aging and Distinguished Professor of Psychiatry and Neurosciences, University of California, San Diego, California 92093, USA

Florence Pasquier, MD, PhD,
University Lille Nord de France UDSL and Memory Clinic, CHU, 59000 Lille, France

Jane Paulsen, PhD [Professor],
Psychiatry, Neurology, Psychology and Neurosciences, The Carver College of Medicine, The University of Iowa, Iowa City, IA 52242, USA

Niels Prins, MD,
Alzheimer Centre and Department of Neurology, VU University Medical Centre, Amsterdam, the Netherlands

Kenneth Rockwood, MD [Professor],
Medicine (Geriatric Medicine & Neurology) and Kathryn Allen Weldon Professor of Alzheimer Research, Dalhousie University Halifax NS Canada B3H 2E1

Gustavo Roman, MD, and
Jack S. Blanton Distinguished Chair, Director Nantz National Alzheimer Center, Methodist Neurological Institute, 6560 Fannin Street, Suite 802, Houston, Texas 77030, USA

Philip Scheltens, MD
Alzheimer Centre and Department of Neurology, VU University Medical Centre, Amsterdam, the Netherlands

Abstract

Background—Several sets of diagnostic criteria have been published for vascular dementia (VaD) since the 1960s. The continuing ambiguity in VaD definition warrants a critical re-examination.

Methods—Participants at a special symposium of the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) in 2009 critiqued the current criteria. They drafted a proposal for a new set of criteria, later reviewed through multiple drafts by the group, including additional experts and the members of the Neurocognitive Disorders Work Group of the DSM-5 Task Force.

Results—Cognitive disorders of vascular etiology are a heterogeneous group of disorders with diverse pathologies and clinical manifestations, discussed broadly under the rubric of vascular

cognitive disorders (VCD). The continuum of vascular cognitive impairment is recognized by the categories of *Mild Vascular Cognitive Disorder*, and *Vascular Dementia or Major Vascular Cognitive Disorder*. Diagnostic thresholds are defined. Clinical and neuroimaging criteria are proposed for establishing vascular etiology. Subtypes of VCD are described, and the frequent co-occurrence of Alzheimer's disease pathology emphasized.

Conclusions—The proposed criteria for VCD provide a coherent approach to the diagnosis of this diverse group of disorders, with a view to stimulating clinical and pathological validation studies. These criteria can be harmonized with the DSM-5 criteria such that an international consensus on the criteria for VCD may be achieved.

Keywords

Vascular dementia; vascular cognitive disorder; vascular cognitive impairment; diagnostic criteria; cerebrovascular disease; multi-infarct dementia; post-stroke dementia; subcortical dementia

1. INTRODUCTION

Cerebrovascular disease (CVD) has long been recognized as an important cause of cognitive impairment, but the conceptualization of the consequent disorder has had a chequered history. The long-standing concept of 'hardening of the arteries' or cerebral atherosclerosis as a cause of 'senility'[1] was challenged in the 1960s by the neuropathological studies from Newcastle-Upon-Tyne, England which suggested that vascular dementia (VaD) was related to multiple brain infarctions exceeding a certain threshold, and distinct from Alzheimer's disease (AD).[2] The concept was further elaborated in a 1974 paper[3] which stated that "… when vascular disease is responsible for dementia it is through the occurrence of multiple small or large cerebral infarcts". This led to the widespread use of the term multi-infarct dementia (MID) as being synonymous with VaD.[3] The last two decades have witnessed a major challenge to this narrow conceptualization of VaD, with the publication of several sets of criteria for VaD[4–8] which expanded the concept to include not only multiple cortical and/or subcortical infarcts, but also strategic single infarcts, non-infarction white matter lesions, hemorrhages, and hypoperfusion as possible causes of VaD. Much ambiguity in the definition of VaD continues to beset the field, which warrants a critical examination and updating of the extant criteria.

1.1. Limitations of current criteria sets for VaD

The four commonly used sets of criteria for VaD are: the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria,[4] the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) criteria,[5] the DSM-IV criteria[6] and the ICD-10 criteria,[7] with the latter two being more general and less operationalized than the first two. Many clinicians and researchers continue to use the ischemic score[8] and its modifications to diagnose VaD even though it was not designed for this purpose. Less commonly used are criteria that are specific for subcortical vascular dementia.[9] The NINDS and the Canadian Stroke Network, at a workshop convened in 2006,[10] harmonized the standards of assessment of various aspects of cognitive impairment due to vascular factors and made a number of

recommendations to improve the quality of the data. As a result, many limitations of the currently available criteria for VaD were highlighted, some of which were common to the various criteria, while others applied only to specific sets.

First, the emphasis on 'dementia' in 'vascular dementia' appears to be misplaced for two reasons. The term dementia has increasingly become equated with AD in the popular mind, even though AD accounts just over one-half of all cases of dementia.[11] Secondly, it prejudices against the early recognition of cognitive impairment due to vascular pathology. While it is generally accepted that such impairment lies on a continuum, and the category of VaD uses a severity-based threshold which identifies the disorder at a late stage. Yet potentially disease-modifying treatments may be more effective before this stage is reached. Thus there have been repeated calls to abandon VaD in favor of an overarching description of vascular cognitive impairment (VCI)[12,13] to overcome this limitation.

Third, the domains of cognitive functioning that are considered for the diagnosis of VaD have been criticised.[11,14] Three of the four commonly used criterion sets mentioned above require memory impairment as necessary for the diagnosis of VaD, using a definition of dementia based on clinical features of AD. There is substantial evidence to suggest that disturbance in frontal-executive functions, rather than memory, is often the more salient feature of VaD,[14] memory impairment may in fact be absent in some cases with significant cognitive deficits or its characteristics may be different from those seen in AD[14].

Fourth, the criteria sets differ significantly on the requirements for levels of cognitive impairment, number and location of strokes, neuroimaging abnormalities and neurological features, such that when applied to the same data set, the prevalence estimates can vary by many orders of magnitude.[15,16] It is therefore necessary that each aspect of the criteria is critically examined, preferably with sound empirical evidence.

Fifth, VaD is not one disease but rather has diverse etiologies, only some of which have well-characterized clinical manifestations.[17] The extant criteria do not necessarily take this diversity into consideration.

Sixth, while VaD is generally regarded as the second most common single cause of dementia after AD,[18] many older individuals with dementia suffer from a combination of vascular and Alzheimer-type pathology with an additive effect on cognition,[19] which is sometimes referred to as 'mixed' dementia. Furthermore, there is increasing recognition that vascular and neurodegenerative processes may interact, so that risk factors for CVD also increase the risk of AD.[20] The co-occurrence of the two pathologies may therefore be more frequent than by chance, and any classification should recognize this overlap.

This proposal addresses some of these limitations in light of recent developments, not only in VaD but also in relation to the development of new criteria for AD at the dementia and pre-dementia stages,[21,22] and to the publication of the fifth revision of the Diagnostic and Statistical Manual (DSM-5) of the American Psychiatric Association.[23] Recently, the American Stroke Association also published a comprehensive consensus statement on vascular cognitive impairment, including new proposed criteria for probable and possible VaD and Vascular Mild Cognitive Impairment (VaMCI).[24]

2. METHOD

A special symposium on the classification of vascular cognitive disorders (VCD) was organized as part of the 4th Congress of the International Society for Vascular Behavioural and Cognitive Disorders (VASCOG) in Singapore on 13 January, 2009. Experts in this field who attended that meeting reviewed the current evidence and critique the extant criteria. Based on the discussions, a draft proposal for a new set of criteria was drafted and reviewed by the group, including additional experts who had not attended the symposium. Multiple further drafts were similarly circulated after recommendations had been incorporated. The criteria were discussed at the 5th VASCOG conference in September 2011 in Lille, France and the 6th VASCOG conference in June 2013 in Toronto, Canada before being finalized.

3. RESULTS

3.1. Criteria for vascular cognitive disorders (VCD)

There are two aspects to the diagnosis of a VCD: i) the establishment of the presence of a Cognitive Disorder; and ii) the determination that vascular disease is the dominant if not exclusive pathology that accounts for the cognitive deficits. While the history of cerebrovascular disease often prompts the careful physician to explore the presence of cognitive deficits, the usual clinical process is that the cognitive disorder is established first and then its etiology is interrogated.

3.1.1. Establishing the presence of a cognitive disorder—The term ‘cognitive disorder’ has previously been applied to this entity,[25] while the term used in DSM-5[23] is ‘neurocognitive’. Recent authors have used the term ‘vascular cognitive impairment (VCI)’ as an overarching term for the vascular cognitive syndromes.[12,13]

The term ‘impairment’ in this context has two limitations: a) Impairment is used in medicine to indicate a reduction or loss of function in any domain of functioning, and is applied either as a statistical construct based on normative data or a demonstration of disability; and b) VCI has sometimes been used in the literature to also denote mild cognitive impairment due to vascular factors insufficiently severe to be diagnosed as dementia. Our proposal for the use of ‘vascular cognitive disorder (VCD)’ recognizes that there is often a need for a categorical diagnosis, which encompasses mild impairment, pre-dementia and dementia syndromes. It can embrace many syndromes and diseases, and also acknowledge the fact that many patients with cerebrovascular disease also have non-cognitive syndromes such as depression, anxiety and psychosis. Functional ‘impairment’ is then understood as a consequence of the disorder rather than a diagnostic criterion for it. The use of the plural term ‘disorders’ acknowledges that VCD comprises many diseases, each with varying severity and patterns of dysfunction. Implicit in the term is the recognition that there has been a decline from a previously higher level of functioning, either documented with longitudinal data or inferred from a premorbid level.

There are two requirements for a cognitive disorder to be diagnosed: a subjective report and objective or test evidence of deficits.

3.1.1.a. Subjective report: A clinical encounter for a cognitive disorder usually results from a *concern* by the patient or a knowledgeable other person (informant) that there has been a decline in cognitive functioning. In some instances, this concern may primarily arise in the mind of the physician or other caring professional, especially if the patient or a family member has a lack of appreciation of the decline. The concern may stem from perceived impairment or disability, or fear of future decline. Concern from any source is sufficient to meet this criterion and prompt the search for objective evidence of decline. The requirement of 'subjective report' is in line with the DSM-5 proposal,[23] the recently proposed criteria for MCI in general,[26] and that due to AD.[22] In VaD (or Major VCD, see below), the subjective report will typically be that the individual has to rely on others to plan or make decisions, has had to abandon complex projects, repeats self in conversation, needs frequent reminders to orient to task at hand, has significant difficulties with expressive or receptive language, has difficulty in navigating in familiar environments or has a clear disturbance in body schema, calculation ability, reading or writing. In Mild VCD, the disturbance is more subtle, and the individual, while still independent, performs tasks with greater effort than before and resorts to compensatory strategies. He/she may therefore have difficulty multi-tasking or complain of fatigue from the extra effort needed to organize and plan. Their work may contain more errors than before and may therefore require double-checking. Word-finding difficulties may be noticeable, and the individual may need additional help to navigate.

3.1.1.b. Objective evidence of impairment: The physician making the diagnosis must obtain some objective evidence to support decline in functioning using a validated measure of cognitive functions. A formal neuro-psychological test battery administered by a trained practitioner is ideal, but a shorter "bedside" test such as a global or screening test may be adequate. This recognizes the reality that formal neuropsychological testing may be unavailable or impractical, even in resource-rich settings, and an equivalent clinical evaluation would have to suffice. The testing examines cognitive functioning in a range of cognitive domains (Table 1), and bedside testing should ideally cover these domains. The criteria are not prescriptive in relation to the test instruments used so long as these are standardized, and normative data for comparison are available. A harmonized battery has however been suggested by a consensus process and is undergoing validation in several languages.[10] A significant departure from most previous definitions of dementia is that memory impairment is not a pre-requisite for the diagnosis. A considerable body of literature has concluded that the preponderance of disturbance in vascular cognitive disorders is in processing speed and frontal-executive functions, manifesting as slowed information processing, poorer working memory and reduced set-shifting ability.[10,14] Slowed information processing may be especially important in Mild VCD, which necessitates the use of timed tests.[10] Episodic memory is frequently impaired in VCD, but the pattern may be different from that seen in AD, with retrieval of information being more affected than retention, such that the individual fares better on a recognition task than on free recall of a word list.[14] These are generalizations, however, as the cognitive profile of VCD is very varied, reflecting the wide variety of brain lesions that underlie these deficits.[10] Moreover, it is recognized that motor or speech deficits may impede an accurate overall cognitive assessment, and efforts have to be made to overcome this limitation.

3.1.2. Diagnostic thresholds—The concept of VCI recognizes that cognitive impairment in VCD is on a continuum from normal functioning to dementia.[12] This is not dissimilar to the situation in cognitive disorders with many other etiologies, be they neurodegenerative, traumatic, or substance-related. The diagnostic process entails the imposition of a categorical system on this continuum, and the approach to have Mild VCD and Major VCD categories, with the latter equating to dementia, has been adopted in the DSM-5[23] and is similar to the recent recommendations for AD.[21,22] Vascular brain damage can exist without any evident cognitive impairment, and such asymtomatic individuals may be at an increased risk of future decline and are worthy of medical attention to prevent such decline. This has been referred to as the pre-Mild VCD stage or the 'brain-at-risk' stage.[12] While preclinical diagnosis is of growing importance in chronic disease, the current criteria are for clinical use and therefore restricted to Mild and Major (or Dementia) categories.

The asymmetrical use of 'mild' and 'major', instead of the 'mild and severe' or 'minor and major' wording, was the accepted compromise in DSM-5.[23] 'Severe' is strongly associated with the degree of disability to be used to define a category, and 'minor' runs the risk of trivializing what is an important disorder worthy of clinical attention and intervention. The term 'dementia', while not favored by the majority of the group, was considered historically too important to be abandoned, and has been used synonymously with 'major' VCD, except that the DSM-IV[6] and ICD-10[7] definitions of dementia warranted impairment in at least two cognitive domains of which one was necessarily memory. The distinction between the Mild and Major (or dementia) levels is based on the severity of cognitive deficits, and more importantly on the functional impairment secondary to them. The traditional approach has been to diagnose dementia (or Major) when the cognitive deficits are severe enough to impair social or occupational functioning, such that instrumental activities of daily living (IADL) are affected and the individual is not able to function independently. This threshold of 'loss of independence' has been retained in the criteria. It is also particularly important in the vascular cognitive disorders to note that impairment should be attributable to cognitive and not motor, sensory or speech impairment for this criterion to be met.

It is true that Mild disorder can also affect functioning, especially in individuals with intellectually demanding occupations, but in general such individuals can function close to their previous levels by instituting compensatory strategies, and their IADLs remain essentially intact, with maintenance of independent functioning. This criterion does raise the dilemma, however, that the degree of impairment produced by a disorder is being used to diagnose the disorder. This is against the recommendations of the World Health Organization that the classification of functioning and disability be kept separate from the classification of diseases.[27] In view of this, thresholds based on cognitive test performance norms are also recommended as guidelines, to be used in conjunction with functional level and based on the clinician's judgment.

As a guide for Mild VCD, deficits would typically fall between one and two standard deviations below the mean (or between the third to 16th percentiles for test scores not normally distributed) of people of similar age, sex, education, and sociocultural background. For Dementia or Major VCD, deficits would typically fall two or more standard deviations below the mean (or below the third percentile). If appropriate normative data for the

measure(s) are not readily available (e.g. for those with very high or very low education or premorbid intellectual capacity or unfamiliar sociocultural-linguistic background), the clinician may infer from the combination of history and cognitive performance that there has been a real but modest level of decline in Mild VCD, and clear and significant level of decline in Dementia or Major VCD. It is also recognized that formal neuropsychological evaluation is not available in all settings, but it is considered important that some objective documentation of the cognitive deficits be made rather than relying solely on the clinician's "gestalt." In research settings, the use of standardized tests with the above recommended thresholds is recommended.

Ideally, when serial measurements are available, decline from an individual's own previous level would serve as more definitive evidence of decline, and this may be used in lieu of normative data. The decline may be in one or more cognitive domains. The evaluation of decline should take practice effects of repeated test administration into consideration. The commonly used definitions of VaD, e.g. NINCDS-AIREN,[4] DSM-IV[6] and ICD-10,[7] require impairment in two or more cognitive domains, with memory being one of these domains. However, an individual with severe impairment in one cognitive domain, e.g. severe aphasia following a stroke, may in some cases have enough consequent disability to justify a diagnosis of Major VCD, although it is more likely that in situations with impairment in one domain only, the disorder will be Mild. Detailed assessment of patient with predominant disturbance in one domain may reveal impairment in other cognitive domains as well. The criteria for Mild and Major Cognitive Disorder are summarized in Table 2.

3.1.3. Establishing a predominantly vascular etiology for the cognitive disorder—Vascular disorder involves an abnormality in the wall or lumen of a blood vessel of any size. The pathological basis of this can be very varied, and some of the common pathologies have been previously reported[5,10,17,28] as summarized in Table 3. The heterogeneity stems from the type of vascular lesion and the nature, extent and location of parenchymal injury. The lesions may be focal, multifocal or diffuse, and occur in various combinations.[17] The nature and severity of cognitive impairment will usually depend upon the nature of the lesions (whether completed infarction, non-infarct ischemic change, hemorrhage, or sclerosis), the volume of parenchymal lesions, the number and location of lesions, and a number of other factors such as age, sex and brain reserve.[29] Vascular risk factors such as hypertension,[30] diabetes,[31] or hyperhomocysteinemia[32] that are implicated in vascular pathology may be related to cognitive impairment through other mechanisms as well. There are also abnormalities in key neurotransmitter systems in some individuals with VCD, in particular in the basal forebrain cholinergic system.[33] The picture is further complicated by the presence of other changes, such as those characterizing AD. Since some degree of vascular pathology is very common in brains of older individuals, a question that has been consistently posed is how best to determine whether a certain degree of pathology, as observed on neuroimaging or neuropathology, is sufficient to account for the observed cognitive deficits. As will be discussed later, there is no simple answer to this vexing question. Expert clinical 'judgment' is frequently necessary for such determination, and when vascular and Alzheimer pathologies are combined, this may become a moot point.

In order to clinically establish a predominantly vascular etiology for a cognitive disorder, the following must be considered:

3.1.3.a. Clinical features of the cognitive syndrome: The heterogeneity of pathology in VCD suggests that the cognitive deficits will vary according to the brain regions affected and the mode of onset of the lesions. The classical description of multiple infarct dementia (MID) was that of an acute step-wise or fluctuating decline in cognition, with intervening periods of stability and even some improvement.[12] This pattern is temporally related to cerebrovascular events of infarction, hemorrhage or vasculitis, and the temporal relationship is not difficult to establish clinically. The cognitive impairment is at its peak soon after a stroke and may show significant improvement over the next three months; persistence beyond this period is generally considered necessary for the cognitive disorder to be diagnosed.[5] Further improvement may occur beyond the three months, but its rate is much slower.[34] Many individuals with VCD do not, however, present this picture and show a gradual onset with slow progress, or a rapid development of deficits followed by relative stability, or some other complex presentation.[13] VCD with a gradual onset and slow progression is generally due to small vessel disease leading to lesions in the white matter, basal ganglia and/or thalamus. The gradual progression in these cases is often punctuated by acute events which leave subtle neurological deficits such as focal weakness, unilateral incoordination, asymmetric reflexes, unsteadiness, small-step gait or parkinsonian signs.[35] The cognitive deficits in these cases can be attributed to disruption of cortical-subcortical circuits, and speed of information processing, complex attention, and frontal-executive function are likely to be affected.[36] White matter lesions (WMLs), often ischemic in origin, are commonly associated with frontal-executive deficits, irrespective of their distribution in the brain.[37] In cases of mild VCD, frontal-executive deficits are therefore more likely to be present than in mild cognitive impairment due to AD in which impairment in episodic memory, in particular the ability to learn and retain new information, is a prominent early feature.[22]

Since vascular lesions may disrupt many thalamocortical, striatocortical and prefrontal-basal ganglia pathways, and may affect cortical and limbic brain structures, VCD is often associated with disturbance in behavior and emotion.[13] As these neuropsychiatric features are not specific to vascular etiology, they are not considered to be core diagnostic features, yet may be the presenting symptoms. Their diagnosis and management are therefore important in the treatment of patients.

3.1.3.b. Determining evidence of significant cerebrovascular disease: This is a key feature of the diagnostic process, and relies on history, physical examination and neuroimaging. The demonstration of abnormalities on neuroimaging is critical for increased certainty in the diagnosis, and the lack of neuroimaging data can result in significant diagnostic inaccuracy by overlooking silent brain infarction and WMLs.[37] Neuroimaging is also important to rule out some less common causes such as brain tumor or normal pressure hydrocephalus (NPH), and it may be important to distinguish vascular from AD or frontotemporal degeneration as the etiology of cognitive impairment.

Neuroimaging: Evidence for significant vascular pathology in the brain usually relies on computed tomography (CT) or structural magnetic resonance imaging (MRI), with the latter being more sensitive, especially if the standardized protocols recommended by the harmonization group are followed.[10] The findings are varied and there is no feature that is pathognomonic of VCD. The neuroimaging findings must therefore be interpreted in the clinical context, and their nature, severity and location must be considered. Attempts have been made to define the minimal radiological evidence necessary. The California criteria[5] require 'two or more' ischemic strokes, with at least one infarct outside the cerebellum for a diagnosis of VaD. The NINDS-AIREN criteria[4] require 'multiple large-vessel stroke' or 'a single strategically placed infarct' (angular gyrus, thalamus, basal forebrain or posterior carotid artery or anterior carotid artery territories) or 'multiple basal ganglia and white matter lacunes' or 'extensive periventricular white matter lesions'. The SIVD criteria[9] require extensive confluent white matter lesions along with lacunar infarcts. It must also be pointed out that the terminology used to describe neuroimaging abnormalities is quite varied as well, and there was a recent attempt to standardize the reporting of neuroimaging abnormalities in relation to small vessel disease[38].

Large infarcts: It is generally accepted that VCD can occur without evidence of brain infarcts, although the latter are usually present. This is in contrast with the traditional view in which multiple large vessel cerebral infarcts were considered necessary to support a diagnosis of VaD.[3] A single large vessel infarct may be sufficient to produce mild VCD, but it must either be strategically placed, as described above, or be very extensive to cause a Major VCD (or VaD). For the latter, multiple (>1) large vessel infarcts are usually necessary, which are more likely to be in the left hemisphere and are often bilateral.[39,40] If multiple large infarcts are to be considered as being sufficient for the diagnosis of major VCD, at least one of these should be outside the cerebellum.[4] A temporal association between the cerebral infarction and the occurrence of cognitive impairment is supportive of its etiological significance, with the impairment being evident within three months of the infarction and persisting beyond that period.[41]

Lacunar infarcts: VCD may also be associated with lacunar infarction, although there is a lack of consensus on the specific number and location of the lacunes required for a VCD diagnosis. It is well recognized that 1–2 lacunes are not uncommon in older individuals with no cognitive impairment, and may be incidental findings.[42] More than two lacunes outside the brain stem would generally be regarded as necessary to support a diagnosis of VCD.[43] Single lacunes placed strategically in the striatum or the thalamus, usually above a certain size threshold,[44] may produce a VCD,[45] but a temporal relationship between lacunar infarction and the cognitive syndrome must be present to be able to attribute VCD to a single lacune. Single lacunes may also be sufficient when associated with extensive periventricular and deep white matter lesions.[8,9] Whether single lacunes, either strategically located or in combination with mild WMLs, are sufficient for Major VCD is uncertain, however. To support the latter diagnosis, multiple lacunes must be present and these must be associated with at least moderate extent of WMLs.[8] The Newcastle neuropathological criteria for VaD[28] suggested >3 lacunar infarcts as being sufficient evidence, but this must

of course be considered along with other vascular pathologies, in particular WMLs which are generally present concurrently.

Lacunar infarction is best detected on T1-weighted or T2-weighted MRI using a fluid-attenuated inversion recovery (FLAIR) sequence on a 1.0 T scanner or greater. It appears as a small hypointense area, which is surrounded by a rim of hyperintensity in the FLAIR image, although in some cases the central cavity fluid is not suppressed on FLAIR and it can appear entirely hyperintense despite a clear CSF-like intensity on other sequences. A lacune has most commonly been regarded as a lesion between 3–15 mm,[28, 38] a definition favored by this group and the STRIVE criteria,[38] but definitions vary with maximum diameter from 1 cm[10] to 2 cm.[46] The VCI harmonization standards recommend that up to 1 cm be classified as 'small' infarcts,[10] with the main feature being that they are deep in the brain and are consistent with a previous acute small deep brain infarct or hemorrhage in the territory of one perforating arteriole. Given their small size, an MRI sequence with contiguous slices that are not too thick (4mm or less) is most likely to image these lesions satisfactorily. On a CT scan, lacunes are seen as small discrete hypodensities, but because of poorer spatial resolution of CT, they are more likely to be missed. Micro-infarcts, which are not visible on gross neuropathological examination, are also not seen with neuroimaging and therefore cannot be considered for clinical diagnosis even though their pathophysiological importance is well established.[28] Infarctions should be distinguished from dilated perivascular spaces, and the neuroimaging characteristics used in the Cardiovascular Health Study[47] are often applied, further elaborated in the STRIVE criteria[38]. While dilated perivascular or Virchow-Robin spaces may represent an early stage of cerebrovascular disease with underlying microvascular degeneration,[28] they have not commonly been considered a feature supporting VCD,[48] thereby needing further study.

White matter lesions (WMLs): VCD may be present in the absence of lacunar or large infarcts if extensive WMLs are present. On CT, WMLs are seen as hypodensities or *leukoaraiosis*. On MRI, which is much more sensitive to white matter pathology than CT, WMLs are hypointense areas on T1-weighted and hyperintensities on T2-weighted imaging. WMLs may be focal or multifocal, and as they become more extensive, they become confluent and may involve much or all of the white matter. The white matter of the basal ganglia and thalamus also show these lesions.[49] When mild, these lesions appear as small 'caps' on the frontal and/or occipital horns and fine 'rims' along the walls of the lateral ventricles on transverse sections (periventricular lesions, PVLs), or punctuate foci in the deep white matter (deep WMLs). The identification of these lesions on neuroimaging, in particular T2-weighted MRI, presents two main problems of interpretation in relation to their significance: i) They are non-specific, and a large number of pathologies, which include multiple sclerosis, cerebral edema, neurosarcoidosis, brain irradiation etc., can cause similar appearing lesions.[50] While the differential diagnosis is long, there is evidence from clinical and pathological data to suggest that the majority of these lesions in the brains of older people are ischemic in origin.[51] They are caused by arteriosclerosis, lipohyalinosis and fibrinoid necrosis of small vessels, in particular the long perforating arteries, with or without occlusion.[17] Importantly, WMLs are more extensive in the periventricular regions and extend to the deep white matter, but spare areas protected from hypoperfusion, such as the

subcortical U-fibers and the external capsule-claustrum-extreme capsule.[52] However, WMLs are also commonly detected in individuals with AD, dementia with Lewy bodies and fronto-temporal dementia, and the pathophysiology of the lesions in these settings is uncertain, and may relate to coexisting small vessel disease, periventricular venous fibrosis,[53] white matter, gliosis,[17] etc.; ii) WMLs are highly prevalent in the brains of elderly and even middle-aged individuals,[54,55] and the lesions have to be extensive to be clinically significant. If the WMLs are focal and visible only on T2-weighted MRI, they are unlikely to be significant enough to explain the development of a cognitive disorder. How much of the white matter must be affected before the VCD can be attributed to them has been difficult to determine, probably because other factors such as age, sex, brain reserve, topography of the lesions, associated infarction or atrophy, and other pathology are all relevant. One set of criteria for subcortical VaD[8] determined that on CT, these should be "extensive… patchy or diffuse areas of low attenuation with ill-defined margins extending to the centrum semiovale (from the ventricular margin)", and on MRI: "hyperintensities extending into the periventricular and deep white matter; extending caps (>10 mm as measured parallel to the ventricle) or irregular halo (>10 mm with broad, irregular margins and extending into deep white matter) *and* diffusely confluent hyperintensities (>25 mm, irregular shape) or extensive white matter changes (diffuse hyperintensity without focal change)". These criteria also required that at least one lacunar infarct should also be present. Some investigators[56,57] have suggested that at least 25% of the total white matter should be affected to support a diagnosis of VaD, and one study in normal elderly noted the threshold for cognitive impairment was 0.5% of total intracranial volume.[58]

It is therefore not possible to provide strict guidelines on the extent of WMLs considered sufficient for Mild VCD or VaD. A general rule is that these should be *extensive and confluent*, and some of the descriptions above should be considered as guidelines. A temporal relationship to the cognitive impairment, if previous imaging has been undertaken, would also be highly supportive. For Mild VCD, WMLs may be sufficient in the absence of other vascular pathology. For VaD (or Major VCD), the additional presence of one or more lacunes is necessary,[8] which is not uncommon in individuals with extensive WMLs.[17]

With the development of newer MRI techniques such as diffusion tensor imaging (DTI), it has been demonstrated that white matter which appears normal on T2-weighted imaging may also have abnormal anisotropy or diffusivity which relates to neuropathology[59] and may have relevance for cognitive function.[60] Abnormalities on DTI are, however, not delineated well enough at present to be incorporated into diagnostic criteria.

Hemorrhages: Cognitive disorders have been associated with subdural hemorrhage (SH) and subarachnoid hemorrhage (SAH), the presence of which on an MRI scan should alert the diagnostician to their possible significance. Cognitive deficits have been reported in 19–62% of patients following SAH,[61] and their severity is related to the severity of SAH,[62] although other factors such as older age, the presence of arterial vasospasm and delayed cerebral infarction, increased intracranial pressure, intraparenchymal and intraventricular hemorrhages, hydrocephalus, and location of the aneurysm are all important.[61] Subdural hemorrhage is an uncommon cause of cognitive disorder, with reports that older individuals with chronic SH have cognitive deficits in about one in two cases,[61] which may be

progressive and not always reversible with surgical drainage.[63] Since SH is usually a result of trauma and not vascular pathology, it should be not be regarded as a VCD. SAH is due to vascular pathology and its associated cognitive deficits are appropriately regarded as VCD. Multiple hemorrhages or hemorrhagic infarcts are often associated with VCD, the common causes being sporadic or hereditary conditions associated with cerebral amyloid angiopathy (CAA)[64] and other genetic disorders,[65] although hypertension may have a role. VCD has also been associated with cortical and subcortical microbleeds, which may be related to hypertension or CAA.[66] These lesions are best visualized on T2*-weighted GRE sequences and susceptibility weighted MRI scans. Since microbleeds are not uncommon in cognitively normal older individuals, attribution of the VCD to these, especially VaD, should follow a careful exclusion of other causes of cognitive impairment and only if numerous such lesions are present. Microbleeds associated with hypertension are seen in the deep nuclei and brainstem and those with AD are generally lobar in location.[67,68]

Other neuroimaging evidence: While structural imaging with CT and MRI are generally used to investigate parenchymal brain injury due to cerebrovascular disease, other modalities of imaging may be useful in such determination. Reviews of the roles of these techniques in the diagnosis of cerebrovascular disease[69,70] and dementia[71] have recently been published. Diffusion-weighted imaging (DWI) is used in the assessment of acute injury due to stroke. Diffusion tensor imaging (DTI) is an MRI technique capable of evaluating the integrity of white matter in greater detail, and will often detect abnormality not visible with other modalities. Its utility in discriminating VCD from other cognitive disorders remains to be established, however. Gradient-recalled echo (GRE) MRI is as good as non-contrast CT for assessing acute intracerebral hemorrhage. Other techniques useful in the evaluation of cerebrovascular disease include angiography and perfusion imaging with CT and MRI, the latter now possible without an intravenous contrast agent using arterial spin-labeling (ASL). Other techniques currently used mainly for research include magnetization transfer ratio (MTR), T1 mapping, permeability imaging and microatheroma and arteriolar imaging. MRI is in general superior to CT in assessing cerebrovascular disease, but it is less readily available and about 10% of patients have contra-indications to its use. Ultrasound technology provides useful information about the status of blood vessels in the neck and the cranium, thereby complementing the imaging of parenchymal brain injury. Cerebral perfusion is also assessed using single photon emission tomography (SPECT) and xenon contrast CT. Positron emission tomography (PET) enables the imaging of regional glucose metabolic rates, using ^{18}F fluorodeoxyglucose, which may assist in the differential diagnosis of the various types of cognitive disorders. PET also enables the imaging of specific molecular abnormalities. More recently, the imaging of amyloid with compounds such as the radiolabeled Pittsburgh compound B (^{11}C-PiB) has received much interest and been proposed as a biomarker of AD.[21,22] Amyloid imaging has recently been used to support the diagnosis of pure subcortical vascular dementia[72] as well as post-stroke dementia,[73] suggesting that the latter is generally a combination of AD and vascular dementia. Neuroimaging is a rapidly developing field and it is likely that developments in the future will increase the certainty with which specific cognitive disorders can be diagnosed.

3.1.3.c. Clinical evidence of cerebrovascular disease: While neuroimaging, in particular the various modalities of MRI, provide the most sensitive evidence for CVD currently available, the clinical history and a neurological examination may provide additional information, or may be the only sources of objective evidence in the absence of neuroimaging.

- **i.** A well documented history of stroke is evidence of CVD, either primarily of the cerebral blood vessels or secondarily through embolism. The decline in cognition should have occurred following the stroke.
- **ii.** Sufficient evidence is also provided by a neurological examination that reveals signs indicative of one (generally for Mild VCD) or multiple (generally for VaD or Major VCD) brain infarctions (e.g., hemiparesis, lower facial weakness, sensory loss including visual field defects, pseudobulbar syndrome {supranuclear weakness of muscles of face, tongue and pharynx, spastic dysarthria, swallowing difficulties and emotional incontinence}).
- **iii.** The following are supportive of the presence of cerebrovascular disease but in themselves are not sufficient to establish vascular disease as a likely cause of VCD. However, in the presence of a characteristic cognitive syndrome, they acquire salience in determining likely vascular etiology:
  - **a.** Early presence of a gait disturbance (small step gait or *marche à petits pas*, or magnetic, apraxic-ataxic or parkinsonian gait).
  - **b.** Early urinary frequency, urgency and other urinary symptoms not explained by urologic or other neurological diseases.
  - **c.** Personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

  The criteria for establishing vascular etiology for a cognitive disorder are summarized in Table 4.

3.2. Exclusion criteria

Since incidental brain infarctions and WMLs are common in brains of older individuals, it is important to consider other possible etiologies when a cognitive disorder is present. If the history, physical examination and/or investigations suggest another etiology sufficient to account for the cognitive impairment, VCD should not be diagnosed. However, in many cases, CVD may be considered to make a contribution to the cognitive disorder, in which case it is important to recognize dual or multiple etiologies. A history of early onset of memory deficit, and progressive worsening of memory, language (transcortical sensory aphasia), motor skills (apraxia) and perception (agnosia), in the absence of corresponding focal lesions on brain imaging, is suggestive of AD as the primary diagnosis. A diagnosis of VCD is not made if other diseases, e.g. brain tumor, multiple sclerosis, encephalitis, toxic or metabolic disorders, etc. are present and are of sufficient severity to account for the cognitive impairment. If the patient is suffering from a Major Depression, and the onset of cognitive impairment is temporally related to the likely onset of the depression, VCD should

again not be diagnosed. It must be noted, however, that patients with VCD may develop a superimposed depression, in which both disorders should be diagnosed. Importantly, VCD should not be diagnosed if neuroimaging with CT or MRI reveals nil or minimal evidence of cerebrovascular disease. A diagnosis of VCD is also inappropriate if the patient has a diagnosis of delirium, although delirium may sometimes be superimposed on a pre-existing VCD, in which case both diagnoses can be made.

3.3. Risk factors for cerebrovascular disease

A number of 'vascular' risk factors, variably referred to as 'cardiovascular' or 'cerebrovascular', have been identified as increasing the risk of cognitive disorders. These include demographic factors such as age and ethnicity; lifestyle factors such as education, physical activity, complex mental activity, alcohol intake, diet, obesity and smoking; physiological risk factors such as hypertension, diabetes, insulin resistance, metabolic syndrome, hyperlipidemia, hyperhomocysteinemia and inflammation; and the concomitant presence of vascular disease such as coronary artery disease, atrial fibrillation, peripheral artery disease, chronic kidney disease and low cardiac output. The evidence in relation to these factors and cognitive impairment has been previously reviewed.[24] Some factors, such as hypertension, diabetes, smoking and hyperlipidemia act through an increased risk of cerebrovascular accidents. Others, such as education and complex mental activity influence the brain's reserve capacity, thereby influencing the impairment associated with brain pathology. Some of the factors are related to cognitive dysfunction through multiple pathways, only one of which is the exacerbation of cerebrovascular disease. Risk factors such as hypertension, diabetes, high cholesterol and high homocysteine have been independently linked to an increased risk of Alzheimer's disease although the evidence remains inconsistent.[74–76] In view of this, the presence of vascular risk factors should raise the index of suspicion for cerebrovascular disease and possibly VCD, but the presence of these risk factors alone cannot be considered evidence for the presence of parenchymal brain injury due to cerebrovascular disease. Risk factors should not be conflated with diagnostic criteria.

3.4. Neuropathological diagnosis

A definitive diagnosis of VCD warrants a neuropathological verification.[17] This will confirm the clinical or radiological evidence of vascular brain injury, or detect such injury not detected by brain imaging, e.g. small lacunes, microinfarcts and selective neuronal loss. It identifies the type of underlying cerebrovascular lesions, e.g. arteriolosclerosis, cerebral amyloid angiopathy, etc. It also ascertains the presence of other brain pathology of relevance to cognitive dysfunction. For instance, if the pathological examination reveals plaques and neurofibrillary tangles of sufficient severity to suggest AD as the major cause of cognitive impairment, a diagnosis of VCD cannot be sustained, although dual etiology can still be diagnosed. The same is true for other pathological findings. The heterogeneity of vascular pathology has made it difficult to establish validated criteria for VCD. Some attempts have been made to characterize and quantify vascular brain pathology[17,28,77] and to harmonize criteria,[10] but have thus far not achieved general consensus.

3.5. Level of certainty

For a clinical diagnosis of VCD two levels of certainty are recommended: probable and possible, consistent with the approach taken in diagnosis of neurodegenerative disorders.[21,22] For a diagnosis of *probable* VCD, both the clinical and neuroimaging criteria must be met. Albeit rare, evidence of a genetic cerebrovascular disorder will support a level of probable certainty. Examples include 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; and collagen type IV, alpha1 (COL4A1) related disorders. If the clinical criteria are met but neuroimaging is not available, a *possible* VCD diagnosis is made. Neuropathological examination will greatly enhance the certainty of a pre-mortem diagnosis, although the term ‘definitive’ VCD is not being proposed as these are clinical criteria.

3.6. Subtypes of VCD

Subcategories of VCD have been described, but they have been used inconsistently since overlap between the subcategories is common. A majority of patients with VCD have a combination of cortical and subcortical lesions, thereby being called *cortico-subcortical VCD*. This term subsumes *cortical VCD*, since it is rare for vascular lesions to be exclusively cortical. It also partially subsumes the older term ‘multi-infarct dementia’ which is characterized by multiple cortical and subcortical infarcts, although multiple infarcts can also be exclusively subcortical and lead to VCD.

It is now well-recognized that VCD may be exclusively due to subcortical vascular lesions, and various attempts have been made to characterize *subcortical* VCD.[8,9,36] The pathological basis of this includes multiple lacunes and/or WMLs. VCD may be related predominantly to white matter lesions of vascular origin, which has sometimes been referred to as Binswanger’s disease. However, the historical usage of this term has made it controversial.[78] Pure subcortical VCD with a slowly progressive course that simulates AD but which does not have the characteristic brain amyloid burden of AD has recently been documented.[71] A special case of subcortical VCD is *thalamic dementia*, due to infarctions located in the thalamus with relatively little involvement of other brain structures.[79] VCD may also be subcategorized according to etiology as being largely *ischemic* or *hemorrhagic*. Another subcategory referred to is *post-stroke VCD*, although this has complex etiology with a varying combination of large and small vessel disease as well as non-vascular pathology such as AD contributing to the picture.

3.7. Multiple causality

Post-mortem examinations of the brains of older people who had cognitive disorders in life usually reveal a combination of pathologies with vascular lesions and Alzheimer-type pathology predominating, but stigmata of other etiologies, such as Lewy body disease, are also present.[80] The concurrent presence of CVD is more common in AD than other neurodegenerative disorders, and has been noted to lower the threshold of diagnosis of

dementia due to AD and α-synucleinopathies.[81] The overlap between vascular and Alzheimer-type changes has received the greatest attention, and this has been referred to as 'VaD with AD' or often 'AD with CVD' (the term 'mixed dementia' is ambiguous and is not recommended). The concept covers a wide spectrum, from individuals with predominant AD pathology who also have large or small infarcts or white matter lesions, to those with a predominantly vascular picture with minimal plaques and neurofibrillary tangles in the brain. The clinical expression of major or mild cognitive disorder will depend upon the severity of AD pathology as well as the location and type of vascular lesions, with cortical microinfarcts and thalamic and basal ganglia lacunar infarcts often being implicated.[82] A clinician, however, may find it difficult to accurately attribute cognitive disorder to one or the other etiology, or decide which has primacy. Modern imaging techniques, which include various modalities of MRI for vascular lesions and volumetry of the hippocampus and entorhinal cortex, and amyloid imaging for Alzheimer-type pathology, may assist in the process, but are not always definitive. The increasing evidence that the so-called vascular risk factors also promote Alzheimer-type pathology in the brain suggests that pure VCD or AD are far less common than previously thought.[83] The recommended approach for the clinician is to initially make a syndromal diagnosis of mild or major cognitive disorder and then decide which is the more prominent pathology. At the same time other contributing pathologies need to be acknowledged, e.g. dementia or major cognitive disorder due to vascular etiology with AD pathology (VaD or Major VCD with AD), or AD with VCD if AD is the more predominant pathology. In such situations, the level of certainty of the first or primary diagnosis, be it AD or VCD, is 'possible' and not 'probable'. This system also allows depression, alcohol dependence and other causes of cognitive disorder to be diagnosed concomitantly, and their contribution to the cognitive impairment acknowledged.

3.8. Associated psychiatric and behavioral symptoms

VCD is often associated with psychiatric or behavioral symptoms that may pose special challenges for their treatment. In particular, depression, psychosis, agitation and apathy are of interest. While some attempts have been made to develop specific criteria for syndromes such as depression and psychosis associated with cognitive disorders,[84] there is no one profile that is specific to VCD. A diagnostician should, however, note the presence of these symptoms and disorders because of their likely impact on the patient and because they are often amenable to effective intervention.

3.9. Biomarkers

The heterogeneity of VCD has made the development of reliable non-imaging biomarkers extremely challenging. Some suggested cerebrospinal fluid (CSF) biomarkers of cerebrovascular disease are the albumin index as a marker of damage to the blood-brain barrier, sulfatide for demyelination, neurofilament for axonal degeneration and matrix metalloproteinases for vascular disease.[10] As none of these is specific to VCD, they are not currently recommended for use for this diagnostic purpose. CSF markers for AD are, however, better developed, with lower levels of Aβ42 and elevated levels of tau/phosphorylated-tau being indicative of AD pathology.[21,22] These, along with amyloid imaging using positron emission tomography (PET), may help determine AD as the main or contributory cause of the cognitive disorder. Their use is encouraged in clinical trials and

research studies of VCD to rule out AD. Other neuroimaging to determine the rate of brain atrophy, hippocampal or mesial temporal atrophy, cerebral blood flow and cerebral metabolic rate may be useful in the differential diagnosis in some cases, but their status as biomarkers of AD is uncertain.[22] Emerging markers include carotid intimal-medial thickness and arterial stiffness, which are associated with arterial ageing and may serve as risk markers of VCD.[24]

4. CONCLUSION

The proposed criteria and guidelines present a rational clinical approach to the diagnosis of VCD in its various manifestations, and should now be examined for their reliability and validity. The proposal recognizes the heterogeneity of the nature, location and severity of pathology underlying VCD, and acknowledges that the clinical data available to the clinician will vary depending upon the setting. The criteria are in line with the DSM-5 criteria and take into consideration the developments in other cognitive disorders such as AD. It is expected that the criteria will be modified as new knowledge becomes available. While this approach results in some lack of comparability with historic data, refinement of criteria must proceed to keep pace with advancement of knowledge.

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Prof. Sachdev is an executive member of VASCOG, and was a member of the Neurocognitive Disorders Work Group of the DSM-5 Task Force and a member of the WHO ICD-11 Expert Working Group on Neurocognitive Disorders. He is funded by the National Health and Medical Research Council of Australia (grants # 568940, 568969 and 401162) and the Australian Research Council (grant # DP120102078). He has received occasional lecture fees (<$2000) from Pfizer and Eli Lilly.

Prof. Kalaria has served on a scientific advisory board for Alzheimer's Research UK (ARUK); serves on editorial advisory boards for Neuropathology and Applied Neurobiology, Alzheimer's Disease and Associated Disorders, European Neurology, NeuroReport, and Behavioral and Brain Functions; has received speaker honoraria from Pfizer Inc; and receives research support from the Alzheimer's Research UK, Medical Research Council, the Dunhill Medical Trust, UK and Mitsubishi Tanabe Pharma, Japan. None of these are associated with this report.

Prof. O'Brien serves as an editorial board member for Psychological Medicine, is Deputy Editor of International Psychogeriatrics and was previously an editorial board member of the American Journal of Geriatric Psychiatry. He has been a consultant for GE Healthcare, Servier and Bayer Healthcare and has received honoraria for talks from Pfizer, GE Healthcare, Eisai, Shire, Lundbeck, Lilly and Novartis. Dr. Skoog has served as a consultant for Nycomed and has served on the Speakers Bureau for Lundbeck, Jansen, Pfizer, Esai, GE, Shire, Pfizer and GE.

Dr. Black has received ad hoc honoraria for serving on the scientific advisory boards for Pfizer, Roche, Elan, and GE Healthcare, and for CME lectures from Eisai, Novartis and Pfizer. She has a patent pending regarding INCAS (Integrate Neuro-Cognitive Assessment System)-Cognitive Assessment Tool and Method, and has conducted contract research paid to her institution by Roche, Elan, GlaxoSmithKline, Pfizer, Novartis, Bristol-Myers Squibb, Lundbeck. She also has peer-reviewed grants from Brain Canada, Alzhiemer's Drug discovery Foundation, the Canadian Institutes of Health Research, the Canada Foundation for Innovation, the Canadian Stroke Network, the Heart and Stroke Foundation of Canada, and the National Institutes of Health. She also has received some salary support from the NIH, Brill Chair in Neurology, Department of Medicine, Sunnybrook Health Sciences Centre and University of Toronto, and Sunnybrook Research Institute.

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chapter of the Alzheimer's Association. She was a member of the Neurocognitive Disorders Work Group of the DSM-5 Task Force.

Dr. Blazer was a member of the Neurocognitive Disorders Work Group of the DSM-5 Task Force.

Dr. Chen serves or has served on the following advisory boards: Abbott, member Nutritional Advisory Board; ESASIS, chairman of the Data Safety Monitoring Board, Early Stent-assisted Angioplasty in Symptomatic Intracranial Stenosis (ESASIS) study; Baxter, member Advisory Board on IVIG in AD; Allergan, member, Global Stroke Community Advisory Panel; Pfizer, member, Asian Alzheimer's Disease Advisory Board. He has served/serves on the following journal editorial boards: Practical Neurology, member editorial board, 2004-present; International Journal of Stroke, member editorial board, 2005-present; Stroke, member editorial board, 2010-present; Journal of Neurology, Neurosurgery and Psychiatry, member editorial board, 2010-present. Dr. Chen has received or receives research support from the following commercial entities: Pfizer, Site Principal Investigator, A 78-Week Noninterventional Longitudinal Study to Validate the ADAS-Cog, DAD, and NTB in Asian Subjects with Mild to Moderate Alzheimer's Disease; Merck, Principal Investigator, A pilot exploration into arterial spin labeling and USPIO-enhanced MRI methodologies for measuring hemodynamic responses to non-drug stimuli; GSK, Co-PI, Retinal Vascular Signs as Novel Biomarkers of Dementia. He has received or receives research support from the following government entities: National Research Foundation, NRF- CRP 3 - 2008 – 01, Co-PI, 2009–14; National Medical Research Council, NMRC/xxxx/2011, PI, 2011–13; National Medical Research Council, NMRC/1288/2011, PI, 2010–13.

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Dr. Pasquier participates in several pharmaceutical trials for AD, served on advisory boards for Bayer, Eisai, Lilly, Servier, Ipsen, received funding from the Ministère de l'Enseignement Supérieur et de la Recherche and from the Direction Generale de l'Offre de Soins (Ministry of Health).

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Dr. Prins serves on the advisory board of Boehringer Ingelheim and Envivo Pharmaceuticals, has been a speaker at symposia organized by Janssen and Novartis, has a senior fellowship at the Alzheimer Center VUmc and receives research support from the Brain Foundation of the Netherlands (project number H07.03) and Alzheimer Nederland (project number WE.03-2012-02). He receives no personal compensation for the activities mentioned above.

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Dr. Scheltens serves/has served on the advisory boards of: En Vivo, GE Healthcare, Novartis, Pfizer, Roche, Danone, Jansen AI. He has been a speaker at symposia organized by Lundbeck, Lilly, Merz, Pfizer, Jansen AI, Danone, Novartis. He is co-editor in chief of Alzheimer’s Research & Therapy and is a member of the scientific advisory board of the EU Joint Programming Initiative and the French National Plan Alzheimer. The Alzheimer Center receives unrestricted funding from various sources through the VUmc Fonds. Dr Scheltens receives no personal compensation for the activities mentioned above.

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Table 1

Description of cognitive domains assessed in vascular cognitive disorders

1	Attention and processing speed (sustained attention, divided attention, selective attention, information processing speed)
2	Frontal-executive function (planning, decision-making, working memory, responding to feedback/error correction, novel situations, over-riding habits, mental flexibility, judgment)
3	Learning and memory (immediate memory, recent memory [including free recall, cued recall], and recognition memory)
4	Language (naming, expressive, grammar and syntax, receptive)
5	Visuoconstructional-perceptual ability (construction, visual perception and reasoning)
6	Praxis-gnosis-body schema (Praxis, gnosis, right/left orientation, calculation ability, body schema, facial recognition)
7	Social cognition (recognition of emotions and social cues, appropriate social inhibitions, theory of mind, empathy)

Table 2

Proposed criteria for Mild Cognitive Disorder and Dementia (or Major Cognitive Disorder)

Mild Cognitive Disorder:

A. Acquired decline from a documented or inferred previous level of performance in *one or more* cognitive domains (listed in table 1) as evidenced by the following:

- **a.** Concerns of a patient, knowledgeable informant or a clinician of mild levels of decline from a previous level of cognitive functioning. Typically, the reports will involve greater difficulty in performing the tasks, or the use of compensatory strategies; and
- **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) in one or more cognitive domains listed in table 1. The test performance is typically in the range between 1 and 2 standard deviations below appropriate norms (or between the 3rd and 16th percentiles) when a formal neuropsychological assessment is available, or an equivalent level as judged by the clinician.

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[*] *or Major Cognitive Disorder:*

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:

- **a.** Concerns of the patient, a knowledgeable informant, or the clinician, of significant decline in specific abilities; and
- **b.** Clear and significant deficits in objective assessment based on a validated objective measure of neurocognitive function (either formal neuropsychological testing or equivalent clinical evaluation) in one or more cognitive domains. These typically fall two or more standard deviations below the mean (or below the 3rd percentile) of people of similar age, sex, education, and sociocultural background, when a formal neuropsychological assessment is available, or an equivalent level as judged by the clinician.

B. The cognitive deficits are sufficient to interfere with independence (e.g., at a minimum requiring assistance with instrumental activities of daily living, i.e., more complex tasks such as managing finances or medications).

[*] Note that the DSM-IV[6] and ICD-10[7] concept of dementia requires deficits in at least two domains, one of which being memory.

Table 3

Pathological basis of vascular cognitive disorders

Parenchymal lesions of vascular etiology:*

1. Large vessel or atherothromboembolic disease:
   - **a.** Multiple infarcts
   - **b.** Single strategically placed infarct
2. Small vessel disease:
   - **a.** Multiple lacunar infarcts in white matter and deep gray matter nuclei
   - **b.** Ischemic white matter change
   - **c.** Dilatation of perivascular spaces
   - **d.** Cortical microinfarcts and microhemorrhages
3. Hemorrhage:
   - **a.** Intracerebral hemorrhage
   - **b.** Multiple cortical and subcortical microbleeds
   - **c.** Subarachnoid hemorrhage
4. Hypoperfusion:
   - **a.** Hippocampal sclerosis
   - **b.** Laminar cortical sclerosis

Types of vascular lesions:

1. Atherosclerosis
2. Cardiac, atherosclerotic and systemic emboli
3. Arteriolosclerosis
4. Lipohyalinosis
5. Amyloid angiopathy
6. Vasculitis – infectious and non-infectious
7. Venous collagenosis
8. Arteriovenous fistulae – dural or parenchymal
9. Hereditary angiopathies – cerebral autosomal dominant arteriopathy with subcorticalinfarcts and leukoencephalopathy, CADASIL; cerebral autosomal recessive arteriopathy with subcortical autosomal recessive leukoencephalopathy, CARASIL, etc.
10. Giant cell arteritis
11. Berry aneurysms
12. Miscellaneous vasculopathies - fibromuscular dysplasia, Moya-Moya
13. Systemic microangiopathies without vascular inflammatory cell infiltrates
14. Cerebral venous thrombosis

* Microinfarcts may be localized in cortical and subcortical structures due to different etiologies

Table 4

Evidence for predominantly vascular etiology of cognitive impairment

A. One of the following clinical features:

1. The onset of the cognitive deficits is temporally related to one or more cerebrovascular events (CVE). [Onset is often abrupt with a stepwise or fluctuating course owing to multiple such events, with cognitive deficits persisting beyond three months after the event. However, subcortical ischemic pathology may produce a picture of gradual onset and slowly progressive course, in which case A2 applies]. The evidence of CVEs 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 (e.g., hemiparesis, lower facial weakness, Babinski sign, sensory deficit including visual field defect, pseudobulbar syndrome – supranuclear weakness of muscles of face, tongue and pharynx, spastic dysarthria, swallowing difficulties and emotional incontinence)
2. Evidence for decline is prominent in speed of information processing, complex attention and/or frontal-executive functioning in the absence of history of a stroke or transient ischemic attack. One of the following features is additionally present:
    - **a.** Early presence of a gait disturbance (small step gait or marche petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); This may also manifest as unsteadiness and frequent, unprovoked falls
    - **b.** Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
    - **c.** Personality and mood changes: abulia, depression, or emotional incontinence

B. Presence of significant neuroimaging (MRI or CT) evidence of cerebrovascular disease (one of the following):

1. One large vessel infarct is sufficient for Mild VCD, and two or more large vessel infarcts are generally necessary for VaD (or Major VCD).
2. An extensive or strategically placed single infarct, typically in the thalamus or basal ganglia may be sufficient for VaD (or Major VCD).
3. Multiple lacunar infarcts (> two) outside the brainstem; 1–2 lacunes may be sufficient if strategically placed or in combination with extensive white matter lesions.
4. Extensive and confluent white matter lesions
5. Strategically placed intracerebral hemorrhage, or two or more intracerebral hemorrhages
6. Combination of the above

Exclusion criteria (for Mild and Major VCD)

1. History
    - **a.** Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging or history of vascular events.
    - **b.** Early and prominent parkinsonian features suggestive of Lewy body disease
    - **c.** History 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. Other medical disorders severe enough to account for memory and related symptoms
    - **a.** Other disease of sufficient severity to cause cognitive impairment, e.g. brain tumor, multiple sclerosis, encephalitis
    - **b.** Major depression, with a temporal association between cognitive impairment and the likely onset of depression.
    - **c.** Toxic and metabolic abnormalities, all of which may require specific investigations
4. Other medical disorders severe enough to account for memory and related symptoms
    - **a.** Other disease of sufficient severity to cause cognitive impairment, e.g. brain tumor, multiple sclerosis, encephalitis
    - **b.** Major depression, with a temporal association between cognitive impairment and the likely onset of depression.
    - **c.** Toxic and metabolic abnormalities, all of which may require specific investigations

5 [For research] The presence of biomarkers for Alzheimer's disease (cerebrospinal Aβ and pTau levels or amyloid imaging at accepted thresholds) exclude diagnosis of probable VCD, and indicate AD with CVD.

Table 5

Criteria for Vascular Cognitive disorder: Miscellaneous aspects

Level of certainty

1 *Probable:*

- **a.** Clinical criteria for VCD are supported by neuroimaging.
- **b.** Both clinical and genetic (e.g. 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, alpha1 (COL4A1) related disorders) evidence of cerebrovascular disease

[*For research*: The presence of biomarkers for Alzheimer's disease (cerebrospinal Aβ and pTau levels or amyloid imaging at accepted thresholds) excludes the diagnosis of probable VCD].

2 Possible:

Clinical criteria for VCD are met, but neuroimaging is not available (if appropriate neuroimaging is available and not supportive of VCD, the diagnosis of possible VCD should not be made)

Subtypes of VCD

- **I.** Hemorrhagic or Ischemic
- **II.** Cortical-subcortical or Subcortical ischemic

Multiple causation

1 VCD with concomitant AD (Major or Mild)

- **a.** Meets criteria for VCD (except for exclusion criteria)
- **b.** Meets criteria for AD (possible)

State which etiology is clinically more salient: vascular or Alzheimer's

2 VCD with additional pathology: e.g. Lewy body disease

3 VCD with contribution from depression

Associated behavioral or psychiatric symptoms: with psychotic symptoms, depression, agitation, apathy etc.