Features of cerebral small-vessel disease and their association with long-term outcome in ischaemic stroke patients

Gerli Sibolt

Academic Dissertation
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Abstract

Cerebral small-vessel disease (CSVD) is a common disease causing slowly progressive disability and earlier death. In CSVD, the destruction of subcortical networks leads to cognitive impairment, mood disorders, gait instability, and motor deficits. All those weaken the ability to be independent of help. Imaging features of CSVD can be visible on brain scans years before the first clinical symptoms. The imaging features are: cerebral white matter lesions (WML), cerebral microbleeds (CMB), perivascular spaces, brain atrophy, and lacunar infarcts.

The aim of this thesis was to investigate the features of cerebral small-vessel disease and their association with long-term outcome in ischaemic stroke patients.

The six publications were sub-studies of the Helsinki Stroke Aging Memory (SAM) study. The SAM cohort consists of 486 consecutive patients aged 55 to 85 years with ischaemic stroke who were admitted to Helsinki University Central Hospital. At 3 months, comprehensive clinical, neuropsychological, psychiatric, and radiological data were acquired. The cohort had a follow-up 21 years later using extensive national registers.

The findings of the six publications can be summarised as follows:

In post-stroke patients, the presence of WMLs was an indicator of ischaemic stroke recurrence up to 5 years after a first-ever ischaemic stroke and indicated a high risk of serious traumatic injuries, especially hip fractures requiring hospital treatment. After ischaemic stroke, patients with severe WMLs spent fewer days at home and became permanently institutionalised earlier, especially within the first 5 years.

In post-stroke patients, depression and especially depression-executive dysfunction syndrome were associated with a shorter interval to ischaemic stroke recurrence. Post-stroke dementia predicted the recurrence of ischaemic stroke at the long-term follow-up. Post-stroke dementia was a robust predictor of institutionalisation. Imaging and clinical features of CSVD were associated with unfavourable outcome events, like earlier recurrent stroke, traumatic injuries, and earlier permanent institutionalisation.
Tiivistelmä


Tämä väitöskirjatyön tavoitteena oli, tutkia aivoverenkierron sairauksien ominaisuuksia ja niiden yhteyttä pitkääikaisennusteeseen potilailla, joilla on ollut iskeeminen aivoinfarkti.


Kuuden osatöiden tiivistetyn tulokset olivat:

Potilailla, joilla oli aivovalvonta, valkean aineen muutokset ennustivat iskeemisen aivovalvoksen uusiutumisen jopa viiden vuoden ajan ensimmäisen iskeemisen aivovalvoksen jälkeen ja valkean aineen muutoksiin liittyi suurentunut riski saada sairaalahoitoa vaativia vakavia traumaattisia vammoja, erityisesti lonkkamurtumia. Iskeemisen aivovalvoksen jälkeen potilaat, joilla oli runsaasti valkean aineen muutoksia, viettivät vähemmän päiviä kotona ja joutuivat aikaisemmin pysyvään laitoshoidoon, erityisesti viiden ensimmäisen vuoden aikana.

Potilailla, joilla oli aivovalvonta, masennus ja erityisesti syndrooma jossa sekä masennus että heikentynyttä toiminnanohjaus masennussyndrooma ennustivat aikaisempaa iskeemisen aivovalvoksen uusiutumista. Aivovalvoksen jälkeinen demencia ennustaa iskeemisen aivovalvoksen toistumista pitkääikaisessa seurannassa. Aivovalvoksen jälkeinen demencia ennusti pysyvää laitoshoidoa.

Pienten suonten taudin kliiniiset ja radiologiset ilmentymätennustivat epäsuotuisia lopputulemia, kuten aikaisempaa aivovalvoksen uusiutumista, traumaattisia vammoja ja aikaisempaa pysyvää laitoshoidoon joutumista.
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List of original publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:


VI. Sibolt G, Curtze S, Jokinen H, Pohjasvaara T, Kaste M, Karhunen PJ, Erkinjuntti T, Melkas S, Oksala NK. Poststroke dementia cuts in half the time before institutionalization. (submitted)
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CIND</td>
<td>Cognitive impairment without dementia</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CMB</td>
<td>Cerebral microbleeds</td>
</tr>
<tr>
<td>CSVD</td>
<td>Cerebral small-vessel disease</td>
</tr>
<tr>
<td>CVD</td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td>DES</td>
<td>Depression-executive dysfunction syndrome</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>mRS</td>
<td>modified Rankin Scale</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PSD</td>
<td>Post-stroke dementia</td>
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<tr>
<td>SAM</td>
<td>Helsinki Stroke Aging Memory study</td>
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<tr>
<td>TOAST</td>
<td>Trial of Org 10172 in Acute Stroke Treatment</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischaemic attack</td>
</tr>
<tr>
<td>WML</td>
<td>White matter lesions</td>
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1 Introduction

Alois Alzheimer gave a speech on 14 April 1902 at the *Jahresversammlung des Vereins der deutschen Irrenärzte* (Annual Meeting of the Association of German Physicians for the Insane) in Munich, Germany.\(^1\) The transcript of the speech, *Die Seelenstörung auf arteriosklerotischer Grundlage (The mental disorder on an arteriosclerotic basis)* is a fascinating read 116 years later, as one notices the preciseness of his description of the disease, which we know today as vascular dementia.\(^1\) Alzheimer andBinswanger had been publishing on this topic since 1894.\(^2\)\(^-\)\(^4\) The speech contains basically all the topics that will be discussed in this dissertation 116 years later. He describes clinical features of cerebral small-vessel disease (CSVD) like depression, dementia, and impairment of cognitive functions which lead to loss of independence, epilepsy, strokes, and finally death.\(^1\) Additionally, he describes neuropathological and vascular abnormalities covering the enlargement of perivascular spaces, arteriosclerosis, brain atrophy, and focal lesions of atherosclerosis in the white matter areas – the imaging surrogates of CSVD in our era.\(^1\) Over the years, understanding of cognitive impairment and dementia has become more precise, including the nomenclature, but a lot was known even back then. The lifetime risk for both stroke and dementia is high: 1 in 3 persons is expected to have dementia, stroke, or stroke and dementia.\(^5\) Vascular diseases of the brain can cause a heterogeneous spectrum of disorders, containing different types and grades of cognitive disorders with diverse pathologies and clinical manifestations. As an umbrella term *vascular cognitive disorders* has been proposed.\(^6\)

The concept of strokes dates back to the 17\(^{\text{th}}\) century when Willis, Wepfer, and Bayle contributed to the understanding of distinguishing ischaemic and haemorrhagic stroke.\(^7\)\(^-\)\(^9\) If a brain vessel, a large or middle size artery, is acutely occluded by a clot, one might suffer a so called stroke. The resulting symptoms depend on the location of brain ischaemia and the size of the affected area with a spectrum from acute fulminate hemiparesis over mild brain dysfunction to silent infarcts, an infarct of brain tissue causing no noticeable deficit.\(^7\)\(^-\)\(^9\) If very small vessels are occluded, only mild symptoms or none occur. However, the occlusion might still lead to infarction or to more chronic damage with atrophy and gliosis.

The term CSVD is used to describe clinical and neuroimaging aspects associated with pathologies of the small vessels of the brain, including small arteries, arterioles, capillaries, and small veins. No clear consensus exists as to whether to define small vessels based on diameter size or on subcortical location.\(^10\) The most important clinical features are stroke and dementia, and the most important neuroimaging aspects are cerebral white matter lesions, lacunar infarcts, cerebral micro-bleeds, brain atrophy, and perivascular spaces. All the features will be discussed later in detail, as they are essential parts of this study. However, in most cases, no definitive proof of the pathological
mechanism can be gathered due to lack of autopsy material of the subjects. In fact, cerebral small-vessel disease is an umbrella-term for several pathological processes with various aetiologies that affect the small arteries, arterioles, capillaries, venules, and probably even the lymphatic system of the brain. The different aetiologic entities will be briefly discussed later on. However, the majority of small-vessel diseases in Finland and in many Western countries are attributable to hypertension-related microhyalinosis, also called arteriolosclerosis, and to cerebral amyloid angiopathy. While arteriolosclerosis seems to share risk factors with common cardiovascular diseases, cerebral amyloid angiopathy is sporadic or hereditary and, except for age, accompanying risk factors are poorly understood.

This underlying dissertation concentrates on conditions in which progressive obliteration and repetitive occlusions of very small arteries and arterioles lead to slow and insidious but remarkable loss of brain function. Frequently, the term arteriolosclerosis is used to distinguish atherosclerosis of small vessels from large- and mid-sized arteriosclerosis. Small arteries have a continuous lamina elastica, while a continuous lamina elastica is absent in arterioles. An arteriole is part of the microcirculation and branches out from an artery and leads to capillaries. Arterioles usually have only one or two layers of smooth muscles. Arterioles are the primary site of vascular resistance, which might play an important role in the pathologic processes of CSVD and might be a target for prevention and treatment. At the transition of arterioles to capillaries, the greatest change in blood pressure and blood-flow-velocity occurs.
2 Background

Acute and clinically symptomatic strokes occur as well in small-vessel disease patients. However, most small-vessel occlusion incidents result in very mild or absent symptoms, and the disease is mostly chronic and the symptomatic strokes are only the tip of the iceberg. Therefore, the short-term outcomes of clinical strokes are often good, while the long-term prognosis is grim.\textsuperscript{11} The main aim of this study, is to elaborate on the prognosis and long-term outcome of stroke patients in a very long follow-up concentrating on those with features of small-vessel disease. The presence of different features of CSVD predicts stroke recurrence, hip fractures, traumatic injuries, and permanent institutionalisation. All six publications were conducted as part of the Helsinki Stroke Aging Memory (SAM) study. The SAM study is a cohort of consecutive stroke patients.

2.1 Stroke definition

The classic definition of a stroke is mainly clinical. The evolution of stroke definitions has been excellently detailed in a doctoral thesis at our institution.\textsuperscript{12} However, the most up-to-date definition of a stroke was formulated by The Stroke Council of the American Heart Association/American Stroke Association.\textsuperscript{13} The consensus statement defines a central nervous system infarction as brain, spinal cord, or retinal cell death attributable to ischaemia based on neuropathological, neuroimaging, and/or clinical evidence of permanent injury.\textsuperscript{13} Stroke also includes intracerebral haemorrhage and subarachnoid haemorrhage,\textsuperscript{13} which were, however, excluded as index events in the SAM cohort. Many definitions distinguishing transient ischaemic attacks (TIA), minor and major stroke from each other exist, but none of them is universally accepted.\textsuperscript{14}

The most commonly used clinical definition of a lacunar stroke includes pure motor stroke, pure sensory stroke, sensori-motor stroke, and atactic hemiparesis.\textsuperscript{15} A widely accepted definition of imaging criteria for a lacunar stroke has been proposed by the STandards for Reporting Vascular changes on nEuroimaging (STRIVE) group:\textsuperscript{16} “A round or ovoid, subcortical, fluid-filled cavity (signal similar to CSF) of between 3 mm and about 15 mm in diameter, consistent with a previous acute small subcortical infarct or haemorrhage in the territory of one perforating arteriole.”

Cerebral microbleeds (CMB) are residuals of blood cells, mostly haemosiderin-rich macrophages in the cortico-subcortical junction and the deep grey or white matter. CMBs are defined by the STRIVE group as small (2-10 mm) areas of signal void with associated blooming seen on T2*-weighted MRI.\textsuperscript{16}
2.2 Stroke epidemiology

One in six people suffers at least one stroke during their lives.\textsuperscript{17} Not only is stroke the third leading cause of death, but it is also an important cause of long-term disability consuming enormous health-care resources.\textsuperscript{18}

The incidence of ischaemic stroke has decreased in the Western world. Globally, however, the incidence had grown by 15.8\% between 2005 and 2015, from approximately 4.7 million to 5.4 million cases per year.\textsuperscript{19}

In high-income countries and in many middle- and low-income countries, the death rates from stroke have declined.\textsuperscript{20} However, probably due to better stroke treatment and better stroke prevention, the strokes are also less severe and less often fatal, leading to higher rates of disabled stroke survivors.\textsuperscript{21} Stroke is a disease of the elderly.\textsuperscript{21} For every 1000 individuals in the Oxford vascular study, the stroke rates increased from 1.8 per year for patients between 55 and 64 years of age to 17 for those aged 85 or older.\textsuperscript{22}

2.3 Risk of recurrent stroke

In a recent meta-analysis, the risk for recurrent stroke was calculated to be 4.3\% per year.\textsuperscript{23} A recent study from Canada reported rates of recurrent stroke to be 3.1\% at 1 year, 6.3\% at 3 years, and 8.8\% at 5 years after the index stroke.\textsuperscript{24} The recurrence rates over 10 years range from 12\% to 42\%.\textsuperscript{25-27}

Patients with large artery atherosclerosis have the highest risk of early recurrent stroke. A significant lowering of the risk, however, is possible with urgent carotid imaging and very early endarterectomy.\textsuperscript{28}

Many factors modify the risk of recurrence. An association between WMLs and recurrent stroke in patients with transient ischaemic attacks or minor strokes has been reported previously,\textsuperscript{29} and lacunar strokes have also been reported to be associated with stroke recurrence.\textsuperscript{30}

We can distinguish between modifiable and unmodifiable risk-factors for ischaemic strokes. The most important unmodifiable risk-factor for recurrent stroke is age.\textsuperscript{22,31,32} The modifiable factors are hypertension, regular physical activity, apolipoprotein (Apo)B/ApoA1 ratio, dietary habits, waist to hip ratio, psychosocial factors, cardiac causes, alcohol consumption, and diabetes mellitus.\textsuperscript{33} Known modifiable risk-factors for stroke recurrence are diabetes,\textsuperscript{31,34} ethanol abuse,\textsuperscript{35} hypertension\textsuperscript{35,36} elevated blood glucose within 48 hours,\textsuperscript{35} hypercholesterolaemia,\textsuperscript{34,36} smoking,\textsuperscript{34} and atrial fibrillation.\textsuperscript{37} A 10 mmHg reduction of systolic blood pressure and a 5 mmHg reduction of the diastolic blood pressure using any commonly used medication reduces the risk of recurrent stroke up to 30-40\% in 5 years.\textsuperscript{38-40} And treatment of atrial fibrillation reduces the recurrence risk by 64\%.\textsuperscript{41} This is proof of the concept that hypertension and atrial fibrillation are
modifiable risk factors. Approximately every fourth stroke is a recurrent one.\(^\text{42}\) The recurrence risk of an ischaemic stroke in patients with CSVD or distinct features of CSVD will be explored in chapter 2.4.

### 2.4 Small-vessel disease

Cerebral small-vessel disease (CSVD) is responsible for about a fourth of ischaemic strokes and, as the main cause of vascular cognitive impairment, it contributes to at least 45% of all memory disorders.\(^\text{43-45}\)

CSVD, as a disease, assumes one distinct pathology. Indeed, the widely used TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification of ischaemic stroke subtypes uses only one category for CSVD.\(^\text{43}\)

In the TOAST criteria, lacunar infarcts are seen in relation to CSVD as the “combination of (1) presentation with one of the traditional clinical lacunar syndromes, (2) normal computed tomography/magnetic resonance imaging (MRI) results or demonstration of a relevant brain stem or subcortical lesion with a diameter <1.5 cm, and (3) exclusion of an alternate etiology, such as cardiac sources of embolism or large vessel disease.”\(^\text{43}\)

However, 100 years afterBinswanger’s and Alzheimer’s reports more and more evidence shows, that the pathological and clinical findings reported by Binswanger, do not qualify as a distinct condition that could be named Binswanger’s disease.\(^\text{2-4,46}\) CSVD is not one single pathology but it should instead be considered a clinical syndrome with different underlying pathologies and risk factors affecting small superficial and deep perforating arteries, arterioles, capillaries, veins, and even the lymphatic system of the brain.\(^\text{47}\)
### 2.4.1 Different types of small-vessel diseases

Table 1 shows an aetiopathogenic classification of CSVDs, as suggested by Pantoni in 2010.

**Table 1: Aetiopathogenic classification of CSVDs according to Pantoni (2010)**

| Type 1 | arteriolosclerosis  
(strongly age- and vascular risk-factor-related) | Pathology: fibrinoid necrosis, lipohyalinosis, microatheroma, microaneurysms (saccular, lipohyalinotic, asymmetric fusiform, bleeding globe), segmental arterial disorganisation |
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<tr>
<td>Type 2</td>
<td>sporadic and hereditary cerebral amyloid angiopathy</td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>inherited or genetic small-vessel diseases distinct from cerebral amyloid angiopathy</td>
<td>For example, CADASIL (cerebral autosomal dominant arteriopathy with subcortical ischaemic strokes and leukoencephalopathy), CARASIL (cerebral autosomal recessive arteriopathy with subcortical ischaemic strokes and leukoencephalopathy), hereditary multi-infarct dementia of the Swedish type, MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes), Fabry’s disease, hereditary cerebroretinal vasculopathy, hereditary endotheliopathy with retinopathy, nephropathy and stroke, CSVD caused by COL4A1 mutations</td>
</tr>
<tr>
<td>Type 4</td>
<td>inflammatory and immunologically mediated CSVDs</td>
<td>Example: Wegener’s granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, cryoglobulinaemic vasculitis, cutaneous leukocytoclastic angiitis, primary angiitis of the CNS, Sneddon's syndrome, nervous system vasculitis secondary to infections, nervous system vasculitis associated with connective tissue disorders such as systemic lupus erythematosus, Sjögren’s syndrome, rheumatoid vasculitis, scleroderma, and dermatomyositis</td>
</tr>
<tr>
<td>Type 5</td>
<td>venous collagenosis</td>
<td></td>
</tr>
<tr>
<td>Type 6</td>
<td>other small-vessel diseases</td>
<td>Example: post-radiation angiopathy and non-amyloid microvessel degeneration in Alzheimer’s disease</td>
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</tbody>
</table>
Types 1 and 2 are the most common forms, especially in stroke cohorts, and therefore require some more attention.

### 2.4.2 Arteriolosclerosis (CSVD Type 1)

In CSVD type 1, the smooth muscle cells from the tunica media degenerate from the arterioles. Additionally, fibro-hyaline material deposits occur in the vessel wall causing thickening of the vessel wall and narrowing of the vessel lumen. Apart from age, this type of pathology is strongly associated with hypertension and diabetes; and is therefore sometimes called hypertensive CSVD. Other organs, like the kidneys and the retina, are frequently co-affected by this type. There is no proven therapy to prevent or slow down the progress of type 1 CSVD; however, treating the underlying risk-factors is a widely accepted, logical, and within-guidelines advocated approach.

### 2.4.3 Cerebral amyloid angiopathy (CSVD type 2)

Progressive accumulation of β-amyloid is responsible for the development of CSVD type 2, which is called cerebral amyloid angiopathy. Neurologists are familiar with this same β-amyloid protein from other diseases. In Alzheimer’s disease, we find that accumulation in neurons and in inclusion body myositis deposits can be found in the muscle cells. In cerebral amyloid angiopathy, however, we find the deposition of β-amyloid in the media and adventitia of small- and medium-sized cortical and meningeal vessels.

In cerebral amyloid angiopathy, the WMLs progress over time and incident lobar haemorrhages start to occur. This underlines the theory of an underlying progressive microangiopathy.

An ability to distinguish cerebral amyloid angiopathy from arteriolosclerotic CSVD with high sensitivity and high specificity would be of high clinical relevance. Cerebral amyloid angiopathy does not relate clearly to vascular risk factors and, thus, a strictly vascular secondary prevention is not beneficial. The bleeding risk might increase without benefit by antithrombotic or anticoagulation treatment, as cerebral amyloid angiopathy is not clearly related to arteriosclerotic processes. Thrombolysis treatment of acute ischaemic stroke in a patient with cerebral amyloid angiopathy is associated with a high risk of symptomatic intracranial haemorrhage, however remote from the ischaemic lesion.

### 2.5 Imaging of small-vessel disease

Larger arteries can be visualised by angiography in vivo. Using ultrasound or contrast agents, even vessel-wall pathologies can be visualised. However, small vessels cannot be visualised in vivo. Therefore, the in vivo diagnosis of CSVD utilises surrogate imaging markers. The surrogate markers of CSVD represent the tissue-damage assumed to be
caused by the disease. The imaging surrogates of CSVD have been elaborated on 2013 in a position paper of the STAndards for Reporting Vascular changes on nEUroimaging (STRIVE) group.16

Six imaging surrogates for CSVD:

1. **Recent small subcortical infarcts**
   - Sometimes, incident findings predict recurrent strokes and dementia.56
   - Lesions are evident within a few weeks of imaging or are due to clinical symptoms from the territory of one perforating arteriole.16

2. **Lacunar infarcts**
   - Long-term prognosis of symptomatic lacunar infarcts, has been claimed to be relatively favourable.57
   - Lobar lacunes seem to be more associated with cerebral amyloid angiopathy (see Type 2 below), whereas deep lacunes relate to arteriolosclerosis (see Type 1 below).58
   - A lacune of presumed vascular origin appears as a round or ovoid, subcortical, fluid-filled cavity with a signal intensity similar to cerebrospinal fluid.
   - The diameter of a lacune is between 3 mm and 15 mm and is in the territory of one perforating arteriole.16

3. **WMLs**
   - WMLs seem to have strong associations with clinically relevant outcomes:
     - Best predictor of post-stroke cognitive performances.59
     - Predictor of symptomatic ICH after stroke thrombolysis treatment.60
     - Predictor of worse outcome after stroke thrombolysis treatment.61

4. **Enlarged perivascular spaces**
   - Enlarged perivascular spaces are associated with age, lacunar stroke subtype and WMLs, but the association with outcomes lacks evidence.
   - The association of enlarged perivascular spaces with worse cognitive function has been established.62
   - This relation, however, has recently been challenged.63

5. **Microbleeds**
   - CMBs can be useful in predicting the bleeding risk in clinical settings as thrombolysis treatment, anticoagulation, or antithrombotic treatment.54,64–67
   - CMBs predict recurrence of ischaemic strokes, and especially predict ICH when comparing with stroke patients without CMBs.68
   - There seems to be an association of cerebral microbleeds and poor functional outcome, but evidence is not as clear as for WMLs.69

6. **Brain atrophy**
   - The association of progressive brain atrophy as a surrogate of CSVD is unknown.
   - Brain atrophy, however, is associated with dementia.70

All these (1-6) are associated with PSD or cognitive decline.71

From the known imaging parameters of CSVD, the WMLs have the strongest association with the clinical outcomes of interest in this thesis.47
2.6 Cerebral white matter lesions

Stroke patients frequently present with reduced areas of X-ray attenuation on CT representing WMLs, previously called leukoaraiosis,\textsuperscript{72} a term introduced in 1987 as a neologism from the Greek words 
leukos (white) and araios (rarefied).\textsuperscript{72} It is used only in connection with CT imaging, not MRI. In MRI imaging, WML can be classified according to the Fazekas scale (see Figure 1).\textsuperscript{73}

In the none to mild degree of WML, periventricular lesions included no more than a small cap or thin lining, and in the other white matter areas, no more than large focal lesions. In moderate WML, periventricular lesions included no more than a large cap and smooth halo, and in the other white matter areas, no more than focal confluent lesions. The severe degree of WML included cases with extending caps or irregular halos in the periventricular area and diffusely confluent lesions or extensive WMLs in other white matter areas.

![Image](image.png)

*Figure 1: Gradings of WMLs according to the modified Fazekas Scale with (a) none to mild, (b) moderate, and (c) severe.*

The underlying pathologies of WMLs were already described in 1854 by Durand-Fardel in \textit{Traité Clinique et Pratique des Maladies des Vieillards (Clinical and Practical Treatise of Diseases of the Elderly)}.\textsuperscript{74} Neuropathologic correlates of the imaging term leukoaraiosis (now white matter lesions) are found to be the same as those described in 1854. Age is one of the strongest risk factors for WMLs, as they usually progress gradually over time. Surprisingly however, in some patients with minor WMLs, they can decrease in the follow-up.\textsuperscript{75}

WMLs summarise the effects of several classical risk factors on the small-vessel brain network, and therefore might estimate the future risk of developing recurrent
cerebrovascular events, such as ischaemic stroke after a first-ever ischaemic stroke. A surrogate marker score of CSVD, including WMLs, could have clinical utility in the risk stratification of stroke recurrence in the same way as the Framingham Risk Score.76

Some studies have found WMLs to be associated with high-degree carotid stenosis,77,78 Another study found associations of WMLs with unstable plaques.79 These studies suggest that WMLs are caused by hypoperfusion and/or repetitive microembolism.

2.6.1 Cerebral white matter lesions and longterm outcomes

According to the LADIS study (Leukoaraiosis and Disability in the Elderly), adverse outcomes associated with WMLs include dependency, cognitive impairment and dementia,80–83 depression,84 and impairment of gait.85,86 Age-related white matter lesions is a frequently used synonym for WMLs. WMLs are claimed to be an even more sensitive predictor of neurological deficit recovery after ischaemic stroke than chronological age.87 Severe WMLs are associated with increased mortality in stroke patients,88–90 and even in patients without stroke.91,92

Patients with WMLs who had transient ischaemic attacks or minor strokes associated with internal carotid artery disease in the North American Symptomatic Carotid Endarterectomy Trial had an increased risk of any stroke compared to patients from the same study without WMLs.93

The association of WMLs and stroke recurrence has been studied in three previous studies only (see Table 3).29,94,95

Table 2: Previous studies on the association of WMLs and stroke recurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Follow-up</th>
<th>Imaging</th>
<th>Association of WMLs with recurrent ischaemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Swieten94</td>
<td>3017</td>
<td>3 years</td>
<td>MRI</td>
<td>HR 1.6; 95% CI 1.2–2.2</td>
</tr>
<tr>
<td>Hénon94</td>
<td>202</td>
<td>3 years</td>
<td>CT</td>
<td>RR 1.7; 95% CI 1.23–2.36</td>
</tr>
<tr>
<td>Fu95</td>
<td>228</td>
<td>&lt;2 years</td>
<td>MRI</td>
<td>HR 4.2; 95% CI 2.0–8.6</td>
</tr>
<tr>
<td>Kim96</td>
<td>2378</td>
<td>90 days</td>
<td>MRI</td>
<td>HR 1.5; 95% CI 1.0–2.3</td>
</tr>
<tr>
<td>Kumral97</td>
<td>9522</td>
<td>5 years</td>
<td>MRI</td>
<td>HR 1.5; 95% CI 1.4–1.7</td>
</tr>
<tr>
<td>Nam98</td>
<td>958</td>
<td>2 years</td>
<td>MRI</td>
<td>HR 1.9; 95% CI 1.1–3.4</td>
</tr>
<tr>
<td>Ntaios99</td>
<td>1892</td>
<td>&lt;10 years</td>
<td>MRI/CT</td>
<td>HR 1.9; 95% CI 1.4–2.6</td>
</tr>
</tbody>
</table>

The first study included 3017 TIA or minor stroke patients from a randomised stroke prevention trial. The WML score was strongly associated with stroke recurrence during the 3-year follow-up (HR 1.6; 95% CI 1.2–2.2).29
In the second cohort 202 stroke patients (median age 75 years, 84% first-ever stroke) had been followed for 3 years.94 The WML score was strongly associated with stroke recurrence during the 3-year follow-up (RR 1.70; 95% CI 1.23–2.36), but the score was determined on CT scans instead of MRI images.

In the third study 228 patients with a first-ever stroke (mean age 68 years) were followed for 23 months.95 In this study, the severity of WMLs was scored on MRI images. The stroke recurrence rate was 43.7% for patients with severe WMLs, and there was an association between stroke recurrence and severe WMLs (HR 4.2; 95% CI 2.0–8.6) after controlling for the classical risk factors.

Since the publication of Study I in 2012, several studies have addressed this relationship between WMLs and stroke recurrence. A retrospective study of consecutive acute ischaemic stroke patients at the Massachusetts General Hospital between March 2003 and April 2011 resulted in a cohort of 2378 patients after excluding 891 patients.96 The follow-up was for 90 days only. The extent of WMLs on MRI predicted 90-day recurrent stroke risk after ischaemic stroke. Data from 9522 patients from the Ege Stroke Registry (n=10930) showed that the cumulative stroke recurrence rate was 22.9% (n = 2181) at 5 years after stroke onset.97 The stroke recurrence rate at 5 years was 10.7% for patients with WMLs vs. 8.6% for patients without them. In a retrospective cohort with 958 patients with first-ever ischaemic stroke severe WMLs were an independent predictor (HR 1.9; 95% CI 1.1–3.4) of the 2-year recurrence rate of ischaemic stroke.98 Among 1892 patients from the Athens Stroke Registry 17% had WMLs, 33% investigated with MRI and 67% with CT. In Cox multivariable analyses WMLs were an independent predictor of stroke recurrence in non-AF stroke patients (HR 1.9; 95% CI 1.4–2.6).99

WMLs are a surrogate marker for CSVD and are associated with clinical outcomes of stroke patients, but the association with recurrent ischaemic stroke, institutionalisation and falls due to gait disturbance lacks sufficient evidence.

2.7 Dementia

Dementia is a syndrome, usually of a chronic or progressive nature, in which there is deterioration in memory, thinking, behaviour and the ability to perform everyday activities.

It mainly affects older people, although it is not a normal part of ageing. (World Health Organization 2017)100

According to the “Global Burden of Disease Study”, dementia affected about 46 million people in 2015.19 It has been estimated that 0.6% of the yearly UK gross domestic product is spent for the institutional care of demented patients and this is expected to rise to 0.96% in 2031.101

With age being the most important risk factor, the prevalence of dementia could be expected to increase with increasing life expectancy. However, the age-specific
The prevalence of Alzheimer’s disease has been reported to decrease in the UK. This has been explained by the reduction of the vascular component due to the primary and secondary prevention of vascular diseases rather than by the reduction of Alzheimer’s disease. Especially in the elderly, incident ischaemic cerebrovascular disease increases the clinical expression of dementia associated with Alzheimer’s disease pathology. Age, medial temporal lobe atrophy, female sex, and family history are associated with dementia. However, those associations are weaker in post-stroke dementia (PSD), suggesting that the degenerative role is less important in post-stroke dementia.

### 2.7.1 Post-stroke dementia

Otto Binswanger and Alois Alzheimer described the connection of dementia and stroke back in 1894. The understanding of this connection has improved over the years.

A stroke causes focal brain damage, often involving the subcortical tracts or otherwise important structures for cognitive functions. Therefore, the decline of cognition after stroke is a direct consequence of the stroke. Despite good physical recovery, many patients suffer from severe cognitive deficits after a stroke.

Irrespective of the underlying cause of the dementia, be it vascular, degenerative, or mixed, PSD includes all types of dementias that occur after an initial stroke. The underlying pathologies consist of a heterogeneous mixture of small to large vascular and non-vascular neurodegenerative processes. PSD is one of the main causes of disability after stroke, and PSD is associated with impaired survival.

PSD is an important category of vascular cognitive impairment, but in addition to the vascular burden, PSD also relates to the degenerative burden of the brain. In up to one-third of the PSD cases, the underlying cause is Alzheimer’s disease; therefore, PSD is not equal to vascular cognitive impairment (see page 23). In one autopsy study, 75% of the demented stroke survivors met the current criteria for vascular dementia.

Many variables have been associated with an increased risk of PSD: increasing age, low education, dependency before stroke, pre-stroke cognitive decline, diabetes mellitus, atrial fibrillation, myocardial infarction, epileptic seizures, sepsis, cardiac arrhythmias, congestive heart failure, silent cerebral infarcts, transient ischaemic attack within weeks before index stroke, global and medial-temporal-lobe atrophy, WMLs, stroke severity, stroke cause, stroke location, and recurrence of stroke.

### 2.7.2 Prevalence and incidence of post-stroke dementia

*Having a stroke doubles the risk of dementia.*

The prevalence of PSD in the SAM cohort varies depending on the used criteria to diagnose dementia from 3.1% (ICD-10) to 29.1% (DSM-III). In other post-stroke cohorts
with different mean ages in the study population, delays of evaluation from 7 days to 3 years and different dementia criteria, the prevalence of PSD ranges from 5.9% to 32% depending on the mean age of the study population, the delay between stroke and cognitive assessment, and the criteria for dementia used. In a meta-analysis, 10% of patients hospitalised with their first-ever stroke had pre-stroke dementia, 10% developed PSD after the stroke, and one of four was diagnosed with dementia within 1 year after the stroke.

The incidence of PSD is about 10% during the first 6–12 months after stroke, but remains double that of the general population even after 12 months and is about 32% at 5 years.

One in six people suffer a stroke, and 30% of these individuals develop vascular dementia or vascular cognitive impairment.

The incidence of dementia in the population of Rochester (Minnesota, USA) was found to be nine times higher than that of the general population in the first year after stroke, and the risk of dementia each year thereafter was about twice the risk in the general population. The increase is not explained by strategic infarcts or severe infarcts, as even after the first year, a 50% increase was observed in Alzheimer’s disease in the cohort compared with that in the community, and they did not find an effect of location or clinical severity of infarct on the rate of occurrence of dementia.

### 2.7.3 Recurrent stroke in patients with post-stroke dementia

Only three previous studies have focused on the incidence of recurrent stroke in patients with PSD before the publication of our study (see Table 3).

**Table 3: Previous studies on recurrent stroke in patients with PSD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Incidence or prevalence of PSD</th>
<th>Population</th>
<th>Follow-up</th>
<th>Mean age (y)</th>
<th>New-onset PSD</th>
<th>Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moroney, 1997</td>
<td>242</td>
<td>62 out of 208 at first follow-up</td>
<td>ischaemic stroke</td>
<td>5 years, prospective</td>
<td>72</td>
<td>62</td>
<td>208</td>
</tr>
<tr>
<td>Hénon, 2003</td>
<td>202</td>
<td>29 out of 110 at 3 months</td>
<td>ischaemic or haemorrhagic stroke</td>
<td>3 years, prospective</td>
<td>75</td>
<td>29</td>
<td>110</td>
</tr>
<tr>
<td>Loeb, 1992</td>
<td>108</td>
<td>25 out of 108 during 4 years</td>
<td>lacunar stroke</td>
<td>4 years, prospective</td>
<td>65</td>
<td>25</td>
<td>108</td>
</tr>
</tbody>
</table>
In all these studies, the association between PSD and stroke recurrence remains uncertain. Two found PSD to be associated with recurrence of stroke. However, in one series, the presence of WMLs, but not PSD, was associated with stroke recurrence.

### 2.7.4 Vascular cognitive impairment

The term *multi-infarct dementia* has been introduced by Hachinski to characterise the cognitive syndrome associated with risk factors for CVD and its manifestations. Later the term *vascular dementia* became more popular. Milder forms of dementia or even pre-dementia can be described as *vascular mild cognitive impairment* as analogous to mild cognitive impairment. The term *vascular cognitive impairment* covers the whole spectrum of cognitive impairments, from a single cognitive domain to severe dementia in combination with a stroke or any vascular brain injury.

Despite the small size of lacunar infarcts, they are associated with cognitive impairment, suggesting that not only the lacunar infarct but also the underlying CSVD are responsible for the cognitive impairment. Vascular dementia or vascular cognitive impairment affects 5% of the population. There is a 9-fold increased risk of incident dementia after the first-ever stroke. Vascular dementia is the second most common dementia after Alzheimer’s disease. The risk for both vascular dementia and Alzheimer’s disease increases after a stroke, and a mixture of both dementia pathologies is common.

Often, there is undiagnosed pre-stroke dementia with the possibility of co-existing neurodegenerative pathology as a cause of PSD. Indeed, subjects with proven Alzheimer-like amyloid beta deposition have a more severe and rapid cognitive decline after stroke compared to subjects without amyloid beta deposition.

However, in the Newcastle CogFAST study 75% of subjects had vascular dementia according to current criteria, and only 25% had mixed pathology. Additionally, in one study, about 70% of stroke survivors did not have evidence of Alzheimer’s disease-like amyloid beta pathology.

Three different scenarios have been distinguished in the development of vascular cognitive impairment:

1. Large-vessel occlusion, artery-to-artery embolism, or cardio-embolism resulting in large cortical infarcts.
2. Infarcts of small volume but in strategic areas such as the thalamus or hippocampus.
3. CSVD

Parenchymal lesions of the brain associated with vascular cognitive impairment are listed in Table 4.
Table 4: Parenchymal lesions of the brain associated with vascular cognitive impairment

<table>
<thead>
<tr>
<th>Haemorrhagic</th>
<th>Ischaemic</th>
<th>Secondary to ischaemia, bleeding, or hypo-perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep haemorrhage</td>
<td>Large vessel infarcts</td>
<td>Brain atrophy</td>
</tr>
<tr>
<td>Lobar haemorrhage</td>
<td>Multiple infarcts</td>
<td>Enlarged perivascular spaces</td>
</tr>
<tr>
<td>Cerebral microbleeds</td>
<td>Strategic infarcts (lacunas)</td>
<td>WMLs</td>
</tr>
<tr>
<td></td>
<td>Micro-infarcts</td>
<td></td>
</tr>
</tbody>
</table>

2.7.5 Evaluation of post-stroke cognitive impairment

Whether there is spontaneous improvement in post-stroke cognitive impairment is not clear. Surprisingly, the prevalence of cognitive impairment after stroke remains persistently high (about 20%) over time, from 3 months after the stroke over the annual follow-up until 5 years post-stroke.125 Any dementia occurring within 3 months after stroke is considered to be a PSD. This is probably due to practical reasons, with follow-up visits at 3 months. A later timepoint would probably not change the ability to predict outcomes.

Dementia is a feature of CSVD. CSVD patients have a high risk of stroke and recurrent strokes. Strokes increase the risk of PSD, and PSD is associated with a grimmer prognosis. This makes PSD a potential predictor of important medical outcomes especially in CSVD patients.

2.8 Post-stroke depression

In the general population of Finland, the prevalence estimate of major depressive disorders over 12 months (in the year 2011) was 7.4%.126

A prevalence four times higher (30%) has been observed for post-stroke depression 3 months after a stroke.127-129 According to a meta-analysis the prevalence of depression after a stroke was 29% and remains stable up to 10 years.130

Post-stroke depression is probably a combination of dysfunctional psychosocial adjustment after often catastrophic illness and neurobiological-pathological changes in the brain, where cerebral WMLs and infarcts interfere with frontostriatal and limbic pathways.131-133

Post-stroke depression is characterised by mild to moderate intensity.134 However, both post-stroke depression and depression-executive dysfunction syndrome (DES) are associated with increased mortality rates.135,136 Major depression increases the risk of
cardiovascular events, including ischaemic stroke. The association between cerebrovascular diseases and depression is suggested to be bidirectional.

Depression is independently related to stroke. If stroke as a cerebrovascular event can cause depression, this so-called post-stroke depression will further increase the risk of recurrent stroke over a defined period of time. Further, this effect will be augmented in patients with concurrent executive dysfunction. A similar interaction exists between dementia and depression after a stroke.

Identified risk factors for post-stroke depression are female sex, history of depression, stroke severity, physical disability, cognitive impairment, level of independence, and social support.

Reports on the association of lesion location with post-stroke depression reveal varying locations. Strategic lesions in different locations can cause post-stroke depression. Imaging markers of post-stroke depression are load of WML, cerebral microbleeds, large-volume lesions, multiple lesions, and atrophy. Post-stroke depression influences the recovery and outcome of a stroke in a negative way as depression interferes with the motivation for active rehabilitation. This connection again, is bidirectional, as immobility and disability are associated with a higher risk of post-stroke depression. Selective serotonin reuptake inhibitors (SSRIs) have been used for many years to manage depression. Recently, small trials have demonstrated that SSRIs might improve recovery after stroke, even in people who are not depressed. SSRIs appeared to decrease dependence, disability, neurological impairment, anxiety, and depression after stroke, but there was heterogeneity between trials and methodological limitations in a substantial proportion of the trials. Currently, the American Heart Association recommends the use of antidepressants for diagnosed post-stroke depression up to 6 months after recovery, although the use of SSRIs is known to be associated with falls, increased risk of haemorrhagic complications, increased risk of stroke, myocardial infarctions, and mortality. Large, well-designed trials are now needed to determine whether SSRIs should be routinely given to patients with stroke.

### 2.9 Depression-executive dysfunction syndrome

Alois Alzheimer describes the progressive arteriosclerotic degeneration of the brain:

… eine Erschwerung des Ablaufs der Auffassung vor, erst später kommt es zu einer gleichmäßig fortschreitenden Verblödung. Die Interessen verschwinden, die Stimmung ist meist leer, manchmal weinerlich. (…difficulty of the execution of understanding, later progressive dumbness. A lack of interest, an empty mood, sometimes sadness.)

In stroke patients, executive dysfunction is often associated with CSVD. The cardinal symptoms of depression-executive dysfunction syndrome (DES) occurring in later life are psychomotor retardation, limited depressive ideation, and lack of interest and insight.
Clinically, dysfunction of the frontostriatal pathways of the brain may present with both depression and executive dysfunction.\textsuperscript{152,153} This subtype of depression is often referred to as depression executive dysfunction syndrome (DES).\textsuperscript{132,151,154} DES is characterised by disturbances in sequencing, organising, planning, abstracting, reduced interest in activities, and psychomotor retardation, but there are less-pronounced vegetative symptoms than there are in depressed elderly patients without significant executive dysfunction.\textsuperscript{155} DES has been recognised as a core feature in vascular depression.\textsuperscript{151,156} A recent study showed, that vascular depression is associated with a transcranial Doppler ultrasound profile of low perfusion and high vascular resistance.\textsuperscript{157} The rise of the resistance probably reflects the end-organ damage, presumably in the small-vessel area with a decreased sum of vessel diameter. Vascular depression is characterised by older age, vascular risk factors, and vascular lesions, such as lacunae and cerebral WMLs that occur in small-vessel disease.\textsuperscript{151,154} Previous cerebrovascular attacks increase the risk of DES.\textsuperscript{158}

Executive dysfunction has shown to be a predictor of worse stroke outcome.\textsuperscript{159}

2.10 Falls, trauma, and hip fractures after ischaemic stroke

Falls after a stroke can be due to residual stroke symptoms, recurrent ischaemic events, or CSVD-related progressive gait disturbance. Between 55\% and 73\% of stroke patients have at least one fall within the first year after the stroke.\textsuperscript{160,161} Falls have even been considered one of the most common medical complications after a stroke,\textsuperscript{162,163} and the leading cause of injury-related deaths in the general elderly population.\textsuperscript{164} As a consequence, falls cause remarkable direct medical costs.\textsuperscript{164}

CSVD, and WMLs as a surrogate of CSVD, are associated with decreasing mobility, gait instability, and falls.\textsuperscript{85,86,165–167}

Only a few previous reports exist on the association of falls with WMLs. The LADIS study showed that patients with severe WMLs have impaired balance and typically have a history of twice as many falls as patients with only mild WMLs.\textsuperscript{85} The association of a higher rate of self-reported falls during 5 years with the presence of WMLs has been reported in a small case-control study with 29 patients and 29 control subjects.\textsuperscript{168} In another study with 820 community-dwelling people, WMLs represented an independent risk factor for hip fractures in persons younger than 80 years.\textsuperscript{169}

Both stroke and CSVD are associated with gait disturbance, leading to the hypothesis that surrogate markers of CSVD might be used to predict clinically significant falls.
2.11 Institutional care

2.11.1 Organisation of long-term care in Finland

Finland has a welfare system to secure the service to all, regardless of age or socio-economic status. Long-term care is mainly financed through taxation and provided by municipalities. The use of long-term care during the last 2 years of life among people 70 years of age and over is about 58% in Finland.\textsuperscript{170}

2.11.2 Permanent institutionalisation

Being strongly dependent on help and care on a daily basis is often considered an unfavourable outcome. In this study, we considered permanent institutionalisation as an unfavourable outcome for stroke patients. Besides the clinical aspect as an outcome measure, exploring institutional care is justified because of expected costs to society; for dementia alone, 0.6% of the UK gross domestic product is spent on institutional care yearly.\textsuperscript{101} The combination of post-stroke dementia and motor disability due to stroke can lead to high rates of institutionalisation. After a stroke 13–45% end up institutionalised.\textsuperscript{171–174} Prevention of stroke and better stroke outcomes would lower the institutionalisation rates. Strategies to identify subjects at high risk of institutionalisation are of interest in order to select patients for interventional trials that aim to prevent institutionalisation.\textsuperscript{175} A recent study from Canada reported long-term care or complex care rates after a stroke of 3.1% at 1 year, 6.6% at 3 years, and 9.6% at 5 years after the index stroke.\textsuperscript{24} Known predictors of institutionalisation after stroke are higher age and more severe strokes.\textsuperscript{176}

2.11.3 Dementia and institutionalisation

Dementia has been identified as the major risk factor for permanent institutionalisation in persons over 70 years old who already received home nursing.\textsuperscript{177} Dementia diagnosed 3 months after a stroke is associated with impaired survival,\textsuperscript{108} but whether the patients are home-dwelling or institutionalised after the stroke is not well known. In the USA, an expected 6.8% of the total direct costs of cerebrovascular diseases will be spent on nursing homes.\textsuperscript{178} With increasing life-expectancy and decreasing stroke mortality, the need for nursing home care might even rise. The risk of developing cognitive impairment and following dementia even after the first 3 months after ischaemic stroke remains increased,\textsuperscript{106,179} which leads to a higher risk of permanent institutionalisation.\textsuperscript{177} Furthermore, both stroke and dementia, are associated with decreased effectiveness and efficiency of rehabilitation.\textsuperscript{180}

Some modifiable risk factors of nursing home admission have already been identified among people with a specified dementia risk.\textsuperscript{181} Modifiable predictors of nursing home
admission were low physical activity, alcohol consumption, and smoking. All of those are also risk factors for stroke, and therefore, the chain of causality remains unclear. However, interventions dealing with modifiable risk-factors can reduce falls, hospital admissions, and nursing home admissions.

In a recent meta-analysis dementia and cognitive impairment were associated with a 2.14 (95% CI: 1.24–3.70) pooled odds ratio with permanent institutionalisation after acute hospitalisation.

The association of PSD with institutionalisation after stroke has been investigated in two studies. First, a national survey of all consecutive hospitalised patients with acute cerebrovascular disease hospitalised in Israel indicated a relative risk of 4.4 that demented patients are discharged to a nursing home, compared with those being sent home. In the prospective population-based registry of Dijon stroke patients were found to have an odds ratio of 5.21 (95% CI: 2.69–10.07) of being discharged to a nursing home instead of to rehabilitation if they were demented. Dementia was diagnosed with a simple standardised clinical approach based on the DSM-IV during the first month after the stroke.

While mortality from strokes has declined, the number of stroke survivors has increased. This results in a growing population of stroke survivors at risk for recurrent strokes, cognitive decline, dementia, falls and fractures due to gait instability, all of which could lead to permanent institutionalisation. One of three survivors of a recurrent stroke can be expected to be demented.

2.11.4 **White matter lesions and institutionalisation**

The international Leukoaraiosis and Disability in the Elderly (LADIS) study has shown that severe WMLs more than doubles the risk of transition from an autonomous to a dependent status in a 3-year follow-up.

The association of WMLs with increased disability and dependence in activities of daily living has been established before for older independent outpatients.

According to a recent review the association of WMLs with institutionalisation has not been investigated.

As the many clinical features of CSVD are known to be risk-factors of institutionalisation, it is worth testing whether the surrogate markers of CSVD could be used to predict institutionalisation in stroke patients.
2.12 Feature and outcomes of small-vessel disease

The connections of the features of CSVD and the outcomes of CSVD are illustrated in Figure 2.
3  **Aims of the study**

The aim of this thesis was, to investigate the features of CSVD and their association with long-term outcomes in ischaemic stroke patients:

I. WMLs as a surrogate for CSVD, have been shown to be associated with a major negative influence on cognition, mood and functioning in daily life. Are severe WMLs a risk factor for recurrent ischaemic stroke in long-term? (Study I)

II. Depression and depression-executive dysfunction syndrome are common neuropsychiatric consequences of stroke. We hypothesised that if stroke as a cerebrovascular event causes depression, this so-called post-stroke depression will further increase the risk of recurrent stroke. Do patients with PSD or depression-executive dysfunction syndrome have increased rates of stroke recurrence? (Study II)

III. Does PSD diagnosis after ischaemic stroke predict recurrent ischaemic stroke in long-term follow-up? (Study III)

IV. WMLs have been shown to be associated with decreasing mobility, gait instability, and falls. Are WMLs in stroke patients associated with increased incidence of hospital admissions because of trauma or hip fractures? (Study IV)

V. WMLs are associated with increased morbidity and mortality in both the general population and in ischaemic stroke patients. Are severe WMLs in ischaemic stroke patients associated with fewer days spent at home or earlier permanent institutionalisation? (Study V)

VI. Dementia is among the most frequent causes of institutionalisation. Is the institutionalisation rate higher or the length of stay in an institutional care facility longer in patients with PSD compared with stroke patients without dementia? (Study VI)
4 Materials, subjects, and methods

All six publications were conducted as part of the Helsinki Stroke Aging Memory (SAM) study.

4.1 Subjects and study protocol

The Helsinki SAM study cohort consists of 1622 consecutive patients with suspected stroke admitted to the Helsinki University Central Hospital between 1 December 1993 and 30 March 1995. All subjects were Finnish/Caucasian. Patients without ischaemic stroke (n=175), intra-cerebral (n=229), or subarachnoid (n=69) haemorrhage were excluded. We further excluded patients younger than 55 years (n=258) or older than 85 years (n=88), those not living in Helsinki (n=158), and those not speaking the Finnish language (n=3). Of the 642 patients initially meeting the inclusion criteria and invited to a baseline visit 3 months post-stroke, 71 (11.1%) had died before the visit, 82 (12.8%) refused, and 3 patients were lost to follow-up due to an unknown cause. The final SAM cohort consisted of 486 patients.189,190
Figure 3: Patient flow in the Helsinki Stroke Aging Memory study

In the whole cohort, there were 98 patients with a previous stroke. None had a recurrent stroke between the index stroke and the 3-month follow-up visit. The Ethics committee of the Department of Clinical Neuroscience, Helsinki University Central Hospital in Finland approved the study. The study was explained to the patients, and informed consent was obtained.

The detailed medical and neurological history has been described in many publications of the SAM study. The patients’ level of education was dichotomised into low, with 0–6 years of formal education, and high, with >6 years of formal education. Smoking habits before the index stroke were categorised on admission as non-smokers or smokers.
Smokers included current and former smokers. All available hospital records were reviewed to collect cardiac risk factors (myocardial infarction, cardiac failure, atrial fibrillation), arterial hypertension, peripheral arterial disease, and diabetes. Those were rechecked by a structured interview of the subject and a knowledgeable informant. Hypertension was defined as the time of study inclusion as systolic blood pressure $\geq 160$ mmHg and/or diastolic blood pressure $\geq 95$ mmHg. Diabetes was defined as current use of insulin or oral antidiabetic medication, or fasting blood glucose $>7.0$ mmol/L, or previously documented diagnosis of diabetes. To categorise the stroke severity, the modified Rankin Scale (mRS) was used.\textsuperscript{191}

### 4.2 Brain-scan analysis

Brain CT scan was done as part of the clinical routine for all patients at the acute phase. An MRI scan was intended per protocol for all patients at 3 months after the index ischaemic stroke. In 63 patients MRI was not done because of severe illness (n=12), obesity (n=1), refusal (n=21), claustrophobia (n=2), or contraindication (n=27). MRI was performed with 1.0 T imaging equipment (Siemens Magnetom).\textsuperscript{190}

The imaging parameters, as previously described in detail, were as follows: The spin echo technique was used for transaxial T2-, PD-, and T1-weighted images. The repetition time (TR) for T2- and PD-weighted images was 3000 milliseconds, echo time (TE) 15–90 milliseconds, and number of excitations (NEX) 1. The corresponding parameters for T1-weighted images were TR/TE/NEX 400/15/2. The slice thickness was 5 mm, gap 0, field of view 230 mm, matrix size 256x256 pixels and number of slices 26 on every pulse sequence. In addition, a three-dimensional gradient echo TR/TE/alpha/NEX 30/5/40/1 - sequence with 65 coronal sections was used, with a thickness of 3 mm.\textsuperscript{190}

A neuroradiologist blinded to the clinical data reviewed all MR-images. WMLs were rated on PD-weighted images in accordance with the LADIS (Leukoaraiosis and Disability in the Elderly) WML rating, as clarified in the following table.\textsuperscript{188}

**Table 5: WML rating on MRI**

<table>
<thead>
<tr>
<th>WML rating</th>
<th>Periventricular lesions</th>
<th>Other white matter areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>None-to-mild</td>
<td>no more than small cap or thin lining</td>
<td>nothing except large focal lesions</td>
</tr>
<tr>
<td>moderate</td>
<td>nothing except large cap and smooth halo</td>
<td>nothing except focal confluent lesions</td>
</tr>
<tr>
<td>severe</td>
<td>extending caps or irregular halo</td>
<td>diffusely confluent lesions or extensive WMLs</td>
</tr>
</tbody>
</table>

33
A good intra- and interobserver reliability for rating basic WMLs in periventricular and other white matter areas has previously been found (weighted kappa 0.72 to 0.95).\textsuperscript{190,192,193}

4.3 Depression

At 12 to 20 weeks after the index stroke, the clinical psychiatric evaluation was carried out as described in many previous publications.\textsuperscript{194} The examination included the computer-assisted structured interview Schedules for Clinical Assessment in Neuropsychiatry.\textsuperscript{195} The Montgomery-Åsberg Depression Rating Scale was used to evaluate the severity of depression. The final diagnosis of depression, according to the Diagnostic and Statistical Manual of Mental Disorders revised 3rd edition (DSM-III-R; APA, 1987) was based on all data from the clinical psychiatric examination, interviews with the close informants (when possible), psychiatric rating scales, and the Schedules for Clinical Assessment in Neuropsychiatry. A senior psychiatrist examined 220 patients, and he also subsequently supervised the data entry for the 37 patients examined by a resident psychiatrist.

4.4 Neuropsychological evaluation

The comprehensive neuropsychological evaluation at 3 months after the index stroke has previously been described in detail.\textsuperscript{196} The Mini Mental Status Examination (MMSE) was used to estimate the global cognitive function with a score of ≤25 indicating cognitive impairment. Executive functions including attention were evaluated in 365 patients using the Trail Making Test,\textsuperscript{197} Stroop colour naming test,\textsuperscript{198} the Digit span subtest of the Wechsler Memory Scale,\textsuperscript{199} the modified Wisconsin Card Sorting Test,\textsuperscript{200} and the verbal fluency test.\textsuperscript{200} The memory functions were evaluated in 379 patients using the Logical memory and Visual reproduction subtests of the revised Wechsler Memory Scale,\textsuperscript{201} and the Fuld Object Memory Evaluation.\textsuperscript{202} For the language evaluation of 395 patients, the short version of the Token Test,\textsuperscript{203} the Boston Naming Test,\textsuperscript{204} and the Verbal fluency test were used.\textsuperscript{200} The overall evaluation of the speech functions in 395 patients was done, using the Boston Diagnostic Aphasia Examination.\textsuperscript{205} Visuospatial and constructional abilities were tested in 391 patients with the Block design subtest of the revised Wechsler Adult Intelligence Scale,\textsuperscript{206} the clock-drawing test,\textsuperscript{207} and the following tests: copy a triangle, a flag, a three-dimensional cube, a Greek cross.\textsuperscript{208} Normative data from a random healthy Finnish population divided into different age groups was used to determine abnormality (impaired vs. not impaired) in each domain (2 SD or, if more than one test was used, 1 SD below the level of the norm in several tests indicated abnormality).\textsuperscript{209}
4.5 Dementia and pre-stroke cognitive decline

Using the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) criteria, dementia was diagnosed in 115 (25.5%) patients. A neurologist assessed the following mental status examination domains: attention; orientation; memory recall; executive functions including abstract thinking, judgment, and problem solving; aphasia; apraxia; agnosia; motor control; constructional and visuospatial abilities; and personality change.\textsuperscript{210} A Folstein Mini Mental Status Examination (MMSE) was performed.\textsuperscript{211} In addition, the following assessments of functioning were performed: index of activities of daily living,\textsuperscript{212} the instrumental activities of daily living scale,\textsuperscript{213} the Functional Activity Questionnaire,\textsuperscript{214} the Blessed Functional Activity Scale,\textsuperscript{215} and the Barthel Index.\textsuperscript{216} Assessment of pre-stroke cognitive decline involved interviews with the patient and a knowledgeable informant.\textsuperscript{217} Structured questions on abnormality in the cognitive domains and of social functions before the index stroke were included. The neurologist asked for the start date of the symptoms and their duration, focusing especially on the period 1 year before the index stroke. A board-certified neurologist independently judged whether the patient had had pre-stroke cognitive decline or not. Patients with pre-stroke cognitive decline included those with borderline or definite dementia. Cognitive impairment without dementia (CIND) was defined as cognitive impairment in any of the above-mentioned domains after the exclusion of patients with dementia, as described previously.\textsuperscript{88}

4.6 Long-term follow-up

Patients were followed 21 years, up to 6 May 2015, using extensive national registers kept by the National Institute for Health and Welfare and the City of Helsinki, Bureau of Social Welfare. All hospital treatment periods until 21 September 2006 were acquired from the National Care Register, and the register of the City of Helsinki contains all nursing home periods and official long-term care decisions. The period of 2006 until 18 January 2015 (Study V) and 6 May 2015 (Study VI) was reviewed from the hospitals’ and the districts’ electronic charts. We pooled the information into two parameters: days spent at home before 21 September 2006 and time to permanent institutionalisation with follow-up until 6 May 2015. Permanent institutionalisation was chosen as an outcome measure of disability and dependency. A patient was considered to be permanently institutionalised when residing for more than two months in a nursing home or hospital at the end of the study or time of death. A cross-check was performed by reviewing the official long-term care decisions until 2006 and from hospital and healthcare charts after 2006. The national ward register contains ICD-9 and ICD-10 diagnosis codes of all hospital treatment periods. ICD-9 codes 820 and 821 and ICD-10 codes S72.0–S72.9, were considered as hip fracture. ICD-9 codes 800–957 and ICD-10 codes S00.0–T14.9 were considered as traumatic injuries. ICD-9 codes 433 and 434 and
ICD-10 codes I63.0–I63.9 were considered as ischaemic stroke. Survival data and causes of death were obtained from Statistics Finland. Patients who had died from brain infarction without registered hospital treatment were considered to have had a fatal recurrent stroke.

4.7 Permanent institutionalisation

Permanent institutionalisation was chosen as an outcome measure of disability and dependency. A patient was considered to be permanently institutionalised when residing for more than two months in a nursing home or hospital at the end of the study or time of death. A cross-check was performed by reviewing the official long-term care decisions until 2006 and from hospital and healthcare charts after 2006.

4.8 Statistical analysis

For the Study I, the statistical analyses were performed by Susanna Melkas (MD) using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). For studies II–VI, the statistical analyses were performed by Sami Curtze (PhD, MD, MSc) and Gerli Sibolt (MD, MSc) using SPSS 20 (Study II+III), 22 (Study IV+V), and 23 (Study VI) for Linux (IBM Corp., Armonk, NY, USA). Table 6 displays a summary of the statistical methods used in the studies. The parameters compared with log-rank analysis are listed in Table 7. Multivariate Cox regression proportional hazards analysis with forced entry was used in all studies, and compared parameters are summarised in Table 8.

Table 6: Summary of the statistical methods used in the studies

<table>
<thead>
<tr>
<th>Study</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson’s chi-squared test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Mantel-Haenszel test</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>One-way ANOVA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Binary logistic regression</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Levene’s test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Significance cut-off p-value: &lt;0.05</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Kaplan-Meier log-rank analysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Life table function cumulative recurrence risks and their 95% confidence intervals (CI). Patients who died from causes other than recurrent ischaemic stroke were considered censored.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Multivariate Cox regression proportional hazards analysis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Proportional hazards assumption tested and met</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
**Study V:** For days spent at home below median and permanent institutionalisation within 5 years after index stroke the same covariates were analysed in univariable logistic regression models. The probability for variable entry in the multivariable models was set at $p<0.10$. To allow comparison to the study of Brodaty,$^{171}$ we also analysed permanent institutionalisation within 5 years.

*Table 7: Parameters compared with log-rank analysis*

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>effect of WMLs on the time to first stroke recurrence</td>
</tr>
<tr>
<td>Study II</td>
<td>time to first recurrent stroke for post-stroke depression</td>
</tr>
<tr>
<td>Study III</td>
<td>post-stroke dementia on the time to first recurrent stroke</td>
</tr>
<tr>
<td>Study IV</td>
<td>WMLs on the time to first hip fracture</td>
</tr>
<tr>
<td></td>
<td>WMLs on the time to admission to hospital due to traumatic injuries.</td>
</tr>
<tr>
<td>Study V</td>
<td>severe WMLs and days spent at home</td>
</tr>
<tr>
<td></td>
<td>severe WMLs and time to permanent institutionalisation</td>
</tr>
<tr>
<td>Study VI</td>
<td>post-stroke dementia and time to permanent institutionalisation</td>
</tr>
</tbody>
</table>
Table 8: Multivariate Cox regression proportional hazards analysis with forced entry

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>Model 1: The association of WMLs on the occurrence of a recurrent stroke was analysed with the potential predictors of age, sex, and years of education. Model 2: Selected variables from the medical history that were associated with stroke recurrence in the Kaplan-Meier analysis were added to the previous model. Collinear covariates, such as dementia in relation to WMLs, were excluded from the model. To estimate the predictive value of severe WMLs for stroke recurrence, a receiver operating characteristic (ROC) test was used.</td>
</tr>
<tr>
<td>Study II</td>
<td>Age, sex, hypertension, atrial fibrillation, hypercholesterolaemia, diabetes, peripheral arterial disease, smoking status. The same model was calculated separately for depression, executive dysfunction, and for DES due to existing collinearity.</td>
</tr>
<tr>
<td>Study III</td>
<td>Variable selection for multivariable regression was done by checking the predictive value of confounders used in previous studies (age, gender, education, smoking status, atrial fibrillation, peripheral arterial disease, hypertension, and diabetes) towards recurrent stroke using a log-rank test with p&lt;0.2. Additionally, we analysed WMLs dichotomised as none to mild versus moderate-to-severe due to their association with CSVD. Three different Cox models were created, separately for PSD and WMLs and a third including both PSD and WMLs.</td>
</tr>
<tr>
<td>Study IV</td>
<td>For the association between WMLs on MRI and traumatic injuries or hip fractures, a complex multivariate Cox regression proportional hazards analysis for multiple cases per subject with forced entry was used to calculate hazard ratios (HR) with their 95% CIs adjusted for gender and age.</td>
</tr>
<tr>
<td>Study V</td>
<td>The association between potential covariates (age in years, sex, mRS, status of living alone at recruitment, and history of education in years, smoking, myocardial infarction, cardiac failure, atrial fibrillation, arterial hypertension, peripheral arterial disease, diabetes, pre-stroke cognitive decline, PSD and severe WMLs) and institutionalisation was analysed in Cox-regression proportional hazards models. The probability for variable entry in the multivariable models was set at p&lt;0.10.</td>
</tr>
<tr>
<td>Study VI</td>
<td>The association between potential covariates (age in years, sex, mRS, status of living alone at recruitment, and history of education in years, smoking, myocardial infarction, cardiac failure, atrial fibrillation, arterial hypertension, peripheral arterial disease, diabetes, pre-stroke cognitive decline, and PSD) and institutionalisation in the 21-year follow-up was analysed in Cox-regression proportional hazards models. The probability for variable entry in the multivariable models was set at p&lt;0.10.</td>
</tr>
</tbody>
</table>

4.8.1 Study I

A binary logistic regression function was used to compare the dichotomous variables. Kaplan-Meier log-rank analysis was used to analyse the effect of WMLs on the time to first stroke recurrence. The actuarial cumulative recurrence risks with 95% confidence
intervals (CI) was calculated using a life-table function. Patients were censored if they had died from causes other than recurrent ischaemic stroke. The proportional hazards assumption was met for each parameter included in further models when using the cumulative hazard function. Two forced entry multivariate Cox regression proportional hazards analysis were constructed to account for potential confounders and to estimate the predictive value of different factors. Model 1: The association of WMLs on the occurrence of recurrent stroke was analysed with the potential predictors of age, sex, and years of education. Model 2: Selected variables from the medical history that were associated with stroke recurrence in the Kaplan-Meier analysis were added to the previous model. Collinear covariates, such as dementia in relation to WMLs, were excluded from the model. To estimate the predictive value of severe WMLs for stroke recurrence, a receiver operating characteristic (ROC) test was used.

4.8.2 Study II

Binary logistic regression functions were used to analyse the association between post-stroke depression, DES, recurrence of stroke, demographics, and risk factors. Kaplan-Meier charts and log-rank analysis were used to analyse the time to first recurrent stroke for post-stroke depression, DES, and other patient groups. The cumulative recurrence risks and their 95% CI were calculated using the life table function. Patients who died from causes other than recurrent stroke were considered censored. The cumulative hazard function was plotted and checked to ensure that the proportional hazards assumption was met for each parameter included in further models. A multivariate Cox regression proportional hazards analysis with forced entry of the following well-known risk factors for ischaemic stroke was used: age, sex, hypertension, atrial fibrillation, hypercholesterolaemia, diabetes, peripheral arterial disease, and smoking status. The same model was calculated separately for depression, executive dysfunction, and for DES due to existing collinearity.

4.8.3 Study III

A binary logistic regression function was used to analyse the association between dementia, demographics, and risk factors. Levene’s test was used to assess the equality of variance of age. Kaplan-Meier log-rank analysis was used to evaluate the impact of post-stroke dementia on the time to first recurrent stroke. The cumulative recurrence risks and their 95% CIs were calculated using the life table function. Patients who died from causes other than recurrent ischaemic stroke were considered censored. The cumulative hazard function was plotted and checked that the proportional hazards assumption was met for each parameter included in further models.

Variable selection for multivariable regression was done by checking the predictive value of confounders used in previous studies (age, gender, education, smoking status, atrial fibrillation, peripheral arterial disease, hypertension, and diabetes) towards recurrent
stroke using a log-rank test with \( p < 0.2 \). Additionally, we analysed WMLs dichotomised as none to mild versus moderate-to-severe due to their association with SVD. A multivariable model with forced entry was used to check the predictive value of these variables for post-stroke dementia because variables predicting PSD might cause a collinearity problem towards recurrent stroke. A multivariate Cox regression proportional hazards analysis with forced entry of significant confounders was used.

4.8.4 Study IV

A binary logistic regression function was used to analyse the association between the grade of WMLs, hip fractures, traumatic injuries, demographics, and risk factors. Kaplan-Meier log-rank analysis was used to evaluate the impact of WMLs on the time to first hip fracture or admission to hospital due to traumatic injuries. The cumulative recurrence risks and their 95% CI were calculated by using the life table function. Patients who died from causes other than hip fracture or traumatic injuries were considered censored. The cumulative hazard function was plotted and checked that the proportional hazards assumption was met for each parameter included in further models. WMLs were dichotomised as none-to-mild versus moderate-to-severe. The association of known risk factors (age, gender, atrial fibrillation, hypertension, diabetes, smoking status, and low education) with moderate-to-severe WMLs on MRI were analysed using a binary multivariable model with forced entry. For the association between WMLs on MRI and traumatic injuries or hip fractures, a complex multivariate Cox regression proportional hazards analysis for multiple cases per subject with forced entry was used to calculate hazard ratios (HR) with their 95% CIs adjusted for gender and age.

4.8.5 Study V

The association between severe WMLs and days spent at home, as well as the association between severe WMLs and time to permanent institutionalisation, was first analysed using Kaplan-Meier log-rank analysis. The cumulative hazard function was plotted and checked to ensure that the proportional hazards assumption was met for each parameter included in further models. Permanent institutionalisation within 5 years was also analysed to compare it with the study of Brodaty.\(^{171}\) The association between potential covariates (age in years, sex, mRS, status of living alone at recruitment, and history of education in years, smoking, myocardial infarction, cardiac failure, atrial fibrillation, arterial hypertension, peripheral arterial disease, diabetes, pre-stroke cognitive decline, PSD and severe WMLs) and institutionalisation was analysed in Cox-regression proportional hazards models. For days spent at home below median and permanent institutionalisation within 5 years after index stroke, the same covariates were analysed in univariable logistic regression models. The probability for variable entry in the multivariable models was set at \( p < 0.10 \).
4.8.6 Study VI
The association between post-stroke dementia and time to permanent institutionalisation was first analysed using the Mantel-Haenszel test and Kaplan-Meier log-rank analysis. The cumulative hazard function was plotted and checked to ensure that the proportional hazards assumption was met for each parameter included in further models. The association between potential covariates (age in years, sex, mRS, status of living alone at recruitment, and history of education in years, smoking, myocardial infarction, cardiac failure, atrial fibrillation, arterial hypertension, peripheral arterial disease, diabetes, pre-stroke cognitive decline, and PSD) and institutionalisation in the 21-year follow-up was analysed in Cox-regression proportional hazards models. The probability for variable entry in the multivariable models was set at p<0.10.

5 Results
<table>
<thead>
<tr>
<th>Variable</th>
<th>Study VI</th>
<th>Study V</th>
<th>Study IV</th>
<th>Study III</th>
<th>Study II</th>
<th>Study I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>(66-77)</td>
<td>(65-77)</td>
<td>(66-77)</td>
<td>(66-77)</td>
<td>(66-77)</td>
<td>(66-77)</td>
</tr>
<tr>
<td>Female sex</td>
<td>50.7%</td>
<td>51.4%</td>
<td>49.0%</td>
<td>48.0%</td>
<td>48.0%</td>
<td>50.3%</td>
</tr>
<tr>
<td>Low education (≤6 yr)</td>
<td>30.0%</td>
<td>29.9%</td>
<td>30.9%</td>
<td>29.0%</td>
<td>31.2%</td>
<td>39.4%</td>
</tr>
<tr>
<td>Severe stroke (mRS 3-5)</td>
<td>33.2%</td>
<td>35.2%</td>
<td>33.2%</td>
<td>32.4%</td>
<td>32.4%</td>
<td>39.4%</td>
</tr>
<tr>
<td>Smoking (current/former)</td>
<td>48.3%</td>
<td>50.1%</td>
<td>49.8%</td>
<td>52.5%</td>
<td>50.3%</td>
<td>50.3%</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>19.0%</td>
<td>18.5%</td>
<td>20.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>17.8%</td>
<td>18.3%</td>
<td>19.1%</td>
<td>19.3%</td>
<td>19.4%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>21.3%</td>
<td>20.9%</td>
<td>21.6%</td>
<td>17.5%</td>
<td>20.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>18.6%</td>
<td>18.8%</td>
<td>18.9%</td>
<td>18.4%</td>
<td>20.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>47.3%</td>
<td>48.0%</td>
<td>47.5%</td>
<td>44.4%</td>
<td>47.2%</td>
<td>47.2%</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>11.2%</td>
<td>11.5%</td>
<td>11.8%</td>
<td>12.6%</td>
<td>12.8%</td>
<td>12.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>23.4%</td>
<td>23.8%</td>
<td>24.6%</td>
<td>23.8%</td>
<td>23.8%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>16.8%</td>
<td>17.1%</td>
<td>16.4%</td>
<td>16.6%</td>
<td>16.6%</td>
<td>16.6%</td>
</tr>
</tbody>
</table>
5.1 White matter lesions and the recurrence of stroke (Study I)

Mean age of the 320 included patients was 70.8 ± 7.7 years, 50.3%. There were 161 female patients, and 31.2% had less than 6 years of formal education (98/312). Current or former smoking was the most frequent stroke risk factor in 50.3% (161/318) of patients, followed by arterial hypertension in 47.2% (151/320), diabetes in 23.8% (76/320), cardiac failure in 20.7% (66/319), atrial fibrillation in 20.7% (66/319), and peripheral arterial disease in 12.8% (41/320).

![Sankey diagram](image)

*Figure 4: Sankey diagram of patients according to white matter lesions (WMLs) and stroke recurrence 5 years after first-ever ischaemic stroke. The number of patients within the cohort is indicated next to the description of each sub-cohort. The width of the flow-bars is shown proportionally to the flow quantity.*

The occurrence of severe and none-to-moderate WMLs within the group of patients with recurrent ischaemic stroke within the 5-year follow-up after index stroke and for
patients with no recurrent stroke is shown in Figure 4. None-to-moderate WMLs appeared in 49.4% (158/320) of the patients, and severe WMLs were found in 50.6% (162/320) of the patients.

Only age was associated with severe WMLs in binary logistic regression analyses (OR 1.10, 95% CI 1.06–1.14, p<0.001). During the first 5 years after the index stroke, at least one recurrent fatal or nonfatal ischaemic stroke had been diagnosed in 76 (23.8%) patients. After 12 years of follow-up, 127 (39.7%) patients had suffered at least one recurrent ischaemic stroke. Five patients had suffered a haemorrhagic stroke (intracerebral haemorrhage in all cases) as the first recurrent event and 4 patients after a recurrent ischaemic event. Due to the low number, no statistical analysis could be performed for the haemorrhagic strokes.

Figure 5: Cumulative recurrence risks of ischaemic stroke stratified by none-to-moderate and severe WMLs.

The risk of stroke recurrence was significantly higher in patients with severe WMLs compared with patients with none-to-moderate WMLs (log-rank test, p=0.004). The
cumulative recurrence risk at 12 years was 48.1% (CI 45.5–50.7%) for none-to-moderate WMLs and 60.9% (CI 56.7–65.1%) for severe WMLs (log rank test p=0.004). The recurrence of an ischaemic stroke was independently associated with severe WMLs at 5 years (HR 1.80, 95% CI 1.11–2.95, p=0.018). Other associated factors were atrial fibrillation, hypertension, and peripheral arterial disease. However, at 12 years, only age remained independently associated (HR 1.04, 95% CI 1.02–1.07; p=0.002).

5.2 Post-stroke depression, depression-executive dysfunction, and recurrence of ischaemic stroke (Study II)

During 1500 patient-years, 85 patients suffered their first recurrent stroke. The first recurrent stroke occurred earlier for the group of depressed patients compared to their non-depressed counterparts (8.15 years; 7.11–9.19 versus 9.63 years; 8.89–10.38). The mean time to first recurrent stroke was shorter still for DES patients (7.15 years; 5.55–8.75) compared to non-DES patients (9.75 years; 9.09–10.41).

The cumulative recurrence risk of ischaemic stroke during the 12-year follow-up was higher in patients with depression (log-rank p=0.04) than in those without depression. In a Cox multivariable regression model, depression was associated with first recurrent ischaemic stroke in the 12-year follow-up (HR 1.68, 95% CI 1.07–2.63).

Patients with executive dysfunction (log-rank p=0.02) and DES (log-rank p<0.01) had higher rates of recurrent ischaemic stroke than the patients without these syndromes. Executive dysfunction alone was not clearly associated with first recurrent ischaemic stroke in the 12-year follow-up after adjustments in a Cox multivariable regression model (HR 1.47, 95% CI 0.92–2.35).

In all models older age was associated with earlier stroke recurrence during the 12-year follow-up in the Cox multivariable analyses (HR 1.05, 95% CI 1.01–1.08). Hypercholesterolaemia was associated with later recurrence of ischaemic strokes (HR 0.24, 95% CI 0.09–0.59). While executive dysfunction alone, was not significantly associated after adjustment (HR 1.47, 95% CI 0.92–2.35), a faster recurrence of ischaemic stroke could be observed for DES (HR 1.95, 95% CI 1.14–3.33). Unfortunately the number of DES patients in this cohort was too small to do further subgroup analyses.

5.3 Post-stroke dementia and recurrent ischaemic stroke (Study III)

In Study III, the total follow-up was 3022 person-years. During this follow-up, 201 patients (41.4%) suffered from at least one non-fatal or fatal recurrent ischaemic stroke. After 12 years of follow-up, 132 patients from the whole cohort (27.2%), but only 15 (13%) in the PSD group, were alive. Only 4 (3.5%) had survived a recurrent stroke. Of the
117 non-demented survivors, 26 (22.2%) had survived at least one recurrent stroke. Median follow-up was 5.4 years (interquartile range 2.4–11.0) until recurrent stroke or the end of the study. Among all patients, and in the first-ever stroke group, the mean age of non-demented patients was lower than that of demented patients (70.4 vs. 72.9 years; p<0.01 and 70.3 vs. 73.2 years; p<0.01, respectively). The stroke recurrence rates for different stroke causes are listed in Table 9. The criteria for the classification of stroke causes in large-artery atherosclerosis (LAA), small-vessel disease (CSVD), cardioembolism (CE), and other cause (OC) are consistent with those used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST). The exact frequencies of vascular imaging and echocardiography in the cohort are not known, but these frequencies were consistent with the clinical praxis at the time of the initial recruitment, when the availability of investigations did not match those available today. More detailed information on classification in this study has been published before.11

Table 10: Stroke causes and stroke recurrence rates for 115 patients with PSD and for 336 patients with no PSD with ischaemic stroke. All values are n (valid column %). PSD was diagnosed 3 months after index stroke. The first recurrent stroke (RS) after index stroke was followed up for 12 years.

<table>
<thead>
<tr>
<th>All strokes</th>
<th>First-ever stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PSD</td>
<td>RS</td>
</tr>
<tr>
<td>CSV D</td>
<td>45 (13.4%)</td>
</tr>
<tr>
<td>LAA</td>
<td>64 (19.0%)</td>
</tr>
<tr>
<td>CE</td>
<td>24 (7.1%)</td>
</tr>
<tr>
<td>OC</td>
<td>203 (60.4%)</td>
</tr>
</tbody>
</table>

In the whole series, PSD patients had a shorter mean time to recurrent stroke (7.13 years; 95% CI 6.20–8.06) than patients without dementia (HR 9.41; 95% CI 8.89–9.92) in Kaplan-Meier log-rank analysis.

When the analyses were limited to patients with first-ever stroke, the time to recurrent stroke was 6.89 (5.85–7.93) years for patients with PSD and 9.68 (9.12–10.24) years for non-demented patients. Recurrent stroke occurred significantly earlier in patients suffering from atrial fibrillation (p=0.02), peripheral arterial disease (p=0.03), and cognitive impairment before stroke (p<0.01).

In Cox univariate analysis, PSD was associated with increased risk for recurrent stroke both in the entire cohort (hazard ratio 2.02; 1.47–2.77) and in those with first-ever stroke (2.40; 1.68–3.42). CIND compared with non-demented post-stroke patients did not significantly predict recurrent stroke (1.49; 0.92–2.41). Variable selection for multivariable regression was done by checking the predictive value of plausible
confounders (age, sex, smoking status, atrial fibrillation, peripheral arterial disease, hypertension, diabetes, and WMLs) for recurrent stroke using the log-rank test with p<0.2 as a selection criterion. Sex, smoking status, and diabetes did not predict recurrent stroke and were therefore excluded from the model. Low education and cognitive impairment before the incident stroke were associated significantly with PSD using a Mantel-Haenszel common odds ratio estimate and in multivariable logistic regression models and were therefore excluded from the Cox regression model due to potential collinearity.

As WMLs are strongly associated with dementia,\textsuperscript{82} collinearity might be suspected with PSD diagnosis. Therefore, three different Cox models were created, separately for PSD and WMLs and a third including both PSD and WMLs. The proportions of severe WMLs versus not severe WMLs are illustrated in Figure 6.

In Cox multivariable regression adjusting for age, atrial fibrillation, peripheral arterial disease, and hypertension, only age (HR 1.07 per year; 95% CI 1.04–1.09) and PSD (HR 1.84; 95% CI 1.34–2.54) were associated with increased risk for recurrent stroke in the entire cohort (see Figure 7). In first-ever stroke patients, age (HR 1.06 per year; 95% CI 1.03–1.08) and PSD (HR 2.16; 95% CI 1.51–3.10) were associated with recurrent stroke. CIND as compared with non-demented stroke patients did not predict recurrent stroke (HR 1.42; 95% CI 0.87–2.32) after Cox multivariable adjustment.
Figure 6: Sankey diagram of patients according to WMLs and status of PSD 3 months after first-ever ischaemic stroke. The number of patients within the cohort is indicated next to the description of each sub-cohort. The width of the flow-bars is shown proportionally to the flow quantity.
5.4 White matter lesions and trauma (Study IV)

There were 44 patients with first ever hip fractures after the index stroke. Of those 8 suffered a second and 1 had a third hip fracture during the 12-year follow-up. There were 50 additional hospital admissions due to trauma other than hip fracture during the follow-up.

The mean length of hospital stay due to hip fracture was 63 days for patients with moderate-to-severe WMLs and only 21 days for patients with none-to-mild WMLs. First hip fractures occurred in 6.5% (7/108) of the none-to-mild WMLs group and in 13.5% (37/275) of the moderate-to-severe WMLs group (p=0.05).
Figure 8: Sankey diagram of patients according to WMLs and first hip fracture during the 12-year follow-up. The number of patients within the cohort is indicated next to the description of each sub-cohort. The width of the flow-bars is shown proportionally to the flow quantity.

During the 12-year follow-up, more first-ever hip fractures after ischaemic stroke occurred in the moderate-to-severe WMLs group as compared to the none-to-mild WMLs group (log-rank p=0.013). In addition, more hospital admissions due to traumatic injury including hip fractures occurred in the moderate-to-severe WMLs group as compared to the none-to-mild WMLs group (log-rank p=0.041).
In the complex samples, a Cox multivariable model adjusting for age, gender, the National Institutes of Health Stroke Scale (NIHSS), infarct size over 60 mm, and PSD, moderate-to-severe WMLs were associated with increased incidences of hospital admissions due to hip fractures (HR 3.98; 95% CI 1.55–10.21) and traumatic injuries including hip fractures (HR 1.72; 95% CI 1.03–2.87).

5.5 White matter lesions and institutionalisation (Study V)

All patients had mRS 0 before the index stroke. Stroke severity at inclusion was as follows: 10 with mRS 5, 56 with mRS 4, 77 with mRS 3, 101 with mRS 2, and 147 with mRS 1.

The 391 patients from Study V spent 96170 days (263 years, 10.8%) in the hospital and 790982 days (2167 years, 89.2%) at home during the follow-up (887152 days, 2430 patient-years) before 21 September 2006. The median number of days in hospital was 110, with a mean 246 days during this follow-up period. Days spent at home after index stroke until 21 September 2006, death or permanent institutionalisation was a median of 1837, with a mean 2023 days. While patients with none-to-moderate WMLs spent 91.6%, those with severe WMLs spent only 86.8% (p=0.003) of the follow-up time at home.

In univariable analysis, patients with severe WMLs spent less time at home compared to those with none-to-moderate WMLs when the time was dichotomised at the median of the whole cohort (OR 2.13, 95% CI 1.42–3.20). Severe WMLs remained associated with days spent at home below median compared with the none-to-moderate WMLs (OR 1.62, 95% CI 1.16–2.25) after adjusting for significant predictors in univariate analyses. At 5-years, 93 (23.8%) patients were institutionalised. At 5 years 71 patients (33.5%) with severe WMLs and 22 (12.3%) patients with none-to-moderate WMLs ended up in institutional care (OR 3.60, 95% CI=2.12–6.10). Severe WMLs were associated with higher rates of institutionalisation within 5 years compared to none-to-moderate WMLs (HR 2.29, 95% CI 1.23–4.29) in a logistical regression model adjusting for age, education, status of living alone at baseline, mRS at 3 months, and history of atrial fibrillation, cardiac failure, PSD, and pre-stroke cognitive decline. Age and mRS were also associated with higher rates of institutionalisation within 5 years.

After 21 years, the patients’ mean and median follow-up times were 8.88 and 7.84 years (SD 6.01), adding up to 3470 patient-years. During the 21 year follow-up, 195 (49.9%) patients were permanently institutionalised and 196 (50.1%) patients were living at home at the end of follow-up or when deceased. Before the end of the follow-up, 122 patients (57.5%) with severe WMLs compared to 73 (40.8%) patients with none-to-moderate WMLs (OR 1.97, 95% CI=1.31–2.95) were permanently institutionalised.
Figure 9: Sankey diagram of patients according to WMLs and institutionalisation during the 21-year follow-up. The number of patients within the cohort is indicated next to the description of each sub-cohort. The width of the flow-bars is shown proportionally to the flow quantity.

Severe WMLs were associated with higher rates of institutionalisation compared to none-to-moderate WMLs (HR 1.64, 95% CI 1.119–2.26) in a Cox regression model adjusting for age, education, status of living alone at baseline, mRS at 3 months, history of atrial fibrillation, cardiac failure, PSD, and pre-stroke cognitive decline. Age, status of living alone at baseline, and mRS were also associated with days spent at home below median (see Table 3). The estimated median time from index stroke to permanent institutionalisation (limited to largest survival time if it is censored) was shorter for patients with severe WMLs compared to those with none-to-moderate WMLs (8.76 years; 95% CI 6.52–10.99 versus 17.12 years; 95% CI 13.17–21.07; log-rank <0.001).
5.6 Post-stroke dementia and institutionalisation (Study VI)

After 21 years the patients’ mean and median follow-up times were 8.37 and 7.03 years (SD 6.45, interquartile range 4.06–13.28), adding up to 3433 patient-years. All patients had mRS 0 before the index stroke. Stroke severity at inclusion was as follows: 9 (2.2%) with mRS 5, 41 (10.0%) with mRS 4, 73 (17.8%) with mRS 3, 100 (24.4%) with mRS 2, and 147 (35.9%) with mRS 1 or 0. Patients that were permanently institutionalised before the end of the follow-up were older at inclusion, were more often living alone at recruitment, and more often had cardiac failure, atrial fibrillation, cognitive decline pre-stroke, and more severe stroke at baseline as assessed by mRS at baseline compared with patients living at home at the end of their follow-up.

Dementia was diagnosed in 115 (25.5%) patients, but follow-up data were available for 103 (25.1%) PSD patients. The mean age of patients that survived at least 5 years was 76 (IQR 70–83) for those with PSD and 74 (IQR 69–80) for those without. The proportion of institutionalisation of survivors at 5 years was 8.9% (24/269) in the whole cohort, 15.1% (8/53) for patients with PSD, and 7.4% (16/216) for those without.

During the 21-year follow-up, 209 (51%) patients were permanently institutionalised, and 201 (49%) patients were living at home at the end of the follow-up or when deceased (see Figure 10).

Patients with PSD were more often permanently institutionalised before the end of the follow-up (n=66, 64%) than those without PSD (n=143, 47%; OR 2.05, 95% CI=1.29–3.24).

The survival time and time spent not institutionalised was shorter for patients with PSD compared to patients without dementia (6.60 vs. 10.10 years, p<0.001; 5.40 vs. 9.37 years, p<0.001). The time spent institutionalised was not significantly shorter for patients with PSD compared to patients without dementia (0.73 vs. 1.10 years, p=0.08; Figure 11).

PSD was associated with higher rates of institutionalisation compared to absence of PSD (HR 1.52, 95% CI 1.05–2.19) in a Cox regression model adjusting for age, sex, mRS at baseline, status of living alone at baseline, years of education at baseline, history of atrial fibrillation, and cardiac failure.

The estimated median time from index stroke to permanent institutionalisation (limited to largest survival time if it was censored) was shorter for patients with PSD compared to those without.
Figure 10: Sankey diagram of patients according to PSD status at 3 months after ischaemic stroke and permanent institutionalisation status during the 21-year follow-up. The number of patients within the cohort is indicated next to the description of each sub-cohort. The width of the flow-bars is shown proportionally to the flow quantity.
Figure 11: Mean time spent permanently institutionalised (grey) and not institutionalised (white) after ischaemic stroke in 410 patients at 21-year follow-up. Stratified for patients with and without PSD. The time spent institutionalised was not significantly shorter for patients with PSD compared to patients without dementia (0.73 vs 1.10 years, p=0.08). 0.73 (SD 1.77), 1.10 (SD 1.92), 9.37 (SD 6.62), 5.40 (SD 4.84)
6 Summary of the results

6.1 Stroke recurrence: association with white matter changes, poststroke dementia and poststroke depression (Studies I, II and III)

In our consecutive cohort of ischaemic stroke patients, recurrent ischaemic strokes were associated with severe WMLs, depression, DES, and PSD (see Figure 12)

<table>
<thead>
<tr>
<th>Variable (Study Number)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe WMLs (I)</td>
<td>1.80 (1.11–2.95)</td>
</tr>
<tr>
<td>Moderate-to-severe WMLs (III)</td>
<td>1.53 (0.99–2.37)</td>
</tr>
<tr>
<td>Depression (II)</td>
<td>1.68 (1.07–2.63)</td>
</tr>
<tr>
<td>Executive dysfunction (II)</td>
<td>1.47 (0.92–2.35)</td>
</tr>
<tr>
<td>DES (II)</td>
<td>1.95 (1.14–3.33)</td>
</tr>
<tr>
<td>Post-stroke dementia (III)</td>
<td>2.16 (1.51–3.10)</td>
</tr>
</tbody>
</table>

Figure 12: Cox regression analysis of the manifestations of small-vessel disease and stroke recurrence after first-ever ischaemic stroke
6.2 Trauma: association with white matter changes (Study IV)

White matter lesions were associated with hip fractures and traumatic injuries leading to hospitalization in our cohort of stroke patients (see Figure 13).

<table>
<thead>
<tr>
<th>Variable (Study Number)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe WMLs and recurrent stroke (I)</td>
<td>1.80 (1.11–2.95)</td>
</tr>
<tr>
<td>Moderate-to-severe WMLs and recurrent stroke (III)</td>
<td>1.53 (0.99–2.37)</td>
</tr>
<tr>
<td>Moderate-to-severe WMLs and hip fracture (IV)</td>
<td>3.98 (1.55–10.21)</td>
</tr>
<tr>
<td>Moderate-to-severe WMLs and trauma (IV)</td>
<td>1.72 (1.03–2.87)</td>
</tr>
<tr>
<td>Severe WMLs and institutionalisation (V)</td>
<td>1.64 (1.19–2.26)</td>
</tr>
</tbody>
</table>

*Figure 13: Cox regression analysis of the association of the white matter lesions and clinical outcomes after an ischaemic stroke*

6.3 Institutionalisation: association with white matter lesions and poststroke dementia (Studies V and VI)

PSD and severe WMLs were associated with higher rates of institutionalisation compared to absence of the factor (See Figure 14).
<table>
<thead>
<tr>
<th>Variable (Study Number)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe WMLs (V)</td>
<td>1.64 (1.19–2.26)</td>
</tr>
<tr>
<td>Post-stroke dementia (VI)</td>
<td>2.43 (1.80–3.28)</td>
</tr>
</tbody>
</table>

*Figure 14: Cox regression analysis of factors associated with institutionalisation after an ischaemic stroke*
7 Discussion

7.1 Stroke recurrence: association with white matter changes, post-stroke dementia and post-stroke depression (Studies I, II, and III)

We showed that PSD, depression, DES, and WMLs diagnosed 3 months after index ischaemic stroke are all significant independent predictors of stroke recurrence. For executive dysfunction and CIND alone, there was a trend for earlier stroke recurrence, but it lacked significance probably due to sample size. PSD, cognitive impairment, depression, DES, and WMLs are all known predictors of post-stroke mortality or morbidity.\textsuperscript{88,136,218,219} PSD, depression, DES, and WMLs are all correlated with CSVD,\textsuperscript{136,187} and the present study adds to existing knowledge regarding the clinical importance and prognostic value of CSVD from a cognitive point of view. As CSVD has a grimmer prognosis than large artery occlusion,\textsuperscript{11} a comparison of CSVD and other causes of stroke would be interesting. In our cohort, we performed classification of the stroke causes consistent with those used in the Trial of Org 10172 in Acute Stroke Treatment (TOAST),\textsuperscript{41} but because more than 60% of stroke causes were not strictly due to small-vessel, large-artery, or cardioembolic aetiology, the analyses would not have been of additional value.

7.1.1 WMLs

We were able to show that the load of WMLs can be used to estimate a person’s 5-year risk of developing a recurrent ischaemic stroke after their first-ever ischaemic stroke. In a 5-year follow-up, the WMLs had a comparable prognostic value to risk factors such as hypertension, atrial fibrillation, and peripheral arterial disease. Increasing age, generally the most important factor of recurrent stroke, became outweighed by the predictive value of WMLs in the 12-year follow-up. The patients of the present study were 55–85 years of age at their index strokes, with a mean age of 70.8 years. One explanation could be a lack of power, as many patients had died during long-term follow-up. A larger study population would have been needed to estimate the stroke recurrence risk according to three grades of WMLs instead of the two that we used. WMLs were a better predictor than PSD for stroke recurrence (OR 1.70; 95% CI 1.23–2.36 vs. OR 1.25; 95% CI 0.47–3.33).\textsuperscript{94}

7.1.2 Post-stroke dementia

In our study, PSD was associated with stroke recurrence (HR 1.84; 95% CI 1.34–2.54), which is in line with a previous study by Moroney and coauthors (HR 2.71; 95% CI 1.36–5.42).\textsuperscript{114} The lower hazard ratio in our study might be due to a higher percentage of non-
stroke deaths during a longer follow-up. The larger cohort size of our study translates to a narrower confidence interval.

An association of CIND with mortality has been shown for our post-stroke cohort, but for stroke recurrence, CIND was a not a significant predictor, although there was a clear trend. This is in line with another study investigating the recurrence of vascular events in post-stroke patients with CIND. The lack of significance might be simply due to a lack of power as a result of missing data for certain neuropsychological domains. Moreover, false positives may exist as stroke deficits might cause impairment in one of the main neuropsychological domains.

Although it has been noted that some patients may still be recovering from cognitive dysfunction at 3 months, the evaluation of cognitive function at 3 months is clinical practice and it is a common time-point of assessment in major studies on PSD. Nevertheless, we were able to show that testing for dementia 3 months after the index stroke can be useful for predicting the recurrence of stroke. Thus far, it remains unclear whether the association between PSD and recurrence of stroke is due to a biological link or to failing secondary prevention of patients with PSD. Suffering from cognitive impairment is known to weaken adherence to medication. On the other hand, an increased number of infarcts have been found in patients with Alzheimer’s disease compared with controls, and evidence suggests a link between CSVD and Alzheimer’s disease.

7.1.3 Post-stroke depression, depression-executive dysfunction

The proportion of patients with depression (37%) in our cohort was in line with that found in other post-stroke follow-up studies for depression. In our study, 17% of depressed patients had DES, and patients with DES were slightly older than those without it. The relative risk for recurrent stroke was 1.68 for depressed patients and 1.95 for patients with DES, adjusted for the classical vascular risk factors.

In our study 17%, of depressed patients also had DES; that is less than reported for a cohort of 126 elderly hospitalised patients with major depression but no history of stroke, of whom 42% had DES. This probably reflects the impact that major depression has on cognitive functions, especially on executive functions. Similarly, we also found that patients with DES were slightly older than those patients without DES in our study.

Although the elevated relative risk of depressed patients for having a recurrent stroke has not been described before, the general deleterious effects of depression on the outcome in stroke patients is known for different clinical settings: For example, in a meta-analysis of 17 studies, the relative risk for first-ever stroke in subjects with depression was estimated to be 1.34 (95% CI 1.17–1.54), compared with controls. Patients with DES have poor long-time survival (HR 1.63; 1.05–2.52). Further, the
relative risk of death due to stroke in depressed patients in one study was estimated to be 1.54 (95% CI 1.06–2.22, n=169), whereas in another study that had only men it was as much as 2.03 (95 CI 1.20–3.44).\textsuperscript{232,233} The relative risk of depressed patients to have either acute myocardial infarction or to die because of coronary heart disease has been estimated to be 1.50.\textsuperscript{234}

Post-stroke depression and PSD should be considered as specific, distinct forms of vascular depression and vascular dementia, with a causal link postulated between the ischaemic lesions and the respective cognitive or affective symptom.\textsuperscript{146,151,154} All these factors seem to be closely linked conditions and might just be different facets of a distinct stroke aetiology such as CSVD.\textsuperscript{136} CSVD is known to have a different risk factor profile from large vessel disease, with hypercholesterolaemia being a clear risk factor.\textsuperscript{235} The risk of stroke recurrence seems to be elevated in the CSVD group, which could explain the negative correlation between hypercholesterolaemia and the recurrence of stroke in our study. The finding of hypercholesterolaemia being protective might be a finding of chance. However, the pleiotropic effects of statins or better monitoring by the general practitioner of patients with hypercholesterolaemia could explain the paradox as well.\textsuperscript{236} A preventive effect of statins, rather than a protective effect of hypercholesterolaemia, could be the underlying explanation for this finding. While CSVD type 1 (arteriolosclerosis) patients have a higher chance of presenting with hypercholesterolaemia compared with CSVD type 2 (cerebral amyloid angiopathy), they are more likely to be prescribed statins for secondary prevention after the index stroke.\textsuperscript{235} However, other pathophysiological changes in depressed patients might also contribute to worse outcomes in stroke patients with depression: increased stress hormone levels associated with depression may contribute to the dysfunction of the immune defence systems, endothelial damage, increased platelet aggregation, clotting cascade activation, increased blood pressure, and cardiac arrhythmias.\textsuperscript{137} Psychosocial factors, such as poor compliance in rehabilitation and secondary prevention, low physical activity levels, smoking, poor nutrition, life stress, and low levels of social support and coping resources have been shown to adversely affect many aspects of outcomes in patients with major depression.\textsuperscript{132,135} Whether the pharmacological treatment of post-stroke depression reduces the frequencies of recurrent stroke is unclear and requires further investigation.\textsuperscript{237}

### 7.2 White matter lesions and trauma (Study IV)

The presented results of Study IV indicate that moderate-to-severe WMLs, compared to none-to-mild WMLs on MRI, were associated with increased incidences of traumatic injuries, especially hip fractures within 12 years after a stroke.

In a prospective community sample study of a population aged 65–80 (not in stroke patients), hip fractures occurred more frequently in those with diffuse WMLs compared
to those without. From the LADIS study, we know that patients with severe WMLs have impaired balance and typically have a history of twice as many falls compared to patients with only mild WMLs. In the present study population the rates of hip fractures were even 4-fold in patients with moderate-to-severe WMLs compared to patients with none-to-mild WMLs. At the same time, the rates of trauma leading to hospital admission rates were 1.7 fold. Besides higher incidence rates, patients with moderate-to-severe WMLs also had longer stays at hospitals for their first hip fracture after stroke compared with patients with none-to-mild WMLs. This might indicate higher complication rates or slower rehabilitation in patients with moderate-to-severe WMLs.

The survival analyses of the present study indicate a higher rate of hip fractures and hospital admissions due to traumatic injury in the whole post-stroke cohort for patients with moderate-to-severe WMLs compared to those with none-to-mild WMLs. Female sex and age, in addition to WMLs, independent factors associated with hospital admission due to traumatic injuries. However, age is a well known risk factor for impaired gait, falls, and hip fractures. The gender difference might therefore be partially confounded by the higher life expectancy of women. The effect of WMLs may even be underestimated in our study setting as age is such a strong predictor of falls. Increasing morbidity and age in the 12-year study period might also make the population less mobile and more bed-ridden, which would decrease the risk of falls – and therefore hip fractures and other injuries.

7.3 Institutionalisation: association with white matter lesions and poststroke dementia (Study V and VI)

We found that severe WMLs and PSD are independently associated with institutionalisation in ischaemic stroke patients. The other factors associated with permanent and earlier institutionalisation in our cohort (age, sex, mRS at baseline, status of living alone at baseline, years of education at baseline, history of atrial fibrillation, and cardiac failure) are still controversial in the literature and are dependent on the setting of the study; however, in the present study, there are no surprising findings in the associated factors when comparing to the literature. Age and stroke severity have been previously shown to be predictors of institutionalisation at 5 years after a first-ever stroke. It has been suspected that being unmarried or living alone is associated with earlier institutionalisation in stroke patients. We could confirm this in adjusted multivariable analyses.

Longer educational history associates with less post-stroke cognitive decline, dementia, and favourable long-term survival independent of covariates in patients with ischaemic stroke. Therefore, higher education should have a preventive effect on lower risk of permanent institutionalisation. However, in our adjusted multivariate models, we found only a non-significant trend towards a preventive effect of longer education similar to
the study of Brodaty and coauthors. A permanent institutionalisation rate of 23.8% within 5 years in the present study is within the previously reported range of permanent institutionalisation rates of stroke (ischaemic and haemorrhagic) patients (15–48%).

### 7.3.1 WMLs

Patients with severe WMLs spent fewer days at home, had increased incidence of institutionalisation, and ended up in permanent institutional care during 21 years of follow-up.

Less time spent at home before permanent institutionalisation can be interpreted as an outcome measure of disability, dependency, and quality of life. The patients in our study were institutionalised for 10.8% of the follow-up time in average, which is lower than in a previously published work (20%). However, the studies are not comparable, as our study did not have patients who were institutionalised (all were mRS=0) before their index stroke. In the study population of Leibson, 11% of the patients had been in nursing homes before having had their index stroke.

The association of WMLs with nursing home admissions was investigated in a cohort of 167 ischaemic stroke patients, in which a subgroup of 86 patients underwent MRI scans. In the MRI subgroup WMLs predicted nursing home admissions, but not when corrected for age. The proportion of follow-up spent in institutions was not detailed and could only be roughly estimated due to many drop-outs and cases in which the date of institutionalisation was estimated to be somewhere between two visits. In our study, follow-up data were missing for only 5 cases (1.3%), which were excluded from the study. In the study of Brodaty the drop-out rate not related to death was 20%.

In the SAM cohort, patients with severe WMLs were older, less educated, and had more severe strokes assessed by the mRS 3 months post-stroke. This association is in line with previous findings. Cumulative survival at home at five years was lower in the present study than in the study by Brodaty et al., (59% vs. 76%), but as we stated before, the comparability of the studies is limited.

When looking at the cumulative hazard curve in the original publication, one can see, that the curves diverge until 5 years. After 5 years, the divergence is less obvious. An explanation for that could be that other medical conditions also start to contribute to functional decline and need for institutional care. However, due to the nature of our study, we do not know, how many patients of the none-to-moderate WML group have progressed to severe WMLs during the follow-up of the study.
7.3.2 PSD
The percentage of PSD in our cohort is in line with previous literature and is similar to studies with similar time points and definitions of dementia.\textsuperscript{106,222,245} The association of PSD with institutionalisation was very similar compared with a recent meta-analysis where dementia and cognitive impairment were associated with a 2.14 pooled odds ratio of permanent institutionalisation after acute hospitalisation.\textsuperscript{183} In a cohort of 254 patients with incident dementia the mean time until institutionalisation was 4.1 years,\textsuperscript{246} which is shorter than the 5.4 years for the PSD patients in our cohort. The patients in the cohort of Luppa, however, were older (all over 75 years).\textsuperscript{246} The prevalence of being permanently institutionalised at 5 years in our cohort was high for the whole cohort and especially high for the patients with PSD compared with the general Finnish population. In the year 2000, the rates of permanent institutionalisation were 4.3% for people over 65 years of age, 8.3% for people over 75 years of age, and 19.6% for people over 65 years of age.\textsuperscript{247} Surprisingly, the time spent institutionalised did not significantly differ between patients with PSD and patients without it. However, this is attributable to the shorter survival time of patients with PSD compared to the patients without, as has been reported previously from the same cohort.\textsuperscript{108} This finding is somewhat conflicting, with previously reported data indicating that residents with a history of stroke have longer lengths of stay in nursing homes compared to other causes of stay.\textsuperscript{248} Data on length of stay in nursing homes are rarely obtained and are available mostly from nursing home surveys. In surveys and retrospective analyses the mean length of stay in a nursing home is 13 to 19 months.\textsuperscript{249-253} We could only identify a single study on the length of residence in nursing homes.\textsuperscript{248} The reported mean (5 months) and median (13.7 months) lengths of stay were within the same range as in the present study.\textsuperscript{248} In Finland the mean time spent in nursing homes is about 3 years before death.\textsuperscript{174}

7.4 Strengths and limitations
The strengths of our study are the well-defined, relatively large, homogeneous and consecutive patient cohort and the long follow-up time. The follow-up in post-stroke dementia cohorts had been 3–5 years in previous studies, and the cohort was 446 patients compared with 202, 242, and 108 patients.\textsuperscript{94,114,115} Relative to the previous studies, our study has longer person-years of follow-up (3022 vs. 647), more recurrent ischaemic strokes (201 vs. 45), and more post-stroke dementia patients (115 vs. 62).\textsuperscript{94,114,115} Other strengths include the structured evaluation of depression and neuropsychological features. The follow-up diagnoses can be considered reliable, as stroke diagnoses in the Finnish Hospital Discharge Registries have been validated against a population-based stroke registry with fairly good positive predictive values (85–92%).\textsuperscript{254}
Our data regarding falls can be considered robust compared to frequently used retrospective settings, where the data are self-reported by the patient or caregiver, or follow-up studies, where fall diaries are used.\textsuperscript{86}

We can be confident in stating that the SAM cohort is a representative stroke cohort as the overall recurrence risk of stroke in the whole cohort is similar to the 4.26% per year from a recent large meta-analysis.\textsuperscript{23} A recent large registry study from Canada also reported similar recurrence rates after a stroke of 3.1% at 1 year, 6.3% at 3 years, and 8.8% at 5 years after the index stroke, and confirms similar institutionalisation rates after stroke of 3.1% at one year, 6.6% at three years, and 9.6% at five years after the index stroke.\textsuperscript{24}

Our study included only patients with a first-ever stroke, and all patients were examined by MRI; however, the correlation between CT and MRI findings in severe WMLs is good.\textsuperscript{255}

WMLs, post-stroke depression, PSD, and DES are not independent of each other in the context of CSVD, making it difficult to investigate them in one multivariable model. We do not have follow-up MRI data on the progression of WMLs. We included patients at 3 months after ischaemic stroke, and thus the more severely affected or mortally ill patients were excluded, possibly leading to a selection bias. The worse outcome of patients with WMLs after 3 months might lead to an under-representation of WMLs in our cohort.\textsuperscript{61}

The rate of recurrent strokes within the first weeks up to 3 months is very high in stroke cohorts;\textsuperscript{256} therefore, the stroke recurrence rates in our cohort is probably lower than it would have been if we had included all consecutive patients at index stroke. Patients with very severe PSD or post-stroke depression might not be capable of participating in the study or even giving informed consent leading to the underestimation of those conditions and to a possible underestimation of permanent institutionalisation. Similarly, patients with severe cognitive symptoms and possibly with the most severe DES or severe aphasia were also excluded because their cognitive status for executive functions could not be reliably evaluated. Patients with very severe strokes initially might not be discharged at any time after the index stroke. In the population-based Stroke Registry of Dijon, about 15% of the patients did not survive the acute phase of the index stroke.\textsuperscript{185} This might lead to an underestimation of permanent institutionalisation, but patients not surviving the first 3 months might lead to an overestimation.

Potentially a hip fracture or severe traumatic injury leading to a prolonged initial hospitalisation might have interfered with recruitment in the study, leading to an underestimation of hip fractures and traumatic injuries in patients with gait disturbance due to CSVD. Also, because patients with severe gait disturbance tend to be bedridden, this might have led to an under-representation in the study and, therefore, an
underestimation of permanent institutionalisation of patients with CSVD. Impaired gait is associated with initial admission to long-term facilities after a stroke.\textsuperscript{257}

Due to the above mentioned limitations, our findings are therefore only generalisable to symptom free stroke patients (scoring 0 on the mRS) before the stroke who are able to walk 3-months post-stroke (mRS better than 4). Another limitation is the lack of information on depression treatment and drug compliance during follow-up. Risk factors were evaluated only at 3-months, so a change in risk factors during a long follow-up is possible. Adherence to medication was not followed up. Patients with CSVD who are living at home after the index stroke can be suspected to have worse adherence to medication compared to those without CSVD due to cognitive impairment. Adjustment for medication adherence might decrease the risk of recurrent strokes in patients with features of CSVD compared to patients without.

Use of alcohol has not been surveyed accurately enough to use it as a covariate. Subtypes of the recurrent strokes are not reported in our study because the diagnoses were registry-based. We could not elaborate on the recurrence risk for different stroke aetiologies, but only for ischaemic stroke in general. Additionally, there might be selection bias, as cardiogenic strokes tend to be more severe and more often fatal in the first month, so stroke patients with cardiogenic strokes might have died before the first evaluation at 3-months post-stroke, or their condition was too poor to participate in the study. This could lead to an overestimation of HR for permanent institutionalisation of patients compared to those without CSVD, as patients with severe stroke after cardiogenic strokes might be institutionalised starting at index stroke. The results might not be generalisable to patients suffering a stroke now, as during the very long follow-up time, the diagnostics, treatment options, and secondary prevention for patients have improved. This might have increased the survival time, but the time spent in an institution might be even higher now.

7.5 Future prospects

There are reports of declining rates of Alzheimer’s disease and dementia, which might be due to improving primary prevention strategies.\textsuperscript{102,258,259} The most important benefits for patients, and the best for the economy, can be expected from the primary prevention of CSVD. There is hope to achieve a decrease of strokes, depression, falls, dementia, and institutionalisation for the relevant age-cohorts with effective primary prevention measures. To test preventive strategies, subjects at high risk would have to be identified. For this purpose surrogate markers of early disease states are crucial to know.
Recently, a CSVD score has been proposed and validated to have a predictive value for recurrent strokes after an incident stroke.\textsuperscript{260} More generally, potentially modifiable factors of permanent institutionalisation should be a target of future research.\textsuperscript{176}

A transcranial Doppler ultrasound profile of low perfusion and high vascular resistance in patients with CSVD should be investigated further. A cohort of young patients with cryptogenic stroke should be ideal to investigate the resistance of the brain as an end-organ through cerebral arteries. The cohort should be followed up for a long time (at least 10 years), and then the measurement and a follow-up MRI of the brain should be performed. This could give valuable information on the development of CSVD.

Distinguishing the different types of CSVD \textit{in-vivo}, and preferably in a subclinical phase, is needed to investigate tailored preventive strategies.
8 Conclusions

PSD, depression, DES, and WMLs diagnosed 3 months after index ischaemic stroke are all significant independent predictors of stroke recurrence.

The presence of severe WMLs, when compared with none-to-moderate WMLs, was independently associated with increased ischaemic stroke recurrence risk at five years after a first-ever ischaemic stroke. Depression and especially DES were associated with more rapid recurrence of ischaemic stroke. Detection of either post-stroke depression or DES identifies a high-risk post-stroke patient group, which might warrant intensive secondary prevention measures, including psychiatric interventions. PSD diagnosed 3 months after index ischaemic stroke was a significant independent predictor of stroke recurrence during a 12-year follow-up, particularly in patients with a first-ever stroke. Ischaemic post-stroke patients with more than mild WMLs were at high risk of traumatic injuries, especially hip fractures, probably due to gait disturbance and instability related to WMLs.

Severe WMLs and PSD are independently associated with institutionalisation in ischaemic stroke patients. Patients with severe WMLs were at higher risk of spending fewer days at home and being permanently institutionalised in a long-term follow-up compared with patients with none-to-moderate WMLs. PSD is a robust predictor of permanent institutionalisation. However, due to significantly shorter survival, the time spent in nursing homes was not significantly longer in patients with PSD compared with those without it.

A recurrent stroke, in general, is more disabling than a first-ever stroke. Compared to patients without a distinct CSVD feature, patients with features of CSVD suffer recurrent ischaemic strokes earlier, leading to higher disability, gait disturbances with increased risk of falls, earlier dementia, earlier institutionalisation, or earlier death.

In summary, this thesis underlines how deleterious CSVD is for independence and quality of life and how deeply it compromises healthy ageing. The ability to observe sub-clinical changes and to synthesise a patient’s symptoms and findings, thus realising the total load of CSVD, is required to prohibit its insidious progression. Predictive and preventive actions are central, consisting of the control of vascular risk factors both pharmacologically and through a patient’s own lifestyle changes, and hopefully in the near future, with specific interventions that protect small vessels.
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Gerli Sibolt
10 References


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