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The international society of vascular behavioural and cognitive disorders: highlights from VasCog 2025 in the UK.

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1. Introduction

Interest in the vascular contributions to cognitive impairment and dementia—including Alzheimer's disease (AD)—as well as depression and other related behavioural conditions has grown significantly over the past decade. The focus has expanded beyond contributions of stroke, to encompass broader mechanisms through which cerebrovascular (patho)physiology, including both large and small vessel disease, influences cognition and behaviour [1].

The *International Society for Vascular Behavioural and Cognitive Disorders* (VasCog) plays a pivotal role in advancing knowledge in the field, from its pathological mechanisms to clinical manifestations and treatments. Indeed, VasCog's mission is to deepen understanding of vascular influences on cognitive and behavioural disorders, enhance prevention and treatment strategies, and promote brain health across the lifespan. A key part of this mission is training the next generation of researchers and clinicians.

To pursue its vision, VasCog organizes a biennial conference designed to showcase the latest breakthroughs in vascular contributions to cognitive impairment and dementia research, promote multidisciplinary symposia led by international experts in both clinical and research domains, and facilitate open debates on current challenges in the field. VasCog 2025, held in Southampton, UK from September 15–18, brought together ~200 researchers, clinicians, and early career investigators to exchange cutting-edge findings, strengthen professional networks, and explore new strategies for improving early diagnosis, prognosis, and treatment of vascular-related cognitive and behavioural disorders.

2. Congress themes: aims and highlights

VasCog 2025 has centred on understanding how cerebrovascular disorders, particularly cerebral small vessel disease (SVD) contributes to cognitive and behavioural syndromes [2], with a program (link: https://conference2025.vascog.org/programme-2/) designed to reflect the complex and heterogeneous etiological and clinical nature of vascular contributions to cognitive impairment and dementia (hereafter, VCID). The conference featured invited and selected talks, as well as interactive sessions addressing both mechanistic and clinical aspects of VCID. Timely themes, debates, and Early Career Investigator master classes—summarized in Table 1—highlighted key updates and introduced novel artificial intelligence (AI)-based methods with potential to clarify VCID pathophysiology and accelerate biomarker discovery. These advances also enhance our understanding of cerebrovascular lesions, particularly in the context of co-morbidities and multiple neurodegenerative pathologies, pointing to shared mechanisms and reinforcing the need for integrated research and clinical approaches. The conference themes were selected a priori by the Scientific Committee and endorsed by the Executive Committee. The highlights presented below have been agreed upon by the co-authors as representing the main novel findings from the conference.

Theme 1 showcased innovative approaches, using AI-driven methods, to unravel the complex cerebral and molecular mechanisms underlying VCID and related clinical syndromes. These approaches bridge emerging tools with traditional clinical and neuropathological frameworks to better capture the heterogeneity of VCID, revealing patterns often invisible to the human eye. For example, AI-derived in vivo classifier of arteriolosclerosis (ARTS), translated from autopsy data, may aid in identifying individuals at risk of VCID, informing risk stratification for clinical trial and guiding future prevention strategies [3]. These approaches also offer insights into converging biological pathways of VCID, including endothelial and vascular injury, inflammation, immune activation, coagulation, neural and synaptic damage, and hemorrhagic processes [1]. A key focus was on neuropsychiatric symptoms—depression, apathy, and fatigue—grouped under Mild Behavioral Impairment, which may precede overt dementia and interact

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Table 1
Overview of VasCog 2025 themes, focused topic, and debates.

Themes	Aim
Theme 1: New directions in VCID	Showcase cutting-edge approaches to decode the complex mechanisms underlying VCID and its behavioural manifestations.
Theme 2A: Fluid, Retinal, Cardiac biomarkers	Present emerging non-invasive biomarkers from fluid, retinal, and cardiac sources to enhance early detection and monitoring of vascular brain injury and cognitive decline.
Theme 2B: Neuroimaging biomarkers	Demonstrate the developments in and utility of advanced neuroimaging techniques in identifying diverse vascular contributions to VCID and refining diagnostic precision.
Theme 3: Pathophysiology of VCID	Deepen understanding of key processes—arteriolosclerosis, blood-brain barrier leakage, and inflammation—as causal mechanisms underlying SVD and cognitive decline.
Theme 4: Epidemiology & Risk Factors	Examine how cardiovascular risk factors and disorders affect vascular brain injury and cognition, with a focus on sex differences and underrepresented populations.
Theme 5: Treatments updates	Showcase results from clinical trials re-purposing existing drugs for treatments of SVD.
Theme 6: Hereditary SVD and VCI	Deepen our understanding of the genetic basis of hereditary SVD and its links to sporadic forms, aiming to inform precision medicine approaches.
Debate: Is small vessel dysfunction the primary cause of dementia?	Discuss the role of SVD in pathogenesis, progression, and clinical expression of dementia.
Focused Topic: Clearence of interstitial fluid (CLIC)	Focused on mechanisms of interstitial fluid clearance in the brain and its role in cerebral amyloid angiopathy and neurodegeneration.
Early Career Investigator	Promote the involvement and training of a next generation of scientists and clinicians in vascular brain health.

with vascular lesions [4]. Theme 1 also featured the newly updated VasCog-2-WSO diagnostic criteria for VCID, integrating neuroimaging markers with harmonized cognitive assessments (Abstract ID#031) [5]. Additional insights included the stronger impact of vascular pathology on neurofilament light (NfL) levels in amyloid-negative individuals (Abstract ID#079), suggesting NfL reflects axonal injury as a common endpoint to different pathology rather than pure AD degeneration alone. A new integrative scale for post-stroke cognitive and functional outcomes was also introduced (Abstract ID#027). Collectively, these contributions reflect a growing interest in precision tools and multidimensional assessments to advance VCID research and care.

Theme 2A focused on identifying fluid, retinal, and cardiac biomarkers to sensitively detect early vascular brain injury and related cognitive decline. These non-invasive, scalable tools aim to advance VCID research toward mechanistically informed early detection. For the VasCog community, this theme bridged translational research and clinical practice, supporting harmonised multi-domain biomarker use across global cohorts and trials. Theme 2A demonstrated how vascular contributions to brain health can be detected through peripheral markers—broadening opportunities for early intervention and population screening. Plasma and/or CSF biomarkers such as GFAP (astrocytes), NfL, sPDGFR-β (pericyte injury), PDGF-BB (signalling changes), and Lp-PLA2 were linked to white matter injury, blood-brain barrier (BBB) dysfunction, and cognitive decline [6]. Combined into multi-analyte panels, these markers improved differentiation between VCID, Alzheimer pathology, and healthy ageing (Abstract ID#017). Promising retinal biomarkers—via deep learning applied to vasculometry and optical coherence tomography angiography (OCTA) retinal images—can quantify vessel calibre, tortuosity, and perfusion density metrics, mirroring cerebral microvascular health [7]. Altered retinal vessel morphology showed associations with cardiovascular and metabolic disorders, cognitive dysfunction, and early white-matter abnormalities (Abstract ID#020), underscoring the retina's potential as an accessible "window to the brain." Cardiovascular markers, integrating cardiac imaging and vascular proteomics, revealed that subclinical arteriosclerosis, reduced arterial elasticity, and altered cardiac output are linked to both white matter injury and cognitive decline [8]. Studies on cardiac interventions (e.g., pacemaker implantation) highlighted complex heart–brain interactions, cerebral perfusion, and long-term cognitive outcomes (Abstract ID#086). Together, these advances illustrate a transition toward multi-modal vascular phenotyping integrating molecular, retinal, and cardiac data to capture early biological changes before clinical symptoms emerge.

Theme 2B outlined the role of different imaging modalities in uncovering diverse types of vascular contributions to VCID. How we measure and characterize spatial patterns of vascular brain function and injury in vivo is at the core of advancing understanding of VCID in both patients and the wider community [9]. White matter hyperintensities as observed on MRI reflect different underlying pathologies depending on their location (e.g., non-AD vs AD in an anterior-to-posterior gradient) [10]. Risk conditions, such as chronic stress, hypertension, physical strength, and depressive symptoms, are linked to regional variability and morphology of perivascular spaces, suggesting an interplay that may influence brain clearance mechanisms (Abstract ID#029). Diffusion imaging measures of structural connectivity can help differentiate small vessel disease subtypes, distinguishing hypertension-related from amyloid angiopathy-related injury (Abstract ID#118). Furthermore, intracranial arteriosclerosis appears to play a more prominent role than extracranial carotid artery stenosis in VCID, with intimal and internal elastic lamina arteriosclerosis contributing differentially to downstream brain pathology independently of amyloid plaques (Abstract ID#047).

Theme 3 explored the pathophysiology of VCID, focusing on arteriolosclerosis, BBB leakage, and inflammation as mechanisms driving SVD and cognitive decline. Despite progress, a comprehensive understanding of these fundamental processes remains incomplete, but it is essential for identifying therapeutic targets. Presentations highlighted how new emerging techniques are transforming the field, including single-vessel imaging with micro-CT to reveal microvascular structural changes along a single vessel [11]. Compelling evidence was presented that BBB breakdown and inflammation are early, interrelated mechanisms contributing to SVD [12]. Theme 3 also addressed the overlap between vascular and neurodegenerative pathways, which often coexist in patients. Disentangling these processes is essential for precision diagnostics and treatment. In the context of cognitive impairment associated with metabolic dysfunction, findings indicated that prolonged high-fat diet modulates amyloid progression in a mouse model, potentially via upregulation of genes related to synaptic structure and neuronal activity (Abstract ID#069). A study examined microglial-driven neuroinflammation and cerebrovascular dysfunction in AD using post-mortem and in vitro models (Abstract ID#040). The session concluded with preliminary results from the Lacunar Intervention Trial (LACI), testing whether cilostazol and isosorbide mononitrate improve white matter blood flow in mice (Abstract ID#075)—drugs now under investigation in the LACI-3 randomized clinical trial.

Theme 4 showcased how traditional and advanced epidemiological methods can help identify risk, protective, and modifiable factors for VCID. It was shown that biological sex at birth interacts with cardiovascular risk factors to influence cardiometabolic risk prediction and small vessel disease, emphasizing the need to account for sex in both analysis and interpretation of epidemiological studies [13]. The session also highlighted the importance of sociocultural background in precision medicine, with a focus on cardiovascular risk and cognitive assessments in underrepresented populations—including Asian Americans, non-Hispanic white Americans, and adults with HIV in Eastern Europe and Central Asia (e.g., Georgia and Kazakhstan) [14]. Differences in white matter hyperintensity volumes, segmented using Bayesian methods, across disaggregated Asian and non-Hispanic white American were reported (Abstract ID#087). Advanced modelling

approaches, such as Bayesian Network, were proposed to better capture the complexity of interactions between multiple risk factors and clinical outcomes, improving individualized risk prediction (Abstract ID#060). These models are being developed and validated using large datasets from population-based, community, and clinical cohorts. Finally, chronic stress—measured via allostatic load—emerged as a risk factor for post-stroke dementia, with higher scores three months after stroke associated with a two-fold increased risk (Abstract ID#032), underscoring mind-body interactions.

Theme 5 focused on treatments for VCID, which remain limited, though recent progress is encouraging [15]. The session highlighted three trends. First, re-purposing existing drugs is gaining traction. PDE5 inhibitors (i.e., sildenafil) show promise, increasing cerebrovascular reactivity and perfusion [16,17] and potentially cognitive benefits [18]. Data from the OX-HARP trial data showing modest increases in brain blood flow following six weeks of treatment, with plans for a mirodenafil trial [19]. Additional findings showed sildenafil effects in mice (Abstract ID#135) and identified a thiazide drug as a novel candidate derived from patient prescribing data (Abstract ID#007). The LACI-2 trial tested a nitrate NO-donor and PDE3 inhibitor cilostazol [20] to potentially treat VCID caused by SVD. Data on its feasibility in human (Abstract ID#059) and back translated in transgenic rats (Abstract ID#116) were presented. Alongside cilostazol, steroid-based therapy is also being tested as potential treatment for cerebral amyloid angiopathy-related inflammation (Abstract ID#066). Second, new drug targets are emerging from 'omic screens'. Transcriptomic and proteomic data on SVD and large-scale proteomics findings were presented [21], along with candidate targets linking SVD to vascular cells from epigenomic analysis (Abstract ID#134). Third, non-pharmacological treatment approaches such as remote ischemic pre-conditioning in patients with VCID were highlighted [22]. Preliminary findings were also shared on amyloid-related imaging abnormalities and clinical benefits in a cohort of Japanese patients treated with lecanemab (Abstract ID#120).

Dementia prevention is entering a new era of innovation. In a standalone invited talk, Dr Mangialasche summarized a decade of findings from the FINGER trial—a lifestyle-based, multidomain intervention combining exercise, cognitive training, social engagement, and vascular risk monitoring for individuals at-risk of dementia [23]. The FINGER model is now being implemented globally through the Worldwide-FINGERS network. Recent results from the US-POINTER study confirmed cognitive benefits in the intervention arm when the program was structured rather than self-guided [24]. Looking at the future, the next generation of multidomain interventions is moving toward integrating lifestyle components with pharmacological approaches [25].

Theme 6 aimed to deepen understanding of hereditary SVD—particularly CADASIL, caused by pathogenic variants in the *NOTCH3* gene—and its relationship to sporadic SVD typically observed with aging [26]. Discussions focused on genetic mechanisms, pathological findings, and emerging research to clarify shared pathways and key distinctions. Findings from the world's largest CADASIL cohort provided insights into the progression of cognitive and motor impairment, modelling variations in multiple cognitive and motor test performances at the individual level [27]. Region-specific CADASIL-related features (e.g., clinical presentations were highlighted when comparing European and Asian populations [28,29]. A study reported characteristics in Japanese CADASIL patients, including carriers of the *NOTCH3* p.R75P variant, whose cognitive changes can be detected using the Montreal Cognitive Assessment, consistent with findings in Caucasian patients (Abstract ID#049). Two potential therapeutic targets were highlighted: active immunization and PDE-5 inhibitors. Experimental work demonstrated the interplay between the cerebral microvasculature, microglia, and neurodegeneration in a mouse model and presented immunization strategies that reduced the number and size of *NOTCH3* extracellular domain accumulation around capillaries (Abstract ID#034). Additional findings showed selective vulnerability of cerebral microvessels to *NOTCH3* variants, with PDE-5 inhibitors rescuing vascular smooth muscle cell phenotype, function, and survival (Abstract ID#055).

Aligned with the VasCog's tradition, a **debate** was held on the topic: *Is small vessel dysfunction (SVD) the primary cause of dementia?* Arguments for the motion emphasized that healthy small vessels are essential for brain function, that SVD impairs brain clearance pathways, contributes to proteinopathies such as cerebral amyloid angiopathy, and is present in most dementia cases. Supporting evidence included that SVD causes BBB breakdown, hypoperfusion, and neuroinflammation, which are linked to cognitive decline. Arguments against the motion highlighted dementia's multifactorial nature, noting that SVD is often a consequence or secondary factor. Pathological data show that only a minority of dementia cases are purely vascular, with the majority involving neurodegenerative etiologies. Further, genetic studies highlight amyloid and tau as primary drivers with SVD only modulating or interacting with these pathologies.

The **Clearance of Cerebrospinal and Interstitial Fluids** (CLIC) group updated on the brain–nose communication pathways and the potential for nasal biomarkers to monitor the progression of neurodegenerative diseases. Mitochondrial therapeutic targets in AD and cerebral amyloid angiopathy were discussed. The Leducq Foundation consortium was represented through the analysis of whether cerebral amyloid angiopathy represents a perivascular clearance disorder. The impact of systemic inflammation on the cerebral vessels and their impairment for clearing amyloid was also discussed within the CLIC symposium.

3. An Early career investigator perspective

As highlighted in the Introduction, a core mission of VasCog is to promote the involvement and training of a next generation of scientists in vascular brain health. In line with this goal, Early Career Investigator (ECI) representatives, developed a dedicated program for VasCog 2025, featuring masterclasses, career panels, roundtables focusing on research (biomarkers, AI, neuropathology, genetics) and professional development (grant writing, collaboration, and mentorship), a poster blitz, and networking events. These activities were designed to strengthen both the technical skills and professional development of ECIs. The program was shaped by feedback from the ECI roundtable at VasCog 2023 and a post-conference survey, which emphasized the need for greater support in career planning, soft skills, and networking opportunities.

Structural changes were introduced to make masterclasses more interactive, including roundtable-style layouts to foster discussion and collaboration. The pre-conference masterclass was structured into two thematic sessions designed to equip ECIs with foundational knowledge within the conference themes. The first masterclass "*Emerging tools*" introduced innovative methods for early-detection of VCID. The first talk highlighted current digital technologies for cognitive assessment. The second talk provided an overview of AI tools—including machine learning and deep learning—and their applications in VCID research (e.g., biomarker quantification, multimodal integration, lesion mapping), highlighting both strengths and limitations. The second masterclass "*Mechanisms in VCID*" focused on biological mechanisms underlying VCID, including vascular biology of the BBB and disease mechanisms and clinical features of cerebral amyloid angiopathy.

Together, these initiatives reflect the sustained commitment that VasCog has to empower the next generation of VCID researchers.

4. Overall direction in the field

Vascular contributions to behavioural and cognitive outcomes are recognized as heterogeneous, involving multiple pathophysiological processes. While some of these processes appear mainly linked to functional or structural changes of the cerebral microvasculature, others will overlap with neurodegenerative processes. The field is moving towards a more integrative mechanistic understanding, where co-

pathologies are seen as the norm rather than exceptions, particularly in advanced stages of disease. Impaired clearance of products like amyloid, is emerging as a central mechanism, bridging vascular and neurodegenerative processes. It is unknown to what extent these clearance mechanisms also affect the build-up of other proteins (e.g., tau, alpha-synuclein) and future studies are warranted. These newer directions were also brought forward during the debate. Yet we lack a common language to define these vascular contributions to behavioural and cognitive outcomes—while ensuring an equal emphasis on cognition and behaviour.

Peripheral biomarkers (e.g., cardiac dysfunction, inflammation) are gaining traction alongside central markers, suggesting converging biological pathways across major vascular risk factors/disorders and SVD. Some of these processes intersect with beta-amyloidosis—whether in vessels or parenchyma—while others are independent of AD pathology. In vivo imaging, supported by post-mortem validation, continues to illuminate disease mechanisms, refine diagnosis, and ultimately guide treatment selection.

A key emerging direction is the integration of multimodal data—i.e., proteomics, neuroimaging, and peripheral biomarkers—within the brain-body axis to refine VCID prediction modelling. AI-driven methods (e.g., deep learning) are increasingly used to detect latent patterns in, for example, neuroimaging markers of SVD (e.g., white matter hyperintensities, perivascular spaces), accounting for spatial distribution and severity across large datasets and supporting early detection and precision diagnostics. Advanced statistical modelling is also showing promise in refining cardiovascular and metabolic risk profiles for better patient stratification for targeted interventions.

There is a strong need for low-cost, AI-enabled screening tools suitable for diverse populations, alongside harmonized longitudinal studies linking blood, retinal, imaging, and cognitive markers. Growing emphasis is placed on sex- and socioculturally tailored approaches to improve diagnostic and therapeutic precision. The newly proposed VascCog-2-WHO diagnostic criteria [5] provide a framework that facilitate their adoption in epidemiological and clinical settings, supporting large-scale implementation in the future, and allowing continuous refinements on emerging evidence. Similarly, neuroimaging standards (e.g., STRIVE-2) are evolving [2,30], while blood-based biomarkers are being validated for use in low-resource and routine clinical environments.

Technological advances include ultra-sensitive detection of single molecules via digital platforms (e.g., Simoa), development of multiplex kits, and improved imaging modalities. Genomic research is reshaping our understanding of sporadic SVD, with NOTCH3 variant heterogeneity prompting a redefinition of CADASIL as a spectrum disorder.

From an intervention standpoint, SVD is not a single pathology. Therefore, SVD treatments demands multi-targeted strategies, including pharmacological treatments, lifestyle modifications, and multidomain approaches. Hybrid interventions—combining multidomain lifestyle and pharmacological components targeting vascular health from multiple angles—are emerging as a promising avenue to slow cognitive decline. Ongoing trials will be critical to validate their efficacy.

Overall, the emphasis in VCID research is towards a more specific and tailored diagnosis of vascular contributions to a cognitive phenotype, and timely detection of subclinical pathology for the prevention of vascular-related cognitive, motor, and behavioural disorders. Key pillars of this transition will be multimodal approaches that integrate central and peripheral biomarkers, supported by advanced computational methods—marking a strategic priority for VasCog's agenda.

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Declaration of generative AI use

During the preparation of this work the authors used M365 Co-pilot to edit the English in the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Anna Marseglia: Writing – review & editing, Writing – original draft, Conceptualization. **Roxana O. Carare:** Writing – review & editing, Writing – original draft, Conceptualization. **Jessica L. Teeling:** Writing – review & editing, Resources, Conceptualization. **Saima Hilal:** Writing – review & editing, Writing – original draft, Conceptualization. **Vera Yuan Cai:** Writing – review & editing, Writing – original draft, Conceptualization. **Russell Chander:** Writing – review & editing, Writing – original draft, Conceptualization. **Hugues Chabriat:** Writing – review & editing, Writing – original draft, Conceptualization. **Deborah Gustafson:** Writing – review & editing, Writing – original draft, Conceptualization. **Atticus H. Hainsworth:** Writing – review & editing, Writing – original draft, Conceptualization. **Gurpreet Kaur Hansra:** Writing – review & editing, Writing – original draft, Conceptualization. **Sarah-Naomi James:** Writing – review & editing, Writing – original draft, Conceptualization. **Audrey Low:** Writing – review & editing, Writing – original draft, Conceptualization. **Julie Ottoy:** Writing – review & editing, Writing – original draft, Conceptualization. **Satoshi Saito:** Writing – review & editing, Writing – original draft, Conceptualization. **Annemieke ter Telgte:** Writing – review & editing, Writing – original draft, Conceptualization. **Hilde van den Brink:** Writing – review & editing, Writing – original draft, Conceptualization. **Frank J. Wolters:** Writing – review & editing, Writing – original draft, Conceptualization. **Prashanthi Vemuri:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

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

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