Alzheimer’s disease—subcortical vascular disease spectrum in a hospital-based setting: Overview of results from the Gothenburg MCI and dementia studies

Anders Wallin¹, Arto Nordlund¹, Michael Jonsson¹, Kaj Blennow¹,², Henrik Zetterberg¹,³, Annika Öhrfelt¹, Jacob Stålhammar¹, Marie Eckerström¹, Mårten Carlsson¹, Erik Olsson¹, Mattias Göthlin¹, Johan Svensson⁴, Sindre Rolstad¹, Carl Eckerström¹ and Maria Bjerke¹

Abstract
The ability to discriminate between Alzheimer’s disease (AD), subcortical vascular disease, and other cognitive disorders is crucial for diagnostic purposes and clinical trial outcomes. Patients with primarily subcortical vascular disease are unlikely to benefit from treatments targeting the AD pathogenic mechanisms and vice versa. The Gothenburg mild cognitive impairment (MCI) and dementia studies are prospective, observational, single-center cohort studies suitable for both cross-sectional and longitudinal analysis that outline the cognitive profiles and biomarker characteristics of patients with AD, subcortical vascular disease, and other cognitive disorders. The studies, the first of which started in 1987, comprise inpatients with manifest dementia and patients seeking care for cognitive disorders at an outpatient memory clinic. This article gives an overview of the major published papers (neuropsychological, imaging/physiology, and neurochemical) of the studies including the ongoing Gothenburg MCI study. The main findings suggest that subcortical vascular disease with or without dementia exhibit a characteristic neuropsychological pattern of mental slowness and executive dysfunction and neurochemical deviations typical of white matter changes and disturbed blood–brain barrier function. Our findings may contribute to better healthcare for this underrecognized group of patients. The Gothenburg MCI study has also published papers on multimodal prediction of dementia, and cognitive reserve.

Keywords
Alzheimer’s disease, cognitive impairment, magnetic resonance, neurochemistry, neuropsychology, subcortical vascular dementia, white matter changes

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Introduction
Several attempts have been made, largely based on results from animal models and familial Alzheimer’s disease (AD) cases, to counteract the effects of amyloid-β (Aβ) mismetabolism, which is assumed to be one of the key pathogenic events in AD. However, there are not yet efficient ways of treating or preventing AD.¹ Reasons for this lack of success may include trials being performed too late in the course of the disease; trials being too short; inadequate treatment targets stemming from a lack of crucial pathogenic knowledge; inclusion of heterogeneous groups of patients in trials;
and insufficient knowledge on the specific clinical features of the diseases. One way to overcome the nosological shortcomings is to use the information provided by longitudinal, clinical-observational studies on patients seeking care for cognitive disorders in specialist clinics. By using adequate clinical and biomarker tools, such studies may provide important information about treatment targets in patients with ongoing neurodegenerative disease. Such studies have been relatively uncommon, but focus in AD research is increasingly moving toward clinical pathogenic and nosological longitudinal studies. Indeed, the agenda of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and the Australian Imaging, Biomarkers and Lifestyle studies intend to fill this gap of knowledge.2,3 This is also the purpose of the Gothenburg mild cognitive impairment (MCI) and dementia studies. Whereas the ADNI and Australian Imaging, Biomarkers and Lifestyle studies focus solely on AD, the Gothenburg studies also include related disorders, in particular subcortical vascular disease. Alzheimer’s disease is the most commonly diagnosed disorder causing cognitive dysfunction among adults.4 AD is characterized by deposition of plaques containing Aβ aggregates, neurofibrillary tangles composed of tau fibrils, loss of synapses and degeneration of neurons leading to memory impairment and other cognitive impairments. However, it has gradually become clear that the clinical-pathologic correspondence is inconsistent. Widespread AD pathology can manifest itself without obvious symptoms and clinically atypical presentations are relatively frequent.5 In addition, presence of vascular involvement is very common, and has been reported in 80% of over 4,500 brains from patients with neuropathologically verified AD.5 One of the core pathophysiologic processes in AD is assumed to be mismetabolism of Aβ initiating a series of processes that eventually lead to neuronal degeneration with brain atrophy and cognitive decline, as has been outlined in the so called amyloid cascade hypothesis.6 Increased basic knowledge about Aβ-related issues has resulted in various pharmaceutical attempts to counteract the Aβ-related disease process using enzymatic inhibition of the secretases involved in Aβ generation7 and different variants of Aβ immune therapy,1 however, yet without much success.

Cerebrospinal fluid (CSF) markers—a key focus in the Gothenburg studies—are assumed to reflect pathogenic events as they occur in the brain directly in living patients. Incipient and manifest AD are characterized by increased CSF levels of phosphorylated tau (P-tau) linked to formation of neurofibrillary tangles, and ‘total’ tau (T-tau) mirroring axonal degeneration together with decreased levels of Aβ1-42 reflecting the amount of amyloid plaques.8,9 Most studies have compared AD patients with cognitively normal elderly people and with patients with other disorders without detailed specification. There is a paucity of CSF studies comparing AD with other specific diagnoses. It remains to be clarified how specific the CSF pattern of high P-tau and T-tau and low Aβ1-42 is for incipient and manifest AD when compared with other neurodegenerative diseases.

Subcortical vascular disease in white and gray matter is a common disorder, especially among the elderly, but often overlooked in clinical practice. In one prevalence study, it was found to constitute as much as 50% of cases with vascular dementia.10 In its pronounced pure form, subcortical vascular disease gives rise to a characteristic phenotype with predominant speed/attention and executive impairments called subcortical (ischemic) vascular dementia (SVD).11 Not only angiopathic lesions of the nonamyloid hypertensive type (arteriolosclerosis) but also cerebral amyloid angiopathy may play a role in the pathogenesis of SVD. Both types of lesions may lead to parenchymal changes involving white matter microinfarcts, lacunar infarcts, rarefaction, and microbleeds.12 Hitherto there are only few CSF studies on patients with SVD.13

The neuropathology underlying cognitive impairment in later life is often a combination of AD and microvascular brain damage, which may overlap and synergize to amplify the risk of clinical symptoms.14 The clinical counterpart of the combination of AD and subcortical vascular disease, mixed-type dementia (MixD), is less studied and its prevalence among patients with dementia is unclear. A significant span in reported prevalence rates (2% to 60%) for the combination of AD and vascular dementia have been reported.15 Dementia means cognitive dysfunction pronounced enough to lead to impaired activities of daily living, whereas cognitive impairment refers to the whole range of severities from the very mild to the most pronounced manifestations. Diagnostic criteria for AD and cerebrovascular disease associated with cognitive impairment have focused on the most severe form of cognitive impairment, i.e., dementia. However, the focus has shifted to identify the early characteristics of pathologic changes taking place in patients with MCI that will progress to dementia. They are better candidates for clinical trials since they are in the early phases of disease with lower burden of pathology.

In addition, most data suggest that pathologic brain changes start to accumulate many years, perhaps even decades, before they result in readily identifiable clinical symptoms.14 Here, refined biomarker tools, representing cognitive, neuroimaging, and neurochemical alterations, may prove particularly useful to outline the underlying disease process.
The Gothenburg MCI and dementia studies attempt to increase the knowledge about subcortical vascular disease with and without AD and its relationship to pure AD at early and manifest stages. The design of the Gothenburg MCI study is presented in a sister publication (Wallin et al., p. 114, this issue). Here, we summarize the results of the ongoing Gothenburg MCI study and its predecessors.

The Gothenburg mild cognitive impairment and dementia studies

Publications from the Gothenburg MCI and dementia studies and the Gothenburg part of the LeukoAraiosis and DISability (LADIS) study are included in the current overview. The dementia studies consist of the prospective dementia study (P study) and the revised prospective dementia (P-rev) study; both predecessors to the Gothenburg MCI study.

The P study comprised 243 inpatients with dementia observed at a hospital ward aiming at finding out symptomatological and neurochemical characteristics of the patient group along the axis of vascular burden. The patients were included in the study between 1987 and 1991. The P-rev study is an update of the P study comprising 210 inpatients with mild to moderate dementia or in a few cases isolated cognitive impairment classified along the vascular burden axis. They were included in the study between 1991 and 1997. All P- and P-rev-study patients were assessed according to a detailed case report form and some of them were also followed up. Single reports relevant for the present topics are presented in Tables 1, 2, 3.

The Gothenburg MCI study is an ongoing longitudinal, clinical-observational, single-center study using a predefined case report form. It is designed to obtain clinical, neuropsychological, neurochemical, genetic, and imaging/physiologic knowledge about cognitive impairment in patients seeking care or referred to an outpatient memory clinic. In particular, the study deals with AD, SVD, and associated disorders at their early and manifest stages. The nosological approach is in agreement with the basic ideas of the P and P-rev studies. However, the Gothenburg MCI study specifically focuses on the earlier manifestations of the diseases, which is at variance with the P and P-rev studies. The recruitment of patients started in December 1999 and the examinations performed are part of the clinical practice. Details about the design of the study, diagnostic procedures, methodology and baseline, and follow-up characteristics after 2 and 6 years have been described in a sister publication (Wallin et al., p. 114, this issue). The diagnostic procedures were strictly standardized in accordance with established criteria. The syndromal and etiological entities were systematically diagnosed by experienced clinicians masked to psychometrics, CSF, and quantitative imaging data.

The examinations included methods from various modalities. The cognitive modality consisted of neuropsychological testing comprising speed and attention, learning and episodic memory, visuospatial-, language-, and executive functions. Within each cognitive domain several aspects of function were assessed to obtain a picture as complete as possible of the cognitive status of the subjects. Two magnetic resonance imaging scanners were used in the study. A 0.5 T scanner (Philips NT5, Eindhoven, The Netherlands) was used from year 1999 to 2004 and a 1.5 T scanner (Siemens Symphony, Siemens Medical Systems, Erlangen, Germany) since 2005. Single photon emission computed tomography (SPECT) imaging and electroencephalography (EEG) have also been part of the study. Cerebrospinal (CSF) neurochemical markers have been the main focus of the study. The core AD biomarkers (T-tau, P-tau181, and Aβ1-42) were analyzed in the Clinical Neurochemistry Laboratory by experienced laboratory technicians following analytically and clinically validated and strictly standardized laboratory procedures. The laboratory leads the Alzheimer’s Association QC Program for CSF T-tau, P-tau181, and Aβ1-42, and is also part of the Alzheimer’s Association Global Biomarker Standardization Consortium and the International Federation of Clinical Chemistry and Laboratory Medicine working group on CSF proteins. Other biochemical measurements have been described in detail in the respective research papers.

The LADIS study is a European multicenter collaboration that started in 2001 with the aim of assessing the role of white matter changes (WMC) in predicting disability in subjects aged 65 to 84. One of the centers, the Gothenburg center, also collected CSF of the patients included in the study. The majority of the included patients were also examined under the umbrella of the Gothenburg MCI study; the others as regular patients at the memory clinic. As the general idea of the LADIS study is in agreement with that of the clinical Gothenburg studies, the LADIS CSF papers have been included in this overview.

Depending on the major modality under investigation the publications were roughly divided into neuropsychological, brain imaging/physiologic, and biochemical groups of papers (Tables 1, 2, 3). In addition, multimodal prognostic papers and papers on the course of the disease and cognitive reserve (CR) formed other groups (Tables 4 and 5). According to the major aim of the study, the various groups of modalities were then subgrouped into AD and SVD. To emphasize various aspects of the work, a specific reference may be listed more than once. The AD and SVD
subclassification implies that a reference dealing with these disorders should be reported at least twice. Specific studies on MixD have not yet been published.

The term MCI has not been consistently used. In some earlier papers, patients with subjective cognitive impairment (SCI) have been included in the MCI group whereas in others they have been explicitly excluded. When it is obvious that the MCI group also includes patients with SCI, it has been renamed SCI/MCI. If it is not clearly stated whether MCI includes SCI a # sign has been added in the table column.

### Results

In the following section, results from different outcome modalities in the Gothenburg MCI and dementia studies are presented.

### Neuropsychology

In the P study, it was found that parietotemporal symptoms, i.e., impairments in interpreting sensory information and performing practical tasks, were typical of
Table 2. Brain imaging and physiologic findings.

| Subjects | Method | Aim | Results | Macro study | References |
|----------|--------|-----|---------|-------------|------------|
| Cognitive impairment | | | | | |
| Dementia | EEG | To compare EEG indicators with clinical symptoms | EEG indicators were correlated with degree of dementia and parietal lobe dysfunction | B | Edman\(^{41}\) |
| Dementia | EEG | Investigate if examination of clinical symptom profile can improve EEG diagnostics | Parietal lobe syndrome was more closely correlated to EEG findings than the other brain syndromes | B | Matousek\(^{42}\) |
| HC, dementia | EEG | To examine if dementia patients have decreased daytime alertness | Decrease in alertness occurred more often in dementia patients and was proportional to the degree of dementia | B | Edman\(^{43}\) |
| HC, stable MCI, MCI–dementia | MRI | To examine if hippocampal atrophy predicts conversion from MCI to dementia | Hippocampal atrophy at baseline predicts dementia | A | Eckerström\(^{37}\) |
| Stable MCI, MCI–dementia | SPECT | To examine if patterns of rCBF is related to cognitive impairment | Reduced CBF particularly the left medial temporal lobe indicates an elevated risk of cognitive decline | A | Edman\(^{38}\) |
| Alzheimer’s disease | | | | | |
| AD (EAD, LAD) | CT | To study the relationship between WMC and EAD, LAD | Almost no WMC in EAD; high percentage of WMC in LAD | C | Wallin\(^{33}\) |
| HC, AD (EAD, LAD) | SPECT | To study discrimination between AD and HC using rCBF | rCBF reduction in parietotemporal cortical areas, the medial temporal lobes, the hippocampi, and the white matter in AD | B | Sjögren\(^{40}\) |
| HC, AD (EAD, LAD) | SPECT | To examine differences in rCBF and CSF markers between two clinical subgroups of AD patients | EAD patients had decreased levels of monoamine metabolites and LAD had decreased rCBF | B | Sjögren\(^{44}\) |
| Subcortical vascular dementia | | | | | |
| SVD | CT | To study the relationship between WMC and VaD defined as dementia with vascular burden | High percentage of WMC\(^a\) in patients with vascular burden | C | Wallin\(^{33}\) |
| SVD | CT | To study the relationship between clinical symptom profile and WMC\(^a\) | Subcortical symptom profile was associated with WMC\(^a\) | B | Wallin\(^{34}\) |
| SVD | CT/MRI | To examine the relationship between WMC\(^a\) and neuropsychiatric symptoms | WMC\(^a\) were associated with a dys-executive-related behavioral symptom profile | B | Jonsson\(^{35}\) |
| SVD | MRI | To examine if depressive symptoms are associated with WMC\(^a\) | No relationship between WMC\(^a\) and depressive symptoms was found | B | Lind\(^{36}\) |
| HC, SVD | SPECT | To study discrimination between SVD and HC using rCBF | rCBF reduction in parietotemporal cortical areas, the medial temporal lobes, the hippocampi, and the white matter | B | Sjögren\(^{40}\) |
| HC, MCI | MRI | Examine if hippocampal atrophy is related to WMC\(^a\) | Hippocampal atrophy was related to WMC\(^a\) in the high WMC\(^a\) quartile of the sample | A | Eckerström\(^{39}\) |

AD, Alzheimer’s disease; CSF, cerebrospinal fluid; CT, computed tomography; EAD, early-onset AD; EEG, electroencephalography; HC, healthy control; LAD, late-onset AD; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; rCBF, regional CBF; SCI, subjective cognitive impairment; SVD, subcortical vascular dementia; VaD, vascular dementia; WMC, white matter changes; SPECT, single photon emission computed tomography. Macro study A: Gothenburg MCI study, 1999; B: revised prospective dementia study (P-rev), 1991 to 1997; and C: prospective dementia study, 1987 to 1991. In the MCI group no patients with SCI have been included. \(^a\)Model for incipient and manifest dementia of the subcortical type.
Table 3. Biochemical findings.

| Subjects | Aim | Results | Macro study | References |
|----------|-----|---------|-------------|------------|
| SCI/MCI  |     |         | B           | Lind⁶⁵     |
| HC, MCI  | To study the feedback control of the HPA axis in patients with MCI | Increased cortisol awakening response in patients with MCI | A          | Quinlan⁶⁶ |
| SCI/MCI  | To study the association between thyroid hormones and cognitive performance | Low levels of TT3 were associated with a neuropsychological profile typical of prodromal AD | A          | Wallin⁶⁷ |
| Stable SCI/MCI, SCI–MCI | Prediction of progression using AD biomarkers³ and NFL | No differences in biomarker levels between the subjects |             |           |
| Alzheimer’s disease | | |             |            |
| HC, AD   | To study IgG and IgM indices in AD in comparison with HC | In AD 26% displayed intrathecal immunoglobin production in comparison with 0% in HC | C          | Blennow⁹⁰ |
| HC, AD   | To study TNF-α biomarker performance in overt dementia | TNF-α is significantly increased in patients with AD | B          | Tarkowski⁶² |
| HC, AD   | GM–CSF biomarker performance in overt dementia | GM–CSF is significantly increased in patients with AD | B          | Tarkowski⁶³ |
| HC, AD   | VEGF and TGF-β biomarker performance in overt dementia | VEGF and TGF-β are significantly increased in patients with AD | B          | Tarkowski⁶⁴ |
| HC, AD   | To study 5-HIAA, HVA, and HMPG in AD in comparison with HC | Decreased levels of 5-HIAA and HVA were found in AD | C          | Blennow⁹⁹ |
| HC, AD   | To study glial fibrillary acidic protein (GFAP) in AD in comparison with HC | Increased levels of GFAP in AD | B          | Wallin¹⁰⁰ |
| HC, AD; stable MCI, MCI–AD⁵ | AD biomarker³ performance in overt dementia | AD biomarkers³ are significantly altered in patients with MCI–AD compared with HC (or MCI–MCI)⁵ | B          | Sjögren⁵⁷; Mattsson⁶⁰ |
| Stable MCI, MCI–AD⁵ | Diagnostic accuracy for predicting AD in MCI patients using AD biomarkers³ | All AD biomarkers³ individually show high sensitivity and moderate specificity, which is improved by their combination | A          | Zetterberg¹⁰¹; Bjerke⁵⁰; Brys¹⁰²; Mattsson⁶¹ |
| Stable MCI, MCI–other, MCI–AD⁵ | Predictive value of AD biomarkers³ for conversion from MCI to AD⁵ | AD biomarkers³ show high accuracy in predicting future development of AD in MCI patients⁵ | A          | Kruczyk¹⁰³ |
| HC, AD; stable MCI, MCI–AD⁵ | Evaluation of AD biomarker³ performance in different age groups | Age effect on diagnostic performance of AD biomarkers³ | A          | Mattsson⁵⁸ |
| HC, stable MCI, MCI–AD, MCI–other, AD⁵ | Investigate APOE ε4 effect on AD pathology and clinical diagnosis | APOE ε4 is as strongly related to amyloid pathology as to the clinical diagnosis of AD | A          | Andreasson¹⁰⁴ |

(continued)
| Subjects | Aim | Results | Macro study | References |
|----------|-----|---------|-------------|------------|
| HC, AD  | SNAP-25 performance in overt AD | SNAP-25 is significantly increased in patients with AD | A | Brinkmalm94 |
| HC, AD (EAD and LAD) | NFL biomarker performance in overt dementia | NFL is significantly increased in patients with LAD | B | Rosengren46; Sjögren105; Sjögren48 |
| HC, AD  | GAP-43 biomarker performance in overt dementia | GAP-43 is significantly increased in patients with AD | B | Sjögren106 |
| HC, AD  | TACE activity and TNFR I and II biomarker performance in overt dementia | TACE activity and TNFR I and II levels are significantly increased in patients with AD | A | Jiang107 |
| HC, AD  | Chitotriosidase activity in overt dementia | Chitotriosidase is significantly increased in patients with AD | A | Mattsson108 |
| HC, AD  | A/β-binding proteins in overt dementia | Aβ-trace, Cys C, AAT, and TTR are significantly reduced in patients with AD | A | Hansson109 |
| HC, MCI, ADb | BACE1 activity performance in MCI and overt dementiab | BACE1 activity is significantly increased in patients with MCI and ADb | A | Ewers110 |

**Subcortical vascular dementia**

| Subjects | Aim | Results | Macro study | References |
|----------|-----|---------|-------------|------------|
| HC, SVD  | Albumin ratio performance in overt dementia | Albumin ratio is significantly increased in patients with SVD and WMC | C | Wallin55; Wallin47 |
| HC, SVD  | To study IgG index and oligoclonal IgG in SVD in comparison with HC | In SVD 9% displayed intrathecal IgG production whereas 0% in HC; positive correlation between IgG index and severity of dementia | C | Wallin111 |
| HC, SVD  | TNF-α biomarker performance in overt dementia | TNF-α is significantly increased in patients with SVD | B | Tarkowski62 |
| HC, SVD  | GM–CSF biomarker performance in overt dementia | GM–CSF is significantly increased in patients with SVD | B | Tarkowski63 |
| HC, SVD  | VEGF and TGF-β biomarker performance in overt dementia | VEGF and TGF-β are significantly increased in patients with SVD | B | Tarkowski64 |
| HC, SVD  | To study 5-HIAA, HVA, and HMPG in SVD in comparison with HC | Decreased levels of 5-HIAA and HVA were found in SVD | B | Wallin112 |
| HC, SVD  | AChE activity performance in overt dementia | AChE activity is significantly decreased in patients with SVD | B | Wallin113 |
| HC, SVD  | Sulfatide relation between SVD and HC (and AD) | Sulfatide level was increased in SVD in comparison with HC and AD | C | Fredman45 |
| HC, SVD  | To study GFAP in SVD in comparison with HC | Increased levels of GFAP in SVD | B | Wallin100 |
Table 3. Continued

| Subjects | Aim | Results | Macro study | References |
|----------|-----|---------|-------------|------------|
| HC, MCI–SVD, SVD<sup>B</sup> | NFL biomarker performance in MCI or overt dementia | NFL is significantly increased in patients with MCI–SVD<sup>B</sup> | A | Bjerke<sup>50</sup>; Bjerke<sup>49</sup> |
| HC, MCI–SVD, SVD<sup>B</sup> | AD biomarker performance in MCI or overt dementia | Ab1-42 is decreased in SVD, while T-tau and P-tau181 are unaltered | A | Ewers<sup>114</sup>; Jiang<sup>107</sup> |
| HC, SVD | AAT, ApoH, and PAI-1 biomarker performance in overt dementia | AAT, ApoH, and PAI-1 are significantly increased in patients with SVD | A | Ohrfelt<sup>56</sup> |
| HC, SVD | HFABP and TIMP-1 biomarker performance in overt dementia | HFABP and TIMP-1 are significantly increased in patients with SVD | A | Ohrfelt<sup>56</sup>; Bjerke<sup>49</sup> |
| HC, SVD | MMP-9 and MBP biomarker performance in overt dementia | MMP-9 and MBP are significantly increased in patients with SVD | A | Bjerke<sup>49</sup> |
| Elderly individuals with WMC | NFL relation to white matter lesions in elderly individuals | NFL levels were correlated to white matter lesion progression | L | Jonsson<sup>52</sup> |
| Elderly individuals with WMC | Sulfatide relation to white matter lesion in elderly individuals | Sulfatide levels were correlated to white matter lesion progression | L | Jonsson<sup>54</sup> |
| Elderly individuals with WMC | NFL, MBP, MMP-9, TIMP-1, and sAPP<sub>b</sub> relation to white matter lesions in elderly individuals | NFL, MBP, TIMP-1, and sAPP<sub>b</sub> levels were correlated to white matter lesion load. MMP-9 was correlated to white matter lesion progression | L | Bjerke<sup>51</sup> |

AAT, α-1-antitrypsin; Ab, amyloid-β; AChE, acetylcholinesterase; AD, Alzheimer’s disease; APOE/H, apolipoprotein E/H; BACE1, β-site amyloid precursor protein–cleaving enzyme 1; Cys C, cystatin C; EAD, early-onset AD; GAP-43, growth-associated protein 43; GFAP, glial fibrillary acidic protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; HC, healthy control; HFABP, heart fatty acid–binding protein; HPA axis, hypothalamic–pituitary–adrenal axis; HVA, homovanillic acid; HMPG, 4-hydroxy-3-methoxy-phenylglycol; 5-HIAA, 5-hydroxyindoleacetic acid; LAD, late-onset AD; MBP, myelin basic protein; MCI, mild cognitive impairment; MMP-9, matrix metalloproteinase 9; NFL, neurofilament light; P-tau, phosphorylated tau; PAI-1, plasminogen activator inhibitor 1; sAPP<sub>b</sub>, soluble amyloid precursor protein β; SCI, subjective cognitive impairment; SNAP-25, synaptosomal-associated protein 25; SVD, subcortical vascular dementia; TACE, tumor necrosis factor-α-converting enzyme; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of metalloproteinase; TNF-α, tumor necrosis factor-α; TNFR III, TNF receptor III; T-tau, total tau; TTR, transthyretin; TT3, total triiodothyronine; VEGF, vascular endothelial growth factor; WMC, white matter changes. Macro study A: Gothenburg MCI study, 1999; B: revised prospective dementia study (P-rev), 1991 to 1997; C: prospective dementia study, 1987 to 1991; L: LeukoAraiosis and DISability (LADIS study, 2001).<sup>a</sup>AD biomarkers: Ab1-42, T-tau, and P-tau181 (in some studies only Ab1-42 and T-tau).<sup>b</sup>No obvious separation between SCI and MCI has been performed. Therefore, in the MCI group SCI patients may have been included.
Table 4. Multimodal prediction.

| Subjects     | Aim                                                                 | Results                                                                 | Macro study | References |
|--------------|----------------------------------------------------------------------|-------------------------------------------------------------------------|-------------|------------|
| HC, MCI      | To examine the combined predictive value of hippocampal volume and AD biomarkers<sup>a</sup> | Hippocampal volume supplement the prognostic accuracy of AD biomarkers<sup>a</sup> in MCI | A           | Eckerström<sup>68</sup> |
| MCI          | To study prediction of dementia in MCI using neuropsychological tests, commonly used biomarkers, and hippocampal volume | Neuropsychological tests were the best predictors of dementia. A combination of markers improved the predictive ability | A           | Eckerström<sup>69</sup> |
| MCI          | To study how prognosis is related to neuropsychological tests, levels of CSF biomarkers, hippocampal volume, and WMC | All studied markers with the exception of WMC predicted dementia. The absence of pathologic markers provided long-time protection from dementia | A           | Eckerström<sup>70</sup> |

APOE, apolipoprotein E; Aβ, amyloid-beta; CSF, cerebrospinal fluid; HC, healthy (cognitively normal) control; MCI, mild cognitive impairment; AD, Alzheimer’s disease; WMC, white matter changes.

Table 5. The course of the disease and cognitive reserve.

| Subjects     | Aim                                                                 | Results                                                                 | Macro study | References |
|--------------|----------------------------------------------------------------------|-------------------------------------------------------------------------|-------------|------------|
| Longitudinal pattern Dementia | To compare longitudinal change in EEG indicators with clinical symptoms | Increased EEG slow-wave activity was correlated with increased parietal lobe dysfunction and dementia degree | B           | Edman<sup>41</sup> |
| SCI/MCI      | Interactive effects of APOE and Aβ1-42 on memory performance         | Association between memory performance and Aβ1-42 were significant among APOE ε4 carriers | A           | Thorvaldsson<sup>115</sup> |
| HC, SCI, MCI, dementia | To predict cognitive performance on the basis of biomarkers in HC and patients at various impairment levels | Aβ1-42 was associated with cognitive functions from a potentially early to a later disease phase, and T-tau was more indicative of performance in a later phase | A           | Rolstad<sup>71</sup> |
| HC, SCI, MCI, dementia | To predict cognitive performance on the basis of Aβ1-42 and NFL in HC and patients at various impairment levels | NFL was associated with cognitive functions in a putative early phase and Aβ1-42 in a putative later phase | A           | Rolstad<sup>72</sup> |
| Cognitive reserve Stable MCI, dementia | To examine the applicability of biomarkers as surrogates for pathology in relation to cognitive reserve | Highly educated–converting MCI patients displayed more amyloid pathology although cognitively performing equally to lower educated patients | A           | Rolstad<sup>75</sup> |
| Stable MCI, dementia | To study the relation between biomarkers, neuropsychological performance, and cognitive reserve longitudinally | The results provided further support for Aβ42 as a substitute for pathology in relation to cognitive reserve | A           | Rolstad<sup>76</sup> |
| Stable MCI   | To study the relation between biomarkers, neuropsychological performance, and cognitive reserve longitudinally | Stable MCI patients with higher education had lower concentrations of T-tau as compared with those with lower education | A           | Rolstad<sup>77</sup> |
| HC, SCI, MCI, dementia | To examine whether certain cognitive systems may compensate for the effect of CSF Aβ42 and T-tau on other cognitive systems | Most cognitive systems were able to maintain cognitive performance despite CSF burden | A           | Rolstad<sup>78</sup> |

APOE, apolipoprotein E; Aβ, amyloid-beta; CSF, cerebrospinal fluid; EEG, electroencephalography; HC, healthy control; MCI, mild cognitive impairment; NFL, neurofilament light subunit; SCI, subjective cognitive impairment; T-tau, total tau. Macro study A: Gothenburg MCI study, 1999; B: revised prospective dementia study (P-rev), 1991 to 1997.
manifest early-onset AD (onset before 65 years of age), which corresponds to AD without cerebrovascular disease. In contrast, late-onset AD (onset after 65 years of age) was characterized by memory impairment together with confusional symptoms, but absence of or less severe parietotemporal symptoms. In another of the P studies frontosubcortical symptoms with mental slowness and loss of initiative were found to be characteristic of manifest SVD.

The first study that reported results from the Gothenburg MCI study was a cross-sectional study on patients with SCI/MCI. Etiological factors such as the influence of vascular disease were not taken into account. It was found that SCI/MCI was a highly heterogeneous diagnostic entity with significant impairments in all cognitive domains (Table 1).

As for vascular and other markers of potential interest in SCI/MCI, when grouped according to the presence of vascular disease, the cognitive profiles of the groups were found to differ, with SCI/MCI with vascular disease performing generally more poorly. The cognitive profile of MCI subjects with AD-typical neurochemical biomarkers differed from that of those without. Neither vascular disease nor altered levels of neurochemical biomarkers were alone associated with a specific cognitive profile in SCI/MCI, whereas a combination of them was associated with executive impairment.

In a recent follow-up study with comprehensive neuropsychological examination memory, visuospatial, and language symptoms characterized incipient AD, whereas speed/attention deficits and executive dysfunction preceded manifest SVD. In a longitudinal study on MCI subtypes and neurochemical biomarkers, the converting SCI/MCI patients had a very high degree of impairment in all cognitive domains, memory impairment not being more predictive than any other cognitive domain for conversion; however, in combination with neurochemical biomarkers it could predict incident AD and with vascular burden incipient SVD.

**Brain Imaging and Physiology**

An early report from the P study found that WMC are highly prevalent in patients with vascular burden. Later in the P-rev study, WMC were found to be associated with a subcortical symptom profile, and a dys-executive behavioral symptom profile with apathy as the most prominent feature rather than classical depressive symptoms.

In one study from the Gothenburg MCI study using hippocampal volume as a biomarker it was found that MCI patients converting to dementia during the 2-year follow-up time had smaller baseline hippocampi compared with both stable MCI patients and controls, with the left hippocampus as the strongest predictor. Similarly, the left medial temporal lobe was found to be the best discriminator in a subsequent study examining differences in regional cerebral blood flow between stable and progressive MCI patients. The presence of WMC and hippocampal atrophy in patients with MCI, AD, and SVD has also been investigated. It was found that hippocampal atrophy was present both in AD and SVD patients and that there was an association between hippocampal atrophy and WMC in the 25% of patients showing the highest degree of WMC. Interestingly, in an early study, SVD patients had reduced regional cerebral blood flow in the medial temporal lobe and increased gray matter atrophy compared with controls.

In addition, the P and P-rev studies used EEG to investigate neurophysiologic changes in subgroups of dementia patients. The first EEG study found that slow-wave abnormality correlated with dementia severity. In an effort to increase EEG efficacy in dementia diagnostics, EEG changes were analyzed in dementia patients with different brain regional syndromes. It was found that EEG abnormalities could mainly be attributed to parietal lobe dysfunction suggesting that EEG may be most valuable in patients with early-onset AD. The following EEG study applied an automatic method to analyze alertness in dementia patients. The results show that demented patients were less alert compared with controls and that the decrease in alertness was proportional to dementia severity.

Another approach was to use regional cerebral blood flow in combination with CSF monoamine metabolites to examine two clinical subgroups of AD patients. It was found that early-onset AD patients had lower levels of CSF monoamine metabolites and late-onset AD had reduced regional cerebral blood flow.

**Biochemistry**

In the P and P-rev studies, it was found that overt SVD exhibited increased levels of myelin lipid sulfatide and neurofilament light (NFL) in CSF. The findings of increased levels of CSF NFL have been corroborated in overt SVD patients and NFL has also been found to be increased in patients with MCI who later progress to SVD. Furthermore, NFL has been shown to reflect degree of WMC, while sulfatide and the extracellular modulating matrix metalloproteinase 9 (MMP-9) have been shown to predict WMC progression as assessed with the modified Rotterdam Progression Scale in nondisabled patients with WMC. Alterations in the blood–brain barrier (BBB) as indicated by an increased CSF/serum albumin ratio have consistently been found in patients with SVD though not always evaluated as a biomarker.
Increased CSF levels of MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1) together with a higher concentration of myelin basic protein (MBP), NFL, and albumin ratio in this particular patient group suggest an inflammatory involvement in SVD. When assessed with multivariate analysis MMP-9, TIMP-1, MBP, and NFL contributed to the separation of patients with SVD and MixD from patients with pure AD. Albumin ratio was not evaluated in the model.

The alterations in albumin ratio have also been correlated to changes in TIMP-1 not only in patients with pure SVD and MixD but also in nondisabled patients with WMC. Furthermore, TIMP-1, plasminogen activator inhibitor-1, α-1 antitrypsin, and apolipoprotein H have all been shown to be increased in MCI patients that subsequently deteriorate to SVD. Although CSF Aβ1-42 has been shown to be moderately decreased in SVD, T-tau and P-tau are unaltered, though all three markers have consistently been shown to be altered in AD. Other markers have been found to be altered in both SVD and AD, such as tumor necrosis factor-α, granulocyte macrophage colony stimulating factor, vascular endothelial growth factor, transforming growth factor-β, heart fatty acid binding protein, and MMP-10.

One study found an increased cortisol awakening response in patients with MCI, as compared with controls. In another study, a neuropsychological profile similar to that seen in prodromal AD was associated to the thyroid hormone triiodothyronine in patients with SCI/MCI. Furthermore, SCI patients who subsequently progressed with MCI did not exhibit a deviating baseline AD biomarker profile, which is not surprising as the majority of the MCI patients do not exhibit incipient AD.

**Multimodal Prediction**

To optimize the prediction of dementia, a number of studies have analyzed combinations of markers from different modalities. A study comparing the predictive ability of hippocampal volume to the CSF biomarkers Aβ42 and T-tau in MCI patients found that the CSF markers were slightly better than hippocampal volume in predicting conversion to dementia but the best predictive model was the combination of all three studied markers. In another study, a combination of neuropsychological tests, CSF biomarkers (Aβ42, P-tau, and T-tau), and hippocampal volume were studied as predictors of conversion from MCI to dementia of various etiologies. The best predictors of the dementia syndrome were memory tests and the best predictors of AD were a visuospatial test and T-tau. The combination of the markers from all three examined modalities was very successful in predicting conversion to dementia (area under the curve 0.96) and AD (area under the curve 0.98). In a third study using CSF markers, hippocampal volume and neuropsychological tests known to reflect deviations in respectively AD and SVD, result on trail-making test B was the best single predictor of dementia (area under the curve 0.89), and T-tau was again the best predictor of AD (area under the curve 0.97). The combination of hippocampal volume and trail-making test B was the best combination for the prediction of dementia (hazard ratio 25), and the combination of hippocampal volume and T-tau was the best combination for the prediction of AD (hazard ratio 37). In addition, lack of pathologic markers provided long-lasting protection from conversion to dementia.

**The Course of the Disease and Cognitive Reserve**

When simulating the course of an assumed disease using the associations between neurochemical biomarkers and neuropsychological deficits from cognitive health to manifest dementia it was found that Aβ1-42 was associated with cognitive functions from a potentially early to a later disease phase, and T-tau was more indicative of performance in a later phase. To a certain extent the results give support for the amyloid cascade hypothesis. In the model, the strongest associations between biomarkers and neuropsychological deficits were found at the MCI stage suggesting that the degenerative process has accelerated at that stage. In a study that aimed to elucidate the ability of CSF biomarkers, Aβ1-42 and T-tau, to predict future cognitive decline of specific functional domains, it was reported that CSF biomarkers reflect the rate of cognitive decline across the continuum of cognitive impairment from cognitive health to dementia. In a new study in patients with SCI, MCI, and dementia, we found that NFL precedes Aβ42 with regard to influence on cognitive functions in those with vascular burden, which suggests that subcortical involvement is an early manifestation in patients with cognitive impairment. This suggests that a combination of vascular and neurodegenerative components predominate in those with progressive cognitive impairment.

When addressing the concept of CR, i.e., the capacity of cognitive processes to resist damage to the brain, the conclusion was that MCI patients with longer education subsequently converting to dementia display more amyloid pathology as assessed by CSF
determinations than less educated progressive MCI patients. Thus, high education could be used as a proxy for CR. A longitudinal study provided further support for the applicability of Aβ1–42 as a substitute for pathology in relation to CR. Furthermore, the results from another study suggested that higher education may offer protection against tauopathy. It has also been found that most cognitive systems were able to maintain cognitive performance despite CSF biomarker burden.

**Discussion**

The current overview is a summary of the findings from the Gothenburg MCI and dementia studies, i.e., clinical-observational studies on AD and SVD among inpatients and patients seeking care at a memory clinic. The methods used comprise psychometrics, biochemical methods mainly CSF determinations of substances reflecting disturbances of the brain, and imaging/physiologic methods. The majority of the listed papers are biochemical papers but there are also neuropsychological and imaging studies.

In particular the papers focus on subcortical vascular disease, which is a common cause of cognitive impairment and disability induced by cerebrovascular disease. Yet the impact of subcortical vascular disease is under debate and its manifestations are occasionally considered as epiphenomena. This opinion is not supported by the results from the Gothenburg MCI and dementia studies, which clearly indicate that SVD is an entity with features different from those of pure AD. There are also overlapping features between the disorders, which imply that they are both spectrum disorders.

**Neuropsychology**

The early studies showed that patients with manifest dementia and vascular burden showed high degrees of WMC. On the contrary, almost no patients with early-onset AD showed signs of WMC or significant vascular diseases. A high percentage of patients with late-onset AD also displayed WMC, which indicates presence of overlapping pathologies, i.e., late-onset AD appears to be equivalent to MixD as described in the Introduction section. Thus, the distribution of WMC in our early studies fits in the AD–SVD spectrum model. The symptom profiles also vary along the spectrum with mental slowness and executive dysfunction being characteristic of SVD at one end and impairments in interpreting sensory information and practical difficulties being characteristic of AD at the other; in the middle of the spectrum memory problems and concentration difficulties predominate.

Neuropsychological findings also differentiated between AD and SVD at early stages. Executive and speed/attention symptoms were found to characterize incipient SVD, whereas incipient AD was characterized by memory, visuospatial, and language impairments although all of the above cognitive symptoms occurred in both disorders. Our findings are in agreement with those of a recent meta-analysis on patients with vascular cognitive impairment without dementia reporting that individuals with vascular MCI had significantly greater deficits in processing speed than those with non-vascular MCI who exhibited a greater relative deficit in delayed recall. Thus, it is not unreasonable to assume that a large group of the vascular MCI patients in the meta-analysis belonged to the SVD group.

In the Gothenburg MCI study, all patients who converted to dementia had multiple-domain MCI at baseline, the majority had amnestic multiple-domain MCI. This supports earlier reports on impairment in several cognitive domains typically preceding dementia—regardless of specific diagnosis—whereas single-domain MCI seems to be a more benign condition. Our findings clearly contradict a number of even quite recent studies reporting that single-domain amnestic MCI is at the highest risk of developing AD. One conceivable reason for the differing results is that the test batteries used for the MCI subgrouping in the referred studies were limited, which prevents detection of impairments in domains not tested.

**Brain Imaging and Physiology**

The brain imaging research in the Gothenburg MCI study has mainly focused on the impact of WMC on cognition, clinical symptomatology and hippocampal volume, discrimination between specific dementia disorders, and prediction of dementia among patients with MCI.

White matter changes are commonly seen in elderly individuals and their importance for cognitive impairment is under debate. They are, however, viewed as the major hallmark in SVD related to the CSF neurochemical changes and causing the neuropsychological profile of the disease. In the clinical Gothenburg studies, WMC were associated with a subcortical symptom profile and a dysexecutive behavioral profile, with apathy as the most pronounced feature. White matter changes have been linked to depressive symptoms, but although loss of motivation was linked to WMC there was no association between WMC and depressive mood indicating that WMC are directly linked to dysexecutive symptoms. Furthermore, WMC were found to be inversely associated with hippocampal volume in patients with high WMC load. This finding
suggests that the memory impairment often seen in patients with cerebrovascular disease\(^{28}\) may be secondary to hippocampal atrophy caused by axonal disconnection of the hippocampi. Support for this interpretation is provided by a study using a mouse model for SVD where the induction of WMC was followed by hippocampal atrophy.\(^{86}\)

Taken together, the findings from the Gothenburg MCI study provide additional support that WMC are important not only in SVD but also in the development of cognitive impairment, regardless of underlying disease.

Hippocampal atrophy has been found to predict conversion from MCI to dementia, strengthening the view that the hippocampi play a vital role in the pathophysiologic process of cognitive decline. Interestingly, although hippocampal volume as a predictor of subsequent dementia performed in line with findings from similar studies,\(^{87,88}\) it was still less effective than both CSF and neuropsychological markers. A possible explanation for this could be the relatively young patients in the Gothenburg MCI study, who are up to 10 years younger than the patients in comparable studies.\(^{87,88}\) The younger patients may be less affected by age-related white matter atrophy and concomitant pathology, which could hamper the predictive ability of measures of atrophy. Another observation from the Gothenburg MCI study is that the left cerebral hemisphere may be affected before the right hemisphere in the development of cognitive impairment. Both reduced blood flow in the left medial temporal lobe and left hippocampal atrophy outperformed their right counterparts.\(^{37,38}\) Although there is some further support that the left hippocampus is more affected in AD,\(^{89}\) further research is needed to establish a clear pattern.

### Biochemistry

One of the first fluid biomarker findings that spoke in favor of the white matter involvement in SVD patients was the increased levels of NFL found in both overt SVD\(^{47,48,49}\) and also in its incipient form.\(^{50}\) Sulfatide, another component of myelin, was increased in patients with white matter damage even before disease onset\(^{52}\) and in the same study it was also found that increased levels of MMP-9 correlated with progression of WMC.\(^{51}\) Our data indicates that damage to the subcortical white matter is a pathologic hallmark of SVD and that the pathology is possible to identify through biochemical markers. In addition to its extracellular remodeling function, MMP-9 is believed to be involved in the regulation of the BBB opening and its activity is counterbalanced by TIMP-1. Blood–brain barrier dysfunction is another hallmark of SVD that has been visualized in earlier studies through an elevated albumin ratio in patients with SVD and MixD, whereas BBB has been shown to be normal in patients with AD without vascular diseases.\(^{13,47,49,50,90}\) The albumin ratio has also been shown to correlate with the levels of TIMP-1 in both SVD patients and in patients with white matter damage.\(^{39,51}\) which give further support for the notion that BBB dysfunction play a role in SVD. In a pivotal study with carefully defined groups of patients using a multivariate analytic method, which has the advantage of pointing at the relative importance of a group of factors for a specific outcome, it was found that patients with SVD displayed elevated levels of MBP, NFL, MMP-9, and TIMP-1, whereas in AD the CSF levels of P-tau and T-tau were increased reflecting degeneration of cortical regions affected by AD pathology.\(^{49}\) Since MBP and NFL are both major constituents of the subcortical axons and they have been found to correlate to white matter lesion load,\(^{51}\) their increased levels likely reflect subcortical axonal/white matter damage, which could also include the MMP/TIMP system through possible myelin breakdown. Other studies have also found alterations in MMP-9 and other MMPs in patients with SVD.\(^{91,92}\) Furthermore, both TIMP-1 and plasminogen activator inhibitor-1, both involved in the regulatory system connected to MMP activity, have been shown to be increased in CSF in MCI patients that subsequently deteriorate to SVD.\(^{56}\) This would not only support an early inflammatory involvement in the disease process that is related to the BBB, but also suggests alterations in the coagulation system. It is therefore not unreasonable to assume that MMPs and TIMP-1 play a role in both BBB disruption and destruction of subcortical tissue in patients with SVD, as has been previously suggested.\(^{93}\) A combined panel of markers could potentially be very important not only for early detection of patients with MCI that will progress to SVD, but also for early differential diagnostics. There are at present no such established markers for SVD. These markers could therefore in combination with markers that have repeatedly been shown to be altered in AD,\(^{39,57,58,59}\) i.e., T-tau, P-tau, and Aβ1-42, be regarded as potential markers that mirror ongoing biological processes that are connected to disease-specific pathologic changes. Although CSF Aβ1-42 has been shown to be moderately decreased in SVD, T-tau, and P-tau are unaltered and would thus represent AD-specific markers that could aid in the differentiation between pure SVD and AD.\(^{47,48}\) New markers that are under evaluation, such as synaptosomal-associated protein 25 reflecting synaptic degeneration, could possibly also contribute to the formation of a disease-specific panel of biomarkers\(^{94}\) or to monitor disease progression. There is also the possibility in
Multimodal Prediction

Mild cognitive impairment is a heterogeneous condition, and the prognosis differs within the group. To enable prediction of a specific etiological dementia diagnosis in patients with MCI the single-marker approach seems to be insufficient. It also seems that markers from more than one modality are needed to capture the specific features of the manifest disease. In our studies on patients included in the Gothenburg MCI study multivariate analyses revealed that multimodal combinations of variables outperformed the prognostic ability of single variables for dementia and AD. Absence of any pathologic markers greatly reduced the long-term risk of developing dementia. In the Gothenburg MCI study, the markers, alone and in combination, generally have higher predictive values compared with, for example, the ADNI study or the DESCRIPA study. One explanation is the study design; the Gothenburg MCI study is a single-center study whereas the ADNI and DESCRIPA are multicenter studies. Single-center studies can be expected to provide data with less variability related to local interpretation of inclusion/exclusion criteria, demographic differences, sampling techniques, scanner differences, etc., which may explain the high predictive values of the markers. The fact that combinations of markers provided less additional information than expected may be because of the already very high predictive value of the single markers. As mentioned previously, another factor to take into account is the relatively young age of the patients compared with, especially, the patients in the ADNI study. Although it is unclear how patient age affects the results, the main difference between the studies is that hippocampal volume is less predictive and CSF markers and neuro-psychological tests are more predictive in the younger Gothenburg MCI study patient material.

Strengths and Weaknesses

Notably, early detection of cognitive impairment induced by subcortical vascular disease has not attracted a similar level of attention as AD. An important reason for this is certainly the predominant role of AD both in research and in the clinical implementation of knowledge in the field. In addition, subcortical vascular disease gives rise to cognitive symptoms that are difficult to detect or are said to be ‘clinically silent’. It is a strength of the Gothenburg MCI study that this disorder is paid serious attention. Other strengths are our fixed protocol, longitudinal design, inclusion of patients seeking help for cognitive disorders and a healthy control group, strict diagnostic criteria, and diagnostic assessment performed by a physician masked to the outcome variables. The study also has some limitations: few patients have converted from SCI/MCI to SVD, a significant number of patients drop out, overlap between the studies, and there may be potential cohort effects. Some research foci have not been pursued and no solid conclusions can thus be drawn from the preliminary results such as research using EEG and SPECT. Analyses of specific vascular factors and the impact of lifestyle have not yet been performed. We have not yet reported any specific results for MixD. There is also lack of studies on potential markers for congophilic versus arteriolasclerotic lesions.

Concluding Summary

The Gothenburg MCI and dementia studies are longitudinal, clinical–observational studies on the AD–SVD spectrum among patients seeking medical care at a memory clinic. Particular focus is on SVD, which is an underrecognized disorder in clinical practice and research. By using specific criteria for SVD and criteria in agreement with recently published clinical criteria for AD, not only AD but also SVD has been identified in the studies. Furthermore, it has revealed characteristic...
neuropsychological and neurochemical patterns for SVD, which are present also early in the course of the disease. Our nosological findings provide opportunities for trials in SVD and better definition of AD in AD trials.

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**Authors’ contributions**

All authors approved of the final version of the manuscript and agreed to be accountable for all aspects of the work. Drafting and revising the manuscript critically for intellectual content were jointly performed by all authors.

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