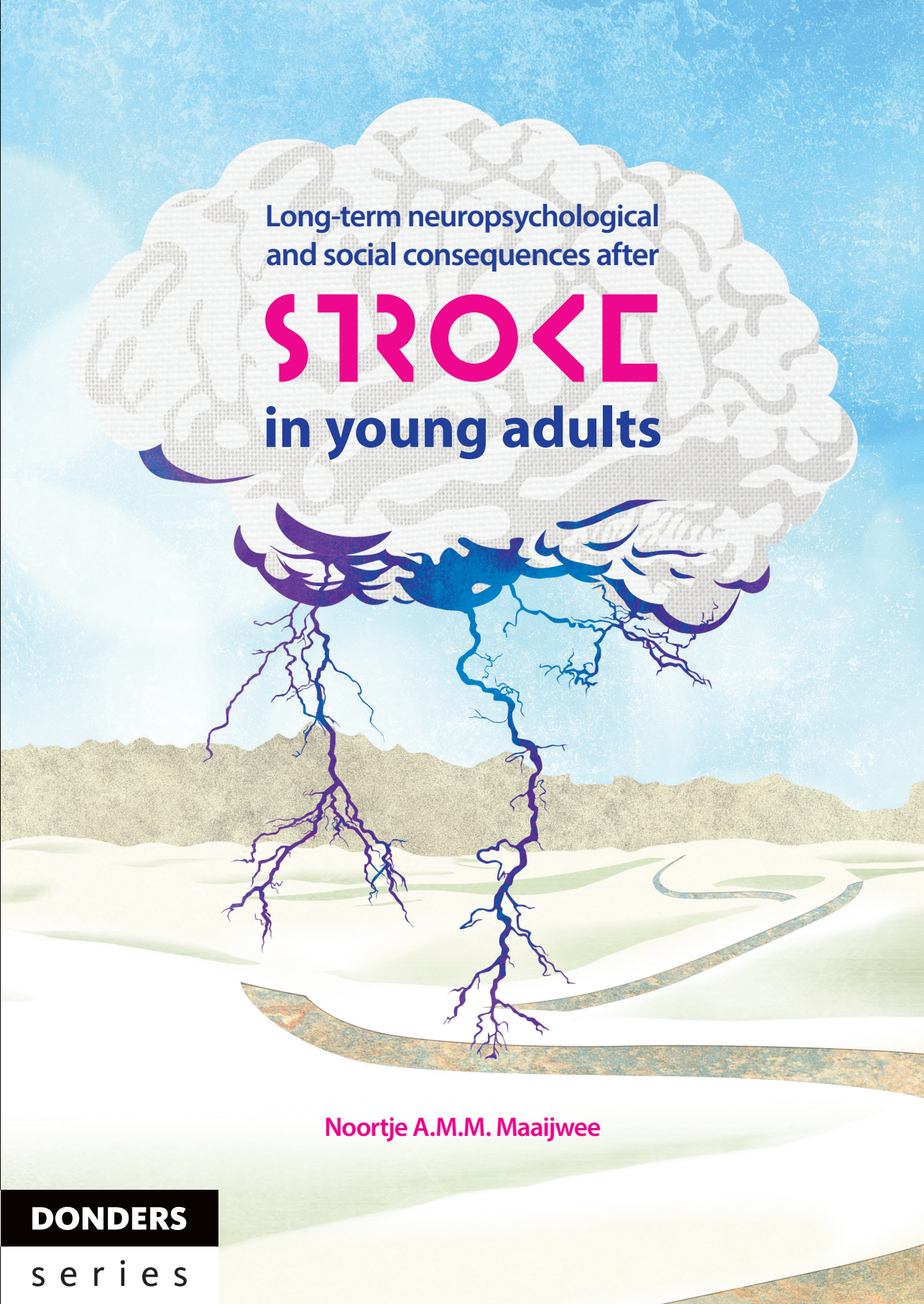
Long-term neuropsychological and social consequences after STROKE in young adults



Noortje A.M.M. Maaijwee

DONDERS series

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Noortje A.M.M. Maaijwee

Colofon

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Long-term neuropsychological and social consequences after STROKE in young adults

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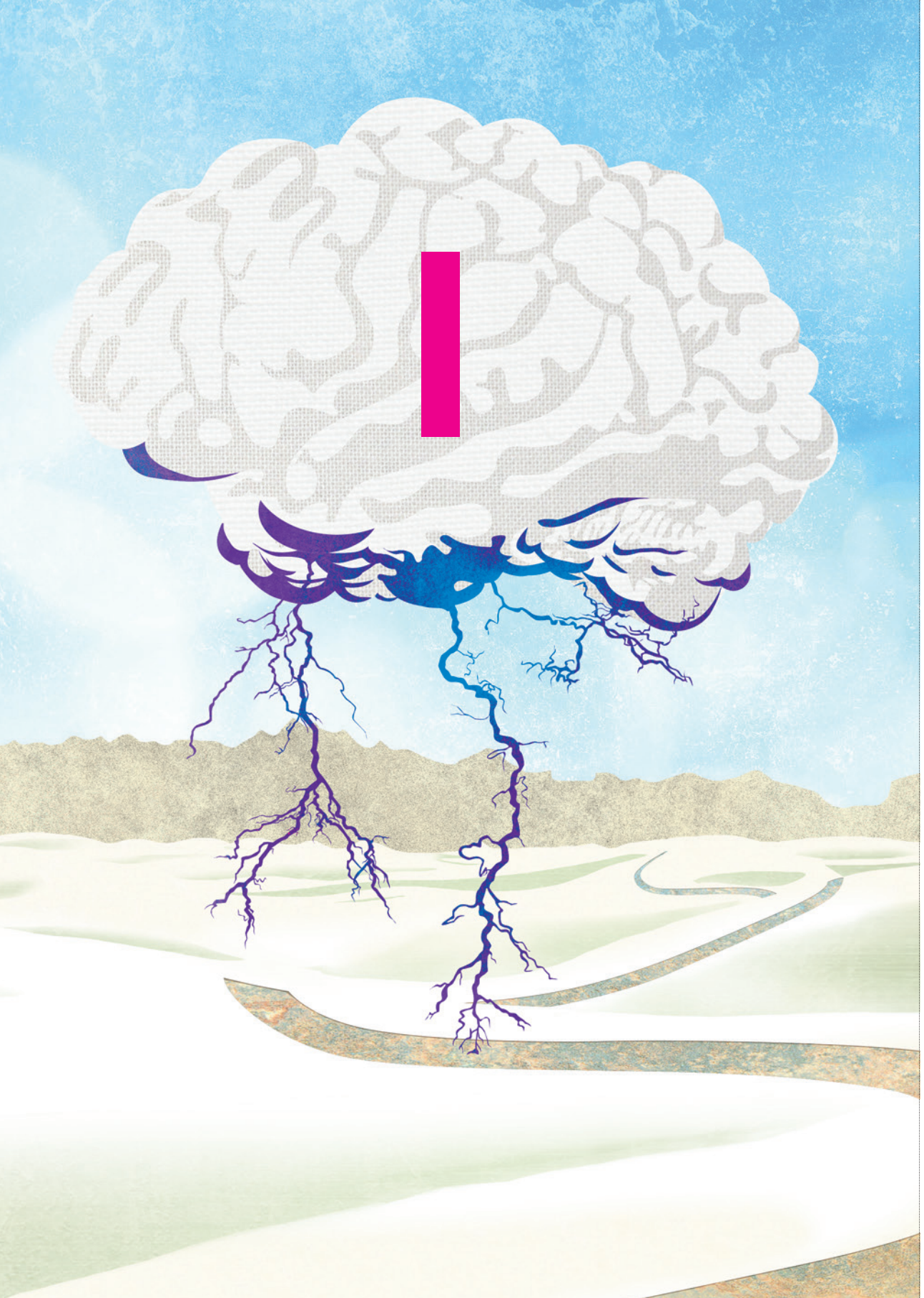
TABLE OF CONTENTS

PART I

Introduction



General introduction, aims, and outline

Stroke in young adults

Stroke affects about 15 million persons worldwide, resulting in death in approximately a third of all cases and significant disability in the survivors.[1]

Stroke is an umbrella term for ischaemic stroke, intracerebral haemorrhage, and a transient ischaemic attack (TIA). Ischaemic stroke is caused by a sudden occlusion of an artery in the brain, impairing blood flow and thus oxygen delivery to brain parenchyma. In a majority of cases, this occlusion is the result of an embolus originating from the systemic circulation (heart, aortic arch, carotid arteries) or a consequence of endothelial damage with clotting of blood platelets and other coagulation factors.[2, 3] TIA's have the same pathophysiological mechanisms as ischaemic stroke. The only difference is the arbitrarily chosen cut-off duration of symptoms of less than 24 hours for a TIA and more than 24 hours for an ischaemic stroke. Intracerebral haemorrhages account for approximately 20% of all strokes. They are caused by the rupture of a cerebral blood vessel.

In the Netherlands, each year approximately 41 000 patients are diagnosed with an ischaemic stroke or intracerebral haemorrhage.[4] Up to 12% of these strokes occur in young adults between 18 and 50 years of age[5] — a so-called 'young stroke' — and the incidence in this age group is rising.[6] Stroke is clinically characterised by a sudden onset of loss of motor, sensory, visual, speech or language function, depending on the localisation of the lesion. Although being an acute event in onset, post-stroke impairments can have a more prolonged course and a life-long negative impact on daily life. These long-term effects are of particular importance in young patients, since they usually have a long life expectancy of decades ahead.

For the studies described in this thesis, we defined 'young stroke' as a TIA, ischaemic stroke or intracerebral haemorrhage in adults aged 18 through 50 years.

Long-term neuropsychological and social consequences

The first thing that usually might come to mind considering post-stroke disability is motor impairment. This is substantiated by the fact that one of the most frequently used functional outcome scales after a stroke, the modified Rankin Scale,[7] predominantly assesses motor performance. In the first weeks after the stroke, patients and caregivers mainly focus on these physical impairments and their recovery. However, less visible consequences may become apparent only after this time, consisting of subjective and objective cognitive impairment, but also fatigue or psychiatric disorders, such as depressive symptoms and anxiety. These consequences have been extensively studied in elderly stroke survivors (>60 years of age).[8-25] Less research has been performed in young stroke patients on these topics,[9, 26-34] although stroke survivors and their family

rate these topics as high priority in research, since these symptoms usually prevent return to pre-stroke life.[35]
Findings from studies in older stroke patients cannot per se be generalised to the younger population. First, the prevalence of cognitive impairment and other neuropsychological consequences may differ from older persons, as a result of different recovery patterns. Age-related neurodegenerative changes, for example amyloid plaques or accumulating small-vessel disease, may contribute to and exaggerate these neuropsychological consequences in elderly stroke survivors. These changes will play a far less pronounced role in the occurrence of neuropsychological symptoms in young stroke patients, given their younger age.
Second, the effects of neuropsychological consequences on daily life are different in younger than in older patients, due to different demands from their social environments. Young patients are in a phase of life during which they have to make important life-changing decisions, such as career movements or family planning. Neuropsychological consequences may possibly have an adverse effect on chances of returning to work.[36] This will not only result in an individual loss, but also in loss of productivity and working years, thereby increasing burden to society.[37]
Third, most studies only included patients with an ischaemic stroke and excluded patients with a TIA or intracerebral haemorrhage. However, evidence is accumulating in older patients that a TIA might not be as transient as previously thought, with respect to less visible symptoms such a cognitive impairment.[38, 39] Survival of intracerebral haemorrhage patients has increased,[40] due to improved intensive and neurological care. So, the need for information on long-term consequences in this condition also arises.
Finally, given their usually long life expectancy, especially information on long-term consequences is of utmost importance for young stroke survivors. However, to date, long-term follow-up studies barely exist.[26]

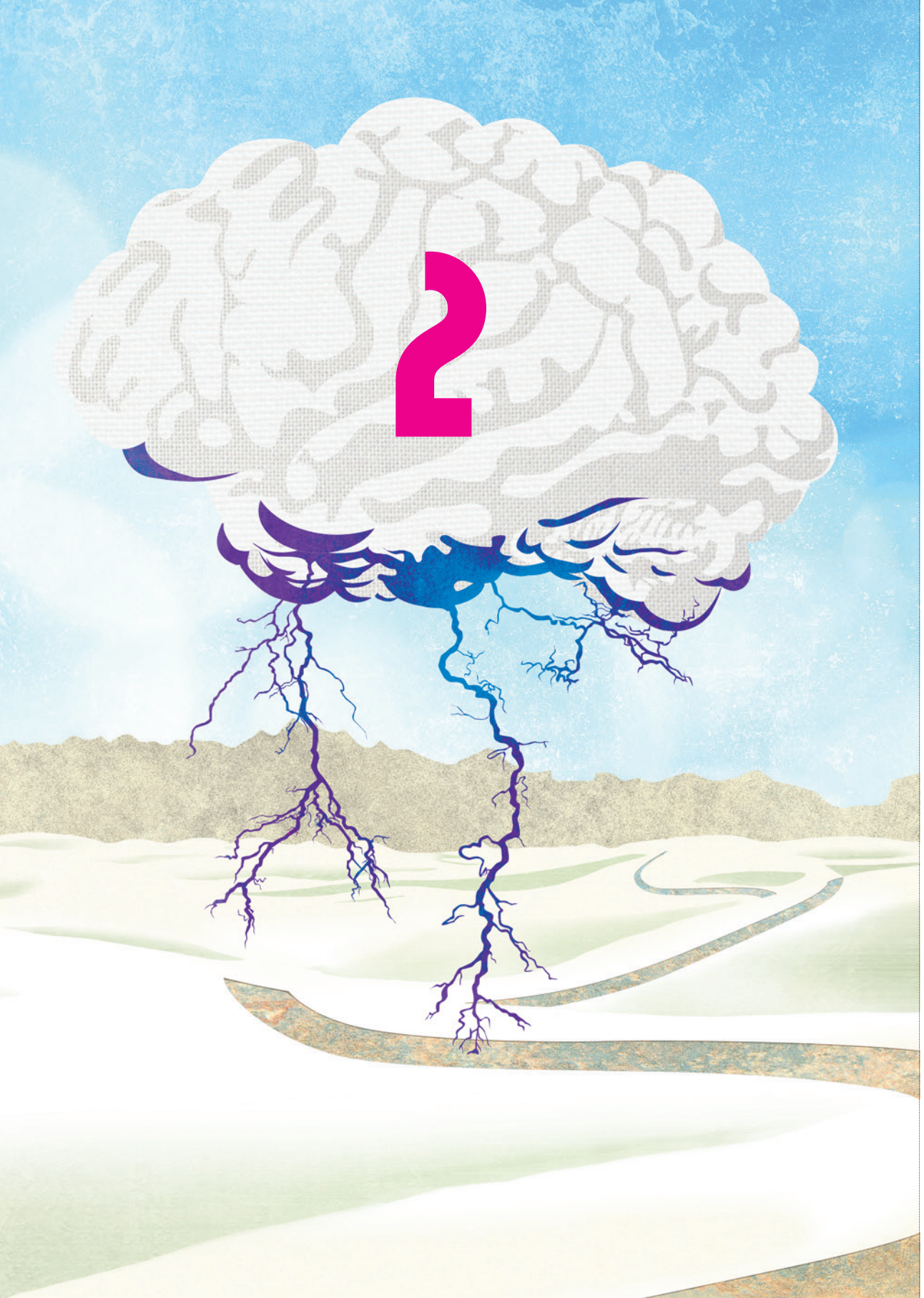
Aims of the thesis and study design

The aim of this thesis was to investigate the long-term prognosis with respect to neuropsychological and social consequences after a stroke in young adults aged 18 through 50 years, including post-stroke depressive symptoms, anxiety, fatigue, subjective and objective cognitive impairment, and post-stroke unemployment.
The studies presented in this thesis are based on the '*F*ollow-*U*p of *T*ransient ischaemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation' (*FUTURE*) study, a large cohort study of 1 005 patients, designed to investigate aetiologies and long-term consequences of a young stroke. All consecutive patients with a TIA, ischaemic stroke

or intracerebral haemorrhage between 18-50 years, admitted to the Radboud University Nijmegen Medical Centre, The Netherlands between January 1, 1980 and November 1, 2010 were included. Patients alive were invited for an extensive follow-up assessment between November 1, 2009 and January 1, 2012.
Exclusion criteria were traumatic haemorrhagic stroke, haemorrhage in known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis, subarachnoid haemorrhage or intracerebral haemorrhage attributable to known ruptured aneurysm, and retinal infarction.
In addition, 147 control subjects were recruited from the same environment as patients, including spouses, siblings, and other relatives. Controls had to be at least 18 years old, without a TIA or stroke in their medical history. They were matched with the patient group on age and sex.

Outline of this thesis

In **part I** of this thesis, **chapter 2** provides a critical review of the literature on risk factors, aetiology, and long-term prognosis of young stroke, including mortality and risk of cardiovascular disease, but also functional outcome and psychosocial consequences. The term 'young stroke' will be discussed and issues that need more investigation are pointed out.
Part II, **chapter 3** describes the rationale and design of the FUTURE study.
In part III, **chapter 4** reports on the long-term cognitive impairments in young ischaemic stroke patients. In **chapter 5**, the prevalence of subjective cognitive failures is reported in patients with a young TIA or ischaemic stroke. Subsequently, we investigated whether these subjective cognitive failures are related to objective cognitive impairment or not. The prevalence of depressive symptoms and anxiety is reported in **chapter 6** and the prevalence of fatigue in **chapter 7**, both in young TIA and ischaemic stroke patients. The association of these symptoms with a poor functional outcome is described in these chapters. In **chapter 8**, we report on the long-term neuropsychological problems in the subgroup of intracerebral haemorrhage patients. **Chapter 9** of this thesis reports on long-term unemployment rates in the young stroke population, compared with nationwide controls.
In **part IV** of this thesis, the main results from the studies in this thesis are summarised (**Chapter 10**) and discussed (**Chapter 11**), including possible implications for clinical practice and directions for future research. **Chapter 12** contains the Dutch summary of this thesis.



Ischaemic stroke in young adults:

risk factors and long-term consequences

Published as

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Abstract

Contrary to trends in most other diseases, the average age of ischaemic stroke onset is decreasing, owing to a rise in the incidence of stroke among 'young' individuals (under 50 years of age). This review provides a critical overview of the risk factors and aetiology of young ischaemic stroke and addresses its long-term prognosis, including cardiovascular risk, functional outcome, and psychosocial consequences. We highlight the diminishing role of 'rare' risk factors in the pathophysiology of young stroke in light of the rising prevalence of 'traditional' vascular risk factors in younger age groups. Long-term prognosis is of particular interest to young patients, because of their long life expectancy and major responsibilities during a demanding phase of life. The prognosis of young stroke is not as favourable as previously thought, with respect either to mortality or cardiovascular disease or to psychosocial consequences. Therefore, secondary stroke prevention is probably a life-long endeavour in most young stroke survivors. Due to under-representation of young patients in past trials, new randomised trials focusing on this age group are needed to confirm the benefits of long-term secondary preventive medication. The high prevalence of poor functional outcome and psychosocial problems warrants further study to optimise treatment and rehabilitation for these young patients.

Introduction

Stroke is a devastating disease that affects 15 million patients worldwide each year, resulting in death in about one-third of patients and severe disability in two-thirds of the survivors.[1, 41] Approximately 80% of all strokes are ischaemic strokes, of which roughly 10% occur in individuals under the age of 50 years — so-called 'young stroke'.[5] In this article, we review the literature on ischaemic stroke in these young patients. Age limits defining young stroke differ across studies,[5, 27, 42, 43] but we chose to define young stroke as an ischaemic stroke in adults aged 18-49 years, as this was the age range generally used in large studies.[26, 43, 44] For the sake of inclusivity, however, we will also report on results from some studies that used upper age limits of 45, 50 or 55 years.[42, 45] Risk factors and management strategies for young stroke differ across the world, depending on factors such as genetic differences, environmental influences, and the development and accessibility of health services. In this review, we will focus on the situation in Western societies, unless otherwise specified.

In recent years, we have witnessed a remarkable, unprecedented decrease in the average age of onset of ischaemic stroke in the overall population, which is mainly attributable to an increased incidence of stroke in young adults.[6, 46] Ischaemic stroke in young adults is often thought to be related to 'rare' risk factors and aetiological features that are very different from the 'traditional' vascular risk factors and aetiology seen in older stroke patients. However, the increase in stroke incidence in young adults has been found to be associated with a rising prevalence of some important 'traditional' vascular risk factors, including hypertension, hypercholesterolaemia, diabetes mellitus, and obesity, in this age group.[6, 47] We will discuss the role of these risk factors from the perspective of the increased incidence of young stroke.

In addition to the identification of risk factors and aetiology, long-term prognosis after stroke is of particular interest from the perspective of young patients, as they usually have a life expectancy of several decades. Following a stroke, these individuals are suddenly confronted with uncertainties about their future in a period of life during which they might be preparing for decisive career moves or planning a family. Therefore, information on long-term prognosis should include not only the risk of vascular and other diseases, but also the expected psychosocial consequences related to life after stroke — a topic reported to be among the top 10 research priorities for patients.[48]

In the first part of this review, we provide a critical overview of the existing literature on risk factors and aetiology of young ischaemic stroke. This section will include a methodological discussion on the rare risk factors and aetiology that have conventionally been regarded as specific for young stroke, followed by a discussion of the

growing prevalence of traditional vascular risk factors among younger individuals. We will then review the life-long consequences of stroke in young adults, not only in terms of cardiovascular disease recurrence, but also with respect to less frequently studied but equally relevant consequences, including cognitive and social impairments, mood disorders, and fatigue.

Risk factors and aetiology

The view that ischaemic stroke in young adults is different from 'old stroke' with respect to risk factors and aetiology originated predominantly from the many publications — mainly based on case series from tertiary hospitals — that reported on the high prevalence of unusual, rare conditions and risk factors among young patients with stroke.[49] These rare risk factors and aetiologies are extensively summarised in previous reviews and textbooks,[2, 49] and will not be outlined in detail here. The term 'risk factor' is used to indicate that a certain factor was found to be associated with stroke in young adults. However, the mere identification of a risk factor does not imply that the aetiology is fully understood. Sometimes the risk factor is somewhere in the 'causal pathway' of the disease, and may give rise to a certain aetiology that in turn is associated with the disease; for example, hypertension is a risk factor, but atherosclerosis might be the underlying causal aetiology of the stroke. For the purposes of this review, we will categorise the aetiology according to the Trial of Org 10172 Acute Stroke Treatment (TOAST) classification, with 'large-artery atherosclerosis', 'small-vessel disease', 'cardioembolic', 'other determined', and 'cryptogenic' as important aetiological subgroups.[3]

'Rare' risk factors and aetiologies

In Tables 1 and 2, we summarise data on 5 rare risk factors and 5 rare aetiologies that have been linked chiefly to stroke in young patients. The choice was based on the relatively high prevalence of these factors and aetiologies in large, Western young stroke cohorts.[43, 44] In other populations, the distribution of conditions in the TOAST category 'other determined aetiologies' differs. For example, in Japan, moyamoya disease will be diagnosed more frequently in young patients with stroke, because the incidence and prevalence of this disease is much higher there than in other parts of the world, such as Europe.[50]

Table 1 Top 5 most prevalent 'rare' risk factors for stroke in young[a] Western populations.

Risk factor	TOAST classification[b]	Prevalence in young patients with stroke[c]	Strength of association	Highest level of evidence[d]
Migraine[51-55e]	Unknown cause	20-24%	Pooled effect estimate ~2.0[56]	A1, association proven for migraine with aura only
Illicit drug use[57-61]	Other (rare) causes	9-20%	OR 2.0 for cocaine;[57] OR 2.3 for cannabis;[60f] no significant association for amphetamines[57]	A2 for cocaine; B for amphetamines, cannabis and heroin
Patent foramen ovale[62-65]	Possible cardiac embolism; low-risk source	24%, up to 50% in stroke, classified as cryptogenic	Hazard ratio ~1.5 (non-significant)[63]	A2, contrasting with evidence from B-level studies
Oral contraceptives[54, 66-71]	Other (rare) cause/ unknown	10-40%	Summary OR 2.1[67]	B
Pregnancy/ puerperium[72-76]	Other (rare) cause/unknown	7.5% in women	Relative risk 8.7 during puerperium, not during pregnancy[74]	A2, conflicting results

a.) Under 50 years of age; **b.)** TOAST classification, according to Ay et al. (2005)[3]; **c.)** Sum of all prevalences exceeds 100%, because data were extracted from different study populations. In addition, conditions are not mutually exclusive in an individual patient; **d.)** Levels of evidence: A1, systematic review, based on at least 2 independent A2-level studies; A2, prospective cohort study of sufficient sample size and duration of follow-up, adequately adjusted for confounding and selective follow-up sufficiently excluded; B, prospective cohort study, not meeting the criteria of A2, or retrospective cohort study, or case-control study; C, non-comparative study; D, expert opinion; **e.)** Note that migrainous stroke is very rare;[35] however, reports on the role of migraine as a risk factor for stroke are abundant; **f.)** Not significant after correction for tobacco use.

Table 2 Top 5 most prevalent 'rare' aetiologies for stroke in young[a] Western populations.

Aetiology	TOAST classification[b]	Prevalence in young patients with stroke[c]	Strength of association	Highest level of evidence[d]
Non-inflammatory arteriopathies				
Arterial dissection (cervical or intracranial)[77-81]	Other (rare) causes	10-25%	Not reported	A2
Reversible cerebral vasoconstriction syndrome[44, 82-84]	Other (rare) causes	1-5%	Not reported	B
Inflammatory arteriopathies				
Inflammatory arteriitis[85e]	Other (rare) causes	3-5% *(all autoimmune vasculitides combined)*	Not reported	B or C, depending on the underlying autoimmune disorder
Cardioembolic				
Cardiomyopathy[43, 44, 86]	Cardioembolism, high-risk source	2-3%	Not reported	A2
Prothrombotic state				
Coagulation factors[87-93]	Other (rare) cause/unknown	Antiphospholipid syndrome: 10%[f]	OR 2.2[94]	A2 for antiphospholipid syndrome, conflicting results; B for other factors, conflicting results
		Factor V Leiden: 3.0-7.5%	OR 1.02[87]	
		Antithrombin III deficiency: 5-8%	Not reported	
		Protein C deficiency: 4-11%	Not reported	
		Protein S deficiency: 6% *(up to 23% in occasional studies)*	Not reported	
		Prothrombin mutation: 2-6%	Not reported	

a) Under 50 years of age; **b)** TOAST classification, according to Ay et al. (2005)[3]; **c)** Sum of all prevalences exceeds 100%, because data were extracted from different study populations. In addition, conditions are not mutually exclusive in an individual patient; **d)** Levels of evidence: A1, systematic review, based on at least 2 independent A2-level studies; A2, prospective cohort study of sufficient sample size and → duration of follow-up, adequately adjusted for confounding and selective follow-up sufficiently excluded. B, prospective cohort study, not meeting the criteria of A2, or retrospective cohort study, or case-control study; C, non-comparative study; D, expert opinion; **e)** Including primary vasculitis and vasculitis secondary to collagen vascular diseases, and other systemic conditions (excluding those secondary to infections)[85]; **f)** Up to 46% in selected populations.

Aetiological subgroups, as described in Table 2, vary across sex and age categories. Extracranial arterial dissections are the most common 'rare' aetiological subgroup. Dissections are found throughout all age categories and account for approximately 20% of strokes in patients under 45 years of age, but only for 2% of all ischaemic strokes. The highest incidence of dissections lies in the fifth decade; men and women are about equally affected, although women are, on average, 5 years younger when the dissection manifests.[77, 78]

Inflammatory arteriopathies, such as vasculitis, are a heterogeneous group, mostly consisting of multisystemic inflammatory disorders affecting arteries of all sizes, depending on the disease.[85] Some of these conditions virtually never occur in young adults; for example, giant cell arteriitis almost exclusively affects individuals over 50 years of age. However, other conditions, such as Takayasu disease, predominate in young females.[85] Of note, infectious diseases underlie a considerable proportion of cases of secondary vasculitis. In the developed world, hepatitis B and C remain the most common underlying infections, whereas HIV is a large problem in the developing world.[95]

Within the subgroup of cardioembolic stroke, cardiomyopathy is one of the most prevalent conditions in young patients with ischaemic stroke.[43, 44] One would expect cardiomyopathy to be associated with strokes earlier in life, because this condition often has an early age of onset. However, 1 study that stratified young patients with stroke by age category found no significant difference in prevalence between patients under 42 years of age and those aged 42 years or older. In this study, cardiomyopathy was more than twice as prevalent in men than in women (15.5% versus 6.1%).[44]

Antiphospholipid syndrome is an important example of a prothrombotic state that is related to stroke in young adults. This condition has predominantly been studied in women. An increased risk of ischaemic stroke was found in association with this condition in women under 50 years of age (OR 43.1, 95%-CI 12.2-152.0).[96] Although some studies showed a clearer relationship in younger women than in older populations, another study showed no age differences in a young stroke population.[97]

Of note, some of the risk factors mentioned in Table 1, such as illicit drug abuse or the presence of a patent foramen ovale (PFO), are seen as being quite specific to young

adults, but they can actually occur throughout the human life span. In older adults, however, the relative presence of these risk factors is much lower than in young adults, as the absolute numbers of patients with traditional cardiovascular risk factors and a proven aetiology, such as large-artery atherosclerosis, small-vessel disease or cardioembolic stroke, is much higher.

For most of the risk factors in Table 1, only weak associations with respect to young stroke have been reported. Moreover, the extent to which a risk factor is judged to be causal in the origin of a disease might depend on the quality of the study. To increase the likelihood of causality, studies would have to show that the effects of risk factors are, among other criteria, dose-dependent and time-dependent.[98] Double-blind randomised trials or large, prospective cohort studies would be needed to meet these requirements.

Associations for most of the reported risk factors were derived from case-control studies or case series, which are prone to various forms of bias because they are hospital-based and often limited with respect to sample size. First, information bias — in particular, recall bias — needs to be considered. Remarkable events in the recent past, such as infections, might be more readily remembered by a patient in the aftermath of a stroke than by a person who has not experienced a stroke. Acute respiratory tract infections have been implicated as trigger factors for stroke, as have chronic infections, such as chronic bronchitis.[99] The potential role of these infections as trigger factors was supported by the fact that their association with stroke was time-dependent and dose-dependent. However, the evidence derives mostly from case-control studies with methodological limitations.

Second, referral bias could be an issue. Young stroke cases described in the literature are often selected from a population that was referred for a second opinion to a tertiary academic centre. These cases usually represent a selection of patients in whom no aetiology could be established on the initial investigations. Subsequent additional investigations may have revealed incidental or presumed abnormal findings (for example, a PFO) that were not necessarily causal factors.

Last, confounding can contribute to bias; for example, in many small studies, traditional risk factors were not appropriately adjusted for in the analysis.

Traditional vascular risk factors

Whereas the role of rare risk factors in the pathophysiology of young stroke seems overestimated, the role of traditional vascular risk factors may have been underestimated.[5, 6, 43, 45, 100-105] The rising incidence of stroke in young adults coincides with an

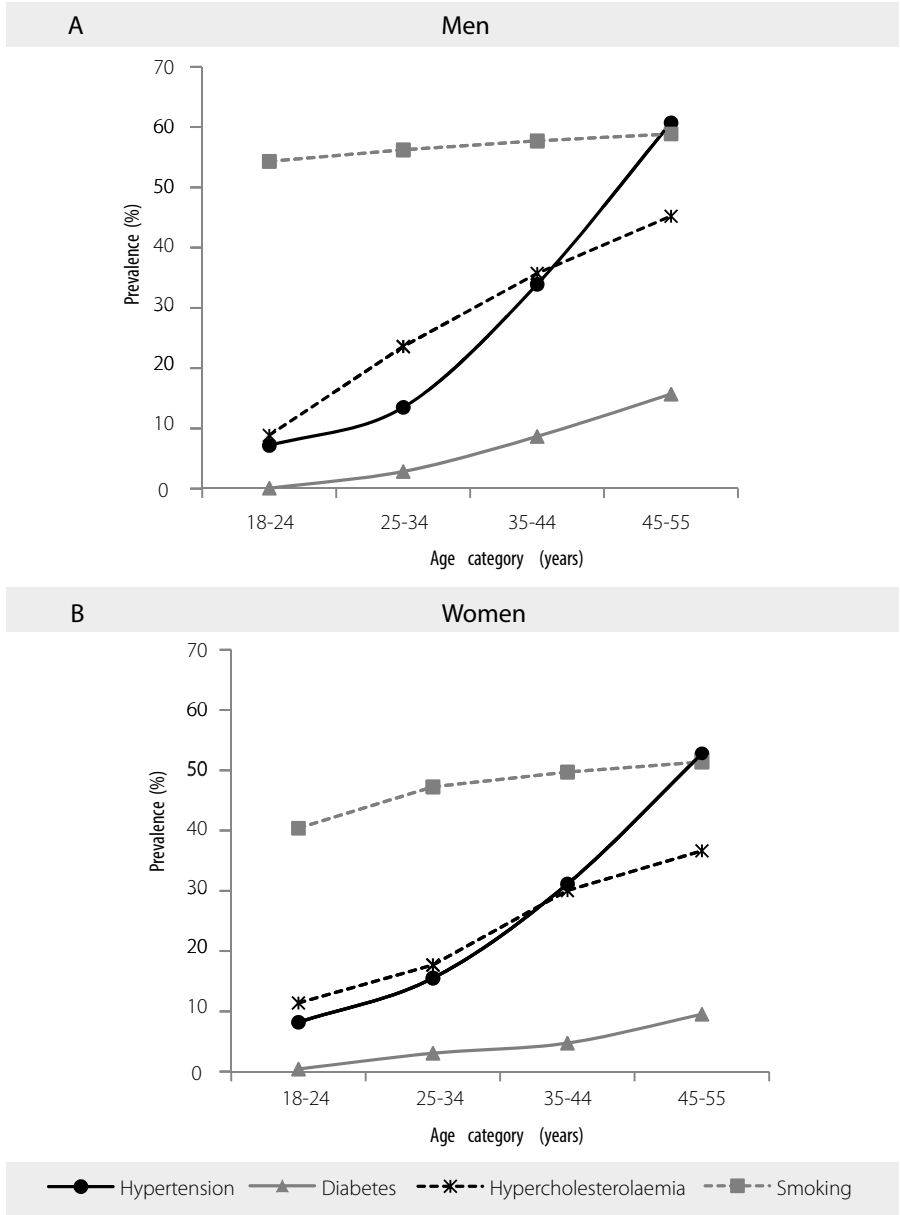
increasing prevalence of traditional vascular risk factors in this age group,[43, 45, 82, 101] which is at least supportive of a relationship between the two, although causality remains to be proven. Hypertension is reported in 19-39% of all young patients with stroke, dyslipidaemia in 17-60%, diabetes in 2-10%, smoking in 42-57%, and obesity in 10-20%.[5, 43, 45, 100-103] Figure 1 illustrates the increase in prevalence of the traditional vascular risk factors with age, indicating a sharp rise in the prevalence of hypertension — and, to a lesser extent, hypercholesterolaemia — over the age of 35 years.

Figure 2 shows that the number of traditional vascular risk factors per patient increases with age: in patients over 35 years of age, only a small fraction of patients has no vascular risk factors.

Despite the high prevalence of traditional vascular risk factors in young adults with stroke, a proven causal aetiology, such as large-artery atherosclerosis, remains to be identified in a large proportion of cases.[82] However, improved diagnostics, including high-resolution plaque and vessel wall imaging, might increase the likelihood of diagnosing a causal aetiology, especially among patients with vascular risk factors, by enabling detection of earlier stages of atherosclerosis.[106]

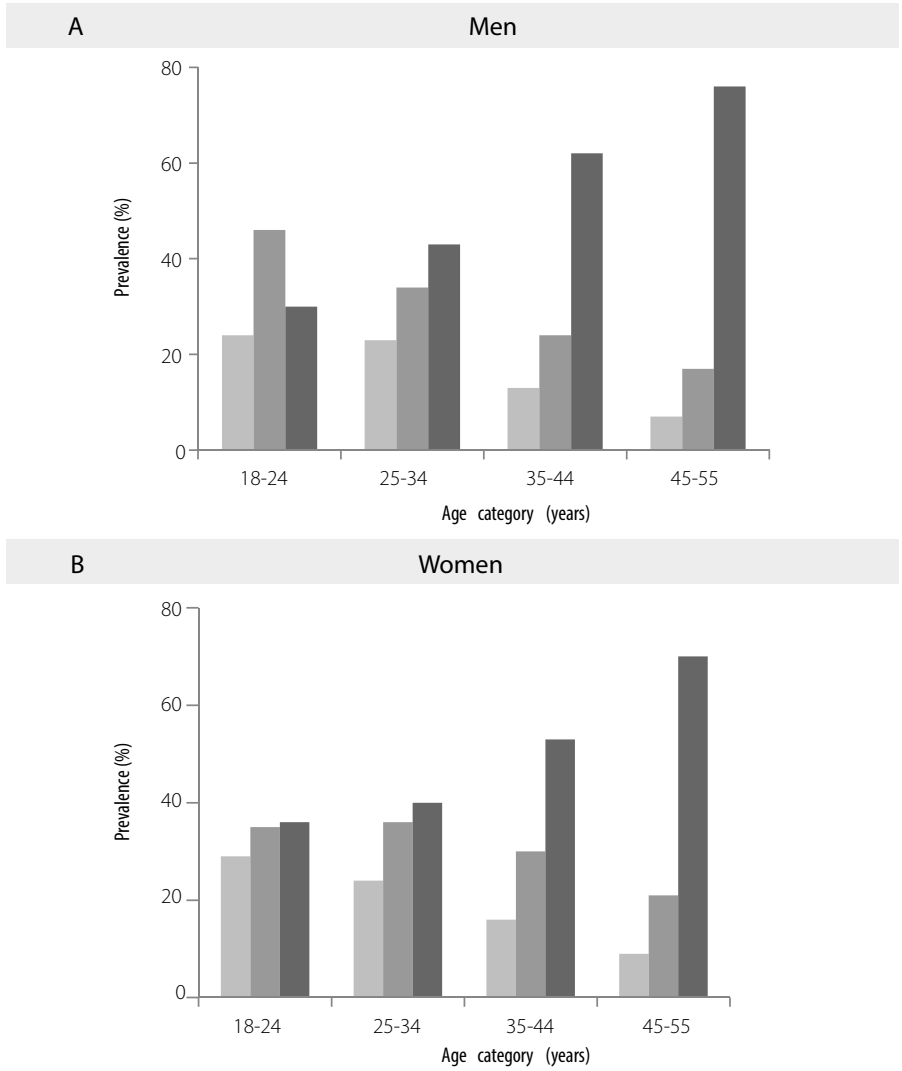
Given the abundance of traditional vascular risk factors, the proven presence of large-artery atherosclerosis might obviate the need for further diagnostic work-up, although the safety of this strategy requires confirmation in diagnostic studies. In patients without any proven aetiology, ancillary investigations are indicated to further unravel potentially treatable rare risk factors and aetiologies.

Figure 1 Prevalence of traditional vascular risk factors in young patients with stroke.



Graphs show the prevalence of various traditional vascular risk factors by age category, for **A** | men and **B** | women. Data were pooled from the 15 Cities study,[101] FUTURE study,[102] and SIFAP1 study.[45]

Figure 2 Age-specific proportions of patients with traditional vascular risk factors, stratified by sex.



Graphs show the prevalence of no, 1, or 2 or more traditional vascular risk factors in different age categories, for **A** | men and **B** | women. Traditional vascular risk factors that were considered were diabetes, hypertension, smoking, and hypercholesterolaemia. Data are extracted from the SIFAP1 study.[45]

Cardiovascular prognosis

Mortality

Prognosis in terms of mortality was usually considered to be favourable in young patients with stroke, given the lower short-term mortality rates compared with older patients.[107] However, long-term follow-up studies in young patients found 5-year cumulative mortality ranging from 9-11%, while the 10-year cumulative risk of death ranged from 12-17%.[27, 103, 108-111] In 30-day survivors of a young ischaemic stroke, 20-year cumulative mortality was reported to be 27%, which is 4 times higher than that of individuals in the general population matched for age and sex.[110] As Figure 3 shows, excess mortality is present across all age groups of young patients with stroke, but especially in those over 35 years of age, in whom vascular risk factors are also highly prevalent.

Figure 3 Long-term cumulative mortality in young patients with stroke and the general population with similar age, sex and calendar-year characteristics.

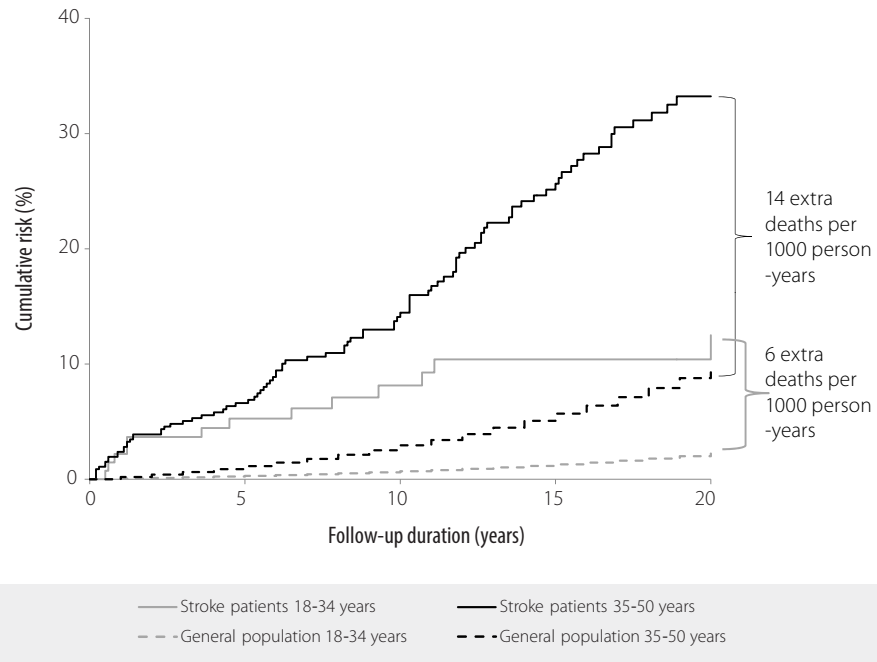


Figure shows the excess mortality of young patients with stroke, compared with the general population, stratified by age <35 years or ≥35 years. Based on data from the FUTURE study.[110]

In young adults who died during a 5-year[109] or a 20-year[110] follow-up period after stroke, vascular disease was the main cause of death. More than half of the deaths resulting from vascular disease were attributable to a vascular cause other than stroke. These findings suggest that the underlying (vascular) disease that caused stroke at a relatively young age continues to put these patients at an increased long-term risk of vascular disease.

Figure 4 Risk of death or recurrent vascular events, stratified by number of traditional vascular risk factors.

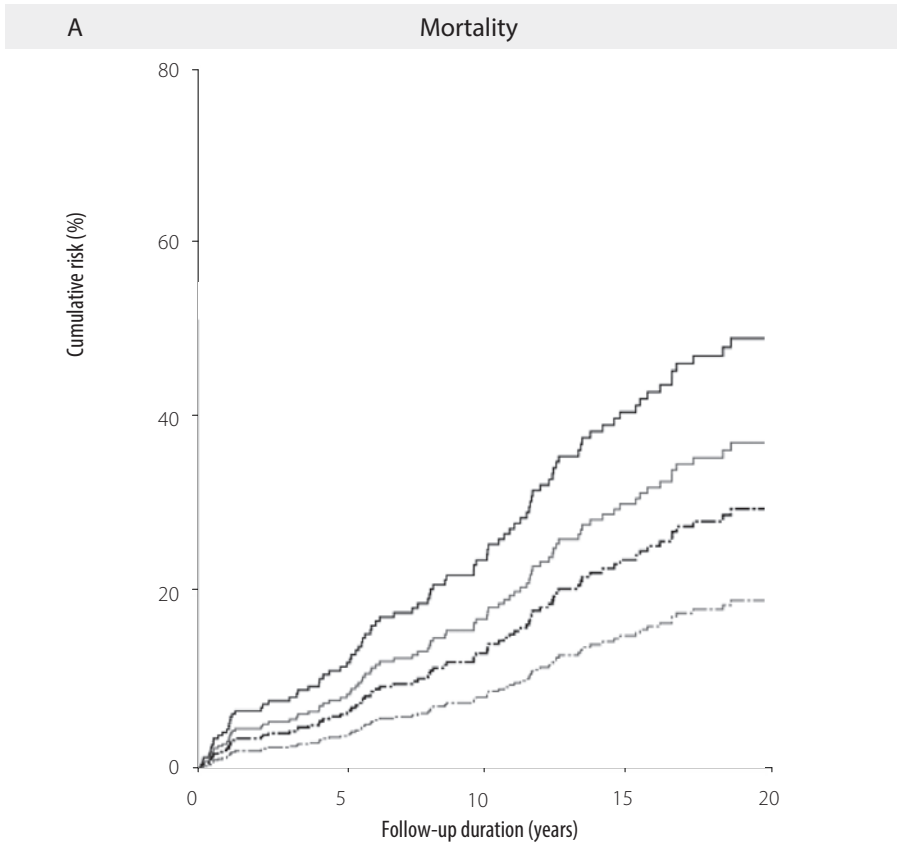
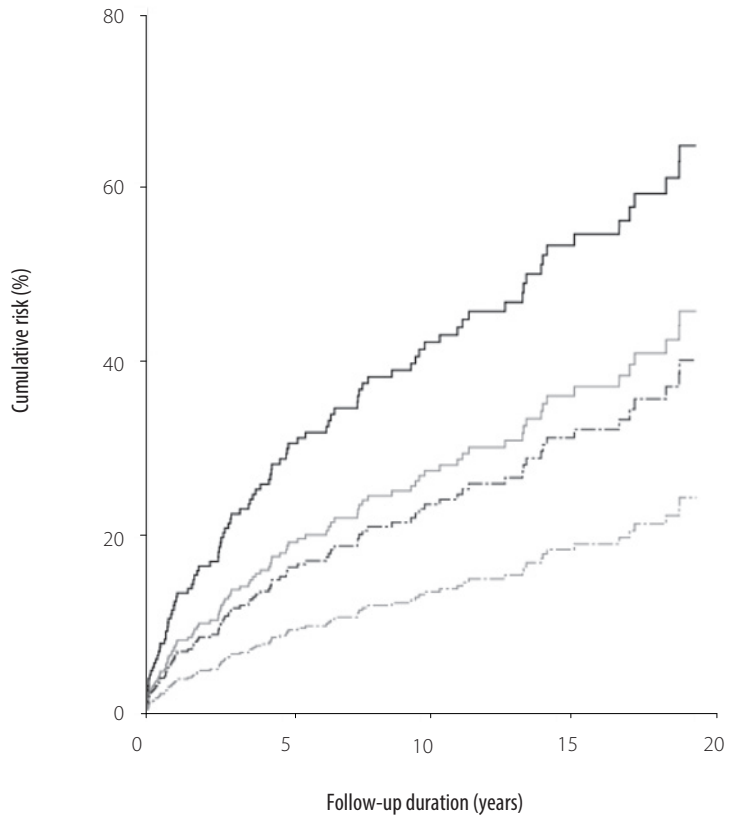


Figure shows risk of **A |** mortality and **B |** recurrent vascular events, stratified by the number of risk factors present. Risks are adjusted for age and sex. Traditional vascular risk factors that were considered were diabetes, hypertension, smoking, and hypercholesterolaemia. Based on data from the FUTURE study.[102, 110]

Figure 4 *Continued*

B Recurrent vascular events



Recurrent vascular events

In the first few years following a young stroke, patients are at a substantial risk of stroke recurrence (annual risk 1-3%)[5, 27, 102, 112-114] and, to a lesser extent, other cardiovascular vascular events (annual risk 0.5-1.0%).[102, 113, 114] In the decades that follow, the risk of recurrent events continues to be elevated, leading to a cumulative risk of 20% for recurrent stroke and 17% for other cardiovascular events.[102, 103, 113]

Identification of high-risk groups

High-risk groups in terms of recurrent mortality and cardiovascular events were identified on the basis of the TOAST classification.[3] The atherothrombotic stroke category was found to have the highest risk of mortality and recurrent stroke, compared with the other TOAST categories.[35, 102, 110, 115]

Risk factors that were associated with the highest 5-year risk of recurrent stroke predominantly included the traditional vascular risk factors, including age over 40 years, history of transient ischaemic attack, type 1 diabetes, and the use of antihypertensive medication.[114] The studies available found that the risk of mortality[109, 111, 116] and recurrent vascular events[102, 114] increased in parallel with the number of traditional cardiovascular risk factors present (Figure 4). Cardioembolic strokes were also associated with higher risks of mortality and recurrent vascular events.[102, 110]

Racial disparities in cardiovascular prognosis after young stroke have also been observed. In a short-term follow-up study of young stroke patients aged 18-45 years, black individuals had the highest 30-day risk of mortality: 10%, about 4 times the risk in Asians.[117] White individuals had an approximately 3.5-fold increased risk of 30-day mortality compared with Asians. These differences were independent of the presence of traditional vascular risk factors.

These findings indicate that prognosis in terms of long-term risk of cardiovascular disease after a young stroke is not as favourable as previously thought.[27, 108, 116, 118] Young patients with stroke, especially those who resemble older stroke patients with respect to the presence of traditional vascular risk factors and aetiology, also seem to show similarity to older patients in terms of long-term cardiovascular mortality and disease.

Of note, the prognosis for stroke patients in the 'other determined' category, which includes arterial dissection, seemed relatively favourable compared with the other categories.[78, 102, 115] However, one must keep in mind that this category includes a mixture of conditions, each with a different disease course and treatment options and, thus, variable prognoses.

Secondary prevention

Young patients with stroke are often under-represented in large secondary prevention trials on antiplatelet drugs, statins and blood pressure lowering agents.[35] Nonetheless, it is common practice to treat young stroke patients in accordance with guidelines based on extrapolated data from elderly patients with stroke.[119] This might be a sensible approach, given that a considerable proportion of these young patients have the risk factors that are targeted in these trials, and some of the trials showed greater benefits

in younger individuals (under 65 years) than in the older ones (65 years or over).[120] These conclusions are, however, mainly based on *post hoc* analyses, as no studies were specifically designed to investigate secondary prevention strategies in young adults with stroke. Although no evidence exists that long-term secondary prevention is particularly harmful in young patients, the question of whether these long-term prevention strategies are truly beneficial in all young adults with stroke — for example, in those patients in whom no risk factor or presumed aetiology could be found — remains to be answered. In addition, treatment strategies without proven benefit are not particularly cost-effective.

Secondary prevention strategies in some subgroups with a specific risk factor or aetiology have been investigated in young adults, for example, those with PFO or antiphospholipid syndrome. For a PFO, current evidence does not show superiority of closure, compared with medical treatment, in preventing recurrent strokes in adults under 60 years of age.[121] Two randomised controlled trials included *post hoc* subgroup analyses in patients aged 45 years or younger (approximately 45% of the study cohort), which showed no beneficial effects of closure in this subgroup.[122, 123] For patients with antiphospholipid syndrome, guidelines from the American Heart Association and American Stroke Association recommend treatment with oral anticoagulants, with an international normalised ratio (INR) between 2.0 and 3.0.[124] However, an expert panel could not reach consensus and noted that the evidence supporting higher or lower INR intensities or other strategies, such as antiplatelet therapy, was uniformly weak.[125]

To discover which patients will benefit the most from secondary prevention strategies, we suggest that recruitment of patients for future (multicentre) trials should be based on aetiological subgroups rather than age, so that younger patients are not excluded.

Physical impairments and complications

The risk factors and aetiology underlying a stroke have a substantial impact on cardiovascular mortality and morbidity. With respect to functional outcome and psychosocial consequences, however, the prognosis is more likely to be determined by a combination of factors, including not only aetiology, but also stroke severity and subsequent cerebral damage, co morbidity, demands from the patient's environment, and the patient's coping strategies. The sections that follow provide an overview of prognosis in terms of physical problems (functional outcome, pain, and epilepsy) and psychosocial consequences (cognitive impairment, depression, anxiety, fatigue, sexual dysfunction, and return to work) after a young stroke.

Functional outcome

Neurological deficits due to a stroke are often registered during hospital admission and discharge, as a measure of stroke severity on the NIH Stroke Scale. However, as no studies have described these neurological deficits in the years after discharge, the frequency of neurological deficit over time is not known.

Functional outcome is assessed in terms of disability, most commonly with the modified Rankin Scale (mRS), a scale that predominantly assesses motor function. Using this scale, functional outcome is usually found to be better in younger than in older adults after short-term follow-up.[126] For young adults, however, information on long-term physical disability is equally important, because of their long life expectancy. Only a few studies have reported long-term functional outcomes after young ischaemic stroke. Proportions of individuals with poor functional outcome (mRS score >2) among young stroke survivors range from 6-20% after a mean follow-up duration of 3-12 years,[103, 118, 127, 128] compared with 40% after short-term follow-up in older stroke survivors.[129]

Independence with regard to basic activities of daily living may not necessarily mean a good outcome for young patients: the ability to live independently as a young adult also requires independence in performing more complex tasks. In addition, demands from society on these young patients might be higher than in the elderly, because of occupational obligations and, in many cases, their role as a caregiver for a young family. The studies performed to date have not addressed these issues. Moreover, one must keep in mind that young stroke survivors with a poor functional outcome have to cope with this consequence for a considerable number of years, given their generally long life expectancy.

Epilepsy

Post-stroke epilepsy is reported to affect 2.4-14.4% of young patients with ischaemic stroke.[103, 113, 118, 130-132] The highest prevalence was found in a study that included patients aged 50 years and under;[132] most other studies only included patients up to 45 years of age. The lowest prevalence was found in a study that only included cryptogenic stroke.[130] Factors that were associated with epilepsy, either with or without recurrent seizures, included a more severe stroke and involvement of cortical structures.[113, 132] A study with a decade of follow-up revealed a long-term association between post-stroke epilepsy and a poor functional outcome, as measured with the mRS.[128]

Pain

The prevalence of post-stroke pain has frequently been studied in the older stroke population, and estimates vary considerably, from as low as 1% to as high as almost 50%.[133-136] This broad range is probably explained by the wide variation in methods used to assess post-stroke pain. Moreover, post-stroke pain originates from multiple sources, including central pain from both thalamic and extrathalamic lesions, and peripheral pain from musculoskeletal abnormalities, such as joint contractures.[133] No studies have specifically addressed the prevalence of pain after stroke in young adults. A recent report suggested a link between post-stroke pain and increased mortality in young patients with stroke.[137]

Psychosocial consequences

Cognitive impairment

Cognitive performance is an important determinant of social functioning in a young patient with stroke.[138] One year after stroke, up to 60% of young stroke patients had impaired cognitive performance compared with stroke-free controls, depending on the cognitive domain tested.[28, 29] In younger patients in particular, cognitive recovery is likely to continue beyond 1 year after stroke. However, 1 study reported that after a mean follow-up of 11 years, 50% of young patients with stroke still had to cope with impairment or below average performance on at least 1 cognitive domain.[139] Elderly patients with stroke commonly exhibit prominent frontal executive impairment,[140] whereas young patients generally show deficits in multiple cognitive domains, including visuoconstruction, delayed verbal memory, attention, and executive function. Most of these deficits are especially pronounced in patients with left-hemispheric lesions, with the exception of visuoconstruction, which seems to be more impaired after right-hemispheric strokes.[139] These findings suggest that cognitive impairment in young patients with stroke displays a more global pattern than one would expect on the basis of a focal lesion,[139] perhaps as a result of diffuse network dysfunction remote from the site of the lesion.[139, 141]

Aphasia has not been specifically tested in long-term follow-up studies.[139] One study that assessed language disturbances in the subacute phase after stroke found that young patients (under 51 years) were prone to non-fluent aphasia, whereas older patients were more likely to exhibit fluent aphasia, probably owing to a higher proportion of posterior infarcts in the older age group.[142]

Cognitive impairment can have life-changing consequences for young adults. For example, return to work may be impaired due to memory problems.[26] A short-term follow-up study found that the number of cognitive deficits predicted later inability to return to work.[143] This is not a surprising finding, as disturbances in multiple domains might interact, thereby diminishing the ability to compensate for impairments. For example, visual field defects can lead to reading disorders, and alexia could exaggerate this effect.[144]

Depression

Depressive symptoms are present in 28-46% of young patients with stroke[26, 27, 32] after follow-up durations of 6-12 years. Depressive symptoms can have a large impact on recovery and daily life after stroke. These symptoms have been associated with poor functional outcomes in an unadjusted analysis, but this association might have been confounded, for example, by recurrent vascular events.[26]

Patients with stroke were also found to have an increased risk of suicide (up to 7%), or suicidal ideations (6-15%) in both the acute and the chronic phase, especially when patients had current or past mood disorders.[145, 146] Young adults seemed to be at particular risk.[146]

In 1 study conducted in the general population, younger individuals tended to be classified as having a 'non-vascular depression' profile, which was characterised by a higher risk of suicide and more psychotic features, whereas older individuals more often displayed a 'vascular depression' profile, with a higher prevalence of functional disability and anhedonia.[147] The small study sample resulted in large confidence intervals, and the findings need further confirmation in large stroke cohorts. One might expect that the proportions of vascular and non-vascular depression profiles would not differ markedly between young and older patients in a stroke cohort, since both age groups have vascular lesions. However, elderly individuals might still exhibit a greater propensity towards a vascular depression profile owing to accumulation of vascular damage with age.

Depressive symptoms should not be confused with emotionalism (that is, emotional expressions outside a patient's normal control), which was reported in 22.5% of the general stroke population the first month post-stroke.[148] Although the 2 conditions co-occurred in 1 patient, and depressed mood was more likely to be present in patients with emotionalism, most patients with emotionalism were found not to be depressed. No studies on emotionalism versus depression have been conducted specifically in young patients with stroke.

Anxiety

Anxiety is present in 19% of patients with young ischaemic stroke after 12 years of follow-up,[26] but no studies exist on its influence on daily life.

Fatigue

Post-stroke fatigue is present in about 50% of young patients with stroke,[33] and seems to be associated with poor functional outcome[33] and inability to regain pre-stroke activities.[34, 149] However, most of the studies that assessed this complaint were limited with respect to sample size[34] or follow-up duration.[34, 149]

Some short-term follow-up studies in older stroke patients found fatigue to be associated with certain lesion locations.[24, 150] In young patients with stroke, however, fatigue could be the result of an imbalance between demands from society and reduced cognitive or physical capacity after stroke. Moreover, factors that underlie fatigue in the short term after stroke may differ from those in the long term, but these factors remain to be clarified.

Sexual dysfunction

One short-term follow-up study on sexual dysfunction, focusing on young patients with stroke (aged 18-45 years), found diminished sexual function in 22.5% of patients.[131] In the general stroke population, sexual dysfunction is caused by multiple factors, varying from neurological deficits (for example, hemisensory neglect[151] or aphasia) to psychological problems such as depression.[152] The relative contributions and long-term effects of the various factors in a young stroke population are unknown.

Hypersexuality may also be an issue after a young stroke. One study found this problem in just 1 of 71 young stroke patients, which may have been an underestimation, as the opinion of the patients' partners was not investigated.[131] Hypersexuality is thought to result from disinhibition due to lesions in the frontostriatal circuits, and also in the temporal lobe after ischaemic stroke.[153]

Return to work

Return to work after young stroke is an important determinant of life satisfaction,[36, 154] and might even be a necessity for many people to provide for themselves. In addition to the personal implications for patients, inability to return to work after stroke imposes an economic burden on society as a whole, owing to loss of productive years of employment.[37] However, only a few studies have addressed this important subject.

Reports to date indicate that 50-80% of stroke patients returned to work after a maximum follow-up of 4 years.[34, 155-158] However, most young patients with stroke will be of vocational age for more than a decade of their remaining life, which stresses the need for further studies on the very long-term prognosis with respect to return to work. In 1 study with a follow-up of almost 12 years,[26] only 40% of patients had returned to full-time employment by the end of the study period. However, these data must be regarded with caution, since the study was retrospective with a relatively low response rate.

Screening and treatment

Cognitive impairment, mood disorders, and fatigue seem to be very common in young patients with stroke, and functional outcome is poor in a substantial proportion of these young adults. If not actively screened for, these consequences often go unnoticed by caregivers, possibly leading to frustration in young patients when they are not able to return to their pre-stroke activities.[159] The first step in treatment of these 'invisible' psychosocial issues, therefore, is their recognition.

The next step is to start treatment for these symptoms. The current treatment strategies, which are suboptimal, consist primarily of occupational therapy[160] or medical treatment, for example, with antidepressants.[161, 162]

Directions for future research

Currently, only limited data exist on long-term psychosocial consequences and their impact on daily life functioning after stroke in young adults. Future studies should focus on the influence of these psychosocial factors on daily life and try to find clinical and demographic factors that can predict future psychosocial effects. Large, prospective cohort studies are needed for this purpose. These predictors might, in turn, provide insight into the pathophysiological mechanisms that underlie these psychosocial consequences, although imaging studies, postmortem studies or animal models would provide us with more fundamental insights.

In addition, treatment strategies should be developed, and their effects quantified, in clinical trials. Individuals who experience a stroke at a younger age have different rehabilitation goals from their older counterparts,[159] and specific programmes need to be developed that are adjusted to the specific needs of these young patients.

Conclusions and recommendations

In the past, stroke in individuals under 50 years of age ('young stroke') has been viewed as a disease with different risk factors and aetiology — and usually a better prognosis — in comparison with stroke in older patients. After a critical review of the available literature, however, this view may be challenged.

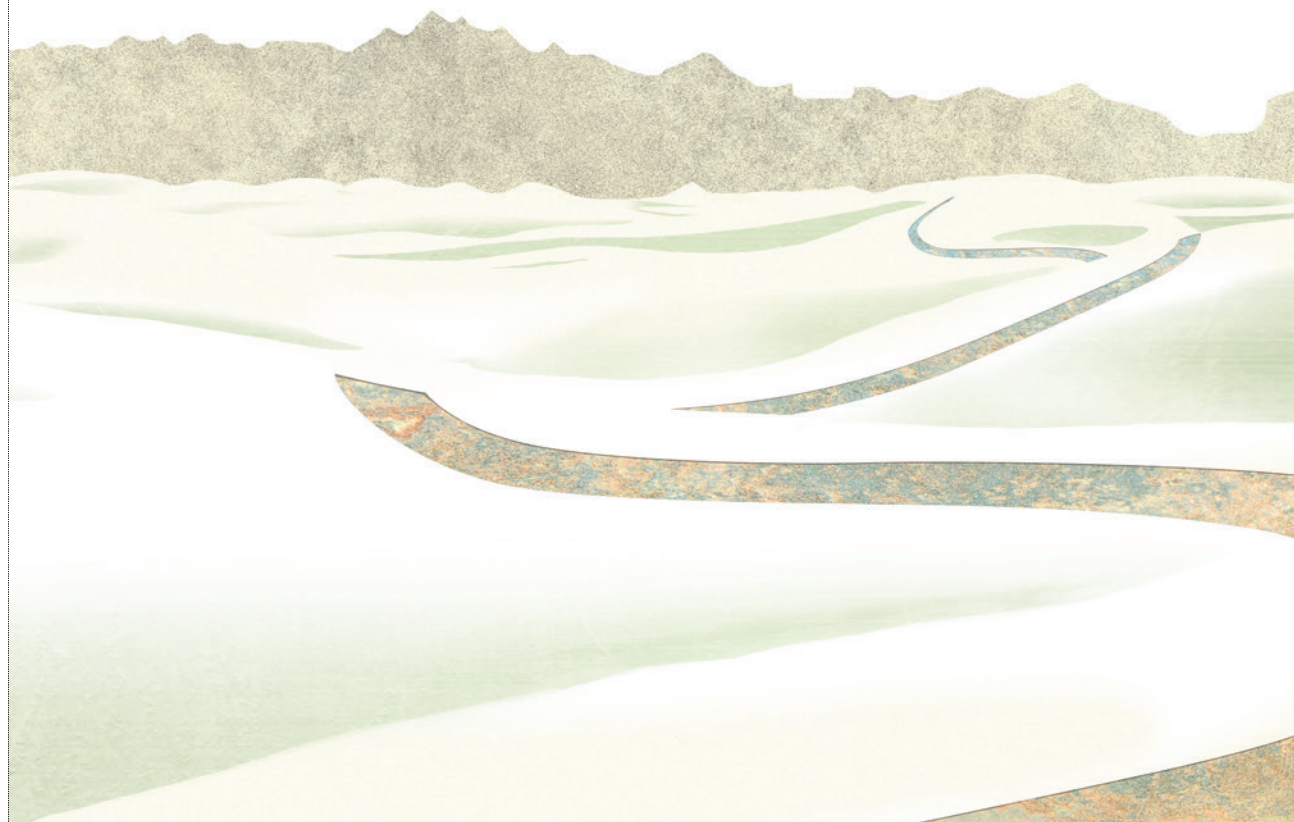
Traditional vascular risk factors in young adults with stroke have been somewhat neglected in the literature, which seems unjustified given their high prevalence,[35] especially in young patients between 35 and 50 years of age. This high prevalence coincides with a rising incidence of stroke in young adults, suggesting that traditional vascular risk factors might contribute more to the aetiology of young stroke than was previously thought. The presence of these risk factors, however, is not always related to causal aetiologies such as large-artery atherosclerosis, as assessed with current diagnostic tools. Young patients with stroke are at increased risk of cardiovascular mortality and morbidity compared with the general population, sometimes even approaching the risks observed in the older stroke population. The patients whose condition is classified as atherothrombotic stroke, with highly prevalent traditional risk factors, have the highest risk. In these patients, life-long treatment with secondary prevention seems to be a plausible approach. However, further trials are needed to establish which patients will benefit from different forms of secondary prevention. Recruitment of patients for these trials should be based on aetiological subgroups rather than age.

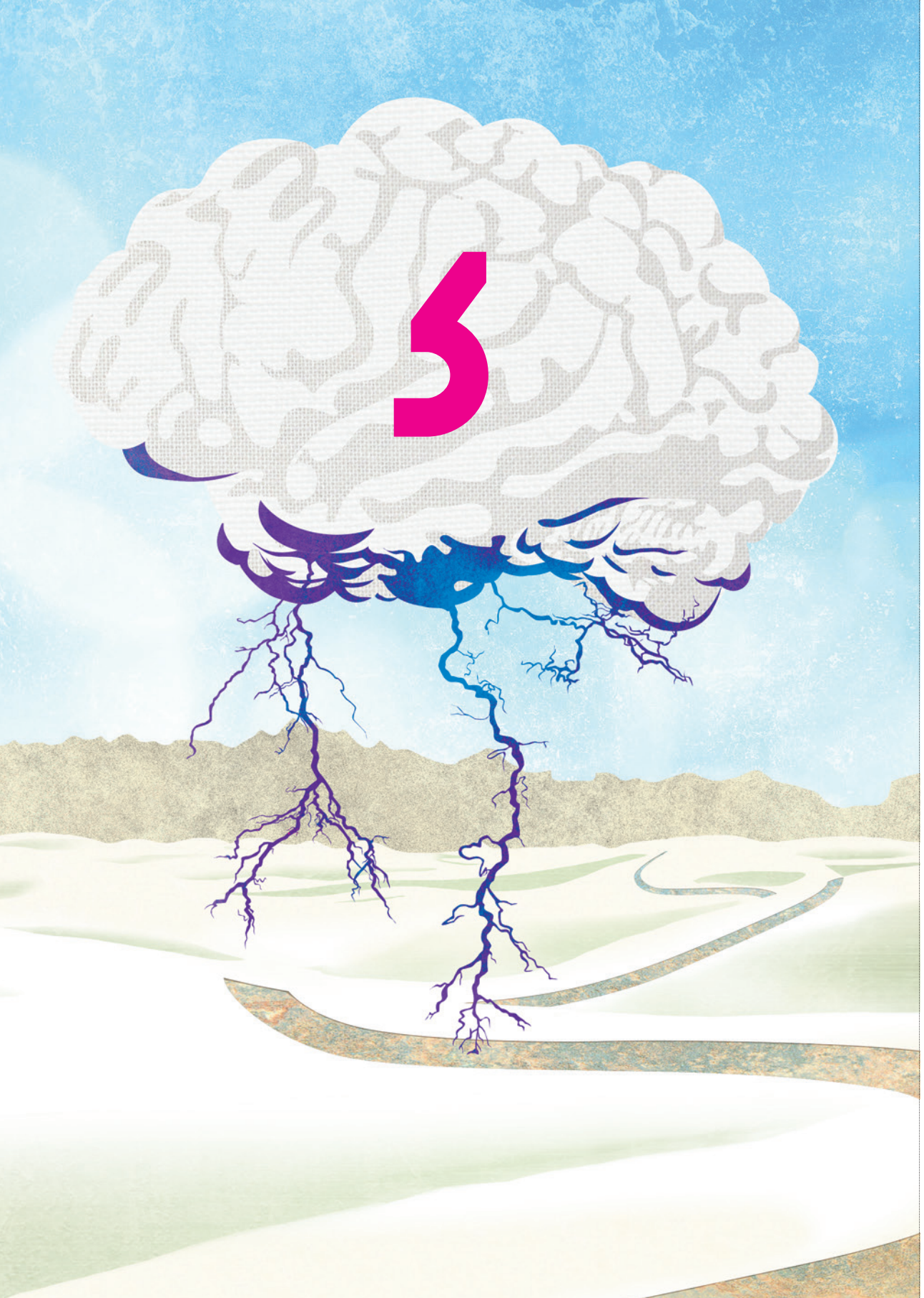
Although many 'young' stroke patients are 'old' with respect to aetiology and prognosis, they are 'young' when psychosocial consequences come into play, as most patients have a life expectancy of decades that includes phases of their lives in which important life-changing decisions have to be made. To fulfil these needs, treatment strategies tailored to the needs of young patients must be developed.

Stroke in young adults is an acute disease, but its life-long consequences are becoming increasingly recognised. Treatment and guidance, accompanied by a life-long perspective, should be offered to each young stroke survivor in order to attain the highest possible quality of post-stroke life.

PART II

Rationale and study design





The Follow-Up of Transient ischaemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study:

rationale and study design

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Risk factors and prognosis of young stroke. The FUTURE study: a prospective cohort study. Study rationale and protocol.

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Abstract

Background and objective

Young stroke can have devastating consequences with respect to quality of life, the ability to work, plan or run a family, and participate in social life. Better insight into risk factors and the long-term prognosis is extremely important, especially in young stroke patients with a life expectancy of decades. To date, detailed information on risk factors and the long-term prognosis in young stroke patients, and more specific risk of mortality or recurrent vascular events, remains scarce.

Methods/Design

The FUTURE study is a prospective cohort study on risk factors and prognosis of young ischaemic and haemorrhagic stroke among 1 006 patients, aged 18-50 years, included in our study database between 1-1-1980 and 1-11-2010. Follow-up visits at our research centre take place from the end of 2009 until the end of 2011. Control subjects will be recruited among the patients' spouses, relatives or social environment. Information on mortality and incident vascular events will be retrieved via structured questionnaires. In addition, participants are invited to the research centre to undergo an extensive sub study including MRI.

Discussion

The FUTURE study has the potential to make an important contribution to increase the knowledge on risk factors and long-term prognosis in young stroke patients. Our study differs from previous studies by having a maximal follow-up of more than 30 years, including not only TIA and ischaemic stroke but also haemorrhagic stroke, the addition of healthy controls and prospectively collect data during an extensive follow-up visit. Completion of the FUTURE study may provide better information for treating physicians and patients with respect to the prognosis of young stroke.

Introduction

Up to 12% of all strokes occur in patients between 18-50 years ('young stroke'),[103] affecting about 5000 patients each year in the Netherlands and about 2 million young people each year worldwide. In a substantial proportion of roughly one third the aetiology remains unelucidated. In terms of prognosis a young stroke has a dramatic influence on independency and quality of life as it occurs in the period of life that people start to form families, make decisive career moves, and have an active social life. Uncertainty about long-term prognosis affects choices and planning affiliated with these life events.

Whereas risk factors and prognosis in patients who develop a stroke at higher ages (usually over 70 years) are among the best studied topics in clinical medicine, this does not hold true for young stroke. At higher ages, almost all risk factors have atherosclerosis in their final common pathway. However, this cannot simply be extrapolated to young stroke as the underlying cause of stroke is usually different from that in elderly and may therefore also have a different prognosis both with respect to functional stroke outcome as to risks of recurrent stroke or other major vascular events. Even more, the identification of risk factors for young stroke so far has often been based on the occurrence of presumed risk factors in consecutive series of young stroke patients, without methodological sound comparison with controls.

The 'long-term' perspective in an on average over 70 years old stroke patient differs from that of a 30 years young stroke patient, and particularly studies with a long-term follow-up of more than 10 years are lacking in the young stroke field. Studies thus far, usually with a mean follow-up duration of less than 7 years, report highly variable post-stroke mortality and risk of incident vascular disease.[5, 103, 112-114, 163] These large differences across studies are well explained because young stroke is a heterogeneous disease and most studies were small, had different selection criteria, did not investigate patients in person but relied on telephone interviews, and outcome assessments and follow-up planning was not uniform and often suboptimal. Although stroke includes both ischaemic and haemorrhagic stroke, almost all studies have excluded the investigation of aetiology and prognosis of young haemorrhagic stroke.

Except for recurrent vascular disease and persistent motor and language impairments, post-young stroke quality of life will most likely also be determined by cognitive dysfunction, depressive symptoms, fatigue, and specific post-stroke complications such as epilepsy, because those determine the ability to (return to) work and to have a normal family and social life. Data on those aspects in the very long-term follow-up of young stroke patients are even more scarce.

Although the absolute number of young stroke is lower than stroke among the elderly,

the total number of years that young stroke patients as a whole will live with the consequences of the stroke exceeds that of older stroke survivors due to far longer survival. This justifies a properly designed and executed study on risk factors and prognosis of young stroke, compared with controls. We therefore set up the *FUTURE* study (*F*ollow-*U*p of *T*ransient ischaemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation study), the largest single-centre prospective cohort study on risk factors and prognosis of young TIA, ischaemic stroke and haemorrhagic stroke patients (n=1 006) and controls.

Methods/Design

The FUTURE study is a prospective cohort study that aims to investigate the causes and consequences of a young stroke. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

Patients

The department of neurology has a long-standing interest in the aetiology and prognosis of young stroke and therefore maintains a prospective registry of all consecutive young stroke patients with a standardised collection of baseline and clinical characteristics (see 'baseline') since the 1970'ies.[164] For the current *FUTURE* study, all consecutive TIA, ischaemic stroke patients with presumed arterial origin or those with an intracerebral haemorrhage that sought medical attention for these disorders at the department of neurology of the Radboud University Nijmegen Medical Centre between 1-1-1980 and 1-11-2010 will be eligible for participation in the study.

Inclusion criteria

- TIA, ischaemic stroke of presumed arterial origin or intracerebral haemorrhage
- Date of onset between 1-1-1980 and 1-11-2010
- Age 18-50 at onset

Exclusion criteria

- Traumatic haemorrhagic stroke
- Intracerebral haemorrhage in known cerebral metastasis or primary brain tumor
- Ischaemic/haemorrhagic stroke due to cerebral venous sinus thrombosis
- Intracerebral haemorrhage due to ruptured cerebral aneurysm
- Any subarachnoid haemorrhage
- Retinal infarct

TIA was defined as a rapidly evolving focal neurological deficit with no other than a vascular cause lasting less than 24 hours. Stroke was defined similarly, but with symptoms lasting more than 24 hours. On the basis of radiological findings, stroke was further subdivided into haemorrhagic and ischaemic stroke.
As the diagnostic process may have changed during a more than 30-year period all initial diagnoses were reviewed by a panel of 2 experts from a pool of 4 (FEdL, EvD, RA, LJD) and in cases of disagreement a consensus meeting was held to adjudicate the event.
1 006 patients who had sought medical attention at our University Medical Centre between 1-1-1980 and 1-11-2010 fulfilled inclusion and exclusion criteria for our study. Characteristics of our baseline population (at the time of their qualifying event) are reported in Table 1.

Table 1 Baseline population characteristics.

	Total population	Time of index event		
		1980-1989	1990-1999	2000-2010
n	1006	223	249	534
Men, n (%)	470 (46.7)	110 (49.3)	128 (51.4)	232 (43.4)
Age at index event, mean (SD)	40.2 (7.9)	39.3 (8.3)	39.7 (8.6)	40.8 (7.4)
Index event				
TIA, n (%)	277 (27.5)	52 (23.3)	40 (16.1)	185 (34.6)
Infarction, n (%)	630 (62.6)	146 (65.6)	189 (75.9)	295 (55.2)
Haemorrhage, n (%)	99 (9.8)	25 (11.2)	20 (8.0)	54 (10.1)

Controls

Control subjects will be recruited among the patients' spouses, relatives or social environment. They have to be at least 18 years old without a history of any TIA or stroke before the age of 50 at the moment of inclusion.

Baseline

At baseline (during the occurrence of the qualifying event for the study) a minimal dataset has been collected that consists of demographics, stroke subtype, risk factors, and additional investigations (Table 2). The completeness of the baseline dataset varies

among patients due to changes in standard diagnostic procedures over the last 30 years. Current common rating scales for the severity and cause of stroke did not exist at the time when a substantial proportion of our patients experienced their qualifying event. Therefore, a rating of both the severity (NIHSS) and cause (TOAST) was done for all cases retrospectively by a validated approach.[165]

Follow-up

Information on the vital status will be available either from hospital data or through coupling of patient records with data from the municipality registry. All patients alive will be approached for the follow-up assessment according to a 2-step approach.

First, all patients will be contacted by letter to inform them about the study; subsequently they will be contacted by phone. In case the patient has moved, the municipality register of the last known residence will be contacted to trace the patient. In cases of an invalid phone number, a second letter will be sent asking the patient to contact our centre to provide a correct phone number. Subsequently, when a patient does not respond to the second letter, the last known general practitioner will be contacted to provide us with updated contact details. The patient will be considered lost to follow-up when known alive, but when untraceable via the procedure described above.

Subsequently, patients will be given the opportunity to participate in an extensive sub study. If they agree to do so, they will be invited to visit our research centre for additional investigations including a structured interview, cognitive assessment, physical and neurological examination, an extensive MRI protocol, an electrocardiogram, and an ultrasonography of the carotid arteries (Table 2). In addition, blood samples (serum/plasma/DNA) will be taken for future analysis. When patients are not able to visit our research centre the same investigations will be performed at their homes, except for the ultrasonography of the carotid arteries, electrocardiogram, and MRI scan. Controls will undergo the same protocol as patients.

The follow-up has started at the end of 2009 and is planned to finish at the end of 2011. All these participants signed an informed consent.

Table 2 Schedule of assessments in the FUTURE study.

Assessment	Baseline	Follow-up
Demographics		
Ethnicity		X
Education		X
Marital status		X
Social/living status		X
Stroke Characteristics		
Qualifying event	X	
Symptoms at onset	X	
Discharge date and destination	X	
TOAST	X	
NIHSS at admission and at discharge	X	
Modified Ranking Scale at discharge	X	
Medical History		
History of any cardiovascular disease	X	X[a]
Cardiovascular risk factors	X	X[a]
Family history of cardiovascular disease	X	X
Medication use	X	X[a]
Stroke related surgical procedures	X	X[a]
Epilepsy	X	X[a]
Neuropsychological examination		
Global cognitive function		
Mini Mental State Examination (MMSE)	X	X
Verbal memory function		
Rey Auditory Verbal Learning Test		X
Visuospatial memory		
Rey's Complex Figure Test		X
Speed of information processing		
Symbol-Digit Substitution Task		X
Stroop test		X
Working memory		
Paper and Pencil Memory Scanning Tasks		X

Table 2 *Continued*

Assessment	Baseline	Follow-up
Neuropsychological examination		
Executive functioning		
Animal Fluency task		X
Attention		
Verbal series attention test		X
Subjective cognitive failures		
Cognitive failures questionnaire		X
Depressive symptoms		
Structured questionnaire depressive symptoms		X[a]
Mini International Neuropsychiatric Interview (MINI)		X
Centre of Epidemiological Studies Depression Scale (CES-D)		X
Hospital Anxiety and Depression Scale (HADS)		X
Physical examination		
Length and weight	X	X
Waist circumference		X
Blood pressure	X	X
Heart rate	X	X
Neurological examination		
Babinski sign	X	
Sensory system		
Quantitative measurement by vibration tuning fork		X
Muscle strength		
Medical Research Council Scale (MRC)		X
Mobility and activities of daily living		
TUG-test		X
Exercise expressed in metabolic equivalent value		X[a]
Tinetti test (body balance and gait)		X
Modified Ranking Scale (MRS)	X	X
Barthel Index		X
Instrumental activities of daily living questionnaire (IADL)		X

Table 2 *Continued*

Assessment	Baseline	Follow-up
Additional questionnaires		
Fatigue		
CIS20R		X
Health related quality of life		
Short Form 36		X
EQ-5D		X
Stroke impact scale 3.0		X
Sleep disturbances		X[a]
List of Threatening Experiences (LTE)		X[a]
Work		X[a]
Radiological examination		
Confirmation of index event (CT or MRI)	X	
Angiography	X	
MRI		
T1 magnetization-prepared rapid gradient echo		X
FLAIR pulse sequences		X
Transversal T2* weighted gradient echo sequence		X
Diffusion Tensor imaging		X
Resting state imaging		X
Time-of-flight angiography		X
Ancillary investigation		
Electrocardiogram	X	X
Ultrasonography of the carotid arteries	X	X

a) Variables were collected both for the period before and after the index event.

Outcome events

The primary outcome of the study will be all-cause mortality and the composite endpoint of death from all vascular causes; non-fatal stroke, non-fatal (silent) myocardial infarction, cardiovascular procedures (coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy, and other arterial revascularisation procedures), whichever occurred first. We will perform separate analyses for the occurrence of fatal or non-fatal stroke. Causes of death will be categorised into

ischaemic stroke, intracerebral haemorrhage, cardiac causes, other vascular causes or non-vascular causes. If we cannot obtain information about the cause of death, the event will be classified as unspecified.
Secondary outcomes are seizures (classified according to the ILAE[166]) and dementia (according to DSM-IV).
Whenever an outcome event is suspected with the aid of a standardised, structured questionnaire, information retrieved will be verified and adjudicated by physicians from the appropriate specialty. In case a patient has died, this information will be retrieved from their general practitioner or a relative. If there is no information available, the event will be classified as a possible event.

Assessment of variables during follow-up

Demographics and life style
Standardised questionnaires on demographics, education (classified using 7 categories; '1' being less than primary school and '7' reflecting an academic degree),[167] marital status, living conditions, and life style habits (alcohol consumption, smoking, exercise) will be administered. Alcohol consumption will be defined as units per day and the age at which alcohol consumption had started (and ended if stopped) will be noted. Cigarette smoking behavior will be defined as never, former, and current. Subsequently, former and current smoking behavior will be quantified as the number of pack-years, calculated as the number of packs of cigarettes smoked per day multiplied by the number of years a participant had smoked. Exercise will be expressed in the metabolic equivalent value (MET) according to accepted standards.[168]

Medical history
Structured, standardised questionnaires will be used to assess participants, history of hypertension, diabetes mellitus, atrial fibrillation, TIA, stroke, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, carotid endarterectomy and other arterial revascularisation procedures, [169-172] migraine with or without aura,[173] pregnancy, and malignancy. Whenever a primary or secondary outcome event is suspected with the aid of this standardised, structured questionnaire, information retrieved will be verified and adjudicated by physicians from the appropriate specialty (see outcome events). The presence of a family history of myocardial infarction, cerebrovascular disease, and diabetes mellitus in next of kin will be recorded.

Epilepsy
Each patient will be evaluated for a history of epilepsy by means of a standardised, structured questionnaire. Whenever epilepsy is suspected, information will be retrieved from the treating physician and verified and adjudicated by a neurologist (FEdL). Epilepsy will be classified according to the ILAE criteria.[166] Post-stroke epilepsy will be subdivided into early (≤7 days post-stroke) and late (>7 days) post-stroke epilepsy.

Current medication
Current medication use and the age at which medication use started will be noted and classified according to the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization, WHO Collaborating Centre for drug statistics and methodology, http://www.whocc.no/atcddd/).

Neuropsychological assessment
We will administer an extensive neuropsychological test battery that encompasses items from other large-scale epidemiological studies covering the main cognitive domains.[174, 175] Global cognitive function will be assessed using the Mini Mental State Examination (MMSE).[176] Verbal episodic memory function will be assessed by the 3-trial version of the Rey Auditory Verbal Learning Test (RAVLT) that also includes a delayed free-recall and recognition trial, a test used to evaluate the ability to acquire and retain new verbal information.[177] Visuospatial episodic memory will be administered by the Rey Complex Figure Test (RCFT), that consists of 3 trials: a copy trial, an immediate recall trial after 3 minutes and a delayed-recall trial after 30 minutes.[178] To evaluate speed of information processing and executive function, 2 tests will be used; the abbreviated Stroop Color Word Test (3 subtasks, the interference trial measuring response inhibition)[179] and the Symbol-Digit Substitution Task, which is a modified version of the Symbol Digit Modalities Test.[180] A verbal fluency task in which as many animals as possible have to be named within 60 seconds will be used to test semantic memory and executive functioning (response generation). To assess working memory, the Paper and Pencil Memory Scanning Task (4 subtasks)[181] will be used. To evaluate attention, the verbal series attention test (VSAT) will be used. [182] To register subjective cognitive failures we will administer the modified Cognitive Failures Questionnaire (CFQ).[183] The assessments will be carried out under standard circumstances in quiet rooms.
A standardised structured questionnaire used in previous large-scale epidemiological studies will be used to assess the history of depressive symptoms; normal reactions to stressful events or normal grief will carefully be excluded.[184] In case of a depres-

sive episode, age of onset, the medical advice and medication use will be registered. We defined 'depression' as those depressive episodes that have required attention of a general practitioner, psychologist or psychiatrist. This definition includes minor depression, as well as more severe depression syndromes such as major depression and bipolar depression.[184]
In addition, participants will be screened for current depressive symptoms by means of the Mini International Neuropsychiatric Interview (MINI), part A, which is a short diagnostic structured interview based on the DSM IV.[185] Additionally, presence of actual depressive symptoms will be assessed by 2 self report questionnaires, the Centre of Epidemiologic Studies Depression Scale (CES-D)[186] and the Hospital Anxiety and Depression Scale (HADS).[187]

Physical and Neurological Examination
Height and weight will be measured without shoes in light clothing. The body mass index (BMI) will be calculated as weight divided by height (in meters) squared. The maximal waist circumference will be measured without shirt, in standing position, between the lowest rib and the iliac crest, at the end of normal expiration.[188] Blood pressure and pulse rate will be measured in triplicate in supine position after 5 minutes rest. Subsequently 1 measurement is performed after 1 minute in upright position.[171]
The strength of the biceps, hand grip, iliopsoas, quadriceps, and foot extensor muscles on both sides will be scored according to the medical research council scale (MRC).
The sensory system will be assessed by a quantitative measurement by vibration tuning fork (Rydel-Seiffer®) on both first toes and both medial malleolus, also registering ankle edema and the ankle jerk reflex.

Gait and balance
We will use a widely used modified version of the original Tinetti test with 17 items: 9 for body balance (score 0-16) and 8 for gait (score 0-12), with a maximum score of 28.[189] It grades balance while sitting, standing with eyes open and closed, nudging and turning, gait initiation, stride length and width and symmetry. Functional mobility will be classified by using the widely-used timed-up-and-go(TUG)-test which is a timed test during which the participant is asked to rise from a standard armchair, walk 3 m, turn, walk back, and sit down again.[190] Each participant will perform the test 3 times.

Functional performance
As a measure of disability the Barthel Index and modified Ranking Scale will be used.[191] The activities of daily living will be assessed by the instrumental activities of daily living questionnaire.[192]

Additional self-report questionnaires
Several primary sleep disorders are addressed using a number of screening questions. The presence of possible sleep disordered breathing is based on a history of snoring, witnessed sleep-related apneas, and non-restorative sleep. Non-REM and REM parasomnias are addressed based on a history of sleepwalking or dream-enacting behaviour. Excessive daytime sleepiness will be assessed based on the presence of continuous feelings of sleepiness, sleep attacks or a combination of both. Finally, the presence of sleep-onset and/or sleep-maintenance insomnia is recorded.
For the assessment of fatigue we will use the Checklist on Individual Strength (CIS20R).[193] The overall health status (quality of life) will be assessed with the Short Form 36 (SF-36),[194, 195] the EQ-5D,[196] and the Stroke Impact Scale 3 (SIS-3).[197]
Adverse life events will be assessed with the 12-item List of Threatening Events (LTE), 6 months before the index event and subsequently the period after the index event.[198]
Patients will be asked for their employment status in the month before their index event, within the first year after their index event and at time of the follow-up visit. Each period includes a description of occupation, working hours a week, adjustments in tasks, use of supporting devices and reasons for not working.

Ancillary Investigations

MRI protocol
MRI scanning will be performed on a 1.5-Tesla Magnetom scanner (Siemens, Erlangen, Germany). The scanning protocol includes whole brain 3D T1 magnetisation-prepared rapid gradient-echo (MPRAGE) sequence (TR/TE/TI 2730/2.95/1000ms; flip angle 7°; voxel size 1.0x1.0x1.0mm); FLAIR pulse sequences (TR/TE/TI 12220/85/2200 ms; voxel size 1.0x1.2x3.0mm; slice gap 0.6 mm); transversal T2-weighted turbo spin echo sequence (TR/TE 7440/96ms; voxel size 0.9x0.9x3.0 mm; slice gap 0.6 mm); Multi-slab 3D time of flight angiography sequence (TR/TE 24/7ms; voxel size 0.8x0.5x1.0mm) will be made of the carotid arteries and the circle of Willis. Gradient echo susceptibility weighted imaging sequence (TR/TE 49/40ms; voxel size 0.8x0.7x1.0mm); DTI (TR/TE 9100/98ms; voxel size 2.2x2.2x2.2mm; 7 unweighted scans, 61 diffusion weighted scans, with non co-linear orientation of the diffusion-weighting gradient, and b value 1000s/mm^2) and

resting state imaging using a gradient echo EPI (TR/TE 1870/35ms; voxel size 3.5x3.5x3.0 mm; slice gap 0.5mm). During resting state, participants will be told not to concentrate on any particular subject, but just to relax with their eyes closed. The complete scanning protocol takes approximately 60 minutes.

ECG

An electrocardiogram (ECG) will be performed and evaluated by a standardised assessment by an experienced cardiologist, registering frequency, cardiac rhythm, cardiac ectopias, cardiac axis, conduction time over the PQ, QRS, and QTC intervals, conduction disturbances, left ventricle hypertrophy, pathologic Qs, infarction, repolarisation disturbances, and acute ischaemia. A final diagnosis is defined as normal, abnormal without clinical significance, abnormal with clinical consequences or pathologic ECG with immediate consultation of a cardiologist when necessary.

Carotid ultrasound

A carotid ultrasound assessment will be performed at which the intima media thickness (IMT) will be measured in the distal (near the bulbus) left and right common carotid artery. All measurements will be performed using a phased array real-time scanner (Philips i-u22, The Netherlands) with a 17-5 MHz broadband linear transducer. The IMT will be automatically measured by QLab® qualification software (V. 4.2.1.) according to previously described procedures.[199] All ultrasound measurements will be performed by 3 experienced and specific trained clinical neurophysiology technicians.

Vena puncture

Fasting blood samples will be taken. Immediate analysis will include glucose, creatinine, lipid profile and complete blood count. Additional serum, plasma and DNA will be stored (-80°C) for future biochemical and genetic analyses.

Statistical analysis

Cumulative risk of primary and secondary outcomes will be estimated with Kaplan-Meier analysis. In the analysis of vascular events, patients who had died from other than the defined fatal endpoints will be censored at the time of death. Cox proportional hazard models will be used to calculate the risk of suffering from any of the primary or secondary outcomes in the follow-up period, with adjustments for the necessary covariates. The relative risk (hazards ratios) will be calculated with their corresponding 95% confidence intervals.

Cross-sectional analysis (for example in the comparison between patients and controls of data acquired during the follow-up) of continuous variables will be done with Student's *t*-test or analysis of variance or in case of skewed distributions which cannot be normalised corresponding non-parametric tests will be used. Chi-squared test will be used for cross-sectional analysis of categorical variables.

Discussion

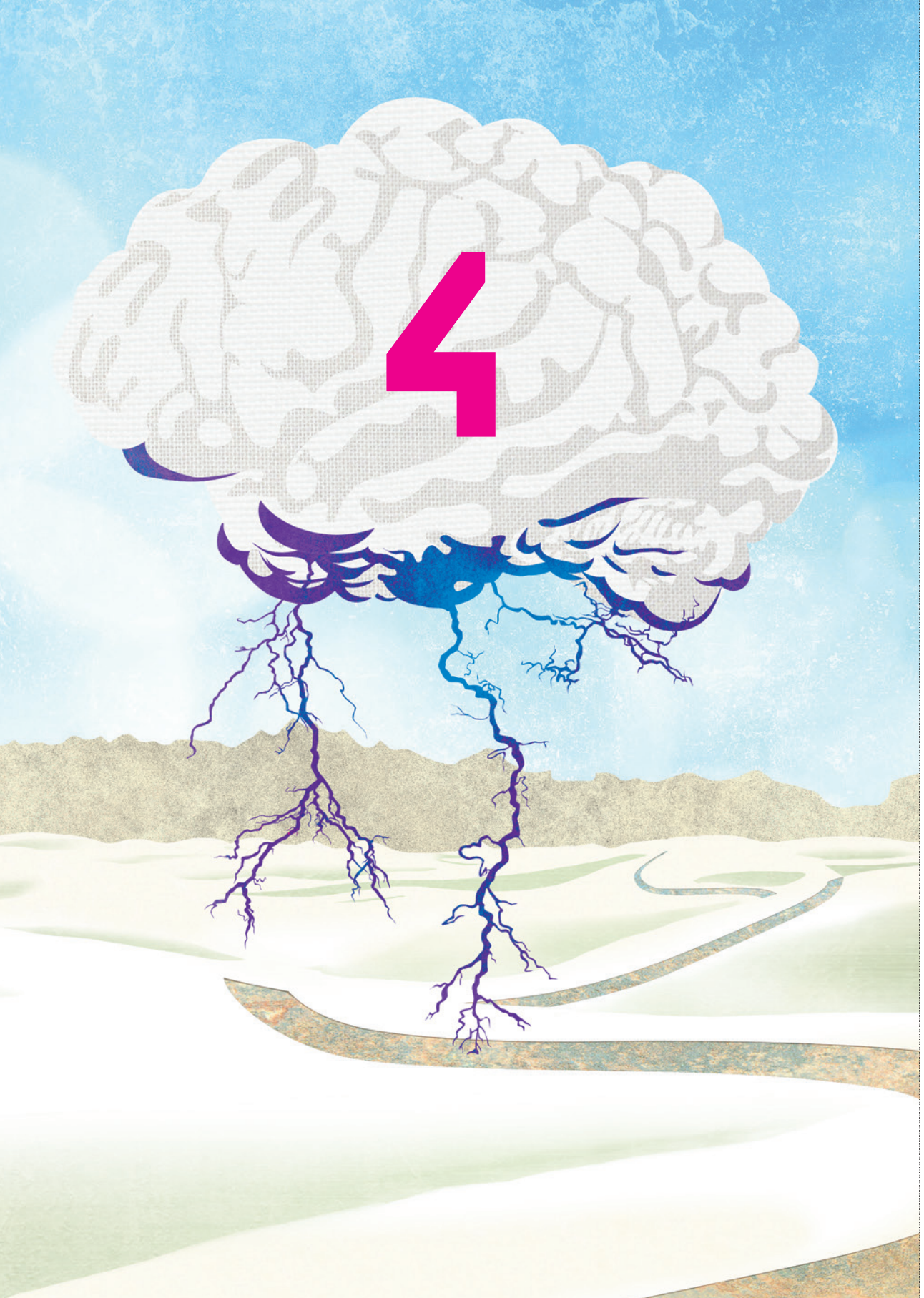
Detailed information on risk factors and the long-term prognosis in young stroke patients, and more specific the risk of mortality and recurrent vascular events, remains scarce. These data are often derived from selected patients (often with the exclusion of TIA and haemorrhagic stroke patients) in small sized studies with short follow-up without in person assessment of risk factors and outcomes. We therefore performed the FUTURE study, designed to investigate risk factors and to prospectively assess prognosis in a large cohort of young stroke patients.

Strong elements of our study are the inclusion of both TIA and haemorrhagic and ischaemic stroke patients, the very long follow-up (up to 30 years), its sample size of over 1 000 potential participants and the availability of baseline data of all consecutive patients in a single university medical centre. In addition, the extensive investigation during a follow-up visit, including advanced neuroimaging has the potential of major contributions to the field. Our study differs from many other young stroke studies due to the inclusion of controls that enable us to compare the frequency of some presumed, but also unknown, risk factors between patients and controls. Detailed risk factor analysis can be done, not only for commonly documented risk factors but also for those that are rarely documented in medical records, like physical inactivity and sleep disturbances. Moreover, the inclusion of healthy controls provides the opportunity to distinguish consequences of a young stroke from other factors like ageing effects.

We feel that completion of our study may contribute to a better understanding of the aetiology of young stroke and may provide better information for treating physicians and patients with respect to the prognosis of young stroke.

PART III

Long-term neuropsychological and social consequences after stroke in young adults



Cognitive performance after young ischaemic stroke

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Long-term cognitive impairment after first-ever ischaemic stroke in young adults.

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**shared first authorship*

Abstract

Background and objective

Up to 14% of all ischaemic strokes occur in young adults (<50 years). Post-stroke cognitive performance is a decisive determinant of their quality of life. However, virtually no studies report on cognition after young stroke, especially not on the long term. This long-term perspective is important since young patients have a long life expectancy during which they start forming a family, have an active social life and make decisive career moves. We aimed to evaluate the long-term cognitive outcome.

Methods

All consecutive patients between January 1, 1980 and November 1, 2010 with a first-ever young ischaemic stroke were recruited for cognitive assessment, using a matched stroke-free population as a reference. Composite Z-scores for 7 cognitive domains were calculated and the ANCOVA model was used (Bonferroni correction). A below average performance was defined as >1.0 SD below the age-adjusted mean of the controls and cognitive impairment as >1.5 SD.

Results

277 patients and 146 matched controls completed cognitive assessment (mean follow-up 11.0 (SD 8.2) years; mean age 50.9 (SD 10.3) years. Long-term cognitive outcome after an ischaemic stroke was worse in most cognitive domains compared with a non-stroke population. Up to 50% of the patients had a below average performance or cognitive impairment. Deficits in processing speed, working memory, and attention were most common.

Conclusions

Even 11 years after ischaemic stroke in young adults, a substantial proportion of patients must cope with permanent cognitive deficits. These results have implications for information given to patients and rehabilitation services.

Introduction

Approximately 10% to 14% of all ischaemic strokes occur in young adults (aged 18-50).[43, 104, 200-204] The incidence of stroke in young adults is rising, which is a major concern.[6]

Their outcome is usually considered fairly good, since these patients usually have a good motor recovery,[118, 129] and outcome after stroke is usually assessed with rating scales that predominantly measure motor performance.[7] However, post-stroke outcome is also very much dependent on cognitive performance after stroke. Surprisingly, there are only a few studies that addressed cognitive outcome on the short term (4-12 months)[28, 29] and none on the long term. Although these short-term studies found somewhat lower cognitive performance in ischaemic stroke patients compared with controls, that may still very well be compatible with the common observation of gradual cognitive recovery, that may continue for at least 1 year or longer after stroke.[205, 206] Since life expectancy of most of these patients exceeds by far 1 year,[109] patients need to be informed about their cognitive prognosis, not only on the short term, but particularly for the coming decades as they are in a period of life in which they start forming a family, have an active social life, and make decisive career moves. It is exactly this long-term perspective that is currently missing. The aim of the present study was to investigate the long-term cognitive performance after a first-ever young ischaemic stroke.

Patients and methods

Study design

This study is part of the '*F*ollow-*U*p of *T*ransient ischaemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation' (*FUTURE*) study, a large cohort study which investigates causes and consequences of stroke in young adults.[42] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study and the recruitment of controls. The present study comprises all consecutive patients with a first-ever ischaemic stroke of presumed arterial origin, aged 18-50 years, admitted to Radboud University Nijmegen Medical Centre from January 1, 1980, until November 1, 2010. This hospital is a large academic centre, receiving patients from both the direct environment as well as serving as a tertiary referral centre. Our hospital is the only academic medical centre in our region.

Patients were identified through a prospective registry of all consecutive young ischaemic stroke patients that has been kept at the department since the 1970s with a

standardised collection of baseline clinical characteristics and neurological exam. Ischaemic stroke was defined as focal neurologic deficit persisting more than 24 hours. The diagnosis of ischaemic stroke and lesion location were based on medical records and radiological findings.
The diagnostic techniques improved during a 30-year period and to minimise bias all initial diagnoses were reviewed by a panel of 2 experts from a pool of 4 (FEdL, EvD, RA, LJD) and in cases of disagreement a consensus meeting was held to adjudicate the event.
Primary exclusion criteria for ischaemic stroke patients in the FUTURE study were cerebral venous sinus thrombosis and retinal infarction. There were additional exclusion criteria for cognitive assessment based on the neurological exam, which was also a part of the FUTURE study (Figure 1).
Controls were recruited among patients' spouses, relatives, or social environment. They had to be at least 18 years old without a history of TIA or stroke. The control group and patient group were matched for age, sex, and level of education. Controls were all living independently, none fulfilled the clinical criteria of dementia. They were recruited from the same environment as patients.
Written informed consent was obtained from all participants.

Cognitive assessment

Neuropsychological tests were administered between November 2009 and end 2011. They covered the main cognitive domains and these tests have been previously applied in large-scale epidemiological studies in cerebrovascular disease.[174, 175] Strict instruction protocols were used to assess cognitive performance and researchers were trained. The following cognitive domains were examined: *Processing speed* (the written administration of the Symbol-Digit Modalities Test, Abbreviated Stroop Color Word Test, parts I and II), *Visuoconstruction* (Rey-Osterrieth Complex Figure (ROCF) - Copy trial), *Working memory* (Paper and Pencil Memory Scanning Task (PPMST)), *Immediate memory* (ROCF - Immediate recall and the total number of words immediately recalled in the 3-trial version of the Rey Auditory Verbal Learning Test (RAVLT)), *Delayed memory* (delayed recall on the ROCF and the RAVLT), *Attention* (Verbal Series Attention Task (VSAT)), and *Executive functioning* (Verbal Fluency and Stroop Interference). To account for speed-accuracy trade-off on the Stroop test, PPMST, and VSAT, composite scores were calculated (accuracy(%)/reaction time).[207] Stroop Interference was computed by dividing the composite Stroop part III score by the mean of the composite scores of parts I and II. To prevent potential bias in scoring the ROCF, 2 researchers independently rated 10% of the complex figures in both patients and controls, with high inter-rater

reliability using the Spearman's correlation coefficients (Copy: r_s=0.90; Immediate recall: r_s=0.97; Delayed recall r_s=0.95). Detailed information on the neuropsychological examination is described extensively elsewhere.[42]

Other measurements

Age, sex, level of education, depressive symptoms, and fatigue were considered possible confounders. Level of education was scored with a Dutch scoring system (1=less than primary school; 7=university degree).[208]
Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS),[187] and fatigue was assessed using the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[193, 209]
Marital status (married, divorced, widowed, and never married) at follow-up was reported. Employment status at follow-up was defined as the number of patients who worked/studied at the time of their event and were unemployed, still employed or retired at follow-up assessment. Employment status of controls was defined as employed, unemployed, and retired at follow-up assessment. Functional outcome during follow-up visit was evaluated using the Barthel Index[210] and modified Ranking Scale (mRS).[7] A good functional outcome was defined as a mRS score of 0-1 and a Barthel Index of ≥85.[211]
Furthermore, assessment of both the aetiology (TOAST)[212] and severity (National Institutes of Health Stroke Scale; NIHSS)[213] was performed retrospectively in all cases using a validated approach,[165, 214] because these scales did not exist at the time when a substantial proportion of the patients experienced their qualifying event.
We assessed vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking (current/former/never), current alcohol use (>2 units/day)), and vascular disease (myocardial infarction and recurrent stroke) on the basis of medical history using a standardised, structured questionnaire and/or the use of medication. Whenever a myocardial infarction or recurrent stroke was suspected information retrieved was verified and adjudicated by physicians. The body mass index (BMI) at follow-up was calculated as weight (kilograms) divided by height (meters) squared.

Statistical analysis

Baseline characteristics were presented as means (±SD), median (Q1-Q3) or number of cases (%). All statistical analyses were performed with SPSS 20.0 software for Windows. Baseline characteristics in young ischaemic stroke participants and ischaemic stroke patients who refused cognitive assessment were compared using a Pearson's chi-

square test, Mann-Whitney *U* test, or Student's *t*-test when appropriate. To adjust for multiple comparisons in all analyses a Bonferroni correction was applied (p-values <0.0071 were considered significant, since there were 7 pairwise comparisons for each analysis).
The mean raw cognitive test scores (±SD) for each test were calculated. The Rey Complex Figure - Copy trial showed a left skewed distribution, therefore this variable was transformed (e^5) to obtain a normal distribution to use in all subsequent analyses.[215]
For the purpose of data reduction, across-domain comparison, and statistical considerations, raw test scores were converted to Z-scores, using the mean and standard deviation of the controls. Z-scores of tests assigned to the same cognitive domain were averaged and were used in all subsequent analyses as composite Z-score, or domain score. If 1 test of a particular domain was missing, the domain score was occasionally based on the remaining tests of that domain (always <5.1%).
A 1-way ANCOVA model was used for each cognitive domain with a 2-level factor adjusting for age, sex, level of education, depressive symptoms, and fatigue severity. All p-values reported were 2-sided and confidence intervals were calculated at the 95%-CI. Linear regression was used to explore the effect of differences in follow-up duration and performance on cognitive domains adjusting for age, sex, level of education, depressive symptoms, and fatigue. Results were reported as standardised beta coefficients.

Below average performance and cognitive impairment

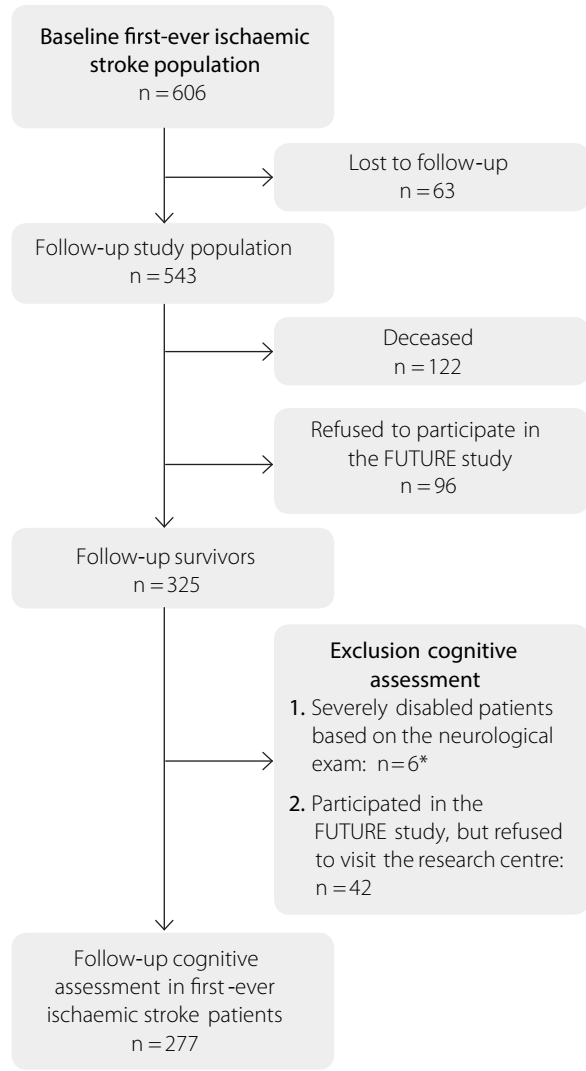
Due to the long-term follow-up patients differed in age at follow-up cognitive assessment. Obviously, age has an influence on cognitive performance apart from stroke.[216]
To account for differences in age, age-adjusted Z-scores for each neuropsychological test were calculated using the mean and SD of the controls in 3 different strata of age at follow-up: 20-40, 40-60 and 60-80 years. Next, Z-scores of cognitive tests assigned to the same cognitive domain were averaged.
The frequency of a below average performance (>1.0 SD below age-adjusted mean of controls) and cognitive impairment (>1.5 SD) was determined.[140]
A Pearson's chi-square test (or Fisher's exact test when an expected cell count was less than 5) was used to investigate differences between patients and controls in the proportion of participants with cognitive impairment.

Lesion location and cognitive outcome

The frequency of cognitive impairment or a below average performance for each cognitive domain in patients with supratentorial infarction (left vs. right) and infratentorial infarction was determined. The proportion of patients with cognitive impairments

were compared with controls using a Pearson's chi-square test (or Fisher's exact test when an expected cell count was less than 5).

Figure 1 Flowchart of the study population.



*Severe psychiatric disorder (1), inability to communicate in Dutch (1), blind and deaf (1), severe fatigue (1), severe aphasia (only sounds) and bilateral hemianopia (1), severe physical disabilities (1).

Recurrent stroke

All above described analyses were conducted including and excluding patients with a recurrent stroke to investigate whether patients with recurrent events influenced the results.

Results

The study population consisted of 277 ischaemic stroke participants and 146 controls (Figure 1).

Basic demographic and clinical characteristics of the study population are described in Table 1 and neuropsychological test scores are presented in Table 2.

Mean age of patients was 40.0 (SD 7.7) years at stroke onset; 55.6% was female. Mean follow-up of the study population was 11.0 (SD 8.2) years, while 48.0% had a follow-up of 10 years or longer. Participants did not significantly differ on basic demographical and clinical characteristics from ischaemic stroke patients who refused to participate or who did participate in the FUTURE study but did not want to visit the research centre (Table 1).

Ischaemic stroke patients had a worse cognitive performance on 6 cognitive domains after a mean follow-up of 11 years compared with controls (processing speed: F(1,406): 35.4, p<0.0001; working memory: F(1,407): 41.7, p<0.0001; immediate memory: F(1,412): 14.0, p=0.0002; delayed memory: F(1,408): 17.7, p<0.0001; attention: F(1,396): 28.6, p<0.0001; executive functioning: F(1,409): 17.2, p<0.0001) (Figure 2).

Follow-up duration

In ischaemic stroke patients longer follow-up duration was associated with a lower immediate memory (β: -0.23, p=0.001), delayed memory (β: -0.30 , p<0.0001) and executive functioning score (β: -0.22, p=0.004).

Below average performance and cognitive impairment

Ischaemic stroke patients showed a substantial higher proportion of patients with a below average performance (-1.5 SD ≤ composite Z-score <-1 SD) or cognitive impairment (>1.5 SD) compared with controls (Figure 3A). Up to 50% of all ischaemic stroke patients had a below average performance or cognitive impairment. Cognitive impairments were frequent among patients, affecting up to 34.5%. Deficits in processing speed, working memory, and attention were most common.

Table 1 Demographic and clinical characteristics of the study population and ischaemic stroke patients who refused cognitive assessment.

	Ischaemic stroke participants (n=277)	Refusals[a] (n=138)	p-value[b]	Controls (n=146)
Age at index event (years)	40.0 (7.7)	40.1 (8.0)	0.84[c]	NA
Men	123 (44.4%)	59 (42.8)	0.75[d]	61 (41.8%)
Follow-up duration	11.0 (8.2)	NA		NA
<10 years	144 (51.9%)	NA		NA
≥10 years	133 (48.0%)	NA		NA
Lesion location				
Supratentorial stroke	218 (79.0%)	NA		NA
Left	116 (42.0%)	NA		NA
Right	102 (37.0%)	NA		NA
Bilateral	7 (2.5%)	NA		NA
Infratentorial stroke	51 (18.5%)	NA		NA
Age at follow-up examination	50.9 (10.3)	NA		48.6 (11.7)
Education	5 (4-6)	NA		5 (5-6)
NIHSS score at admission	4 (2-8)	4 (2-7.75)	0.79[e]	NA
Barthel Index at follow-up	96.9 (9.7)	NA		99.6 (1.5)
Good outcome (BI ≥85)	262 (94.6%)			146 (100%)
modified Ranking Scale at follow-up	1 (1-2)	NA		0 (0-0)
Good outcome (mRS 0-1)	191 (69.0%)	NA		139 (95.2%)
Marital status at follow-up				
Married	180 (65.7%)	NA		97 (66.4%)
Widowed	5 (1.8%)			4 (2.7%)
Divorced	22 (8.0%)	NA		6 (4.1%)
Never married	67 (24.5%)	NA		39 (26.7%)
Employment status at follow-up[f]				
Working	120 (51.9%)	NA		101 (70.1.2%)
Unemployed	94 (40.7%)	NA		35 (24.3%)
Retired	17 (7.4%)	NA		8 (5.6%)
MMSE at follow-up	26.3 (2.6)	NA		27.2 (1.9)
HADS - depressive symptoms	4.0 (3.6)	NA		2.5 (2.7)

Table 1 *Continued*

	Ischaemic stroke participants (n=277)	Refusals[a] (n=138)	p-value[b]	Controls (n=146)
CIS-20R - fatigue severity	30.3 (13.9)	NA		22.5 (12.8)
TOAST			0.21[d]	
Large-artery atherosclerosis	66 (23.8%)	42 (30.4%)		NA
Cardiac source of embolism	26 (9.4%)	10 (7.25%)		NA
Small-vessel occlusion (lacune)	38 (13.7%)	16 (11.6%)		NA
Stroke of other determined aetiology	47 (17.0%)	33 (23.9%)		NA
Multiple aetiologies	7 (2.5%)	3 (2.2%)		NA
Stroke of undetermined aetiology	93 (33.6%)	24 (24.6%)		NA
Vascular medical history				
Myocardial infarction	16 (5.8%)			3 (2.1%)
Recurrent stroke	30 (10.8%)			NA
Vascular risk factors				
Hypertension	150 (54.2%)			44(30.1%)
Diabetes mellitus	34 (12.3%)			6 (4.1%)
Dyslipidaemia	185 (66.8%)			26 (17.8%)
BMI at follow-up	26.9 (5.1)			26.9 (4.7)
Smoking				
Current	78 (28.2%)			38 (26.0%)
Former	129 (46.6%)			55 (37.7%)
Never	70 (25.3%)			53 (36.3%)
Alcohol (>2 units/day)	19 (6.9%)			14 (9.6%)

Data are expressed as mean (SD), number (%) or median (Q1-Q3). NIHSS: National Institutes of Health Stroke Scale, MMSE: Mini Mental State Examination, HADS: Hospital Anxiety and Depression Scale, CIS-20R: Checklist Individual Strength, TOAST: Trial of Org 10172 in Acute Stroke Treatment. NA: not applicable. Missing data in ischaemic stroke participants: Lesion location: 0.4%, education: 1.1%, NIHSS at admission: 0.7%, marital status: 1.1%, employment status: 2.5%. MMSE: 2.9%, HADS depression: 1.1%, CIS-20R: 1.1%, BMI: 3.2%, alcohol: 0.4%. Missing in the control group: employment status: 1.4%, BMI: 1.4%. Missing in the refusals: NIHSS at admission: 1.4%. **a.)** Ischaemic stroke patients who refused to participate in the FUTURE study (n=96) + patients who participated in the FUTURE study, but refused to visit the research centre (n=42); **b.)** Comparisons between ischaemic stroke participants and those who refused cognitive →

← assessment; **c.)** Student's *t* test; **d.)** Pearson's chi-square test; **e.)** Mann-Whitney *U* test; **f.)** The proportion of ischaemic stroke patients with baseline employment (n=231) and who were unemployed, still employed, or retired at follow-up. Controls: employment status at follow-up.

Table 2 Neuropsychological test scores of patients with a previous young stroke and controls.

Cognitive domain & test	Ischaemic stroke	Controls
Processing speed		
SDMT	42.6 (13.7)	53.3 (10.2)
Stroop part I[a]	4.0 (1.1)	4.7 (0.8)
Stroop part II[a]	3.2 (0.9)	3.7 (0.6)
Visuoconstruction		
ROCF copy	30.7 (5.4)	32.4 (2.8)
Memory		
Working memory		
PPMST '%'[a]	2.8 (1.0)	3.6 (0.8)
PPMST 'S'[a]	2.4 (0.8)	3.1 (0.7)
PPMST 'MP'[a]	1.6 (0.5)	2.0 (0.5)
PPMST 'DHN'[a]	1.3 (0.4)	1.6 (0.4)
Immediate memory		
RAVLT trial 1-3	18.3 (6.3)	22.1 (6.1)
ROCF immediate recall	16.4 (6.5)	18.3 (5.8)
Delayed memory		
RAVLT delayed recall	5.3 (2.8)	6.9 (2.8)
ROCF delayed recall	15.8 (6.3)	18.0 (5.7)
Attention		
VSAT[a]	1.2 (0.5)	1.5 (0.4)
Executive functioning		
Verbal fluency	21.3 (6.8)	24.4 (5.8)
Interference[a]	0.51 (0.1)	0.56 (0.1)

Data are expressed as mean (SD). SDMT: Symbol-Digit Modalities Test, ROCF: Rey-Osterrieth Complex Figure, PPMST: Paper & Pencil Memory Scanning Test, RAVLT: Rey Auditory Verbal Learning Test, VSAT: Verbal Series Attention Test. **a.)** Speed-accuracy composite score. Higher scores indicate better performance on all measures.

Figure 2 Cognitive performance after first-ever ischaemic stroke in young adults compared with controls.

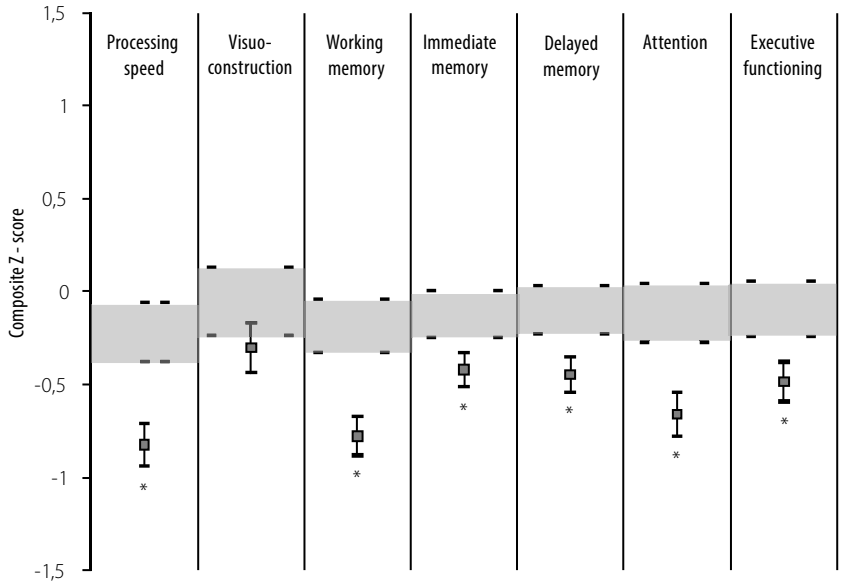


Figure shows cognitive performance about 11 years after first-ever ischaemic stroke in young adults compared with controls. Adjusted mean composite Z-score (95%-CI) per cognitive domain (adjusted for age, sex, education, depressive symptoms, and fatigue). Grey band represents the 95%-CI of the adjusted mean composite Z-score of controls. Missing values in different domains: 0.7-6.5%. No missing values in the control group.

* Denotes a significant difference between ischaemic stroke patients and controls. p-value <0.0071 was considered significant.

Lesion location and cognitive outcome

One patient could not be classified as supratentorial or infratentorial infarction (infarction in basal ganglia or brainstem). Seven patients with bilateral supratentorial infarction were excluded from the analysis since the number of patients was too small for further analyses. The results showed that patients with a left supratentorial infarction had the worst cognitive outcome, up to 45.5% of patients had cognitive impairments on the long term (Figure 3B).

Recurrent stroke

After exclusion of patients with a recurrent stroke (n=30) there was no longer a significant negative relation between follow-up duration and executive functioning score in ischaemic stroke patients.

Figure 3 Below average performance or cognitive impairment in ischaemic stroke patients and controls.

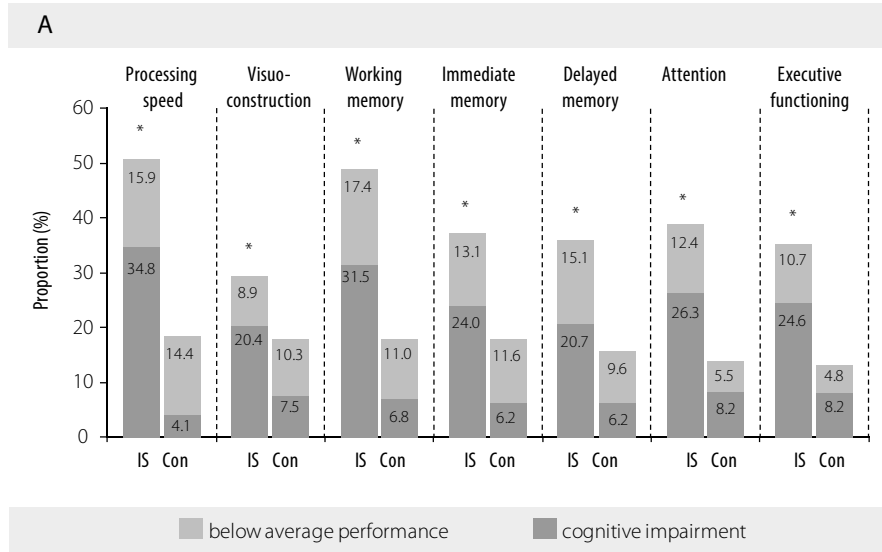


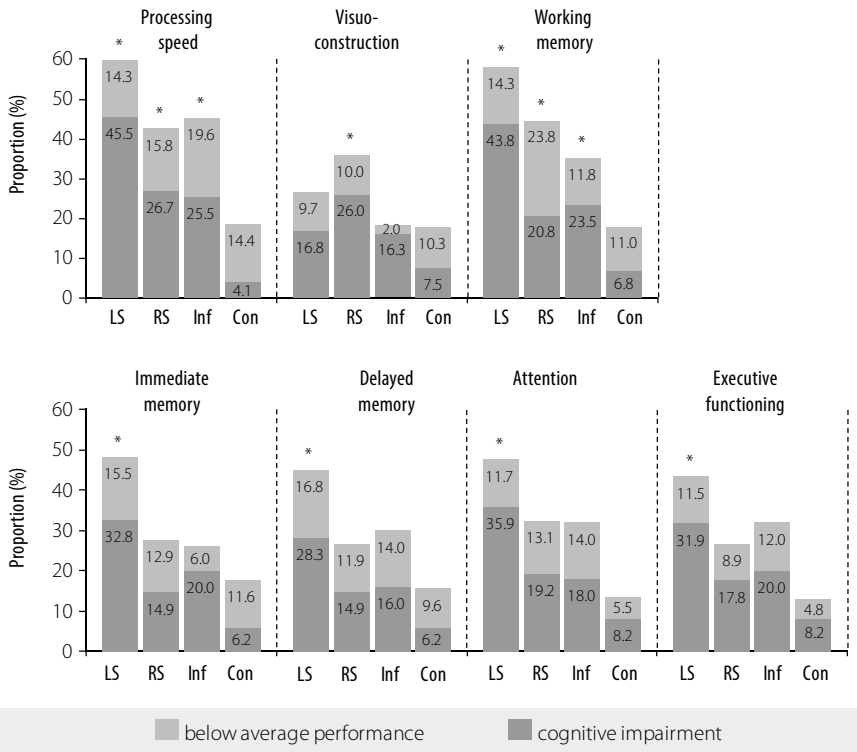
Figure 3 shows the proportion (%) of ischaemic stroke patients and controls with a below average performance (composite Z-score >1.0 SD below the age-adjusted mean of controls) or a cognitive impairment (>1.5 SD) about 11 years after stroke **A |**. The relationship between lesion location and the proportion of patients with a below average performance or a cognitive impairment compared with controls **B |**. *(page 72)*

IS: Ischaemic stroke, Con: Control group, LS: left supratentorial infarction, RS: right supratentorial infarction, Inf: Infratentorial infarction.

* Denotes a significantly higher proportion of patients with cognitive impairment compared with controls. p-value <0.0071 was considered significant.

Figure 3 *Continued*

B



Discussion

This study showed that a substantial proportion of young ischaemic stroke patients after a mean follow-up of 11 years showed a worse cognitive performance on a wide range of cognitive domains compared with a matched stroke-free population. Patients with a left supratentorial infarction had the worst cognitive outcome.

Strong elements of our study include a large sample size in a single centre, with a high response rate.[28, 29] We used extensive neuropsychological testing rather than a short cognitive screen and we included a representative control group as a reference for neuropsychological examination.

However, some methodological issues need to be addressed. First, the study was not

community-based, but hospital-based and therefore our sample may not represent all young stroke survivors in our catchment area. However, we think that our stroke population is representative to the wider Dutch stroke population. Those who survive usually visit a university medical centre during the course of their disease. Furthermore, the age and sex standardised prevalence of stroke in our region equals that of the age and sex standardised prevalence of stroke in the Netherlands.[217] We therefore believe that our cohort has a good external validity. This is also underlined by the fact that we included all consecutive cases admitted to our hospital.

Second, cognitive data of patients who refused to participate obviously were lacking, but their baseline characteristics did not differ from participants in the present study, making a selection bias unlikely.

Although we investigated a wide range of cognitive domains, agnosia or language comprehension[28] were not included in our neuropsychological assessment. Based on the neurological exam we considered the proportion of patients with these symptoms to be small and therefore we believe that this has not largely influenced cognitive performance.

We found relatively low MMSE scores in both the patients and the controls, compared with others[28] and healthy older adults.[218] However, all controls lived independently and none fulfilled the clinical criteria for dementia. Furthermore, the diagnostic accuracy of the MMSE in detecting cognitive impairment is generally poor, especially outside the Alzheimer domain[219] hence we believe this finding is of little clinical relevance.

Longer follow-up, adjusted for age effects, was associated with a decrease in cognitive functioning in ischaemic stroke patients. Longer time interval might be associated with incident co morbidity that could in turn have negatively affected cognitive performance. Another explanation is that these patients are older and that, apart from the stroke, neurodegenerative pathology might have emerged that interacts with the cerebrovascular disease.[220] A better understanding of this interaction is important as especially those with the longest follow-up are the oldest patients who might be at risk for further cognitive decline, due to this interaction of vascular lesions and neurodegenerative pathology.

Two studies have investigated cognitive performance in 24[29] and 40[28] young ischaemic stroke patients 4-12 months after stroke. Malm and colleagues[29] examined 24 patients with cerebellar infarcts and cognitive domains most affected were mental speed, cognitive flexibility, and working memory. We also found that an infratentorial infarction was associated with impairments in processing speed and working memory. Cao and colleagues[28] investigated 40 young ischaemic stroke patients and assessed other do-

mains and found language comprehension, reasoning and verbal memory to be most affected. Processing speed was not assessed in these patients.[28] Comparing our results with these 2 studies, we found similar deficits in verbal memory, working memory, and processing speed, but also deficits in executive functioning and attention are common on the long term in ischaemic stroke patients. These 2 domains were not addressed in reported studies.[28, 29]

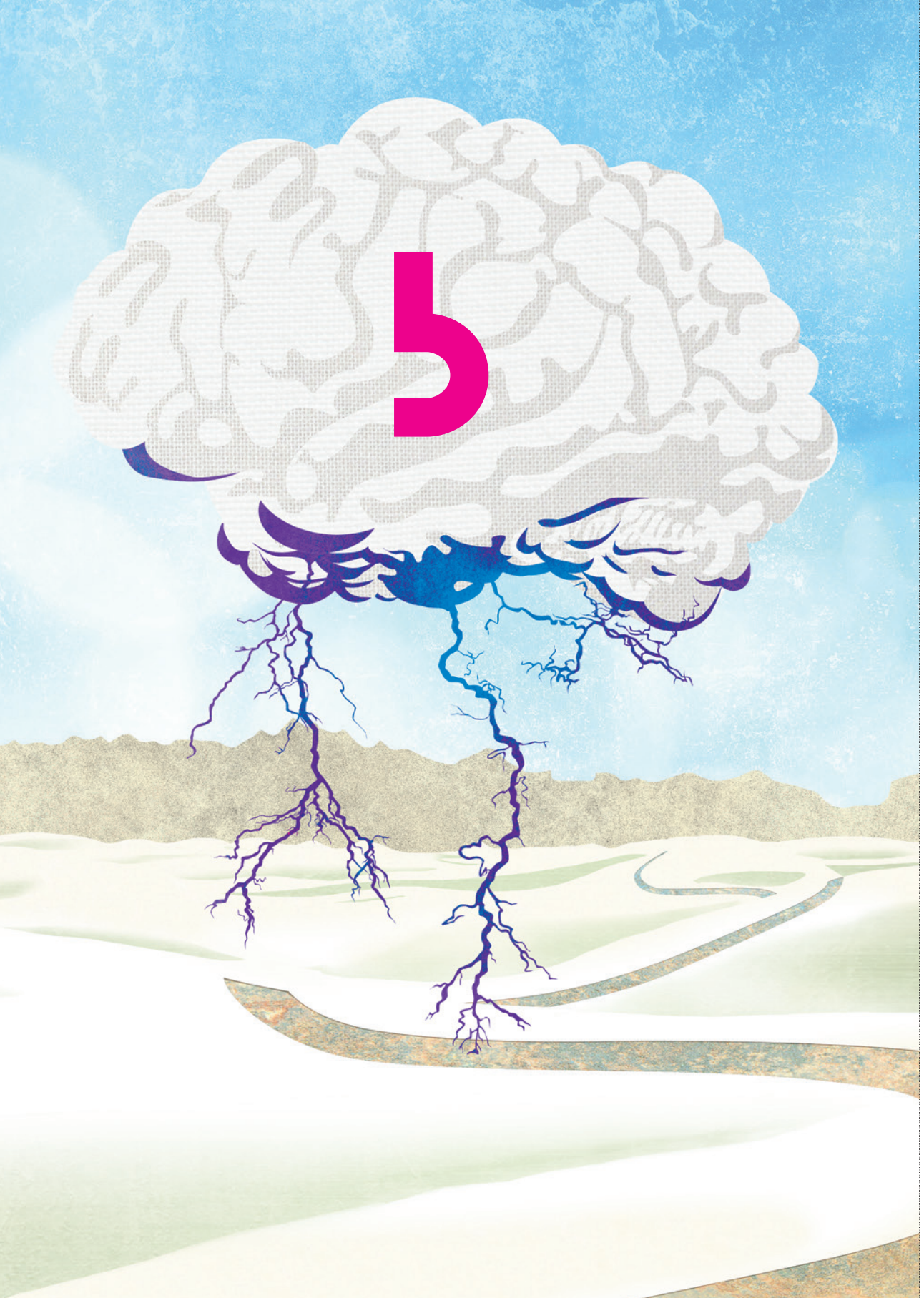
A substantial proportion of up to 50% of young ischaemic stroke patients had below average cognitive performance or impairment, despite the fact that the median of initial stroke severity was relatively mild. This highlights the influence of cerebrovascular lesions on cognitive performance, even decades after the stroke. It could also be that a severity rating scale, which includes predominantly motor signs (NIHSS), may underestimate the effect of stroke on other than motor symptoms. This would justify a basic careful neuropsychological examination of stroke patients in the (sub)acute phase of the disease.

Interestingly, a focal stroke on the long term seems to have a widespread impact on cognition, affecting multiple cognitive domains. Increasing evidence suggests that focal lesions can have a widespread, diffuse impact on brain network organisation,[141] which may explain the cognitive impairments attributable to dysfunction of the brain, remote from the site of the infarction.[221]

It appears that stroke in young adults seems to have a relatively better cognitive prognosis as compared with stroke in the elderly, as we found cognitive deficits in 20.4-34.8% of our young ischaemic stroke patients, whereas 31-77%[222] was reported in elderly stroke survivors. This difference in cognitive prognosis is perhaps due to a better collateral blood supply with an attendant lower volume of the infarction, a more pronounced neuronal plasticity and the absence of neurodegenerative pathology in younger adults.[223]

Summary

To conclude, in young ischaemic stroke patients, with in general a good motor recovery, long-term cognitive impairments are common. Given the importance of cognitive performance for post-stroke quality of life cognitive functioning should be monitored in clinical practice. This may also yield valuable information for treating rehabilitation services and return to work.



Subjective cognitive failures after young TIA and ischaemic stroke

Published as

Maaijwee NA, Schaapsmeerders P, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, van Dijk EJ, Kessels RP, de Leeuw FE.
Subjective cognitive failures after stroke in young adults: prevalent but not related to cognitive impairment.

J Neurol. 2014; 261:1300-08

Abstract

Background and objective

Few studies exist on subjective cognitive failures after a stroke in young adults (≤50 years) and their relation to objective cognitive performance is unknown. Therefore, we investigated the prevalence of subjective cognitive failures in patients with a stroke in young adulthood, and their relation with objective cognitive impairment.

Methods

This study is part of the 'Follow-Up of Transient ischaemic attack and stroke patients and Unelucidated Risk factor Evaluation' (FUTURE) study, including patients, aged 18 through 50 years, admitted to our hospital between 1980 and 2010 with a first-ever TIA or ischaemic stroke. The prevalence of subjective cognitive failures in patients was determined and compared with 146 age- and sex-matched stroke-free controls. The relation of subjective failures with objective cognitive performance was investigated with linear and logistic regression analysis.

Results

160 patients with a TIA and 277 with an ischaemic stroke were included. After a mean follow-up of 10.1 (SD 8.3) years, the prevalence of subjective memory failures was 86.4% and that of subjective executive failures was 67.4% in patients, versus 69.7% (p=0.008) and 41.4% (p=0.002) in controls. A weak association between subjective memory failures and objective immediate (ß: -0.12, p=0.011) and delayed memory performance (ß: -0.13, p=0.010) was observed in patients.

Conclusions

Subjective cognitive failures are prevalent after stroke in young adults, but not strongly related to objective cognitive impairment. Therefore, extensive neuropsychological assessment is essential for determination of objective cognitive impairment. However, it is important that subjective cognitive failures are recognised as they may indicate underlying psychosocial problems.

Introduction

Post-stroke subjective cognitive failures are highly prevalent in the general stroke population.[8-10] They are related to current or forthcoming objective cognitive impairment, in line with findings in the general elderly population.[224, 225] Previous studies reported that in patients with a stroke <55 years, these subjective cognitive failures are very common as well up to 2.5 years after stroke, but whether these were also related to long-term objective cognitive impairment is not known.[9, 30, 31] This information can be of help to either prevent unnecessary concern or provide reliable insight in actual or future cognitive performance and is particularly important in young adults. They are in need for long-term information on possible post-stroke consequences, because they usually have a life expectancy of decades ahead.

Stroke is an umbrella term for, amongst others, also patients with a transient ischaemic attack (TIA). Evidence from older stroke cohorts suggests that a TIA is not as transient as previously thought, with respect to other less visible symptoms, such as mood disorders.[226] Therefore, the aim of our study was to investigate the long-term prevalence of subjective cognitive failures in patients with a TIA or ischaemic stroke at ages 18 through 50 years, compared with a stroke-free control population and to investigate the relation between these subjective cognitive failures and objective cognitive performance.

Methods

Patients and study design

This study is part of the '*F*ollow-*U*p of *T*ransient ischaemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation' (*FUTURE*) study, a large cohort study that investigates causes and consequences of stroke in young adults. Details of the study have been described extensively elsewhere.[42, 110] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

In short, the FUTURE study comprised all consecutive patients aged 18 through 50 years with a TIA, ischaemic stroke or intracerebral haemorrhage, admitted to the Radboud University Nijmegen Medical Centre from January 1, 1980, until November 1, 2010.[110] For the present study, only first-ever TIA or ischaemic stroke patients were assessed. Patients were included prospectively between 1980 and 2010 with a standardised collection of baseline and clinical characteristics.[132] TIA was defined as a rapidly evolving focal neurological deficit with no other than a vascular cause lasting less than 24 hours. Stroke was defined similarly, but with symptoms lasting more than 24 hours.[102, 110, 128, 132]

All patients underwent neurological examination and brain imaging at the time of their index event. Radiological findings were used to differentiate between ischaemic and haemorrhagic stroke.
The assessment of stroke severity (National Institutes of Health Stroke Scale (NIHSS)[213]) was done for all cases retrospectively by a validated approach,[165, 214] as these scales did not exist at the time when a substantial proportion of our patients experienced their qualifying event.[42]
Cerebral venous sinus thrombosis was excluded. There were additional exclusion criteria for cognitive assessment based on the neurological exam, which was also a part of the FUTURE study.
Stroke-free control participants were recruited among the patients' spouses, relatives, or social environment, resulting in a sex- and age-matched control group (n=146). They had to be at least 18 years old, without a history of TIA or stroke. Controls were all living independently, none fulfilled the clinical criteria of dementia.[139]
Written informed consent was obtained from all patients and control participants.

Follow-up

All patients alive were invited to visit our research centre for a follow-up examination between November 1, 2009 and January 1, 2012, including assessment of subjective cognitive failures and an extensive neuropsychological investigation in the same session.

Subjective cognitive failures

The presence of subjective cognitive failures in the past month was assessed, using a 15 items semi-structured interview based on the Cognitive Failures Questionnaire (CFQ).[183] This version was also used in other large scale epidemiologic research.[227, 228]
Our primary outcome measures were the prevalence of subjective memory failures and of subjective executive failures. This subdivision of subjective cognitive failures into memory failures and executive failures was made, in order to correlate these specific failures to the objective cognitive domains of memory and executive functioning, respectively.
Subjective cognitive failures were considered present when a participant scored a '2 (moderate)' or higher on at least 1 item with a scale of 0 to 3 or scored a '1' on at least 1 item with dichotomous answers (failure present or absent). For this study, only items specific for memory failures (missing data in 10 subjects (2.3%)) and executive failures (missing data in 1 patient (0.2%)) were used.

Objective cognitive performance

For the present study, the following cognitive domains were examined: *Working memory* (Paper and Pencil Memory Scanning Task (PPMST)), *Immediate memory* (Rey-Osterrieth Complex Figure Test (ROCF) - Immediate recall and the total number of words immediately recalled in the 3-trial version of the Rey Auditory Verbal Learning Test (RAVLT)), *Delayed memory* (delayed recall on the ROCF and the RAVLT), and *Executive functioning* (Verbal Fluency and Stroop Interference). If 1 test of a particular domain was missing, the domain score was based on the remaining tests of that domain (always <5.1%). Detailed information on the neuropsychological examination and calculation of domain-scores is described extensively elsewhere.[42, 139] The MMSE was administered as a measure of global cognitive performance.

Other measures

Other measures were education, depressive symptoms, fatigue, and current level of performance (assessed by the modified Rankin Scale). Level of education was scored with a widely-used Dutch scoring system (1 = less than primary school; 7 = university degree).[229]
Depressive symptoms and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS), with a cut-off value for the presence of depressive symptoms or anxiety of >7.[230] Fatigue was assessed using the subscale Subjective Fatigue of the revised Checklist Individual Strength (CIS-20R).[193, 209]
We assessed vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, smoking (current/former/never), current alcohol use (>2 U/day)) and vascular disease (myocardial infarction and recurrent stroke) on the basis of medical history using a standardised, structured questionnaire, and/or the use of medication. Whenever a myocardial infarction or recurrent stroke/TIA was suspected, information retrieved was verified and adjudicated by physicians. The body mass index at follow-up was calculated as weight (kg) divided by height (m) squared.

Statistical analysis

Baseline characteristics were compared between participants, non-participants (those patients that refused and patients lost to follow-up), and deceased patients using Student's *t*-test, Mann-Whitney *U* test or chi-square-test when appropriate. Age between stroke subgroups (TIA or ischaemic stroke) and controls was compared with a Student's *t*-test and sex with a chi-square test. P-values <0.05 were considered statistically significant, unless otherwise specified.

The prevalence of subjective memory failures and of subjective executive failure was calculated, defined as the proportion of subjects in whom subjective memory or executive failures were present. Logistic regression was used to calculate the risk of having subjective memory or executive failures as a patient with a stroke ≤50 years, compared with stroke-free controls. Subsequently, the distribution of the total scores of subjective memory and executive failures is reported as a measure of severity of subjective failures. Next, we calculated prevalence of subjective memory failures and of subjective executive failure, stratified by tertiles of follow-up (first tertile: up to 4.43 years, n=145; second tertile: 4.45 to 13.27 years, n=146; third tertile: 13.49 to 30.00 years, n=146)

In addition, we calculated whether fatigue, the presence of depressive symptoms, and the presence of anxiety were associated with the presence of subjective memory failures or with the presence of subjective executive failures.

The association between subjective cognitive failures and objective cognitive performance was calculated in 2 ways. First, for each stroke subtype (TIA or ischaemic stroke) and controls, correlations between total scores of subjective memory failures and domain scores of objective (working, immediate, and delayed) memory and correlations between subjective executive failures and the domain score of objective executive functioning were determined using linear regression. In this analysis, a correction for multiple testing was applied, using the Bonferroni method. Alpha was set at 0.013 (0.05 divided by 4 (number of cognitive domains)). Second, we tested with a chi-square test, whether the presence of subjective memory and executive failures differed between cognitively impaired and unimpaired patients on the memory domain and executive functioning domain, respectively (cut-off point >1.5 SD below the mean of the control group). Controls were excluded from this analysis, because of the small absolute number of cognitively impaired patients in this group.

Age at follow-up, sex, NIHSS-score at admission, education, presence of depression, and fatigue were considered potential confounders and adjusted for in analyses when appropriate. NIHSS-score in controls was set at '0'

All statistical analyses were performed with SPSS 20.0 software for Windows.

Results

Study population and demographics

437 patients were included in the analysis for this study (Figure 1), of whom 160 (36.6%) had a TIA, and 277 (63.4%) had an ischaemic stroke.

Demographics and clinical characteristics are listed in Table 1.

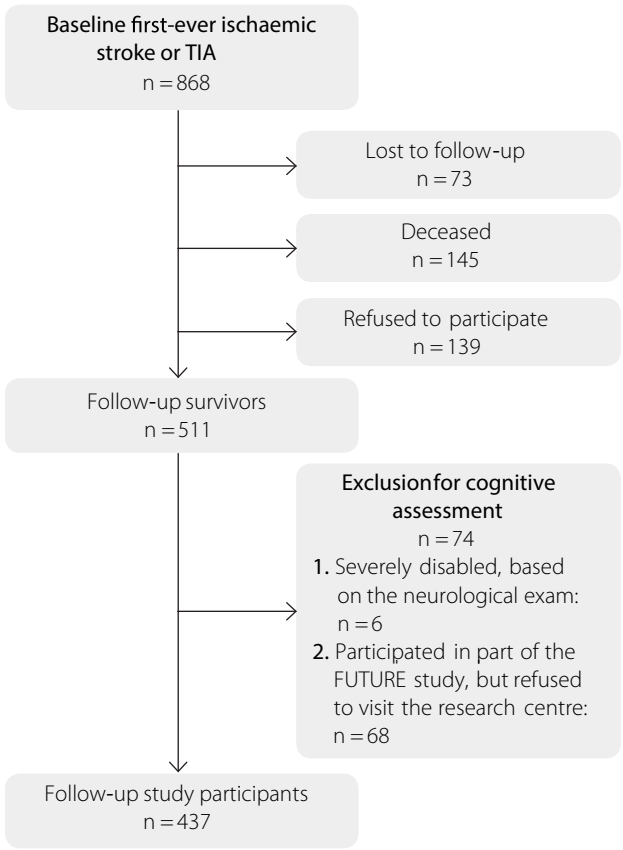
Table 1 Demographic and clinical variables of patients with a stroke at young age and controls.

	TIA (n=160)	IS (n=277)	Controls (n=146)
Baseline			
Age at index event (years); mean (SD)	40.9 (8.0)	40.0 (7.7)	NA
Men, n (%)[a]	75 (46.9)	123 (44.4)	61 (41.8)
NIHSS-score at admission; median (Q1-Q3)	0 (0-1)	4 (2-8)	NA
Follow-up			
Follow-up duration (years)			
Mean (SD)	8.7 (8.3)	11.0 (8.2)	NA
Median (Q1-Q3)	4.8 (4.8-15.4)	9.3 (4.0-16.6)	NA
Age at follow-up (years); mean (SD)[b]	49.7 (11.2)	50.9 (10.3)	48.6 (11.7)
Education; median (Q1-Q3)	5 (5-6)	5 (4-6)	5 (5-6)
MMSE at follow-up; mean (SD)	26.7 (2.3)	26.3 (2.6)	27.2 (1.9)
mRS at follow-up; median (Q1-Q3)	0 (0-1)	1 (1-2)	0 (0-0)
HADS-depressive symptoms; median (Q1-Q3)	3 (1-5)	3 (1-6.25)	2 (0.75-4)
CIS- fatigue; median (Q1-Q3)	30 (17-41)	30.5 (18-43)	19 (12-30)
Incident vascular events			
Incident myocardial infarction; n (%)	7 (4.4)	16 (5.8)	3 (2.1)
Incident stroke/TIA; n (%)	25 (15.6)	47 (17.0)	NA
Vascular risk factors			
Hypertension; n (%)	86 (53.8)	150 (54.2)	44 (30.1)
Diabetes mellitus; n(%)	16 (10)	34 (12.3)	6 (4.1)
Hypercholesterolaemia; n (%)	105 (65.6)	185 (66.8)	26 (17.8)
BMI at follow-up; mean (SD)	26.4 (4.2)	26.9 (5.1)	26.9 (4.7)
Smoking			
Current; n (%)	34 (21.3)	78 (28.2)	38 (26.0)
Former; n (%)	59 (36.9)	129 (46.6)	55 (37.7)
Never; n (%)	65 (40.6)	70 (25.3)	53 (36.3)
Current alcohol consumption (> 2 units/ day); n (%)	9 (5.6)	19 (6.9)	13 (8.9)

TIA: Transient Ischaemic Attack, IS: ischaemic stroke, NIHSS: National Institutes of Health Stroke Scale, MMSE: Mini Mental State Examination, mRS: modified Rankin Scale, HADS: Hospital Anxiety and →

← Depression Scale, CIS-fatigue: Checklist Individual Strength, fatigue subscale, BMI: Body Mass Index, NA: not applicable. **a.)** no significant difference between the overall patient group and controls, tested with a chi-square test, and **b.)** Student's *t*-test. Ischaemic strokes only differed significantly from controls on age at follow-up, p=0.039.

Figure 1 Flowchart of study population.



Patients who refused to participate did not differ from participants with respect to type of index event, sex, age at index event, and NIHSS-score at admission. Deceased patients and patients who were lost to follow-up more often had an ischaemic stroke than a TIA as index event than participants. They also had higher NIHSS-scores at admission than participants (median 5.5 (Q1-Q3: 2-12) and 4 (Q1-Q3: 1-11) versus 2 (Q1-Q3:

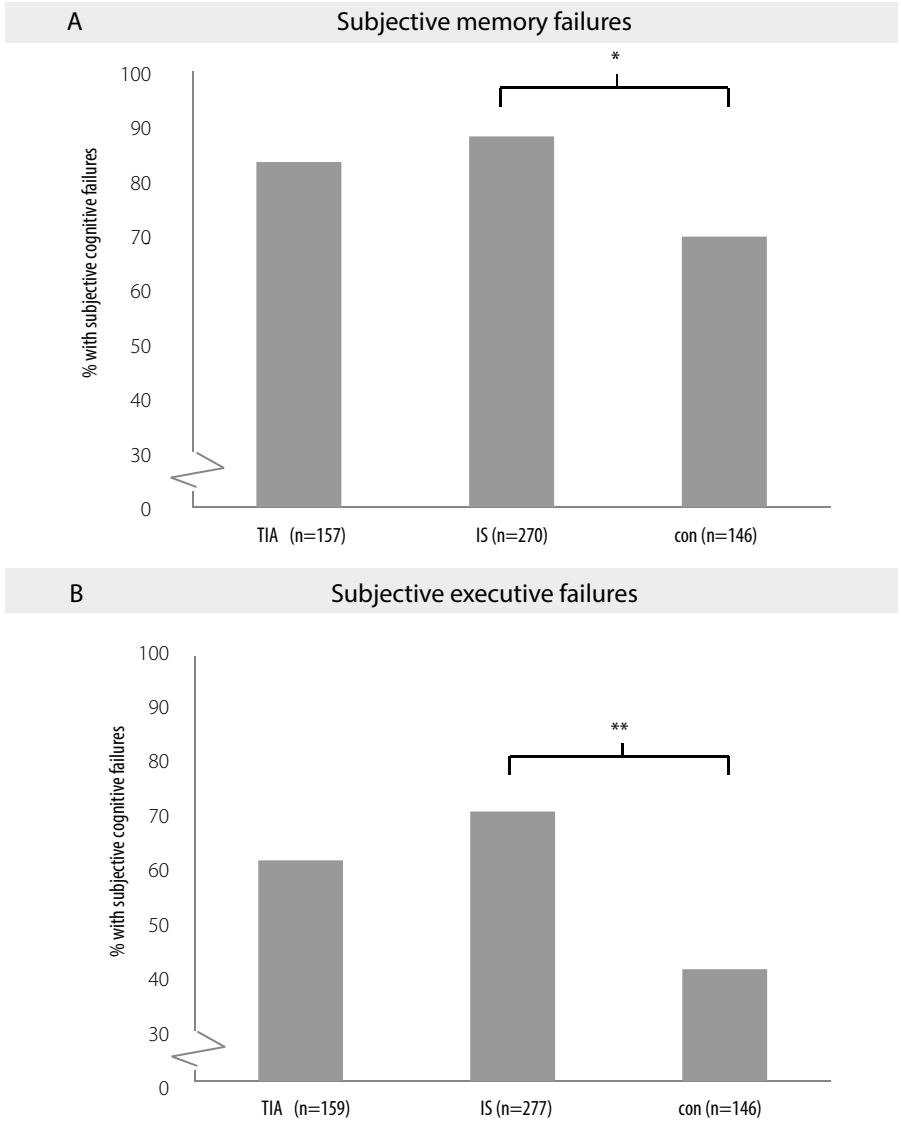
0-6) in participants, p<0.001 and p<0.001, respectively). Deceased patients were more often men (56.4% versus 45.3%, p=0.017) and slightly older than participants at the time of their index event (mean 42.6 (SD 6.6) years versus 40.3 (SD 7.8) years, p=0.002). Patients lost to follow-up were slightly younger than participants at the time of the index event (38.1 (SD 8.5) years versus 40.3 (SD 7.8) years, p=0.025).

Prevalence of subjective cognitive failures

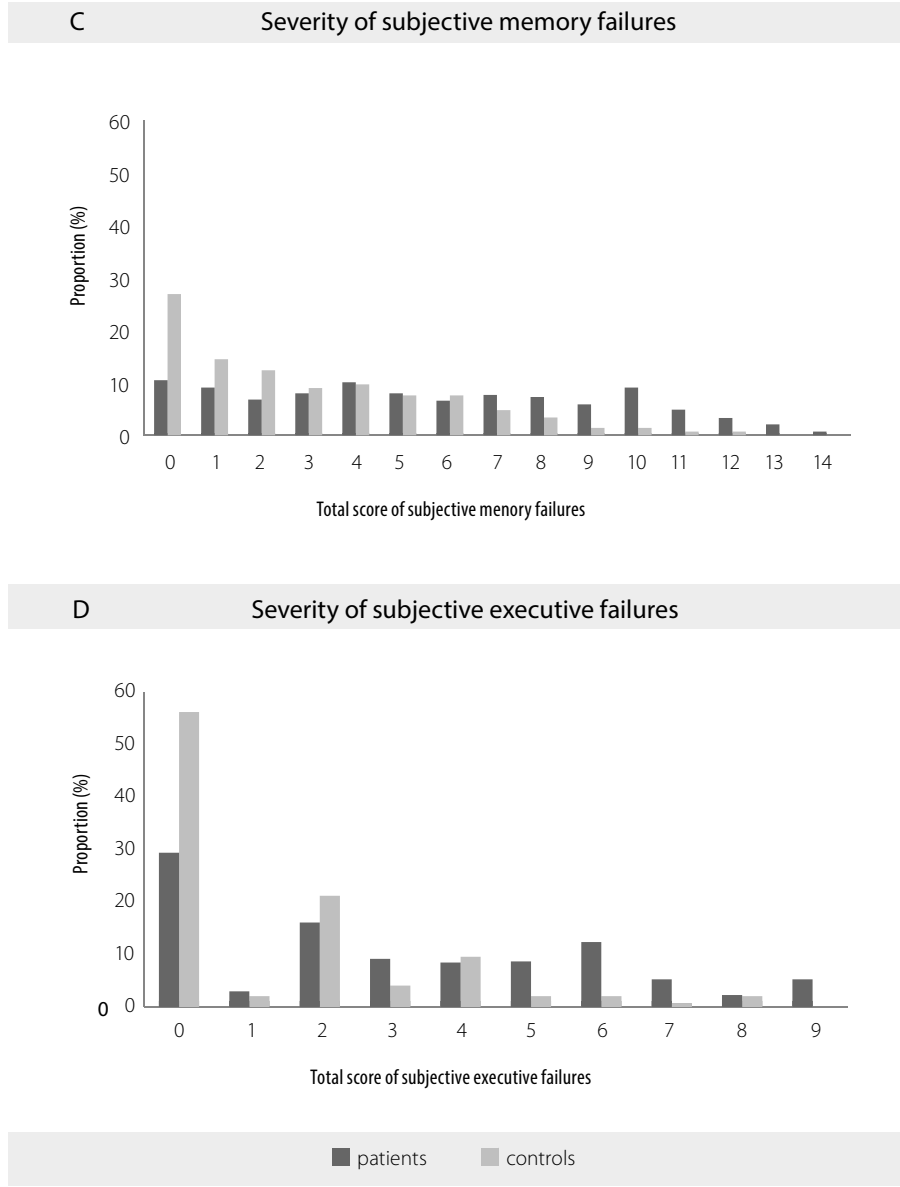
The overall prevalence of subjective memory and executive failures in patients with a stroke ≤50 years was 86.4% and 67.4%. Prevalence of subjective cognitive failures stratified by stroke subtype is shown in figure 2A and 2B. Figure 2C and 2D show the distribution of total scores of subjective memory and executive failures. Patients more often had higher total scores of subjective memory failures (73.5% with a score >2) and subjective executive failures (51.6% with a score >2) than controls (46.2% (p=0.0004) and 20.5% (p=0.00006), respectively). Prevalence of subjective memory and executive failures did not differ between the 3 tertiles of follow-up duration, although there was a trend towards higher prevalence of subjective memory failures among patients in the tertile with the longest follow-up (OR 2.7, 95%-CI 1.0-7.1).

The risk of having subjective memory failures was higher in ischaemic stroke patients (OR 3.0, 95%-CI 1.5-5.9) than in controls, but did not differ significantly between TIA-patients (OR 1.6, 95%-CI 0.9-2.9) and controls. The risk of having subjective executive failures was higher in ischaemic stroke patients (OR 2.9, 95%-CI 1.7-5.1) than in controls, but did not differ significantly between TIA-patients (OR 1.6, 95%-CI 1.0-2.7) and controls.
In the patients, the severity of fatigue (OR 1.1, 95%-CI 1.0-1.1, per point of the subscale Severe Fatigue of the CIS20R-questionnaire), the presence of depressive symptoms (OR 12.7, 95%-CI 1.7-94.3), and the presence of anxiety (OR 4.5, 95%-CI 1.6-13.1) were all associated with the presence of subjective *memory* failures in univariate logistic regression analysis. When these 3 variables were put together in a multivariate logistic regression model, only fatigue was independently associated with the presence of subjective memory failures (OR 1.1,95%-CI 1.0-1.1, per point of the subscale Severe Fatigue of the CIS20R-questionnaire).
In the patients, the severity of fatigue (OR 1.1, 95%-CI 1.0-1.1, per point of the subscale Severe Fatigue of the CIS20R-questionaire), the presence of depressive symptoms (OR 5.1, 95%-CI 2.2-11.6), and the presence of anxiety (OR 3.8, 95%-CI 2.1-7.1) were all associated with the presence of subjective *executive* failures in univariate logistic regression analysis.

Figure 2 Prevalence and severity of subjective cognitive failures.



TIA: Transient ischaemic attack, IS: ischaemic stroke. Missing data in part **A** and **C**: 3 in TIA group, 7 in IS group. Missing data in part B and D: 1 in TIA group. * p<0.01, ** p<0.001.



When these 3 variables were put together in a multivariate logistic regression model, only fatigue was independently associated with the presence of subjective memory failures (OR 1.1, 95%-CI 1.0-1.1, per point of the subscale Severe Fatigue of the CIS20R-questionnaire).
In controls, the severity of fatigue was (OR 1.1, 95%-CI 1.0-1.1, per point of the subscale Severe Fatigue of the CIS20R-questionnaire) associated with the presence of subjective memory failures and executive failures. The presence of depressive symptoms or anxiety was not related to the presence of subjective memory failures and executive failures, in the univariate nor in the multivariate model.

Relation between subjective cognitive complaints and objective cognitive performance

Table 2 shows that there was a statistically significant association between subjective memory failures and cognitive domain scores of immediate memory (ß: -0.12, p=0.011) and delayed memory (ß: -0.13, p=0.010) in the overall stroke population.

In 'Online resource 1', a scatter plot shows that effect sizes of this relation were small, with an R^2 of 0.06 and 0.05, respectively. The statistically significant difference disappeared after stratification by stroke subtype, taking into account the Bonferroni correction. Subjective executive failures and objective executive performance were not associated.
In controls, no significant associations between subjective cognitive failures and objective cognitive performance were found.

In patients with an ischaemic stroke or TIA, the prevalence of subjective cognitive failures did not differ between patients with or without cognitive impairment (defined as >1.5 SD below the mean of the control group) (Figure 3).

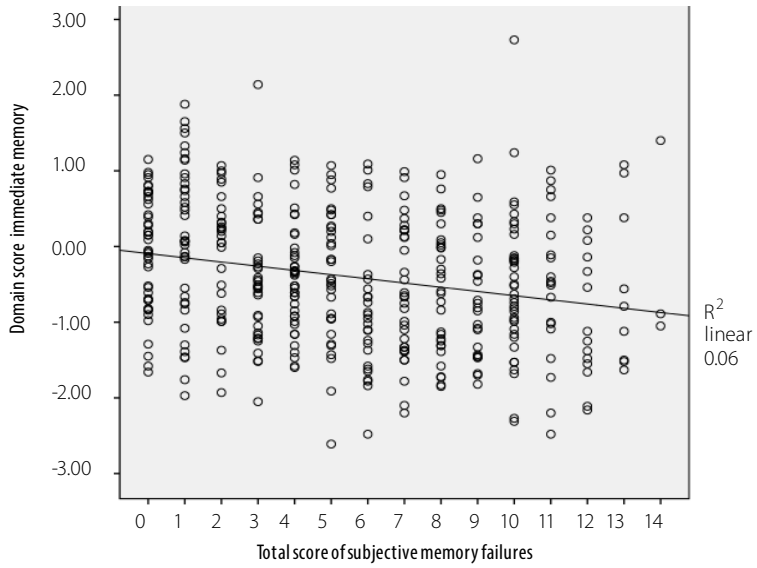
Table 2 Relation between subjective cognitive failures and objective cognitive performance.

	Working memory	Immediate memory	Delayed memory	Executive functioning
Subjective memory failures				
Participants, overall	-0.03	-0.12[a]	-0.13[a]	NA
TIA	-0.08	-0.06	-0.09	NA
Ischaemic stroke	-0.01	-0.15	-0.15	NA
Controls	0.03	-0.10	-0.05	NA
Subjective executive failures				
Participants, overall	NA	NA	NA	0.00
TIA	NA	NA	NA	-0.04
Ischaemic stroke	NA	NA	NA	0.01
Controls	NA	NA	NA	0.04

Table 2 shows correlations between total score of subjective cognitive failures and z-scores of objective cognitive performance, calculated with linear regression analysis (numbers in table are adjusted beta's). NA: correlation not determined. **a.)** p<0.013 (indicating statistical significance after Bonferroni correction).

Online resource 1 → *Page 90*
Relation between subjective memory failures and objective memory performance.
A | Subjective memory performance and objective *immediate* memory performance.
B | Subjective memory performance and objective *delayed* memory performance.

A Subjective memory performance and objective immediate memory performance



B Subjective memory performance and objective delayed memory performance

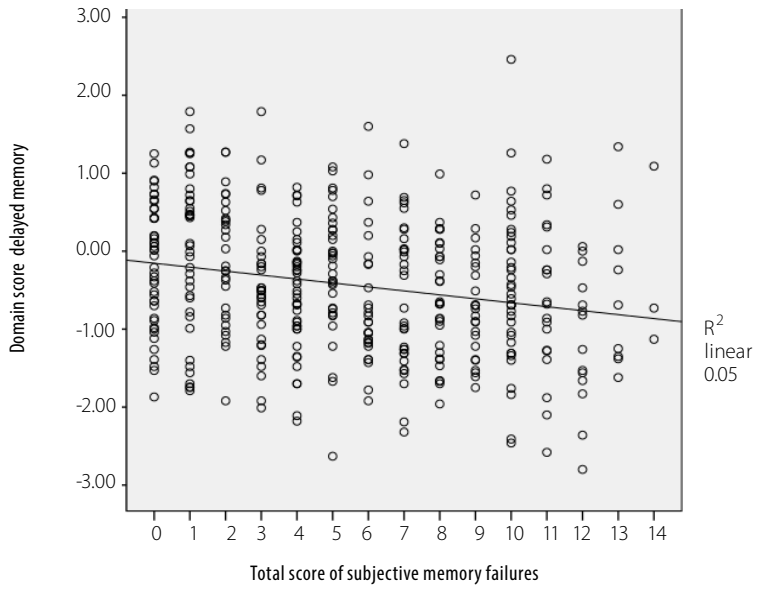
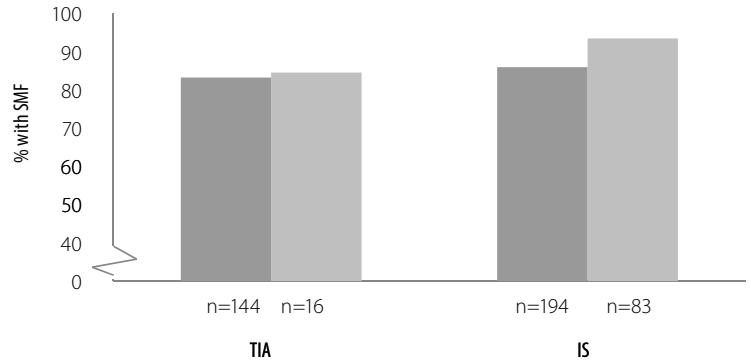
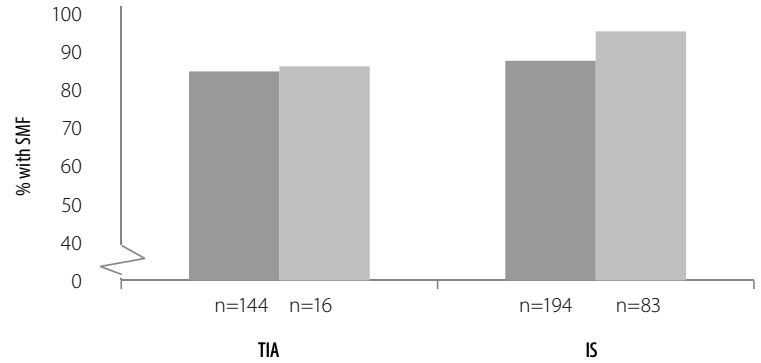


Figure 3 Subjective cognitive failures, stratified by presence of objective cognitive impairment.

A Working memory



B Immediate memory



No cognitive impairment Cognitive impairment

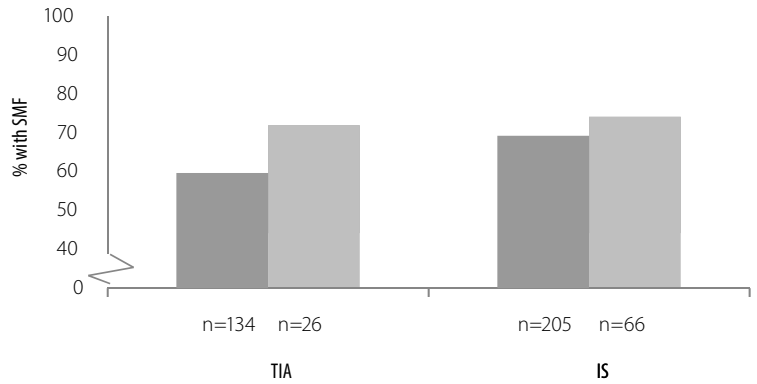
TIA: Transient ischaemic attack, IS: ischaemic stroke, SMF: subjective memory failures, SEF: subjective executive failures.

No statistically significant differences between 'No cognitive impairment' and 'Cognitive impairment' in any of the subgroups or cognitive domains.

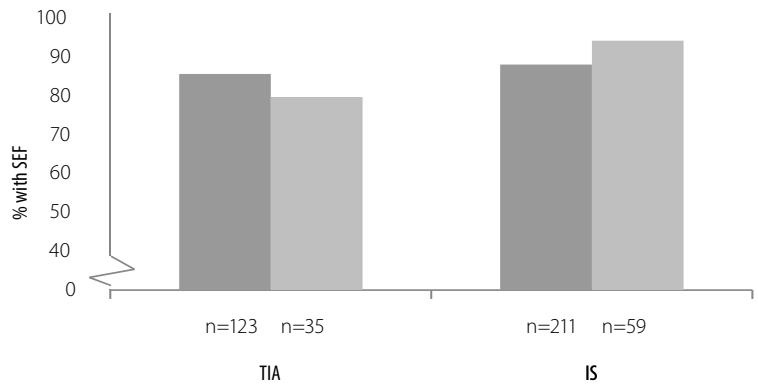
Missing data in part C: TIA, n=2, IS, n=7; and in part D: IS, n=6.

Figure 3 *Continued*

C Delayed memory



D Executive functioning



No cognitive impairment Cognitive impairment

Discussion

Subjective memory and executive failures were highly prevalent in our study population. We found a statistically significant, yet weak association between the subjective cognitive failures and objective cognitive performance in the overall population with a stroke at young age, but this association disappeared when stratified by stroke subtype after correction for multiple testing.

A strength of our study is the large sample size with inclusion of all consecutive cases, admitted to our hospital. Since in the Netherlands all patients with a stroke at young age who survive usually visit a university medical centre during the course of their disease, we believe that our study population is a representative cohort for a Dutch population with a stroke at young age. In comparison with other studies on patients with stroke at a young age, we found similar prevalence of diabetes mellitus and hypertension, a little higher prevalence of hypercholesterolaemia and a somewhat lower prevalence of alcohol consumption and smoking.[43, 231] However, overall, we conclude that the contribution of traditional vascular risk factors was rather comparable to other studies on patients with a stroke at young age. Therefore, our results are generalisable to other cohorts with patients with stroke at young age in Western societies. Another strong element is the inclusion of stroke-free controls. The prevalence of subjective memory failures and subjective executive failures among stroke-free controls was high. This may be due to several reasons. First, the high prevalence in controls may be a reflection of the high prevalence of subjective cognitive failures in the general population. The strict cut-off value from the Cognitive Failures Questionnaire (CFQ) — 1 positive answer already results in classification as 'subjective cognitive failures present' — makes it a very sensitive method for assessing subjective cognitive failures, but maybe not very specific. One population-based study, using the CFQ with the same strict cut-off value found subjective memory failures present in 72%.[227] However, participants in this study were on average 72 years old. Younger individuals may report subjective memory complaints less often; unfortunately this has never been formally assessed with the CFQ. Second, although controls did not suffer from a stroke themselves, they all had a spouse or close relative with a stroke at young age (as controls were recruited from the patients social environment). This might have been a stressful life event to the controls as well, that could have resulted in psychological vulnerability, that on its turn might have contributed to the emergence of subjective memory complaints.[232] However, the presence of depressive symptoms or anxiety was not related to the presence of subjective cognitive failures in our control group. Moreover, prevalence did not differ between controls with a relative who had a stroke <2 years ago and controls

who had a relative with a stroke >2 years ago, a period after which the recovery period of neurological deficits in patients is usually considered to be stabilised. However, the presence of a higher degree of fatigue was associated with the presence of subjective cognitive failures in our control group. The underlying reasons for the presence of fatigue in the control group are unknown. It may be related to co morbidities other than stroke, that were not an exclusion criterion in controls. However, these co morbidities were neither an exclusion criterion in patients. Comparison with this reference group is therefore essential for a realistic comparison with our patient group and a meaningful interpretation of findings.

There are some methodological issues that need to be addressed. First, selection bias might have occurred, due to patients who refused to participate, patients lost to follow-up, and patients who were deceased. However, patients who refused to participate did not differ from participants in baseline clinical and demographic variables (index event, sex, age at index event, and stroke severity), making selection bias unlikely. Patients who were lost to follow-up and deceased patients more often had an ischaemic stroke than a TIA. As the prevalence of subjective cognitive failures was very high in ischaemic stroke patients, this would only have underestimated the overall high prevalence of subjective cognitive failures and would not have altered our conclusions. Information bias in collecting data on cognitive functioning might have occurred, because researchers were not blinded to which group a patient belonged (stroke subtype or control), due to the presence of visible physical disabilities. However, strict instruction protocols were used to assess subjective and cognitive performance by trained researchers.

Potentially, recall bias might have occurred, especially among those with the most outspoken cognitive impairment. However, as we assessed the current subjective cognitive failures, we believe that our results are not largely influenced by recall bias.

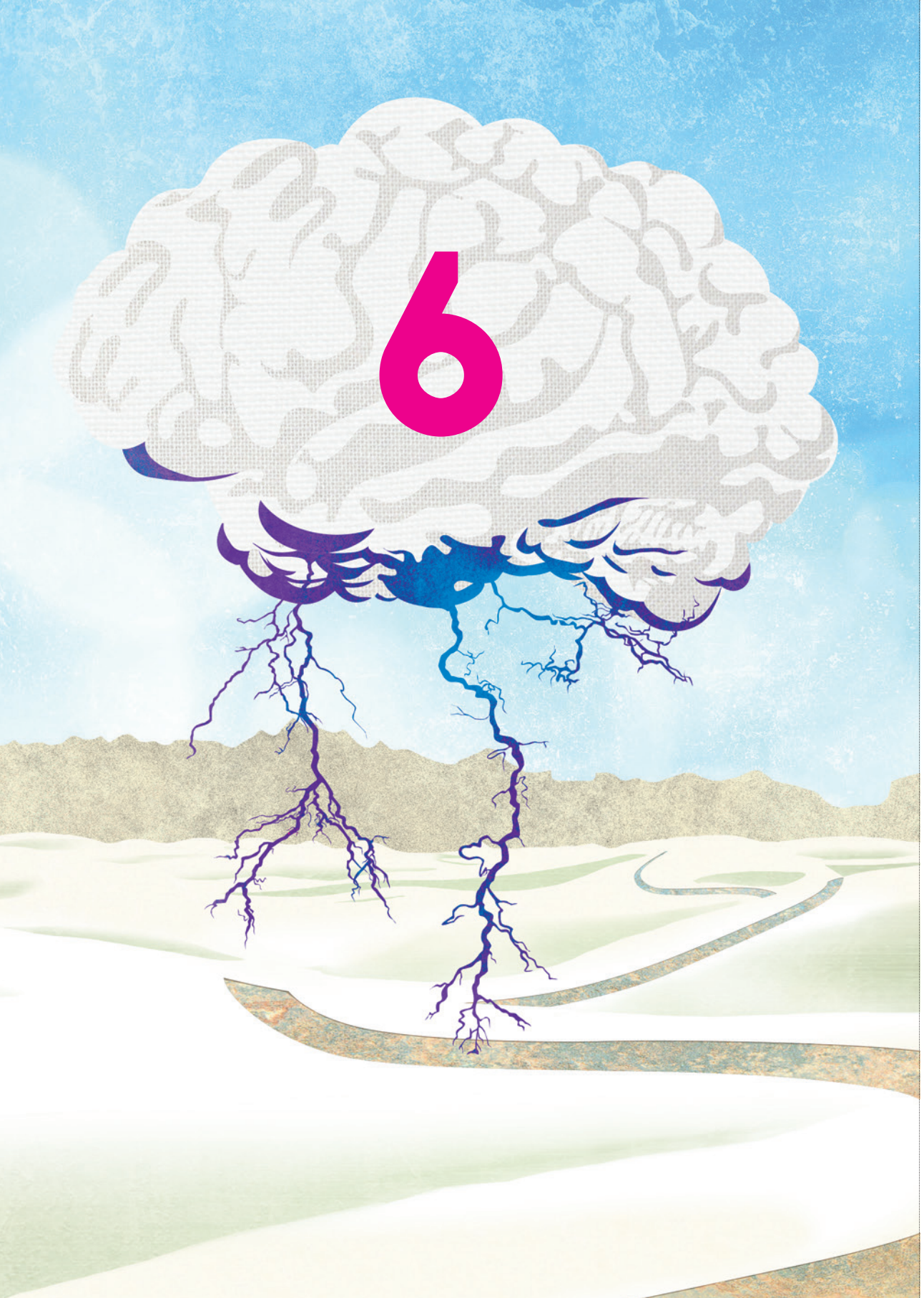
Finally, confounding is another bias to be considered. However, we tried to overcome this by adjusting for several confounding factors in our analysis.

The highly prevalent subjective cognitive failures we found in our study were not strongly related to objective cognitive impairment. Two previous studies investigated the relation between subjective cognitive complaints and objective cognitive functioning in stroke patients in the subacute phase after the stroke[9] and after 3 months of follow-up.[8] Although they reported some contradictory results on the association between subjective cognitive failures and objective cognitive impairment, they both suggested that the subjective cognitive failures are at least in part the result of other factors than objective cognitive impairment, for example mood disorders. This is in line

with our finding that, after long-term follow-up, fatigue, depressive symptoms, and anxiety were associated with the presence of subjective memory and executive failures in the univariate model. Only fatigue was associated with subjective memory and executive failures in the multivariate model, independent from depressive symptoms and anxiety. The fact that depressive symptoms were not independently (from fatigue and anxiety) associated with subjective memory failures in the multivariate model, may however been the result of limited power, suggested by the large confidence intervals. A meta-analysis in elderly concluded that the presence of subjective memory complaints was related to future mild cognitive impairment or dementia.[224] This contradiction with our findings may be because older patients, in addition to the similar cerebral ischaemia as in young patients, may also suffer from co-existing neurodegeneration, such as amyloid pathology.

Future research in patients with a stroke at young age should focus on effective coping strategies with difficulties they are confronted with in daily life, including proper knowledge on factors as the presence of depression, fatigue, or work-related issues. Unraveling these factors will give the opportunity to effectively adjust rehabilitation programmes to these young patients' specific needs.

In conclusion, our study showed that subjective cognitive failures are highly prevalent in patients after a stroke at young age, but these were not strongly related to objective cognitive impairment. Given the rising incidence of stroke in young adults, in combination with a usually long life expectancy in these young survivors, the number of patients confronted with long-term consequences, such as the highly prevalent subjective cognitive failures, will increase. This study provides insight in how these subjective cognitive failures need to be interpreted by the clinician, and how patients can be informed accordingly. For instance, it clearly shows that for the determination of objective cognitive impairment, one should not rely on these self-report measures of subjective cognitive failures, but a more extensive neuropsychological examination is essential. However, it is important that subjective cognitive failures are recognised in these patients, because they might indicate other underlying psychosocial problems that need guidance or psychological problems that need treatment.



Depressive symptoms and anxiety after young TIA and ischaemic stroke

Submitted as

Maaijwee NA, Tendolkar I, Rutten-Jacobs LC, Arntz RM, Schaapsmeerders P, Dorresteijn LD, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE.
Long-term depressive symptoms and anxiety after stroke in young adults.

Abstract

Background and objective

Few studies exist on long-term post-stroke depressive symptoms and anxiety in young adults, although these young patients have a particular interest in their long-term prognosis, given their usually long life expectancy, being in the midst of an active social, working, and family life.

The aims of this study are to investigate the prevalence of depressive symptoms and anxiety and their association with clinical and demographic variables and with functional outcome after stroke in young adults.

Methods

Long-term prevalence of depressive symptoms and anxiety was calculated in 511 patients with a TIA or ischaemic stroke, aged 18-50 years, using the Hospital Anxiety and Depression-scale, compared with 147 controls. Functional outcome was assessed with the modified Rankin Score (mRS) and Instrumental Activities of Daily Living (IADL).

Results

16.8% of patients had depressive symptoms and 23.0% had anxiety, versus 6.1% (p=0.001) and 12.2% (p<0.001) in controls. In ischaemic stroke patients, depressive symptoms and anxiety were associated with poor functional outcome (mRS>2 or IADL<8).

Conclusion

Even after a decade after stroke at young age, depressive symptoms and anxiety were prevalent and associated with poor functional outcome. Therefore, even in the long term, treating physicians should be aware of the long-term presence of these symptoms, as their recognition may be the first step in improving long-term functional independence.

Introduction

Many studies investigate the prevalence of post-stroke depressive symptoms and anxiety in stroke populations, usually with a mean age over 70 years.[11-16] Studies that assess the effect of these symptoms on functional outcome suggest a negative influence on functional outcome after a few months or years.[17-20] Patients with a stroke at a young age (≤50 years) have a particular interest in factors that influence their long-term outcome, as they usually have a life expectancy of decades ahead. Possible adverse effects of depressive symptoms or anxiety on functional outcome in these patients may be more profound, because they are in a vulnerable period of life with respect to socio-economic consequences. However, few studies reported on the long-term prevalence of depressive symptoms and anxiety in this specific age-group.[26, 27, 32] Only 1 of these related them to functional outcome, measured with the modified Rankin Scale, which includes little information on more complex tasks in daily living.[26] Furthermore, no studies exist on depressive symptoms and anxiety in young patients with a transient ischaemic attack (TIA). However, increasing evidence from other stroke studies suggests that less visible symptoms, such as cognitive impairment or mood disorders, may persist after the resolution of the focal neurological deficits caused by the TIA.[38, 39, 226]
Therefore, we investigated the prevalence of depressive symptoms and anxiety and demographic and clinical variables associated with these symptoms, as well as the relation between these symptoms and long-term functional outcome in patients with a TIA or ischaemic stroke at a young age.

Methods

Patients and study design

This study is part of the '*F*ollow-*U*p of *T*ransient ischaemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation' (*FUTURE*) study, a cohort study that investigates causes and consequences of stroke in young adults. Details of the study have been described elsewhere.[42, 110] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.
In short, the FUTURE study comprises 1 005 consecutive patients with a TIA, ischaemic stroke (excluding cerebral sinus thrombosis) or intracerebral haemorrhage, aged 18 through 50 years, admitted to the Radboud University Nijmegen Medical Centre between January 1, 1980 and November 1, 2010. For the present study, only first-ever TIA and ischaemic stroke patients were assessed. Patients were identified through a pro-

spective registry with a standardised collection of baseline and clinical characteristics (including demographics and stroke subtype). TIA was defined as a rapidly evolving focal neurological deficit without positive phenomena such as twitches, jerks or myoclonus, with no other than a vascular cause lasting less than 24 hours. Stroke was defined similarly, but with symptoms lasting more than 24 hours. All patients underwent neurological examination and brain imaging at the time of their index event. Radiological findings were used to differentiate between ischaemic and haemorrhagic stroke. The assessment of stroke severity (National Institutes of Health Stroke Scale (NIHSS)[213]) was done for all cases retrospectively by a validated approach.[165, 214] NIHSS-score in controls was set at '0'. Lesion location was based on review of presenting clinical signs and symptoms and radiological findings, categorised into supratentorial left, supratentorial right, bilateral, and infratentorial.
Control participants were recruited from the same environment as the patients, among the patients' spouses, relatives, or social environment (n=147). The patient group and control group were matched for age and sex. Controls had to be at least 18 years old, without a history of TIA or stroke. They were all living independently.
Written informed consent was obtained from all participating patients and controls.

Follow-up

All patients alive were invited to visit our research centre for a follow-up examination between November 1, 2009 and January 1, 2012. If patients consented to participate, but were not able to visit our research centre, data were collected by means of a standardised, structured questionnaire on paper.

Depressive symptoms and anxiety

Our primary outcome measure was the prevalence of depressive symptoms or anxiety, operationalised as a score higher than 7 on either the depression or the anxiety items of the Hospital Anxiety and Depression Scale (HADS).[230] This is a self-administered questionnaire used to evaluate depressive symptoms and anxiety in the past week and is well validated in stroke patients[233] and in large population-based studies.[184] The cut-off value we used is considered to be suggestive of the presence of depressive symptoms or anxiety.[230, 233] Information on the HADS was missing in 12 participants (2.4%).

Functional outcome

Functional outcome was assessed with the modified Rankin Scale (mRS) and the Instrumental Activities of Daily Living-scale (IADL).[192] The mRS predominantly measures

outcome based on motor function. The IADL complements this with the assessment of more complex tasks necessary for independent living in a community.[128]
In the 68 patients who only filled out questionnaires (because they were not able to participate in person), IADL was not assessed. Information on mRS was missing in 2 participants (0.4%) and on IADL in 5 participants (1.1%).

Assessment of incident vascular events and vascular risk factors

We assessed vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia, current smoking, current alcohol use (>2 U/d)) and vascular disease (myocardial infarction and recurrent stroke) on the basis of medical history taking using a standardised, structured questionnaire, and/or the use of medication. Whenever a myocardial infarction or recurrent stroke/TIA was suspected, medical records were reviewed for verification of the event by physicians from the appropriate specialty, that is, either a cardiologist or a neurologist.[102] The body mass index (BMI) at follow-up was calculated as weight (kg) divided by height (m) squared.[139]
In the patients who only filled out questionnaires only (n=68), vascular risk factors (diabetes mellitus, dyslipidaemia and hypertension) were considered present when diagnosed by a physician. In these 68 patients, BMI, smoking, and alcohol consumption were not assessed.

Other measurements

Educational level, a history of depression, and unemployment at follow-up (excluding retirement) were considered possible confounders.
Level of education was scored with a widely-used Dutch scoring system (1 = less than primary school; 7 = university degree).[229]
A history of depression before index event was assessed by asking the patient if there had ever been a period of depression, verified by additional questions about treatment or professional counseling. 'History of depression before index event' in controls was defined as 'history of depression ever'.
Employment status was assessed in a self-questionnaire, during the follow-up visit.
In the 68 patients who only filled out questionnaires (because they were not able to participate in person), a history of depression before index event and employment status were not assessed.

Statistical analysis

Baseline characteristics were compared between participants, non-participants (patients who refused and patients lost to follow-up), and deceased patients, using Student's *t*-test, Mann-Whitney *U* test or chi-square-test when appropriate. Sex and age were compared between patients and controls, using a chi-square-test and a Student's *t*-test, respectively.

The prevalence of depressive symptoms and anxiety was calculated and compared with controls with a chi-square test. Logistic regression, stratified on sex, was used to calculate the risk of having depressive symptoms or anxiety as a TIA- or ischaemic stroke patient compared with controls.

Age at follow-up, sex, education, NIHSS-score at admission, observation time, and a history of depression before the index event were considered potential confounders and adjusted for in all analyses when appropriate.

Since the present study features a long inclusion period (1980-2010), TIA- and ischaemic stroke patients were stratified into tertiles of observation time (n=170/171 per tertile).

A chi-square test was used to test differences in the prevalence of depressive symptoms or anxiety between lesion locations.

The following analyses were performed only in ischaemic stroke patients, because of too small numbers in TIA-patients to perform meaningful logistic regression analysis.

First, 2 multiple logistic regression models were constructed, 1 with the presence of depressive symptoms as dependent (dichotomous) variable and 1 with the presence of anxiety as dependent (dichotomous) variable. These models contained demographic and clinical factors that may theoretically be associated with depressive symptoms and anxiety as independent variables. Age at follow-up, sex, education, and NIHSS-score at admission were forced into the model. Observation time, recurrent stroke, a history of depression before the index event, current alcohol use (>2 U/day), and unemployment were put into the model with the backward logistic regression method. These variables were removed from the model when they did not significantly alter the model.

Second, the association between the presence of depressive symptoms or anxiety and a poor functional outcome in ischaemic stroke patients was calculated with logistic regression analysis. Poor functional outcome was defined as a mRS>2 or an IADL<8. Separate analyses were performed for each of these 2 dependent dichotomous outcomes, with the presence of depressive symptoms or anxiety as the independent variable and age at follow-up, sex, education, NIHSS-score at admission, and observation time as confounders.

All statistical analyses were performed with SPSS v20.0 software for Windows.

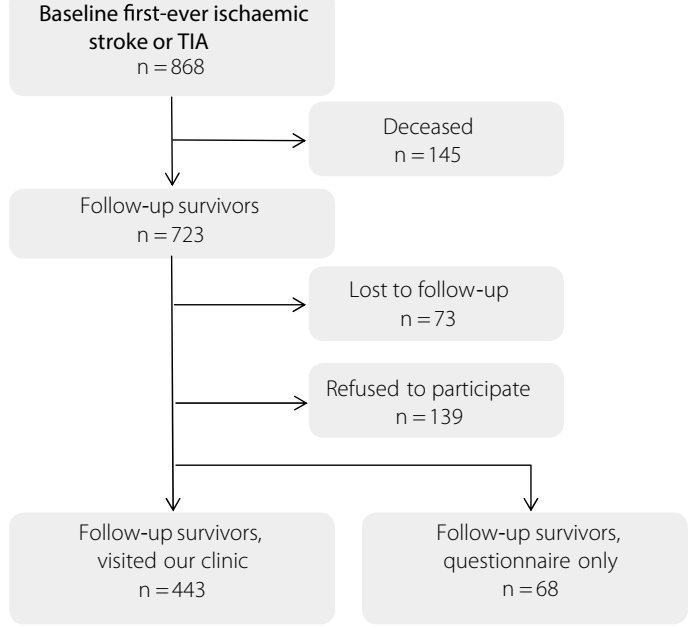
Results

Study population and demographics

For the present study, 511 patients were included, of whom 186 (36.4%) had a TIA and 325 (63.4%) had an ischaemic stroke (Figure 1). Their baseline characteristics are presented in Table 1.

Patients who refused to participate did not differ from participants with respect to index event, sex, age at index event, and NIHSS-score at admission. The proportion of patients with an ischaemic stroke was higher among deceased patients and patients who were lost to follow-up compared with participants. These 2 groups had higher NIHSS-scores at admission than participants (deceased: median 5 (Interquartile range (IQR) 2-12), p<0.001, lost to follow-up: median 4 (IQR 1-11.5), p<0.001, participants: median 2 (IQR 0-6). Deceased patients more often were men (55.8% versus 44.9%, p=0.01). Deceased patients and patients who were lost to follow-up were older than participants at the time of the index event (mean 42.5 (SD 6.7) years, p=0.002 and 38.2 (SD 8.6) years, p=0.04, versus 40.2 (SD 7.8) years).

Figure 1 Flowchart of study population.



TIA: Transient Ischaemic Attack

Table 1 Description of demographic and clinical variables in patients and controls.

	TIA	Ischaemic stroke	Controls
	n=186	n=325	n=147
Baseline			
Age (years) at index event, median (IQR)	42.9 (34.8-47.2)	41.2 (35.7-46.5)	NA
Age (years) at index event, mean (SD)	40.5 (8.0)	40.0 (7.8)	NA
NIHSS score at admission, median (IQR)	0 (0-1)	4 (2-9)	NA
Depression ever before index event, n (%)	33 (20.8)	50 (18.1)	60 (41.1)
Follow-up			
Men, n (%)[a]	83 (44.6)	143 (44.0)	63 (42.9)
Observation time (years), median (IQR)	4.7 (2.5-14.4)	8.5 (3.0-16.6)	NA
Observation time (years), mean (SD)	8.3 (8.1)	10.6-8.4	NA
Age (years) at follow-up, median (IQR)	49.2 (40.7-54.1)	50.0 (44.6-57.6)	48.5 (43.0-55.6
Age (years) at follow-up[b], mean (SD)	48.9 (11.3)	50.7 (10.4)	48.7 (11.7)
Education, median (IQR)	5 (5-6)	5 (4-6)	5 (5-6)
mRS at follow-up, median (IQR)	0 (0-1)	1 (1-2)	0 (0-0)
mRS>2, n (%)	12 (6.5)	41 (12.6)	1 (0.7)
HADS – d, median (IQR)	3 (1-5)	3 (1-7)	2 (0-4)
HADS – a, median (IQR)	5 (2-7)	4 (2-7)	4 (2-6)
IADL<8, n (%)	17 (10.8)	41 (14.6)	1 (0.7)
Unemployment (excluding retirement), n (%)	33 (24.2)	100 (41.8)	35 (23.8)
Current use of antidepressants, n (%)	12 (7.6)	34 (12.1)	9 (6.1)
Incident vascular events			
Incident stroke, n (%)	32 (17.2)	58 (17.8)	NA
Incident myocardial infarction, n (%)	9 (4.8)	19 (5.8)	3 (2.0)
Vascular risk factors			
Diabetes mellitus, n (%)	19 (10.3)	43 (13.3)	6 (4.1)

Table 1 *Continued*

	TIA	Ischaemic stroke	Controls
	n=186	n=325	n=147
Hypercholesterolaemia, n (%)	116 (63.0)	199 (61.6)	27 (18.4)
Hypertension, n (%)	97 (52.4)	175 (54.2)	45 (30.6)
Body Mass Index, mean (SD)	26.3 (4.2)	26.2 (5.2)	26.8 (4.7)
Current smoking, n (%)	35 (22.0)	79 (28.2)	38 (25.9)
Current alcohol consumption (>2 U/d), n (%)	7 (4.5)	13 (4.7)	14 (9.5)

TIA: Transient Ischaemic Attack, IS: ischaemic stroke, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale, HADS-d: Hospital Anxiety and Depression Scale, depressive symptoms, HADS-a: Hospital Anxiety and Depression Scale, anxiety, IADL: instrumental activities of daily living, NA: not applicable.

a.) Pearson chi-square, no significant differences between TIA or ischaemic stroke and controls;

b.) Student's *t*-test, no significant differences between TIA or ischaemic stroke and controls.

Missing data: 1.4% for depression before index event, 13.3% for employment status, 0.9% for diabetes mellitus, 0.9% for hypercholesterolaemia, 0.9% for hypertension, 2.0% for body mass index, 0.9% for smoking 0.9%, and 2.7% for regular alcohol consumption.

Depressive symptoms

The overall prevalence of depressive symptoms in patients with a stroke at young age (TIA and ischaemic stroke together) was 16.8% versus 6.1% in controls. The risk of having depressive symptoms was higher in both TIA-patients (OR 2.8, 95%-CI 1.2-6.6, p=0.02) and ischaemic stroke patients (OR 4.7, 95%-CI 2.0-11.0, p=0.003) compared with controls. Prevalence of depressive symptoms stratified by stroke subtype (TIA or ischaemic stroke) and sex is shown in Figure 2A. Prevalence of post-stroke depressive symptoms by tertiles of follow-up is shown in Figure 3A.

Prevalence of depressive symptoms did not differ between different stroke locations.

In the multiple regression model, ischaemic stroke patients with a lower educational level had higher risk of having depressive symptoms (OR 4.3, 95%-CI 2.0-9.0, p<0.001). Longer observation time was associated with a lower risk of having depressive symptoms (OR 0.9, 95%-CI 0.9-1.0 per year, p=0.03). Furthermore, unemployed patients had a higher risk of depressive symptoms (OR 3.8, 95%-CI 1.9-7.7, p<0.001). Current alcohol use was not associated with the presence of depressive symptoms.

Figure 2 Prevalence of depressive symptoms and anxiety, stratified by stroke subtype and sex.

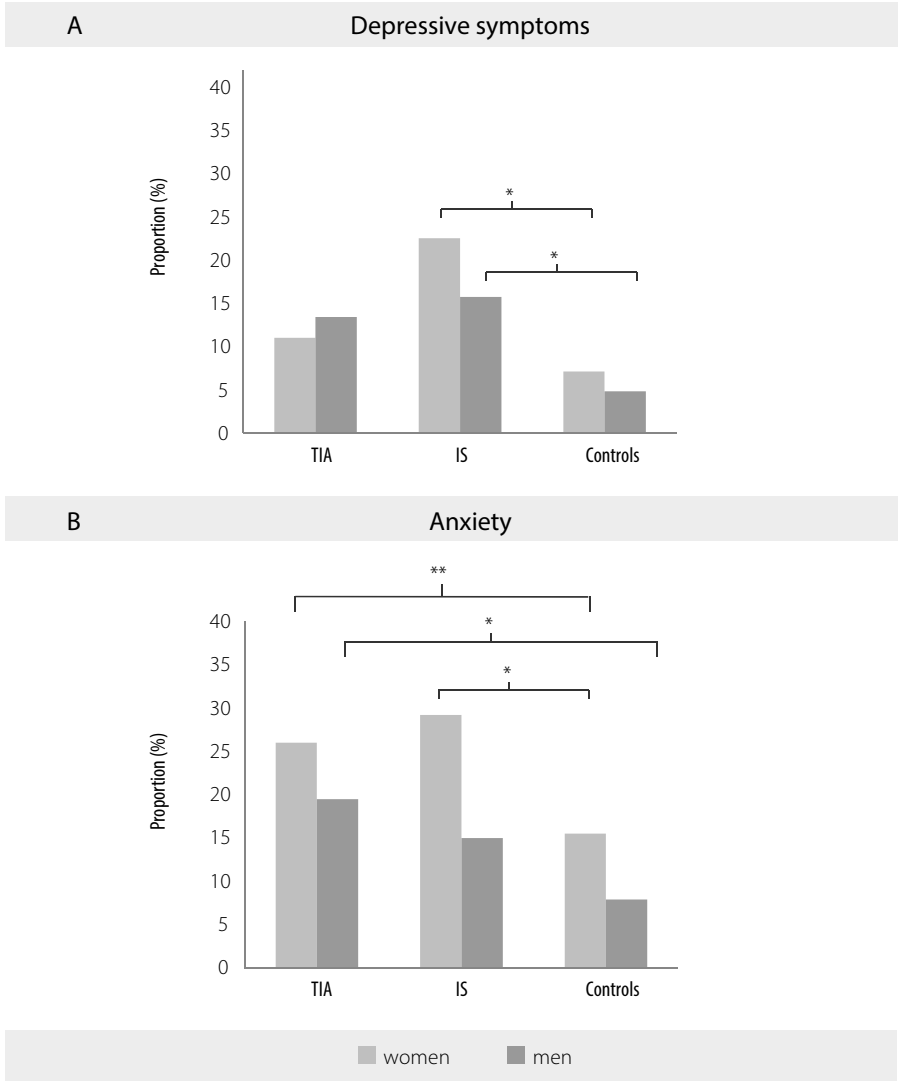
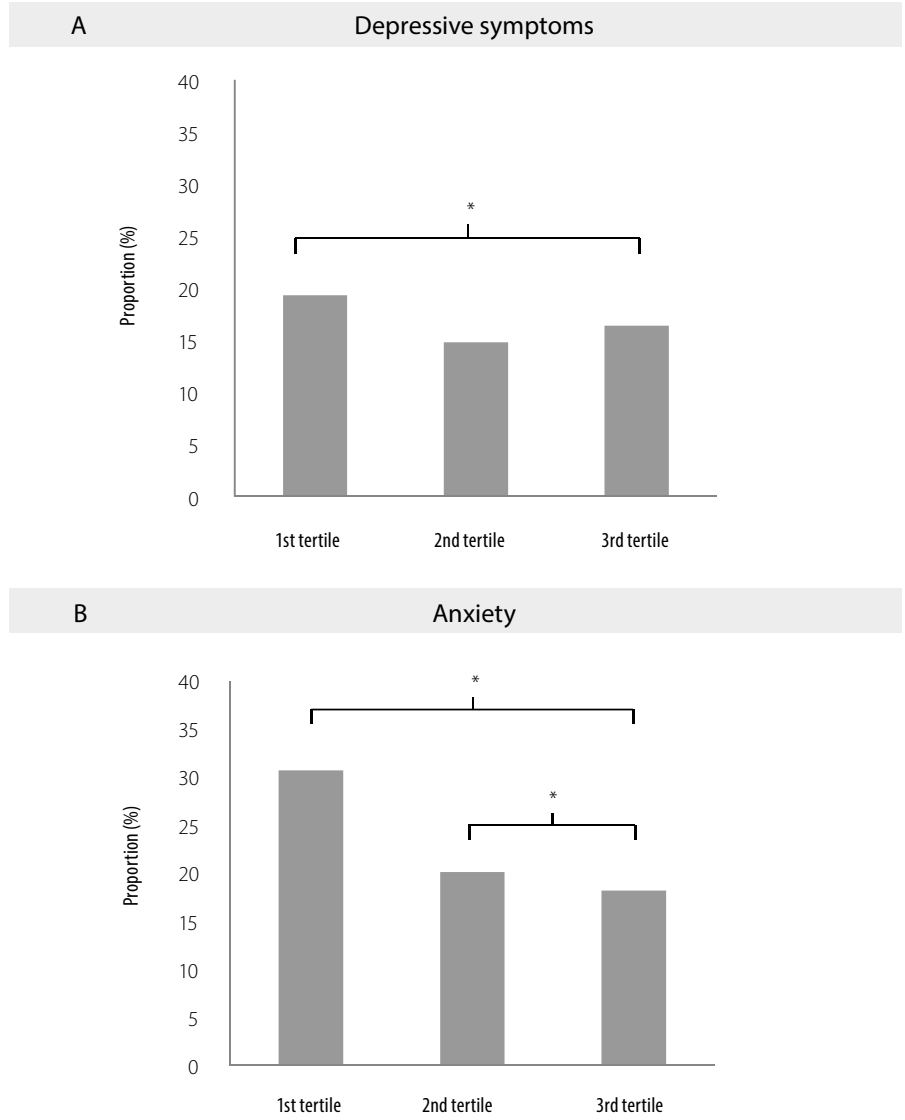


Figure shows prevalence of depressive symptoms and anxiety on average 10 years after the event, stratified by stroke subtype and sex. *Legend:* TIA: Transient ischaemic attack, IS: Ischaemic stroke. *p<0.05, ** p <0.01

Figure 3 Prevalence of depressive symptoms and anxiety, stratified by tertiles of observation time after stroke.



1st tertile: 0.2-4.1 years of observation time, 2nd tertile: 4.1-12.8 years of observation time, 3rd tertile: 12.8-31.0 years of observation time. * p<0.05.

Anxiety

The overall prevalence of anxiety in patients with a stroke at young age (TIA and ischaemic stroke together) was 23.0% versus 12.2% in controls. The risk of having anxiety was higher in both TIA-patients (OR 3.0, 95%-CI 1.6-5.8, p=0.001) and ischaemic stroke patients (OR 2.9, 95%-CI 1.5-5.8, p=0.002) compared with controls. The prevalence of anxiety stratified by stroke subtype (TIA or ischaemic stroke) and sex is shown in Figure 2B.
Prevalence of post-stroke anxiety by tertiles of follow-up is shown in Figure 3B.
Prevalence of anxiety did not differ between different stroke locations.
In the multiple regression model, ischaemic stroke patients with a lower educational level (OR 3.3, 95%-CI 1.5-7.4, p=0.003) and a history of depression (OR 4.3, 95%-CI 2.1-8.8, p<0.001) had a higher risk of anxiety. Younger age was associated with a lower risk of anxiety (OR 1.0, 95%-CI 0.9-1.0, p=0.04). Furthermore, unemployment (OR 2.3, 95%-CI 1.1-4.8, p=0.03) and current alcohol use (OR 4.1, 95%-CI 1.1-15.9, p=0.04) were associated with the presence of anxiety.

Association between depressive symptoms or anxiety and functional outcome

Depressive symptoms were associated with a poor functional outcome, as assessed by both the mRS (OR 11.2, 95%-CI 4.2-29.9, p<0.001) and the IADL (OR 3.8, 95%-CI 1.7-8.9, p=0.002), with adjustment for age at follow-up, sex, education, NIHSS-score at admission, and observation time.
Anxiety was associated with a poor functional outcome, as assessed by both the mRS (OR 6.4, 95%-CI 2.5-16.7, p<0.001) and the IADL (OR 2.4, 95%-CI 1.0-5.6, p=0.04), with adjustment for age at follow-up, sex, education, NIHSS-score at admission, and observation time.

Discussion

We showed that patients with a TIA or ischaemic stroke at a young age have an up to approximately 5 times higher risk of depressive symptoms and anxiety than stroke-free controls. Even after on average a decade after the stroke, these symptoms were associated with poor functional outcome.
Prognosis in patients with a stroke at young age is generally considered to be better than in elderly stroke patients with respect to mortality and cardiovascular risk.[129] Our findings indicate that this is apparently not true for depressive symptoms, as the prevalence of depressive symptoms we found in our young study population, were in the

range of numbers given in older stroke survivors (12-60%).[11-14] Other studies in young patients with stroke found an even higher prevalence of depressive symptoms than we found, up to 28%.[26, 27, 32] The difference is probably explained by the different methods used to assess depressive symptoms.
The finding that the prevalence of depressive symptoms and anxiety was higher in patients than in stroke-free controls, might suggest that these symptoms are attributable to the stroke at young age. However, we found that neither a more severe stroke nor recurrent strokes were associated with a higher risk of depressive symptoms and anxiety, as would be expected if stroke and depressive symptoms are directly associated. Some other studies found recurrent strokes to be associated with depression.[184, 234]
An explanation for these opposite findings might be that it is not the degree of brain damage that gives a higher risk of depressive symptoms, but merely the location of the lesion and associated network destruction.[235] However, we found no differences in prevalence of depressive symptoms or anxiety between different lesion locations.
Therefore, other factors than lesions of brain structure or function may play a role in the presence of depressive symptoms and anxiety after a stroke at young age, for example psychosocial issues.
We found an association between depressive symptoms or anxiety and a poor long-term functional outcome. Our study described this association with long-term poor functional outcome in patients after a stroke at young age, not only defined as poor motor recovery (as 1 previous study has done[26]), but also as a poor outcome on the IADL. Because this questionnaire describes more complex tasks in daily living, it is more recognisable to patients when they are informed on long-term consequences of their stroke.
The relation between psychological symptoms and poor functional outcome may be reciprocal. Possibly, psychological symptoms lead to a more passive lifestyle, which results in more functional dependency in daily life activities. Or maladaptation to functional post-stroke disabilities leads to depressive symptoms or anxiety. A lower educational level might exaggerate this reciprocal relation, due to less effective coping strategies.[236] This is indeed suggested by our finding that a lower educational level was associated with more depressive symptoms and anxiety. The vulnerability of patients with a lower educational level for depressive symptoms and anxiety may be partly explained by other related factors, such as alcoholism and unemployment. Therefore, these factors may be important targets for treatment and guidance in rehabilitation programs, to annihilate their negative effects on mood.
Strengths of our study include the large sample size and long observation time, with inclusion of both ischaemic stroke and TIA-patients. Furthermore, the single centre

design allowed us to collect information systematically, limiting information bias. In addition, since in the Netherlands all survivors of a stroke at young age usually visit a university medical centre during the course of their disease, our study population is a representative cohort for a Dutch population of patients with a stroke at young age.
However, some methodological limitations need to be addressed. Selection bias might have occurred due to patients who refused to participate or were lost to follow-up. However, as participants and patients who refused to participate did not differ in baseline clinical and demographic variables (index event, sex, age at index event, and stroke severity), we have no reason to assume that these patients differed from participants with respect to the prevalence of depressive symptoms and anxiety or their association with functional outcome. Patients who were lost to follow-up and deceased patients more often had an ischaemic stroke than a TIA. As depressive symptoms were most prevalent in ischaemic stroke patients, this might have resulted in an underestimation of our prevalence figures, but would not have altered our conclusions.
Recall bias probably influenced the reported history of depression. Patients who had their index event in the first decade of the inclusion period reported a history of depression less frequently than patients who had their index event in the second or third decade. However, it is unlikely that recall bias has influenced our primary outcome measure, as the HADS-questionnaire assesses depressive symptoms and anxiety in the past week.
Confounding is another bias to be considered. We tried to overcome this by adjusting for previously reported confounding factors in the analysis when appropriate.[237] There may be some residual confounding, especially in the association between depressive symptoms or anxiety and functional outcome. In the group with the longest observation time, there is a risk that co morbidities or other complaints, such as incident vascular disease or pain, may have led to both the depressive symptoms or anxiety and to a poor functional outcome. Future larger studies should take these factors further into account.
In conclusion, the findings of our study indicate that even after more than 10 years after the stroke at young age, lives of the survivors are very much influenced by the psychological consequences of the stroke. These negative effects may be influenced by changing lifestyles and learning better coping strategies. Therefore, even in the long term, treating physicians should be aware of the long-term presence of these symptoms, as its recognition may be the first step in improving long-term functional independence.

Fatigue after young TIA and ischaemic stroke

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Post-stroke fatigue and its association with poor functional outcome after stroke in young adults.

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Abstract

Background and objective

Post-stroke fatigue negatively influences short-term functional outcome in older stroke survivors. In young adults, in the midst of their active working and family life, this influence may even be more pronounced. However, there are only few studies on this topic in young patients with stroke. Therefore, we investigated the long-term prevalence of post-stroke fatigue in patients with a young TIA or ischaemic stroke and its association with functional outcome.

Methods

This study is part of a large cohort study among 511 stroke survivors with a first-ever TIA or ischaemic stroke, aged 18-50 years. After a mean follow-up of 9.8 (SD 8.4) years, we assessed the presence of fatigue with the fatigue subscale of the Checklist Individual Strength questionnaire and functional outcome. Prevalence of fatigue between young patients with stroke and 147 stroke-free sex-matched and age-matched controls was compared. Odds ratios (OR's) for poor functional outcome on modified Rankin Score (mRS>2) and Instrumental Activities of Daily Living (IADL<8) and cognitive performance were calculated using logistic regression analysis.

Results

Of the young patients with stoke, 41.0% experienced symptoms of fatigue, versus 18.4% in controls (p=0.0005). Fatigue was associated with a poor functional outcome, as assessed by the mRS (OR 4.0, 95%-CI 1.6-9.6), IADL (OR 2.2, 95%-CI 1.1-4.6), and impairment in speed of information processing (OR 2.2, 95%-CI 1.3-3.9).

Conclusion

Fatigue was very common in young stroke survivors and was associated with a poor functional outcome, even after almost a decade of follow-up.

Introduction

Post-stroke fatigue is a frequent symptom in the elderly stroke population (>60 years).[21-24] A previous study found that fatigue was associated with a poorer prognosis after 3 years of follow-up.[25] In young patients with stroke (≤50 years), post-stroke fatigue and its negative effects on prognosis may be even more profound, since these patients are confronted with higher demands from their social environment, with a young family to take care of and responsibilities at work. In addition, if fatigue negatively influences functional outcome, this effect may be long-lasting, as most of these patients still have a long life expectancy. Therefore, young patients with stroke form a distinct group and results from the older stroke population cannot just be extrapolated to these young patients.

However, there are only few studies on post-stroke fatigue and its influence on daily functioning in this specific age group.[33, 34, 149, 238] Those that have been performed, were limited with respect to sample size[33, 149, 238] or follow-up duration.[34] Furthermore, no studies addressed the occurrence of post-stroke fatigue in young patients with a transient ischaemic attack (TIA). Increasing evidence suggests that, after a TIA as well as after an ischaemic stroke, despite the first being a transient neurological condition by definition, patients suffer from persistent residual symptoms that may not be directly visible, for example depressive symptoms or anxiety.[239] In patients with stroke, these symptoms were found to be associated with post-stroke fatigue.[240]

Therefore, we investigated the long-term prevalence of post-stroke fatigue in patients with a TIA or ischaemic stroke aged 18 through 50 years, demographic and clinical risk factors that may be associated with fatigue, and the association between fatigue and functional outcome, including cognitive performance.

Methods

Patients and study design

This study is part of the '*F*ollow-*U*p of *T*ransient ischaemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation' (*FUTURE*) study, a large cohort study that investigates causes and consequences of stroke in young adults. Details of the study have been described elsewhere.[42, 110] The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study.

In short, the study comprises all patients with a TIA, ischaemic stroke or intracerebral haemorrhage, aged 18-50 years, admitted to Radboud University Nijmegen Medical

Centre in the Netherlands between January 1, 1980 and November 1, 2010. For the present study, only first-ever TIA and patients with ischaemic stroke were assessed.
Patients were identified through a prospective registry with a standardised collection of baseline and clinical characteristics (including demographics and stroke subtypes). TIA was defined as a rapidly evolving focal neurological deficit, with no other than a vascular cause lasting less than 24 hours. Stroke was defined similarly, but with symptoms lasting more than 24 hours. All patients underwent neurological examination and brain imaging at the time of their index event. Radiological findings were used to differentiate between ischaemic and haemorrhagic stroke. The assessment of stroke severity (National Institutes of Health Stroke Scale (NIHSS)[213]) was performed for all cases retrospectively by a validated approach.[165, 214] Lesion location was based on review of presenting clinical signs and symptoms and radiological findings.
Patients with cerebral sinus thrombosis were excluded.
Control participants were recruited from the same environment as the patients, among the patients' spouses, relatives, or social environment (n=147). The patient group and control group were matched for age and sex. Controls had to be at least 18 years old, without a history of TIA or stroke and were all living independently.
Written informed consent was obtained from all participants and controls.

Follow-up

All patients alive were invited to visit our research centre for a follow-up examination between November 1, 2009 and January 1, 2012. If patients consented to participate, but were not able to visit our research centre, data were collected by means of a standardised, structured questionnaire, which was filled out at home.

Fatigue

Our primary outcome measure was the prevalence of fatigue in young patients with stroke. The presence of fatigue was assessed with the fatigue subscale of the Checklist Individual Strength questionnaire (CIS).[193, 241] This screening instrument is well validated in patients with stroke and has been used in a previous stroke cohort.[24] The fatigue subscale contains 8 items on the level of fatigue perceived over the past 2 weeks. All items are scored on a range from 1 to 7, with higher scores representing more fatigue. The total score ranges from 8 to 56, a score above 35 is considered indicative of severe fatigue.[193, 241] Data on the presence of fatigue were missing in 13 participants (1.9%).

Functional outcome

Functional outcome was assessed with the modified Rankin Scale (mRS) and the Instrumental Activities of Daily Living-scale (IADL).[192] The mRS predominantly measures outcome based on motor function. The IADL complements this with the assessment of more complex tasks necessary for independent living in a community. In the patients who did not visit our research centre, IADL was not assessed. Information on mRS was missing in 2 patients (0.4%) and on IADL in 5 patients who visited our research centre (1.1%).

Cognitive performance

Neuropsychological tests covered the main cognitive domains and these tests have been previously applied in large-scale epidemiological studies in cerebrovascular disease.[174, 175]
The following cognitive domains were examined: *Processing speed* (the written administration of the Symbol-Digit Modalities Test, Abbreviated Stroop Color Word Test, parts I and II), *Visuoconstruction* (Rey-Osterrieth Complex Figure (ROCF) - Copy trial), *Working memory* (Paper and Pencil Memory Scanning Task (PPMST)), *Immediate memory* (ROCF - Immediate recall and the total number of words immediately recalled in the 3-trial version of the Rey Auditory Verbal Learning Test (RAVLT)), *Delayed memory* (delayed recall on the ROCF and the RAVLT), *Attention* (Verbal Series Attention Task (VSAT)), and *Executive functioning* (Verbal Fluency and Stroop Interference). To account for speed-accuracy trade-off on the Stroop test, PPMST, and VSAT, composite scores were calculated (accuracy(%)/reaction time).[207] Stroop Interference was computed by dividing the composite Stroop part III score by the mean of the composite scores of parts I and II.[139]
Per cognitive domain, the prevalence of cognitive impairment (>1.5 SD below the mean domain score of controls) was assessed. If 1 test of a particular domain was missing, the domain score was occasionally based on the remaining tests of that domain.[139]
Detailed information on the neuropsychological examination is described extensively elsewhere.[42, 139]
In the patients who did not visit our research centre, cognitive performance was not assessed. Data on cognitive impairment was missing in 1.4% to 7.7% in patients who visited our research centre, depending on the domain tested.

Other measurements at follow-up

Educational level, depressive symptoms and, anxiety were assessed at follow-up. Level of education was scored with a widely-used Dutch scoring system (1 = less than primary school; 7 = university degree).[229] The Hospital Anxiety and Depression scale (HADS)

was used for assessing depressive symptoms and anxiety.[230, 233]
Information on recurrent cerebrovascular events (TIA's, and both ischaemic and haemorrhagic strokes, defined as any stroke between the qualifying event and time of follow-up), myocardial infarction, and (cardio)vascular risk factors was collected, using a structured questionnaire. Whenever a recurrent event was suspected, information retrieved was verified and adjudicated by physicians from the appropriate specialty.
Diabetes mellitus, hypercholesterolaemia, and hypertension were considered present when diagnosed by a physician or when participants were taking medication for these conditions. Furthermore, body mass index (BMI) (weight/(length^2)), current smoking, and regular alcohol consumption defined as >2 U/day was assessed. In the patients who did not visit our research centre, BMI, smoking, and alcohol consumption were not assessed.

Statistical analysis

Baseline characteristics were compared between participants, non-participants (patients that refused and patients lost to follow-up), and deceased patients using a Student's *t*-test, Mann-Whitney *U* test or chi-square-test when appropriate. Sex and age were compared between patients and controls, using a chi-square-test and a Student's *t*-test, respectively.
The prevalence of fatigue was defined as the proportion of participants in whom these symptoms were present (CIS-fatigue subscale >35). Logistic regression was used to calculate the risk of fatigue in a patient with TIA or ischaemic stroke compared with controls, adjusted for age, sex, NIHSS-score at admission, and the presence of depressive symptoms and anxiety.
Since the present study features a long inclusion period (1980-2010), the prevalence of fatigue was also calculated as a function of follow-up duration (in tertiles; n= 62 per tertile in patients with TIA and n=108/109 per tertile in patients with ischaemic stroke) and compared with a chi-square test. A similar analysis was performed for the different lesion locations (left hemispheral, right hemispheral, bilateral or infratentorial).
We calculated whether clinical and demographic factors were associated with the presence of fatigue with multiple logistic regression, using the presence of fatigue as the dependent variable and including sex, current age, NIHSS at admission, education, follow-up duration, depressive symptoms and anxiety (per point on the HADS), and recurrent cerebrovascular events as independent variables. BMI and alcohol consumption were additionally evaluated for their association with fatigue.
Subsequently, the association between the presence of fatigue and a poor functional outcome was calculated for TIA and patients with ischaemic stroke combined, with a

logistic regression analysis, using either mRS>2, IADL<8, or cognitive impairment on the 7 cognitive domains (>1.5 SD below the mean domain score of controls) as the dependent variable indicating poor functional outcome. For the 7 cognitive domains, a Bonferroni correction was used to define results as statistically significant (p 0.05/7 cognitive domains= 0.007). Sex, age at follow-up, NIHSS-score at admission, presence of depressive symptoms and anxiety, duration of follow-up, and recurrent cerebrovascular events were considered possible confounders and adjusted for in these analyses.
Cases were excluded from the analysis when 1 or more of the used variables contained missing data. This was only the case in 0.4-3.5%, depending on the variable.
All statistical analyses were performed with SPSS 20.0 software for Windows.

Results

Study population

511 Patients were included in the present study of whom 186 had a TIA and 325 had an ischaemic stroke (Figure 1). Their baseline characteristics are presented in Table 1.

Figure 1 Flowchart of study population.

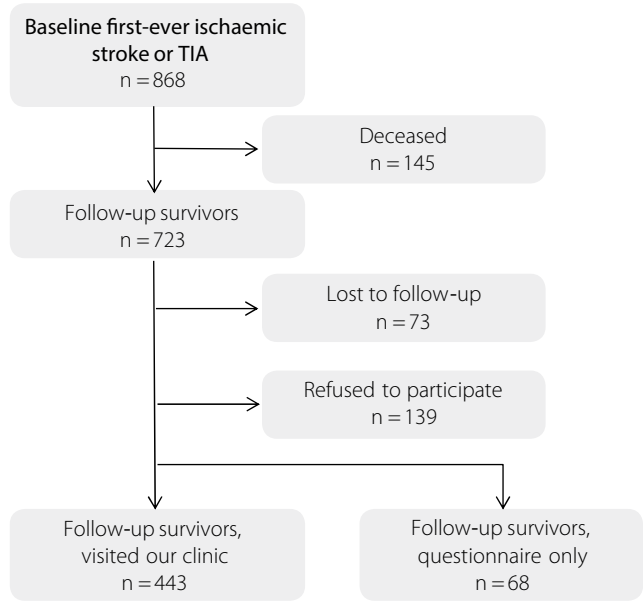


Table 1 Description of demographic and clinical variables in young patients with stroke and controls.

	TIA n=186	Ischaemic stroke n=325	Controls n=147
Baseline			
Age at index event (years)	40.5 (8.1)	40.1 (7.8)	NA
Sex[a] (proportion men)	83 (44.6%)	143 (44.0%)	63 (42.9%)
NIHSS score at admission	0 (0-1)	4 (2-9)	NA
Localisation of index event			NA
Supratentorial left	81 (43.5%)	141 (43.4%)	
Supratentorial right	56 (30.1%)	116 (35.7%)	
Infratentorial	28 (15.1%)	60 (18.5%)	
Bilateral	1 (0.5%)	7 (2.2%)	
Could not be established[b]	20 (10.8%)	1 (0.3%)	
Follow-up			
Follow-up duration (years)			
Mean (SD)	8.3 (8.1)	10.6 (8.4)	NA
Follow-up > 15 years	44 (23.7%)	105 (32.3%)	NA
Follow-up > 20 years	29 (15.6%)	56 (17.2%)	NA
Age at follow-up examination (years)[c]	48.9 (11.3)	50.7 (10.4)	48.7 (11.7)
Education	5 (5-6)	5 (4-6)	5 (5-6)
MMSE[d]	26.7 (2.3)	26.3 (2.6)	27.2 (2.0)
CIS - fatigue	30.0 (13.4)	30.7 (14.2)	22.5 (12.7)
Modified Rankin Scale	0 (0-1)	1 (1-2)	0 (0-0)
Modified Rankin Scale >2	12 (6.5%)	41 (12.6%)	1 (0.7%)
IADL-questionnaire[d]	8 (8-8)	8 (8-8)	8 (8-8)
IADL <8[d]	17 (10.8%)	41 (14.6%)	1 (0.7%)
Cognitive impairment[d]			
Speed of information processing	30(19.1%)	91 (33.8%)	9 (6.2%)
Visuoconstruction	21 (13.6%)	54 (20.1%)	11 (7.5%)
Working memory	16 (10.0%)	83 (30.0%)	13 (8.9%)
Immediate memory	33 (20.6%)	66 (23.8%)	10(6.8%)
Delayed memory	35 (22.2%)	59 (21.9%)	8 (5.5%)
Attention	24 (15.9%)	60 (23.3%)	9 (6.2%)

Table 1 *Continued*

	TIA n=186	Ischaemic stroke n=325	Controls n=147
Executive functioning	26 (16.3%)	66 (24.4%)	11 (7.5%)
Incident vascular events			
Incident stroke	32 (17.2%)	58 (17.8%)	NA
Incident myocardial infarction	9 (4.8%)	19 (5.8%)	3 (2.0%)
Vascular risk factors			
Diabetes mellitus	19 (10.3%)	43 (13.3%)	6 (4.1%)
Hypercholesterolaemia	116 (63.0%)	199 (61.6%)	27 (18.4%)
Hypertension	97 (52.4%)	175 (54.2%)	45 (30.6%)
Body Mass Index[d]	26.3 (4.2)	26.9 (5.2)	26.8 (4.7)
Current smoking[d]	35 (22.0%)	78 (28.2%)	38 (25.9%)
Current regular alcohol consumption[d]	7 (4.5%)	13 (4.7%)	14 (9.5%)

Data are mean (SD), number (%), or median (Q1-Q3). TIA: Transient Ischaemic Attack, NIHSS: National Institutes of Health Stroke Scale, MMSE: Mini Mental State Examination, HADS: Hospital Anxiety and Depression Scale, CIS: Checklist Individual Strength, IADL: Instrumental activities of daily living, NA: not applicable.
a.) Pearson chi-square, no significant differences between TIA or ischaemic stroke and controls; **b.)** uncertainty based on clinical grounds and (lack of) radiological findings; **c.)** Student's *t*-test, no significant differences between TIA or ischaemic stroke and controls; **d.)** The following variables were only obtained at follow-up visit and not in the follow-up questionnaire group (n=68): MMSE, IADL, cognitive performance, body mass index, smoking, and regular alcohol consumption. Proportions and means are of the follow-up visit participants only.

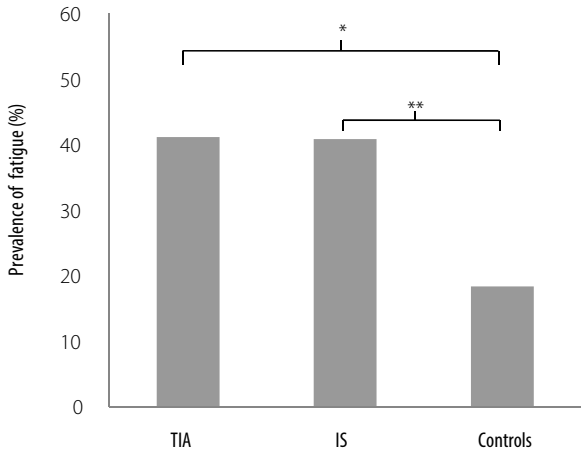
Patients who refused to participate did not differ from participants with respect to index event, sex, age at index event, and NIHSS-score at admission. The proportion of patients with an ischaemic stroke was larger among deceased patients and among patients who were lost to follow-up compared with participants. These 2 groups had higher NIHSS-scores at admission than participants (deceased: median 5 (IQR 2-12), p<0.001, lost to follow-up: median 4 (IQR 1-11.5), p<0.001, participants: median 2 (IQR 0-6)). Deceased patients more often were men (55.8% versus 44.9%, p=0.01). Deceased patients and patients who were lost to follow-up differed in age from participants at the time of the index event (deceased: mean 42.5 (SD 6.7) years, p=0.002, lost to follow-up: mean 38.2 (SD 8.6) years, p=0.04, and participants: mean 40.2 (SD 7.8) years).

Prevalence of fatigue

The overall prevalence of fatigue was 41.0% in young patients with stroke (after a mean follow-up of 9.8 (SD 8.4) years versus 18.4% in controls (p=0.0005). Figure 2 shows the prevalence of fatigue, stratified by stroke subtype.

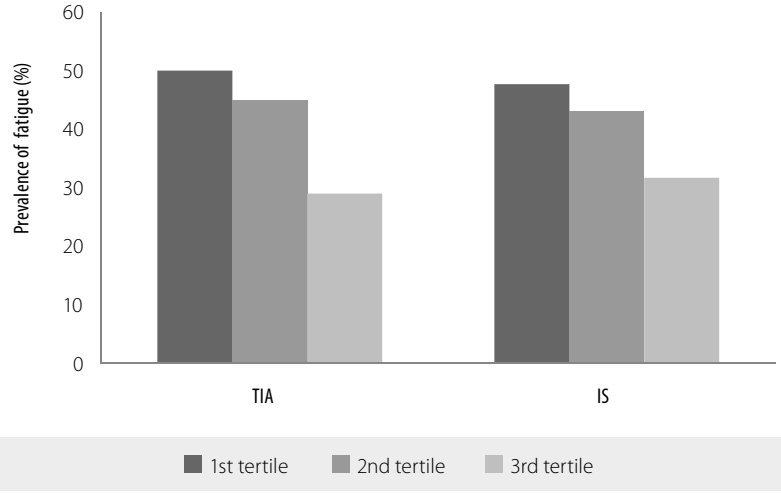
The risk of fatigue was significantly higher in patients with TIA (OR 2.9, 95%-CI 1.6-5.1) and in patients with ischaemic stroke (OR 2.2, 95%-CI 1.2-4.0) than in controls.
The prevalence of fatigue was not influenced by the duration of follow-up (Figure 3).
The prevalence of fatigue did not differ between different stroke localisations.

Figure 2 Prevalence of fatigue.



TIA: Transient Ischaemic Attack, IS: ischaemic stroke, CIS: Checklist Individual Strength.
* p=0.0003, ** p=0.01, adjusted for age at follow-up, sex, NIHSS at admission, presence of depression and anxiety.

Figure 3 Prevalence of fatigue, stratified by follow-up.



TIA: transient ischaemic attack, IS: ischaemic stroke.
TIA: 1st tertile: 0.3-3.1 years, 2nd tertile 3.3-7.8 years, 3rd tertile 7.9-30.4 years. (n per tertile = 62).
IS: 1st tertile: 0.2-5.0 years, 2nd tertile 5.0-14.6 years, 3rd tertile 14.9-31.0 years. (n per tertile =108-109-108).
No significant differences between tertiles of follow-up existed after adjustment for age, sex, NIHSS at admission, and presence of depression and anxiety.

Risk factors associated with fatigue

In patients with an ischaemic stroke, the number of depressive symptoms (OR 1.4, 95%-CI 1.3-1.6, per each point increase on the HADS-d), the number of symptoms of anxiety (OR 1.1, 95%-CI 1.0-1.2, per each point increase on the HADS-a), and recurrent cerebrovascular events (OR 2.4, 95%-CI 1.2-5.0) were associated with the presence of fatigue (Table 2)

In patients with a TIA, the number of depressive symptoms (OR 1.8, 95%-CI 1.4-2.2, per each point increase on the HADS-d), the number of symptoms of anxiety (OR 1.2, 95%-CI 1.0-1.4, per each point increase on the HADS-a), and female sex (OR 2.9, 95%-CI 1.1-7.6) were associated with the presence of fatigue (Table 2).

Table 2 Risk factors for the presence of fatigue.

	TIA		Ischaemic stroke	
Risk factor	OR (95%CI)	p-value	OR (95%CI)	p-value
Female sex	2.9 (1.1-7.6)	0.03	1.3 (0.7-2.2)	0.45
Age, per year	1.0 (0.9-1.0)	0.47	1.0 (1.0-1.0)	0.10
Lower educational level	1.0 (0.3-3.4)	0.96	1.1 (0.5-2.5)	0.78
NIHSS at admission, per point	1.1 (0.9-1.3)	0.36	1.0 (1.0-1.1)	0.59
Follow-up duration, per year	1.0 (0.9-1.0)	0.37	1.0 (0.9-1.0)	0.45
Depressive symptoms[a]	1.8 (1.4-2.2)	0.00001	1.4 (1.3-1.6)	<0.000001
Anxiety[b]	1.2 (1.0-1.4)	0.03	1.1 (1.0-1.2)	0.02
Recurrent cerebro-vascular events[c]	2.3 (0.8-7.1)	0.13	2.4 (1.2-5.0)	0.02

Multiple logistic regression analysis with factors associated with fatigue. All variables were entered simultaneously into the model. Body Mass Index and alcohol consumption did not significantly alter the model and were removed from the model. Legend: NIHSS: National Institutes of Health Stroke Scale. **a.)** per point on Hospital Anxiety and Depression Scale, items on depressive symptoms; **b.)** per point on Hospital Anxiety and Depression Scale, items on anxiety; **c.)** TIA's, ischaemic and haemorrhagic strokes combined.

Table 3 Association between fatigue and cognitive impairment.

	Association between impairment and fatigue	
Cognitive domain	OR (95%-CI)	p-value
Speed of information processing	2.2 (1.3-3.9)	0.006
Visuoconstruction	1.5 (0.8-2.8)	0.18
Working memory	2.3 (1.3-4.3)	0.007
Immediate memory	1.5 (0.8-2.9)	0.17
Delayed memory	0.7 (0.4-1.3)	0.25
Attention	1.6 (0.9-2.9)	0.12
Executive functioning	1.0 (0.6-1.9)	0.94

Multiple logistic regression analysis, showing associations between fatigue and cognitive impairment on 7 cognitive domains. With Bonferroni correction, p<0.007 was considered statistically significant. Odds Ratios (OR) with 95%-Confidence Intervals (95%-CI) and p-values were adjusted for age, sex, stroke →

← severity (National Institutes of Health Stroke Scale), duration of follow-up, presence of depressive symptoms and anxiety, and recurrent cerebrovascular events.

Association between fatigue and functional outcome

In patients with a TIA and ischaemic stroke, fatigue was associated with a poor functional outcome, as assessed by the mRS (OR 4.0, 95%-CI 1.6-9.6) and the IADL (OR 2.2, 95%-CI 1.1-4.6). Odds ratios are presented after adding the variable 'recurrent cerebrovascular events' to the model, and adjustment for NIHSS at admission, duration of follow-up, the presence of depressive symptoms and anxiety.
Table 3 displays the associations between fatigue and cognitive impairment.

Discussion

We found that fatigue was a very common symptom in young patients with stroke. Even after almost a decade of follow-up, fatigue was associated with a poor functional outcome.
Strengths of our study include the large sample size and long follow-up, with inclusion of patients with both ischaemic stroke and TIA and the comparison with a stroke-free control group. Furthermore, the single centre design allowed us to collect information systematically, limiting information bias. Being a tertiary referral centre, our cohort is a representative sample of a Dutch young stroke population, since those young patients with stroke who survive usually visit a university medical centre during the course of their disease.
However, some limitations need to be addressed. Selection bias might have occurred due to patients who refused to participate, patients lost to follow-up, and patients who were deceased. It might be that higher levels of fatigue were an important reason for patients to refuse to participate. This would result in an underestimation of the prevalence of fatigue in our cohort. However, including these patients would then only have magnified the differences we found between patients and controls, and not alter our conclusions.
Patients who were lost to follow-up and deceased patients more often had an ischaemic stroke than a TIA and higher NIHSS-scores. These variables were however not associated with a higher prevalence of fatigue. Furthermore, we have no reason to assume that the nature of the relation between fatigue and functional outcome differs in participants from that in any of the 3 groups of non-participants (eg., refusers, lost to follow-up, and deceased).

Confounding is another bias to be considered. The most important confounders in the relation between fatigue and functional outcome are the presence of depressive symptoms and anxiety. We tried to overcome this bias by making adjustments for the presence of depressive symptoms and anxiety in our analyses.

Statistical power was limited in patients with TIA, so we had to include the variables 'depressive symptoms' and 'anxiety' as continuous scores on the HADS in the model investigating their association with fatigue. They were found to be independently related to fatigue, with modestly elevated odds ratios per point on the HADS-score. If there were more patients in the TIA-group, and we could have included depressive symptoms and anxiety as dichotomous variables, we expect that this would have resulted in larger odds ratios, showing even more clearly that these symptoms are interrelated. Therefore, this probably would not have altered conclusions.

One previous study in young patients with stroke reported a prevalence of fatigue of 51.3% versus 31.6% in controls.[33] These figures were higher than we found (41.0% versus 18.4%). This difference may be explained by the different methods that were used to assess fatigue. It might be that the threshold of detecting fatigue with our questionnaire is higher, but we are not aware of studies that directly compare the 2 different methods that assess fatigue (Fatigue Severity Scale (FSS) and CIS).

A surprising finding of our study was that fatigue was equally common in young patients with TIA as in young patients with ischaemic stroke. This may suggest that the size of the structural lesion caused by the initial TIA or stroke does not play a role in the presence of fatigue after long-term follow-up. In addition, we did not find any difference in prevalence of fatigue in different lesion localisations. Our findings are in contrast with previous short-term follow-up studies. One study found that fatigue was more common after a minor stroke than after a TIA.[242] Other short-term follow-up studies found that the lesion localisation, namely infratentorial or in the basal ganglia, was associated with the presence of fatigue.[24, 150] Our findings indicate that on the long term, initial stroke characteristics (eg., volume of brain damage or lesion localisation) are not an important determinant of the presence of fatigue, in contrast to previous studies that found stroke characteristics to be associated with fatigue shortly after the stroke.

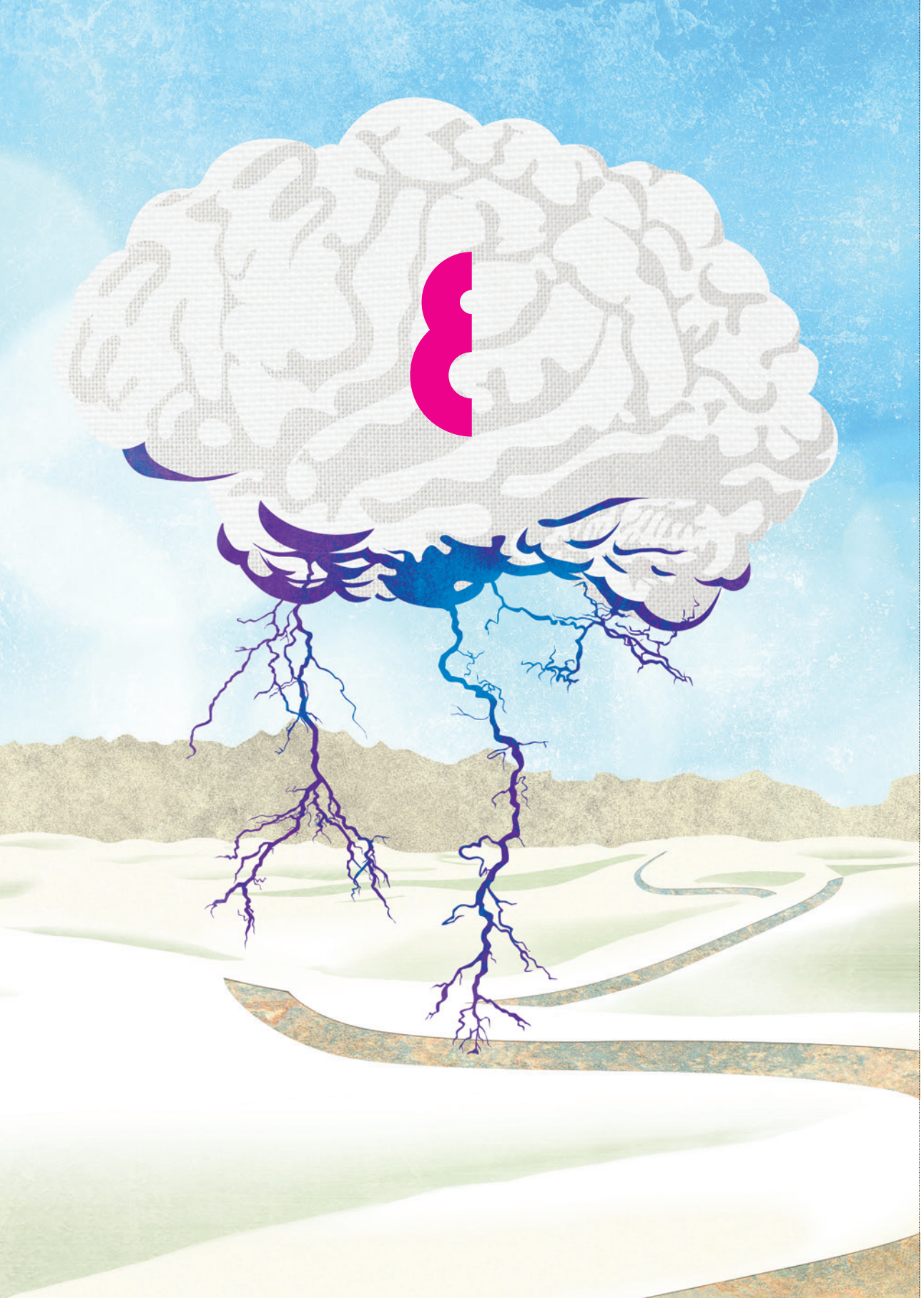
Whereas the initial stroke may not have a large role in long-term post-stroke fatigue anymore, accumulating structural brain damage over the years may have. This is indeed suggested by our finding that recurrent cerebrovascular events were associated with the presence of fatigue (in patients with an ischaemic stroke). However, one would then also expect that the prevalence of fatigue would rise with longer follow-up, during which recurrent cerebrovascular events occur. We did however not find differences in prevalence during different tertiles of follow-up.

Our findings that stroke subtype (TIA or ischaemic stroke), lesion localisation and recurrent cerebrovascular events were not unequivocally related to the presence of fatigue, suggest that other factors may play an important role, for example psychosocial factors. In our study, depressive symptoms and anxiety were associated with the presence of fatigue. These symptoms often co-occur.[243] A study in patients with a mean age of 68 years found that fatigue was associated with poor physical health 1.5 years after a stroke, independent of depressive symptoms.[244] However, younger patients might have to cope with higher demands than older stroke survivors, due to active work participation and a young family. Therefore, results from studies in older stroke survivors cannot necessarily be extrapolated to young patients with stroke. Our study shows that fatigue was related physical health in young stroke survivors, measured with a motor performance scale (mRS), independently from depressive symptoms or anxiety. Moreover, we found that fatigue was also associated with impairment of speed of information processing and showed a trend towards a significant association with impaired working memory. One previous study in older patients with stroke found no longitudinal relationship between fatigue and mental health.[244] This differs from the findings from our study, but this is probably explained by the fact that we assessed each cognitive domain separately, instead of 1 global score for cognitive performance. Although we found that fatigue was associated or showed a trend towards an association with only 2 cognitive domains (speed of information processing and working memory), impairment in these domains may very much interfere with regaining pre-stroke activities, for example returning to work.[245]

One other study also found a relation between fatigue and poor functional physical outcome in young patients with ischaemic stroke.[33] Since our study shows that this association also holds true for cognitive impairment, our study underlines the fact that the less visible (psychological) post-stroke consequences are at least as important to address in rehabilitation programmes as are the more visible motor symptoms.

Our findings can be used to properly inform young stroke survivors and caregivers, which may be a first step in optimising rehabilitation programmes.[246] Although different kinds of treatments for post-stroke fatigue are in development for the general stroke population,[247, 248] no treatments have been proven unequivocally successful in clinical trials in these patients,[249-251] let alone in specific young stroke cohorts.

In conclusion, even after almost a decade of follow-up after a stroke at young age, fatigue was present in approximately 40% of patients. This fatigue was associated with a poor functional outcome. Therefore, reducing fatigue can be an important tool in increasing functional independence in young stroke survivors.



Neuropsychological consequences after a young intracerebral haemorrhage

Submitted as

Maaijwee NA, Schaapsmeerders P, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, van Dijk EJ, Kessels RP, de Leeuw FE.
Neuropsychological consequences of intracerebral haemorrhage in young adults; a long-term follow-up study.

Abstract

Background and objective

The survival of patients with an intracerebral haemorrhage (ICH) has increased due to improved intensive and neurological care. Data on the long-term cognitive and behavioural prognosis of these patients is scarce, especially in young patients (<50 years). Therefore, the aim of this study was to investigate this long-term prognosis.

Methods

All patients, aged 18-50 years, admitted to our hospital between January 1, 1980 and November 1, 2010 who survived an ICH (n=45, mean age: 35.3 (SD 8.5) years), were recruited. We assessed depressive symptoms and anxiety with the Hospital Anxiety and Depression-scale. Fatigue was assessed with the Checklist Individual Strength questionnaire and subjective cognitive failures with the Cognitive Failures Questionnaire. Cognitive performance was examined, using an extensive neuropsychological examination. Prevalence of these symptoms was compared with 45 sex-, age-, and education-matched controls.

Results

After a mean follow-up of 9.8 (SD 8.0) years, fatigue showed a trend towards a significantly higher prevalence in patients compared with controls (40.5% versus 22.2%, p=0.07). Subjective cognitive failures were more prevalent in patients than in controls (93.9% versus 73.0%, p=0.02). Higher frequencies of cognitive impairment on the domains 'speed of information processing' (33.3% versus 5.4%, p=0.003), 'working memory' (29.4% versus 10.8%, p=0.049), 'immediate memory' (26.5% versus 8.1%, p=0.04), and 'delayed memory' (20.6% versus 2.7%, p=0.02) were observed. We found no difference in prevalence of depressive symptoms and anxiety between patients and controls.

Conclusion

Even after almost 10 years of follow-up, neuropsychological problems are prevalent after ICH in young adults. Patients should be informed on these possible long-term consequences of an ICH.

Introduction

Approximately 10% to 14% of all strokes occur in patients under 50 years of age,[5] of which 20% are intracerebral haemorrhages (ICH).[252] The survival of ICH patients has increased due to improved intensive and neurological care.[40] Furthermore, once a patient survives the first 30 days, long-term mortality is comparable to the general population in patients aged 18-40 years,[253] resulting in an increasing number of very long-term survivors after an ICH in young adults. Therefore, the need for information on long-term sequelae of this condition arises. Moreover, young adults are in a demanding phase of life, because of their role as a caregiver for a young family or the presence of occupational responsibilities. This stresses the need for reliable information on possible factors that might interfere with post-ICH activities of daily life.

To date, only limited data exist on long-term consequences of ICH in young adults <50 years,[16, 108, 254] especially with respect to less visible symptoms, such as mood disorders, fatigue or cognitive impairment.[255] Data cannot be extrapolated from findings in elderly patients,[18, 256-258] since patients are much younger and for example have better recovery than elderly. On the other hand, young adults may experience more difficulties as they are more likely to encounter demanding situations in their daily life. Findings from studies in ischaemic stroke patients may neither necessarily be generalisable to patients with an ICH. Although often lumped under the term 'stroke', these are 2 completely different diseases, each with different causes and recovery.[23, 259, 260]

Therefore, we aimed to investigate the long-term prevalence of neuropsychological consequences in a population of ICH-survivors, aged 18 through 50 years, including depressive symptoms, anxiety, fatigue, subjective cognitive failures, and objective cognitive impairment, compared with an age-, sex-, and education-matched, stroke-free control group.

Methods

Patients and study design

This study is a part of the '*F*ollow-*U*p of *T*ransient ischaemic attack and stroke patients and *U*nelucidated *R*isk factor *E*valuation' (*FUTURE*) study, a prospective cohort study designed to investigate the aetiologies and consequences of a young stroke. Details of the study have been described elsewhere.[42, 110] In short, the FUTURE study comprised all consecutive patients aged 18 through 50 years with a transient ischaemic attack (TIA) or stroke admitted to the Radboud University Medical Centre Nijmegen from January

1, 1980 until November 1, 2010. For the present study, only patients with an ICH were included. Patients were identified through a prospective registry that has been maintained at the Department of Neurology of the Radboud University Nijmegen Medical Centre, since the late 1970's with a standardised collection of baseline and clinical characteristics (including demographics and stroke subtype).[42]

Stroke was defined as a focal neurological deficit persisting for more than 24 hours.[261, 262] Stroke was subdivided into ischaemic or haemorrhagic based on radiological findings. To minimise bias resulting from changing diagnostic techniques, the World Health Organization definition for stroke was used.[261, 262] ICH location was determined by neuroimaging reports and medical history. Assessment of stroke severity (National Institutes of Health Stroke Scale (NIHSS)[213]) was performed retrospectively in all cases using a validated approach as previously described,[165, 214] because this scale did not exist when a substantial number of our patients experienced their index event.

Exclusion criteria were traumatic haemorrhagic stroke, haemorrhage in known cerebral metastasis or primary brain tumor, subarachnoid haemorrhage or ICH attributable to known ruptured aneurysm.

Control participants were recruited from the same environment as the patients, among the patients' spouses, relatives, or social environment. Each patient was matched with 1 control participant for age, sex, and education. Controls had to be at least 18 years old, without a history of TIA or stroke. They were all living independently.

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study. Written informed consent was obtained from all participants and controls.

Follow-up assessment

All patients alive were invited for a follow-up assessment between November 1, 2009 and January 1, 2012. If patients consented to participate, but were not able to visit our research centre, a standardised, structured questionnaire was sent out by mail to these participants, including the questionnaires on depressive symptoms, anxiety, and fatigue. The presence of subjective cognitive failures and cognitive impairment was not assessed in these patients.

Depressive symptoms and anxiety

Depressive symptoms and anxiety in the past week were assessed with the Hospital Anxiety and Depression Scale (HADS). Depressive symptoms were considered present with a score higher than 7 on either the depression or the anxiety items of this questionnaire.[230] The cut-off value we used is considered to be indicative of the presence of depressive

symptoms or anxiety,[230, 233] and is well validated in stroke patients[233] as well as in large population-based studies.[184] Data on the HADS were missing in 6.7% of the patients.

Fatigue

The presence of fatigue in the past 2 weeks was assessed with the fatigue subscale of the Checklist Individual Strength questionnaire (CIS).[193, 241] The fatigue subscale contains 8 items on the level of perceived fatigue, with a scoring range from 1 to 7, with higher scores representing more fatigue. The total score ranges from 8 to 56, a score above 35 is considered indicative for severe fatigue.[193, 241] This screening instrument is well validated in stroke patients and has been used in a previous stroke cohort.[24] Data on the presence of fatigue were missing in 6.7% of the patients.

Subjective cognitive failures

The presence of subjective cognitive failures in the past month was assessed, using a semi-structured interview based on the Cognitive Failures Questionnaire (CFQ).[183] This questionnaire contains 5 items with a scoring range from 0 to 3 (none-mild-moderate-severe) and 10 items with a scoring of 0 or 1 (item absent or present). Subjective cognitive failures were considered present when a participant scored a '2 (moderate)' or higher on at least 1 item with a scale of 0 to 3 or scored a '1 (present)' on at least 1 item with dichotomous answers. This version was also used in other large scale epidemiologic research.[227, 228] Subjective cognitive failures were assessed in the patients who visited our research centre for an in-person neuropsychological investigation, n=37. Data were missing in 10.8 % of these patients.

Cognitive performance

Neuropsychological examination covered the main cognitive domains and these tests have been previously applied in large-scale epidemiological studies in patients with cerebrovascular disease.[174, 175] The following cognitive domains were examined: *Processing speed* (Symbol-Digit Substitution Task, Abbreviated Stroop Color Word Test, parts I and II), *Visuoconstruction* (Rey-Osterrieth Complex Figure (ROCF) - Copy trial), *Working memory* (Paper and Pencil Memory Scanning Task (PPMST)), *Immediate memory* (ROCF - Immediate recall and the total number of words immediately recalled in the 3-trial version of the Rey Auditory Verbal Learning Test (RAVLT)), *Delayed memory* (delayed recall on the ROCF and the RAVLT), *Attention* (Verbal Series Attention Task (VSAT)), and *Executive functioning* (Verbal Fluency and Stroop Interference). To account for speed-accuracy trade-off on the Stroop test, PPMST, and VSAT, composite scores were calculat-

ed (accuracy(%)/reaction time).[207] Stroop Interference was computed by dividing the composite Stroop part III score by the mean of the composite scores of parts I and II.
Cognitive performance was assessed in the patients who visited our research centre for an in-person neuropsychological investigation, n=37. Data on cognitive impairment were missing in 8.1-10.8% of these patients, depending on the domain tested. If 1 test of a particular domain was missing, the domain score was occasionally based on the remaining tests of that domain. Detailed information on the neuropsychological examination is described extensively elsewhere.[42, 139]

Statistical analysis

The prevalence of depressive symptoms, anxiety, fatigue, and subjective cognitive failures was compared with controls, using a chi-square test.
Cognitive impairment for each cognitive domain was defined as >1.5 SD below the mean of the control group. Next, the prevalence of cognitive impairments for each cognitive domain between patients and controls was compared by means of a chi-square test. Subsequently, we tested the 'forgetting rate' after 30 minutes by subtracting delayed recall on the RAVLT from the third trial of the RAVLT.
A sensitivity analysis was performed to account for the relatively large percentage of missing data in the 7 cognitive domains, using the automatic multiple imputation methods in SPSS.
Two-sided p-values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS 20.0 software for Windows.

Results

Study population and demographics

45 patients with an ICH and 45 healthy controls were included in this study (Figure 1). Demographics and clinical variables of patients are presented in Table 1. Controls did not differ from patients with respect to sex, age, and education.

Deceased patients were older than participants at the time of the index event (41.2 (SD 7.7) years versus 35.3 (SD 8.5) years, p=0.04) and had a more severe stroke (median NIHSS 17.5 (IQR 11-23) versus median NIHSS 11 (IQR 3-15.5), p=0.0001), but no differences were observed with respect to sex.

Figure 1 Flowchart of study population.

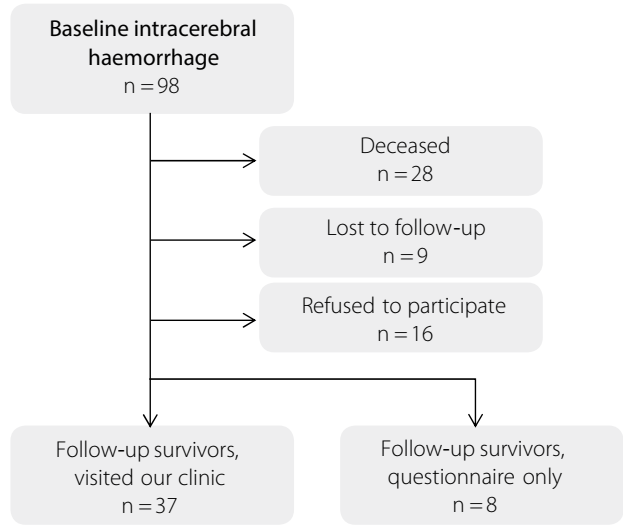


Table 1 Description of demographics and clinical variables in ICH-patients.

	ICH n=45
Baseline	
Men, n (%)[a]	26 (57.8)
Age at index-event, years (SD)	35.3 (8.5)
NIHSS score at admission, median (IQR)	11 (3-15.5)
Location	
Supratentorial, n (% of total)	36 (80.0)
Hemisphere, n (% of all supratentorial locations)	
Left	13 (36.1)
Right	20 (55.6)
Bilateral	3 (8.3)
Localisation, n (% of all supratentorial locations)	
Deep	8 (22.2)
Lobar	15 (41.7)
Ventricular	3 (8.3)
Intraventricular extension	10 (27.8)

Table 1 *Continued*

	ICH n=45
Infratentorial, n (% of total)	9 (20.0)
Cerebellum, n (% of all infratentorial locations)	3 (33.3)
Brainstem, n (% of all infratentorial locations)	6 (66.7)
Etiology, n (%)	
Hypertension	10 (22.2)
Arteriovenous malformation	14 (31.1)
Cavernous angioma	1 (2.2)
Coagulopathy	
Medication use	2 (4.4)
Bleeding disorder	2 (4.4)
Septic embolism	1 (2.2)
Unknown	
Cryptogenic	11(24.4)
Multiple causes	2 (4.4)
Incomplete evaluation	2 (4.4)
Follow-up	
Mean duration of follow-up, years (SD)	9.8 (8.0)
Follow-up >10 years, n (%)	17 (37.8)
Age at follow-up, years (SD)[b]	45.1 (10.4)
Education, median (IQR)[c]	5 (5-6)
Recurrent strokes, n (%)	5 (11.1)[d]

Abbreviations: ICH: Intracerebral haemorrhage; NIHSS: National Institute of Health Stroke Scale; IQR: interquartile range.

a.) In controls: 25 (55.6), p=0.83; **b.)** In controls: 45.1 (10.7), p=1.00; **c.)** In controls: 5 (5-6), p=0.63; **d.)** Of which 1 ischaemic stroke and 4 intracerebral haemorrhages. Missing data: educational level was missing in 1 patient. Level of education was scored with a widely-used Dutch scoring system (1 = less than primary school; 7 = university degree).[229]

Neuropsychological outcomes

After a mean follow-up of 9.8 (SD 8.0) years (with 17 of patients (37.8%) with a follow-up duration of >10 years), subjective cognitive failures were more prevalent in patients than in controls (93.9% versus 73.0%, p=0.02). Fatigue was present in 40.5% of patients and showed a trend towards a significant difference compared with controls (22.2%, p=0.07). No differences in the prevalence of depressive symptoms and anxiety were observed in patients compared with controls (7.1% versus 4.4%, p=0.59 and 11.9% versus 6.7%, p=0.40).

Table 2 shows the neuropsychological test scores of patients and controls.

Figure 2 shows that the prevalence of patients with cognitive impairment (>1.5 SD below mean performance of controls) differed significantly from controls on the domains 'speed of information processing' (33.3% versus 5.4%, p=0.003), 'working memory' (29.4% versus 10.8%, p=0.049), 'immediate memory' (26.5% versus 8.1%, p=0.04), and 'delayed memory' (20.6% versus 2.7%, p=0.02).

After performing a sensitivity analysis with the multiple imputation method, the significant difference in 'working memory' impairment changed into a trend (p=0.06) and the non-significant difference in 'attention'-impairment became a trend (p=0.08).The differences in other domains remained significant.

The large proportion of patients with impairment in delayed memory is mainly attributable to a worse performance in the initial learning trials of the test, as patients did not show a rapid forgetting rate after 30 minutes compared with controls.

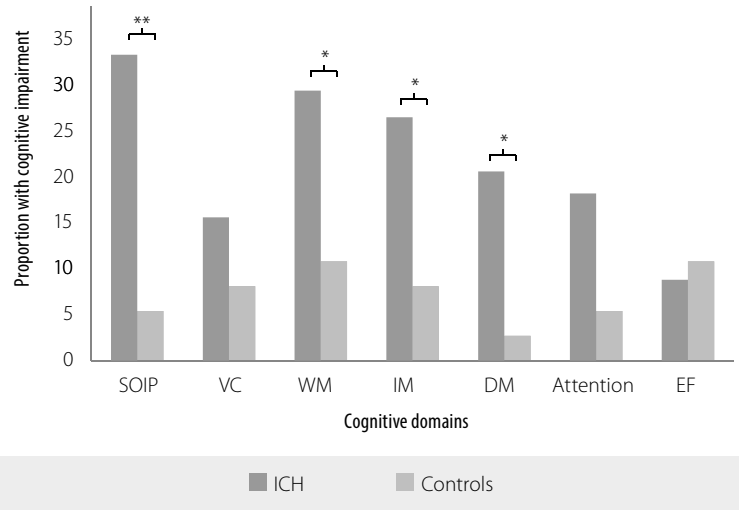
Table 2 Neuropsychological test scores of patients with an ICH and controls.

Cognitive domain and test	ICH N=37	Controls N=37	p-value
Processing speed			
SDMT	45.8 (10.8)	53.9 (8.6)	0.001
Stroop part I[a]	4.4 (1.3)	4.6 (0.7)	0.23
Stroop Part II[a]	3.2 (1.1)	3.6 (0.7)	0.04
Visuoconstruction			
ROCF copy	31.7 (3.7)	32.2 (2.7)	0.57
Memory			
Working memory			
PPMST '%'[a]	2.9 (1.2)	3.6 (1.0)	0.01
PPMST 'S'[a]	2.5 (0.9)	3.0 (0.6)	0.03
PPMST 'MP'[a]	1.7 (0.6)	1.8 (0.4)	0.39
PPMST 'DHN'[a]	1.5 (0.4)	1.6 (0.4)	0.12
Immediate memory			
RAVLT trial 1-3	19.9 (7.0)	22.7 (5.6)	0.07
ROCF immediate recall	14.2 (5.4)	19.5 (5.7)	0.0002
Delayed memory			
RAVLT delayed recall	6.2 (2.8)	7.3 (3.0)	0.12
ROCF delayed recall	13.6 (5.6)	19.3 (5.7)	0.0003
Attention			
Total score of the VSAT[a]	1.3 (0.5)	1.5 (0.4)	0.35
Executive functioning			
Verbal fluency	23.9 (8.5)	24.4 (6.9)	0.81
Interference[a]	0.5 (0.1)	0.5 (0.1)	0.74

Data are expressed as mean (SD). PPMST: paper and pencil memory scanning test; RAVLT: Rey auditory verbal learning test; ROCF: Rey-Osterrieth complex figure; SDMT: symbol-digit modalities test; VSAT: verbal series attention test. S, MP, DHN: these (combination of) letters had to be memorised and found among 120 distracting letters.

a.) Speed-accuracy composite score. Higher scores indicate better performance on all measures.

Figure 2 Proportions of patients and controls with cognitive impairment (<1.5 SD below the mean performance of controls) on 7 cognitive domains.



ICH: intracerebral haemorrhage; SOIP: Speed of information processing; VC: visuoconstruction; WM: working memory; IM: immediate memory; DM: delayed memory; EF: executive functioning.

*p<0.05

**p<0.01

Discussion

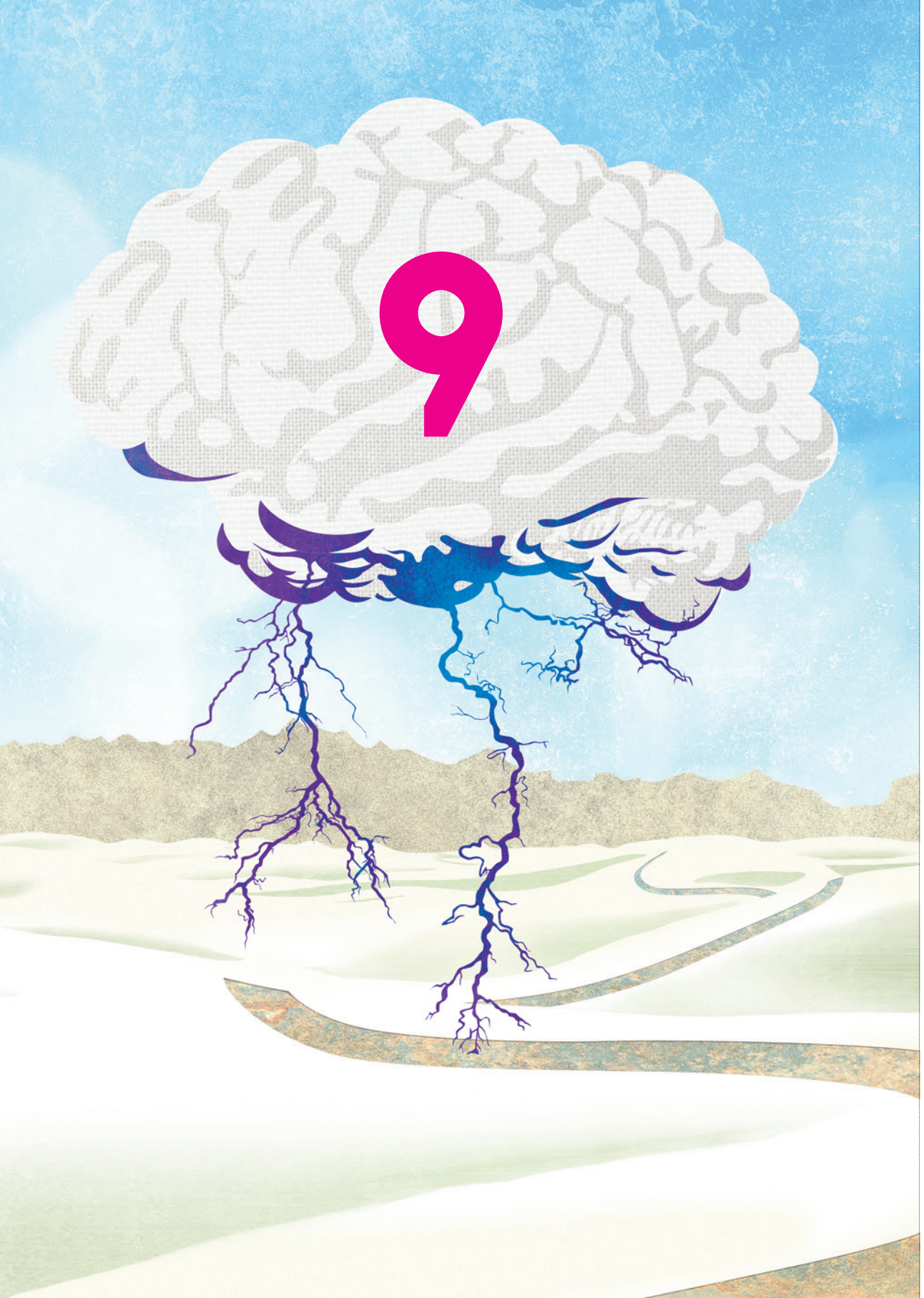
This study showed that up to one third of patients who survived an ICH have cognitive impairment after almost 10 years of follow-up. In addition, subjective cognitive failures and fatigue were also very common symptoms. Depressive symptoms and anxiety were much less prevalent and did not differ between ICH-patients and stroke-free controls.

One strength of our study is the long-term follow-up, which provides unique information on possible long-term neuropsychological consequences a young survivor of an ICH may be confronted with. Another strength of our study is the comparison with a closely matched control sample. This provides insight into the excess risk of neuropsychological problems, attributable to the ICH.

However, our results need to be interpreted with caution. Because of the small sample size, statistical power is limited, which may have introduced bias.

First, selection bias is an issue. Our study included only the long-term survivors of an ICH. Patients who were deceased suffered from a more severe stroke. Therefore, it might be expected that these patients would also have been more cognitively impaired than the participants, resulting in larger differences when included in the analyses, but not in different conclusions.
Second, information bias may have occurred. Researchers who assessed neuropsychological functioning were not blinded to which group a patient belonged (ICH or control), due to presence of possible visible physical disabilities. However, strict instruction protocols were used and researchers were trained.
Third, because of the small sample size, we were not able to adjust for confounders. However, we tried to overcome this by matching controls on some of the important confounding factors, namely age, sex, and education. Recurrent ischaemic strokes or ICH, that might have led to cognitive impairment, were not considered in our analyses because of low numbers. These should be considered in future studies with larger sample sizes.
Our most important finding is that patients with an ICH showed more cognitive impairment than controls, especially on the domain of 'speed of information processing'. This impairment might interfere with other complex tasks, such as working memory or episodic memory performance. As for episodic memory performance, mental slowing might have led to impaired learning trials, resulting in a worse recall ability and thereby lower scores on tests on delayed memory. One would also expect that ICH-patients showed more impairment on the domain of 'attention', because this may also be influenced by mental speed. Possibly, our tests were not sensitive enough to find a difference between patients and controls in our small study sample.
Mental slowness may also result in experienced fatigue or subjective cognitive failures. These symptoms can be caused by an imbalance between high demands from a patients' environment (especially in young adults) and impaired coping strategies due to the cognitive impairment.
A possible underlying pathophysiological mechanism for impaired mental speed may be the destruction of subcortical fiber networks,[263] since mental slowness is usually considered to be due to subcortical disfunctioning. Previous studies hypothesised that an ICH may cause more reversible damage, because the blood would only displace fibers, not destroy them.[257] However, our study suggests that an ICH might lead to subcortical fiber network destruction, with consequent long-term cognitive impairment. Possible mechanisms may be the mass effect of the volume of the haemorrhage itself, causing a raised intracranial pressure[264] and tissue necrosis, or the surrounding

edema, causing secondary hypoxia,[265] although these mechanisms may be partially reversible.[260, 266]
Future studies are needed to confirm this suggestion, using DTI-techniques to measure changes in integrity of subcortical fiber networks over time during and after the clinical recovery phase and taking incident co morbidities into account.
Findings from our study can be used to inform young patients on possible long-term neuropsychological consequences of an ICH, although larger studies are needed to confirm our results and to elucidate underlying mechanisms. These patients are in a period of their lives during which important, possibly life-changing decisions have to be made, for example on career movements or family planning.
In conclusion, even after almost 10 years of follow-up, a large proportion of young adults who survive an ICH are confronted with cognitive impairment, next to fatigue and subjective cognitive failures. Knowing what difficulties may be encountered, will create opportunities for better preparation and adjustments, increasing the chances of functional independence.



Unemployment after stroke at young age

Published as

Maaijwee NA, Rutten-Jacobs LC, Arntz RM, Schaapsmeerders P, Schoonderwaldt HC, van Dijk EJ, de Leeuw FE.
Long-term increased risk of unemployment after young stroke:
A long-term follow-up study.

Neurol. 2014; 261:1300-08

Abstract

Objective

To investigate the prevalence, excess risk, and risk factors of unemployment in patients after a transient ischaemic attack, ischaemic stroke or intracerebral haemorrhage at ages 18 through 50 years of age, compared with nationwide controls.

Methods

We performed a hospital-based cohort study among 694 patients, aged 18-50 years, with a first-ever transient ischaemic attack, ischaemic stroke or intracerebral haemorrhage.

After a mean follow-up duration of 8.1 (SD 7.7) years, we used logistic regression analysis to calculate odds ratios (ORs) with 95% confidence intervals (95%-CI) for being unemployed as a young stroke patient, compared with the Dutch population of vocational age (n = 7 803 000), with subsequent assessment of risk factors of unemployment.

Results

Young stroke patients had a higher risk of being unemployed than their peers in the Dutch population: women: OR 2.3, 95%-CI 1.8-2.9, men: OR 3.2, 95%-CI 2.5-4.0. A higher NIHSS-score at admission (OR 1.1, 95%-CI 1.0-1.1) and a longer follow-up duration (middle tertile: OR 2.8, 95%-CI 1.7-4.7, upper tertile: OR 3.4, 95%-CI 1.9-6.1) were associated with a higher risk of being unemployed.

Conclusion

Young stroke patients had a 2 to 3 times higher risk of unemployment after 8 years of follow-up. Return-to-work programmes should be developed, adjusted and evaluated in order to diminish the negative effects that unemployment can have on patients' life satisfaction and to limit the socio-economic consequences.

Introduction

Approximately 10% of strokes occur in patients under 50 years of age ('young stroke'), but proportions between 20% and 30% are reported, although these higher figures mostly come from studies in developing countries.[5, 267] At this socioeconomically demanding phase of life, post-stroke disability may affect the probability to return to work after stroke,[268] an important determinant of life satisfaction.[36, 154] This is not only an individual loss, but also an economic burden to society, as the expected number of loss of years of employment is high in these young patients.[37]

Assessment of the magnitude of this problem is the first step towards optimising rehabilitation of young stroke survivors. This knowledge is currently hampered by the fact that previous studies on post-stroke employment usually were limited in follow-up duration[155-157, 269] or sample size.[158] One study reported on long-term post-stroke employment after 12 years, but this study was retrospective with a relatively low response rate.[26] In addition, most studies reported only crude numbers of unemployment within the young stroke population. A more meaningful approach would be to compare these numbers with that of the general population, to reveal the excess in unemployment attributable to the young stroke.

The aim of this study was to investigate the prevalence and excess risk of unemployment in patients aged 18 through 50 years with a transient ischaemic attack (TIA), ischaemic stroke or intracerebral haemorrhage (ICH), compared with a nationwide control group. Also, we investigated whether demographic and clinical variables were associated with long-term unemployment, including baseline skills level.

Methods

Patients and study design

This study is a part of the *´Follow-Up of Transient ischaemic attack and stroke patients and Unelucidated Risk factor Evaluation´* (*FUTURE*) study, a prospective cohort study designed to investigate the aetiologies and consequences of stroke in a population of individuals aged 18 through 50 years.[110] Details of the study were described extensively[42] and in summary,[102, 110, 128, 132] and are detailed briefly here.

The FUTURE study comprised all consecutive patients aged 18 through 50 years with a TIA, ischaemic stroke or ICH admitted to the Radboud University Nijmegen Medical Centre from January 1, 1980, until November 1, 2010.[110] For the present study, only patients with first-ever TIA, ischaemic stroke or ICH were assessed. Patients were included

prospectively between 1980 and 2010 with a standardised collection of baseline and clinical characteristics and all patients underwent neurological examination and brain imaging at the time of their index event.[132]

TIA was defined as a rapidly evolving focal neurological deficit without positive phenomena such as twitches, jerks or myoclonus, with no other than a vascular cause lasting less than 24 hours.[132] Stroke, divided into ischaemic and ICH categories on the basis of radiological findings, was defined as focal neurologic deficit persisting for more than 24 hours.[110] We assessed stroke severity retrospectively in all cases with the NIH Stroke Scale (NIHSS)[213] by a validated approach.[165, 214]

Exclusion criteria were as follows: previous stroke or TIA, traumatic haemorrhagic stroke, haemorrhage in known cerebral metastasis or primary brain tumor, cerebral venous sinus thrombosis, subarachnoid haemorrhage or ICH attributable to known ruptured aneurysm, and retinal infarction.[110]

Standard protocol approvals, registrations, and patient consents

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study. We obtained written informed consent from all participants.

Assessment of unemployment

In the Netherlands, a national registry of Dutch citizens who receive a disability payment is kept by the Central Bureau of Statistics (CBS), a government agency that is responsible for collecting statistical information on the Dutch population. We could establish anonymously which patients in our study population received a disability payment on the basis of the registry on disability benefits, provided by the CBS. Our study participants were assigned unique numbers by the CBS, to guarantee anonymity. As most of our follow-up data were collected in the year 2010, we chose to collect data on disability payment from the CBS-registry of 2010.

Data on disability payments of the general Dutch working population (stratified by sex and age category) are freely available on the website of the CBS and were used as the control group.[270]

In appendix 1 on the *Neurology*® website at Neurology.org, the Dutch system of disability benefits is explained.[271, 272]

The 4 types of disability payments that exist in the Netherlands were combined into 1 variable. This variable was used to calculate our primary outcome, unemployment after stroke, defined as the proportion of patients receiving any of these 4 disability payments in 2010.

Appendix 1 Short explanation of the Dutch disability benefit system.

In the Netherlands, 4 types of disability benefits exist, depending on the employer (self-employed or not), age, and the proportion of disability. The proportion of disability is based on the proportion of a persons' last-known salary, that one is still able to earn (in the same or another occupation). The 4 types of disability benefit are: 1.) WAO (Occupational Disability Insurance Act), for employees with chronic disease or disability, utilised until 2005; 2.) WIA (Work and Income according to Labour Capacity Act), comparable with 1.), but partly replacing it, enacted from 29th of December 2005. This benefit consists of 2 parts, 1 for persons who are permanently disabled for at least 80% (IVA) and 1 for persons who are between 35% and 80% disabled or more than 80% but not permanently (WGA); 3.) WAZ (Occupational Disability Insurance Act for self-employed persons); and 4.) Wajong (Occupational Disability Insurance Act in young persons), for those already disabled before turning 18.

When a person is partially disabled, it is possible to be part-time employed at the same time, for example being 70% disabled and 30% employed. However, the sum of these 2 parts cannot be more than 100%. If a patient is able to regain (partial) employment, the disability benefit will be cancelled or adjusted accordingly.

Being retired at follow-up was an additional exclusion criterion for this particular study. Data on receiving a disability payment were missing in 77 patients of the original cohort of 1 005 patients (7.7%).

Other measurements

Apart from baseline demographic clinical variables (age, sex, and stroke severity (NIHSS score)), we collected occupation prior to the index event by structured questionnaires and review of medical records. We subsequently categorised occupations into 4 levels of baseline skills, based on required educational levels for that occupation (ranging from first = primary education only, to fourth = tertiary education with university degree or equivalent), according to the International Standard Classification of Occupations-88.[273] This classification is designed by the International Labour Organization (ILO), a United Nations agency concerned with international labour standards.[273] Data on baseline skills level were missing in 12.2% of patients.

Statistical analysis

We compared age and sex between stroke subtypes using a Student's *t*-test and Pearson chi-square test, respectively.

We calculated the prevalence of unemployment, defined as the proportion of patients receiving a disability payment after the index event, for men and women separately. We calculated prevalence of unemployment in the 3 stroke subtypes (TIA, ischaemic stroke or ICH) similarly and compared differences in prevalence between stroke subtypes with a chi-square test. NIHSS-score at admission, sex, current age, and duration of follow-up were considered possible confounders and adjusted for.

We assessed the risk of unemployment in a young stroke patient, compared with the Dutch population by logistic regression, stratified by sex and age. The Central Bureau of Statistics stratified age groups as follows: <25, 25-34, 35-44, 45-54, and 55-65 years. This was done in an identical manner for young stroke patients. Patients residing in the age groups <25 and 25-34 years were combined, because there were only few cases in each group. We weighted overall proportions of unemployment in men and women in the Dutch working population by age groups. Similar analyses were done for only fully unemployed patients (eg., including only patients who are disabled for at least 80% (defined as being able to earn less than 20% of the last earned salary), as these patients are classified as fully disabled according to the Dutch disability benefit system), and ischaemic stroke and ICH patients only (excluding TIA patients).

We used a multiple logistic regression model to estimate the association (OR with 95%-CI) between unemployment and sex, current age, follow-up duration divided in tertiles (first tertile: up to 3.17 years, n=231; second tertile: 3.20 to 10.05 years, n=232; third tertile: 10.06 to 30.00 years, n=231), stroke severity (NIHSS-score at admission), index event, and baseline skills level. The 2 lower and 2 intermediate skills levels were combined for comparison with the highest skills level.

Two-sided P-values <0.05 were considered statistically significant. We performed statistical analysis, using IBM (Armonk, NY) SPSS Statistics version 20.

Results

Study population and demographics

We included 694 patients in this study (Figure 1). There were 215 (31%) patients with a TIA, 425 (61.2%) patients with an ischaemic stroke and 54 (7.8%) patients with an ICH. Table 1 lists baseline characteristics of all stroke subgroups. Mean follow-up duration was 8.1 (SD 7.7) years. Of the 694 patients, 33.6% had a follow-up of ≥10 years and 21.5% of ≥15 years.

Deceased patients (n=120) and patients who were lost to follow-up (n=77) more often had an ischaemic stroke or ICH than the 694 participants, with higher NIHSS-scores (median 10 (3.5-14) and 5 (1-11) versus 3 (0-7) in participants, p<0.0001). The proportion of men was higher among deceased patients and among patients who were lost to follow-up than among participants (57.1% and 55.8% versus 42.7%, respectively, p=0.007 and p=0.02). Patients who died during the course of the follow-up were older at the time of their index event than participants (42.6 (SD 6.8) years versus 39.1 (SD 8.1) years, p<0.0001).

Figure 1 Flowchart of study population.

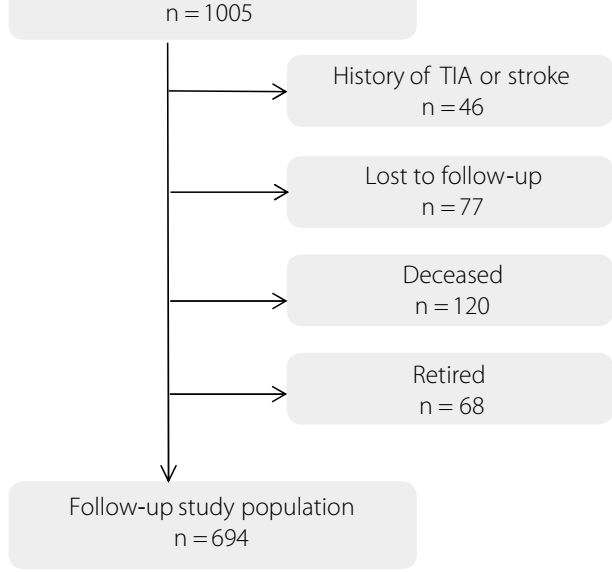


Table 1 Baseline demographic and clinical variables, stratified by stroke subtype .

	TIA n=215	IS n=425	ICH n=54
Baseline			
Men, n (%)[a]	88 (40.9)	182 (42.8)	26 (48.1)
Age (years) at index event	39.7 (8.0)	39.1 (8.1)	36.2 (8.8)
NIHSS score at admission	0 (0-1)	4 (2-8.5)	10.5 (2.8-15.0)
Skills level at baseline, n (%)			NA
None	28 (14.3)	52 (14.1)	3 (6.8)
Primary education only	21 (10.7)	54 (14.6)	6 (13.6)
High school education	73 (37.2)	149 (40.4)	17 (38.6)
Tertiary education, not equivalent to university degree	65 (33.2)	96 (26.0)	15 (34.1)
Tertiary education, (equivalent to) university degree	9 (4.6)	18 (4.9)	3 (6.8)
Follow-up			
Follow-up duration (years)			
Mean (SD)	6.0 (6.9)	9.1 (7.9)	8.9 (7.7)
Median (IQR)	3.6 (1.2-7.4)	7.2 (2.1-14.9)	5.5 (3.3-15.2)
Age (years) at follow-up[b]	45.7 (9.3)	48.2 (9.0)	45.1 (10.8)

Data are expressed as mean (SD) or median (Q1-Q3), unless otherwise specified.

Abbreviations: TIA: Transient Ischemic Attack, IS: Ischemic stroke, ICH: intracerebral hemorrhage, NIHSS: National Institutes of Health Stroke Scale.

a.) No differences between stroke subtypes, tested with Pearson chi-square test.

b.) Difference between TIA- and ischemic stroke patients, tested with Student's t-test (p: 0.004)

Missing data: NIHSS: 0.6%; skills level at baseline:12.2% (Of note, proportions were calculated by dividing the number of cases by the total number of patients in the TIA or ischemic stroke group, excluding cases with missing values for baseline skills level (n=19 in TIA group, n=56 in ischemic stroke group, and n=10 in ICH-group).

Unemployment

A total of 202 young stroke patients (29.1%) were unemployed in 2010. Table 2A shows that young stroke patients had a higher risk of having a disability payment than the nationwide controls in all age groups in both men and women, except for women between 55 and 65 years of age and men <35 years of age. In both women and men, patients between 35 and 44 years had the highest risk (women: OR 4.7, 95%-CI 3.0-7.0, men: OR 9.4, 95%-CI 5.6-15.3).

Of the 202 unemployed patients, 170 patients (84.2%) were fully unemployed. Unemployment rates of these patients only, stratified by age category are also reported in Table 2A.

Table 2B shows the unemployment rates, stratified by age categories, for ischaemic stroke patients and ICH patients only, excluding the TIA-patients.

Table 2 Post-stroke unemployment after stroke in young adults, compared to total Dutch working population.

Part A	Unemployment in Dutch population (n=7 803 000)	All[a] post-stroke unemployment in young stroke population (n=694)	OR (95%-CI)	Full[b] post-stroke unemployment in young stroke population only (n=694)	OR (95%-CI)
Women					
(overall) n (%)	14.2%[c]	xx	2.3 (1.8-2.9)[d,e]	xx	1.8 (1.4-2.2)[d,e]
<35 years	xx	xx	3.8 (1.7-7.8)[f]	xx	3.8 (1.7-7.8)[f]
35-44 years	69015 (7.3)	30 (26.8)	4.7 (3.0-7.0)[e]	24 (21.4)	3.5 (2.2-5.4)[e]
45-54 years	106140 (11.9)	44 (25.9)	2.6 (1.8-3.6)[e]	37 (21.8)	2.1 (1.4-2.9)[g]
55-65 years	150093 (36.7)	28 (40.0)	1.2 (0.7-1.9)	21 (30.0)	0.7 (0.4-1.2)
Men					
(overall) n (%)	12.5%[c]	xx	3.2 (2.5-4.0)[d,e]	xx	2.6 (2.0-3.3)[d,e]
<35 years	xx	xx	3.0 (0.7-9.4)	xx	3.0 (0.7-9.4)
35-44 years	56743 (5.0)	23 (32.9)	9.4 (5.6-15.3)[e]	20 (28.6)	7.7 (4.5-12.8)[e]
45-54 years	106023 (9.4)	37 (26.6)	3.5 (2.4-5.0)[e]	31 (22.3)	2.8 (1.8-4.1)[e]
55-65 years	205203 (29.6)	29 (43.9)	1.9 (1.1-3.0)[h]	26 (39.4)	1.5 (0.9-2.5)

Table 2 *Continued*

Part B	Unemployment in Dutch population (n=7 803 000)	All post-stroke unemployment in young stroke population[i] (n=479)	OR (95%-CI)
Women			
(overall) n (%)	14.8%[c]	xx	2.9 (2.2-3.7)[d],[e]
<35 years	xx	xx	3.6 (1.1-9.9)[h]
35-44 years	69 015 (7.3)	24 (31.2)	5.8 (3.5-9.3)[e]
45-54 years	106 140 (11.9)	38 (32.2)	3.5 (2.4-5.1)[e]
55-65 years	150 093 (36.7)	24 (46.2)	1.5 (0.8-2.6)
Men			
(overall) n (%)	13.3%[c]	xx	4.0 (3.0-5.3)[d],[e]
<35 years	xx	xx	4.5 (1.0-15.0)[h]
35-44 years	56 743 (5.0)	21 (45.7)	16.1 (8.9-28.9)[e]
45-54 years	106 023 (9.4)	31 (33.0)	4.8 (3.1-7.3)[e]
55-65 years	205 203 (29.6)	24 (45.3)	2.0 (1.1-3.4)[f]

Table 2 shows the number (proportion) of patients and controls who are unemployed, for patients defined as the number (proportion) receiving a disability payment after the index event. Part A: all participants were included (with TIA, ischaemic stroke or intracerebral haemorrhage); part B: patients with TIA were excluded.

xx: Number and proportions not shown for men and women <35 years of age; according to CBS (Central Bureau of Statistics)-guidelines, anonymity of data cannot be guaranteed in case of too small absolute numbers.

a.) All post-stroke unemployment includes patients with full and partial unemployment;

b.) Full post-stroke unemployment includes only patients who are disabled for at least 80% (defined as being able to earn less than 20% of the last earned salary). These patients are classified as fully disabled according to the Dutch disability benefit system; **c.)** percentage weighted by age groups; **d.)** OR (95%-CI) weighted by age groups; **e.)** p<0.0001; **f.)** p<0.01; **g.)** p<0.001; **h.)** p<0.05; **i.)** All post-stroke unemployment includes patients with full and partial unemployment, for patients with an ischaemic stroke or intracerebral haemorrhage only, excluding patients with a TIA.

Risk factors for being unemployed

A higher NIHSS-score at admission (OR 1.1, 95%-CI 1.0-1.1, per point increase of the NIHSS) and a longer duration of follow-up (OR 2.8, 95%-CI 1.7-4.7, for the middle follow-up tertile and OR 3.4, 95%-CI 1.9-6.1, for the upper follow-up tertile) were associated with a higher risk of being unemployed (Table 3).

There was no difference in post-stroke unemployment between TIA-patients and ischaemic stroke patients after adjustment for confounding, but patients with an ICH had a higher risk of post-stroke unemployment (Figure 2).

Table 3 Odds ratios for factors associated with post-stroke unemployment.

Risk factor	Unemployment[a] in 2010 OR (95%-CI)	p-value
Female sex	1.0 (0.6-1.4)	0.84
Age, per year	1.0 (1.0-1.0)	0.70
NIHSS, per point	1.1 (1.0-1.1)	<0.0001
Follow-up duration		
1st tertile	1	-
2nd tertile	2.8 (1.7-4.7)	<0.0001
3rd tertile	3.4 (1.9-6.1)	<0.0001
Skills level at baseline		
None or primary school only	1.2 (0.4-3.3)	0.80
High school with or without extra education not equal to university degree	1.9 (0.7-5.3)	0.19
University degree	1	-
Index event		
TIA	1	-
Ischaemic stroke	1.4 (0.9-2.3)	0.18
Intracerebral haemorrhage	2.2 (0.9-4.9)	0.07

Multiple logistic regression analysis.

a.) Unemployment, defined as the proportion receiving a disability payment after the index event.

Figure 2 Unemployment rates, stratified by stroke subtype.

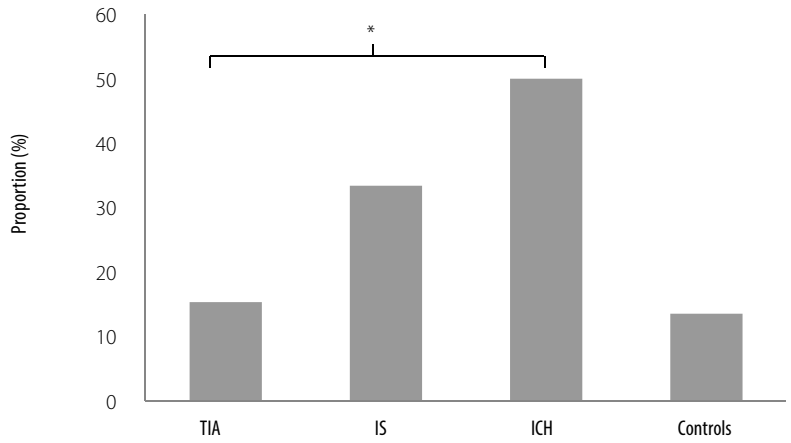


Figure shows proportions of unemployment rates (proportion of patients receiving a disability payment), stratified by stroke subtype. Column of controls (Dutch working population) was added for illustrative purposes.

TIA: Transient ischaemic attack, IS: ischaemic stroke, ICH: Intracerebral haemorrhage.

*TIA versus ICH p=0.02; TIA versus IS p=0.06; (p-value adjusted for sex, age, NIHSS at admission, and follow-up duration).

Discussion

Even after a mean follow-up of 8 years, we found an up to approximately 9 times higher risk of unemployment for young stroke patients, compared with the general population. A more severe stroke (indicated by a higher NIHSS-score at admission) and a longer follow-up duration were associated with an increased risk of being unemployed. Ischaemic stroke and ICH patients as well as TIA patients had a high unemployment rate, although the rate in TIA patients was comparable with that of the general population.

An important finding from our study was that even after on average 8 years of follow-up, the unemployment rate after a stroke at young age was still between 25.9% and 43.9%, and full unemployment rates between 21.4% and 39.4%. This is in line with previous studies with a short-term follow-up, that also reported that 30-50% of young stroke survivors did not return to full-time employment.[156, 157]

The combination of an up to 9 times excess risk of unemployment after a young stroke and the prospect of decades of unemployment results in a considerable social and economic burden by payments of the disability payments. Therefore, the findings of our study are relevant for policymakers.

Previous short-term follow-up studies found lower educational level an independent predictor of returning to work during the first post-stroke years.[156, 157] It may be that higher educated patients use better coping strategies to compensate for post-stroke disabilities.[236] However, we found that a lower baseline skills level was not associated with a higher risk of unemployment. This is somewhat contradictory to the previous studies, assuming that skills level is related to educational level. It may be that patients with both lower and higher skills levels are confronted with difficulties in returning to work, albeit different difficulties. For example, patients with a lower skills level may get fewer opportunities to adjust their work to possible impairments, but patients with a higher skills level may face higher demands from their colleagues or employer. Therefore, personalised chronic care during almost the course of a life should be emphasised.

Strengths of our study include a large sample size and the fact that we included patients with ischaemic stroke, ICH, and those with a TIA. Since in the Netherlands all young stroke survivors usually visit a university medical centre during the course of their disease, our study population is representative for a Dutch young stroke population. Therefore, we used the Dutch working population as a reference group. This makes it possible to assess the excess risk of unemployment due to young stroke.

However, some methodological issues need to be addressed. Selection bias might have occurred. We may have underestimated unemployment risks, due to missing data on 77 unregistered patients who had a more severe stroke. However, this underestimation would not have altered our conclusions. In addition, it might be that the retired patients we excluded were also prematurely unemployed because of the stroke, again leading to an underestimation of unemployment rates. However, we found that only 3 of the 68 excluded retired patients received a disability benefit in the past. Therefore, including these patients would not have largely influenced our results.

Information bias is not likely to be an issue in this study, as the primary outcome variable of both the participants and the controls (Dutch population) was obtained from the same national registry. However, our outcome measure 'unemployment after stroke', defined as the proportion of patients receiving any of the 4 possible disability payment after the stroke may lead to an overestimation of unemployment, due to several reasons. First, it also includes patients who can still be partially employed, when only partially disabled. However, we intentionally chose 'receiving a disability payment' as a measure for excess unemployment in patients with a stroke at young age, as it measures only involuntary unemployment, due to disability, not including voluntary unemployment.

Second, we do not have data on the permanent or temporary status of the unemployment in 2010. Some patients may still be in their recovery phase and may return to work in 2011, leading to an overestimation of long-term unemployment. However, the majority (>90%) of unemployed patients in our study were followed-up for more than 2 years after stroke, after which further recovery is usually considered unlikely.

Confounding is another source of bias to be considered in our study. First, we could not establish whether incident diseases or co morbidities that occurred after the index event rather than the qualifying young stroke, might have led to the unemployment, because these data could not be linked at an individual level to the anonymous data of the Central Bureau of Statistics. Especially in TIA-patients, with signs and symptoms by definition being resolved within 24 hours, the long-term risk of unemployment might be a reflection of the risk of incident disease, for example vascular events.[102] Although we cannot establish a direct causal relation between the young stroke and the unemployment, this does not change our observation that young stroke survivors have a much higher risk of being unemployed on the long-term than the general population; if not caused by the index stroke itself, then maybe by a long-term higher risk of incidental disease or co morbidities after stroke.

Second, educational levels could be an important confounder. We adjusted for baseline skills levels, used as a proxy of education level, based on patients' jobs. As skills levels were similarly distributed in our study cohort and in the Dutch population,[274] we do not expect this confounding factor to largely influence our results or alter our conclusions.

In addition, misclassification may play a role as also in the general population, there will be a few patients with a young stroke in their medical history of whom some receive a disability payment. However, given the size of our control sample, this misclassification of only a few controls would not largely influence our results or conclusions.

Future research is needed to further determine the reasons for being unemployed so many years after the young stroke, which may include impaired motor function, cognitive impairment, or incident diseases. One previous study assessed return-to-work and associated factors after 12 years of follow-up.[26] However, memory problems, anxiety, and depression were assessed with only 1 question each. A more thorough assessment is necessary to reveal more detailed information and strengths of associations. This information can be used to optimise advice and rehabilitation programmes to patients' individual needs.

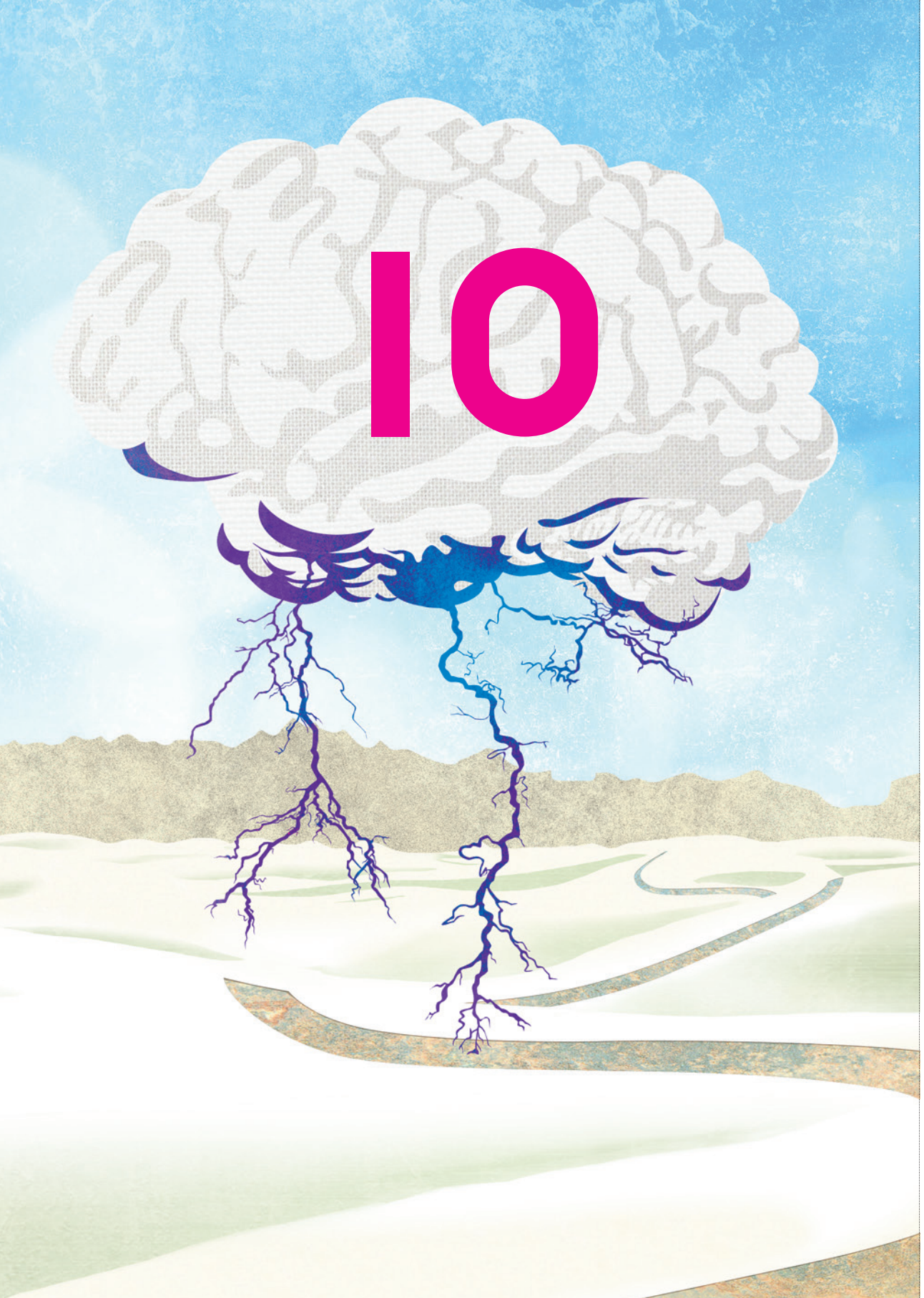
Earlier short-term follow-up studies found high rates of unemployment after stroke.[156, 157] Our study showed that, even after 8 years of follow-up, young stroke patients still had an up to 9 times higher risk of unemployment. Given that these young individuals usually have a long lifespan, long-term unemployment places a disproportionate burden upon stroke survivors in particular and society as a whole. Improving the rehabilitation of survivors after a young stroke and developing policies that assist their reintegration into the work force should be high priorities for health care policy. This would be the first step in diminishing the negative effects that unemployment can have on patients' life satisfaction and to limit the enormous socio-economic consequences.

Acknowledgements

We thank the Central Bureau of Statistics in the Netherlands for providing the anonymous registry on disability payments in our study population.

PART IV

Summary and general discussion



Summary

Summary

Stroke is one of the leading causes of death and disability worldwide. The traditional view is that stroke is mainly a disease of the elderly. However, approximately 10% of all strokes occur in young adults, under the age of 50 years. Despite this considerable proportion, there are only limited data available with respect to their long-term prognosis. However, it is particular this long-term prognosis that matters most for these young patients, since they usually have a long life expectancy and are in a demanding phase of life, during which life-changing decisions have to be made on for example career moves or planning of a family life.

In **part I, chapter 2** of this thesis, we provide a critical review of the literature on causes and consequences of an ischaemic stroke in young adults. Previous literature mainly focused on rare risk factors or diseases as the aetiology of a young ischaemic stroke. However, the evidence for these rare conditions as a cause of stroke is relatively limited. Evidence is accumulating that traditional vascular risk factors are increasingly prevalent in these young patients. Therefore, we challenged the concept of 'young stroke' as a different disease entity opposed to 'old stroke'. We suggested that with respect to aetiology, the 'young stroke' population is rather heterogeneous, with a subgroup of truly young adults (<35 years of age) with rare causes, older young adults (35-50 years) approaching 'old stroke' in prevalence of traditional cardiovascular risk factors, and a group in whom no causal factor can be found at all.

Long-term prognosis in terms of mortality and cardiovascular morbidity is worse than previously thought in these young patients. Although mortality is lower than in older stroke patients, cumulative mortality was 2-4 times increased, compared with nationwide data from an age- and sex- matched population. The long-term risk of recurrent cardiovascular events also remained high.

Cognitive impairment, depressive symptoms, anxiety, and fatigue seem common after a stroke at young age. However, only few studies on these outcomes exist to date, most of them with limited lengths of observation time or with small study samples. Moreover, only limited data exist on the impact of these symptoms on daily life functioning.

Therefore, we performed the FUTURE study. In **part II, chapter 3**, we describe the rationale and design of this study; a prospective cohort study designed to investigate aetiologies and long-term consequences of a TIA, ischaemic stroke or intracerebral haemorrhage in 1 005 adults, aged 18-50 years ('young stroke'), admitted to the Radboud University Medical Centre Nijmegen between January 1, 1980 and November 1, 2010. In this thesis, the focus lies on the long-term neuropsychological and social consequences of a young stroke and their impact on functional outcome.

Long-term neuropsychological and social consequences after stroke in young adults

In **part III, chapter 4**, we report on the cognitive performance of young ischaemic stroke patients. Compared with 146 stroke-free age- and sex-matched controls, patients performed worse on most cognitive domains. After a mean follow-up of 11.0 (SD 8.2) years, up to 50% of the patients had a below average performance or cognitive impairment. A longer follow-up duration was associated with lower scores on the immediate memory, delayed memory, and executive functioning domains. Deficits in processing speed, working memory, and attention were most common. Patients with a left hemispheral stroke had the worst cognitive outcome. In **chapter 5**, we report on a higher prevalence of subjective memory failures and subjective executive failures in young stroke patients (86.4% and 67.4%) than in controls (69.7% and 41.4%). These failures were not strongly related to objective memory performance or executive functioning, assessed with an extensive neuropsychological examination. We found that the presence of these subjective cognitive failures in patients and controls were merely significantly associated with the presence of fatigue. This fatigue was assessed with the Checklist of Individual Strength questionnaire, which consists of items measuring both physical as mental fatigue.

Subsequently, the long-term prevalence of depressive symptoms and anxiety (**chapter 6**) and of fatigue (**chapter 7**) was described. All of these symptoms were very common in patients with an ischaemic stroke or a TIA (depressive symptoms: 16.8%, anxiety: 23.0%, fatigue: 41.0%), and more prevalent than in controls. These symptoms did not differ by stroke localisation. Depressive symptoms and anxiety were prevalent in the first few years after stroke, and became less apparent after longer time after stroke. The prevalence of fatigue also showed this trend, but differences were not statistically significant after adjustment for age at follow-up, sex, education, severity of stroke, and a history of depression. In ischaemic stroke patients, depressive symptoms, anxiety, and fatigue were all associated with a poor functional outcome, measured with the mRS and the IADL. Fatigue was also associated with impairment on the cognitive domain of processing speed and working memory.

In **chapter 8**, prevalence of cognitive impairment, subjective cognitive failures, depressive symptoms, anxiety, and fatigue in 45 patients with an intracerebral haemorrhage was investigated and compared with 45 age-, sex-, and education-matched controls after a mean follow-up of 9.8 (SD 8.0) years. Subjective cognitive failures were more prevalent in patients than in controls (93.9% versus 73.0%, p=0.02), as was cognitive impairment on the following cognitive domains: 'speed of information processing' (33.3% versus 5.4%, p=0.003), 'working memory' (29.4% versus 10.8%, p=0.049), 'immediate memory' (26.5% versus 8.1%, p=0.04), and 'delayed memory' (20.6% versus 2.7%, p=0.02). Prevalence of fatigue showed a trend towards a significant difference between patients and controls (40.5% versus 22.2%, p=0.07).

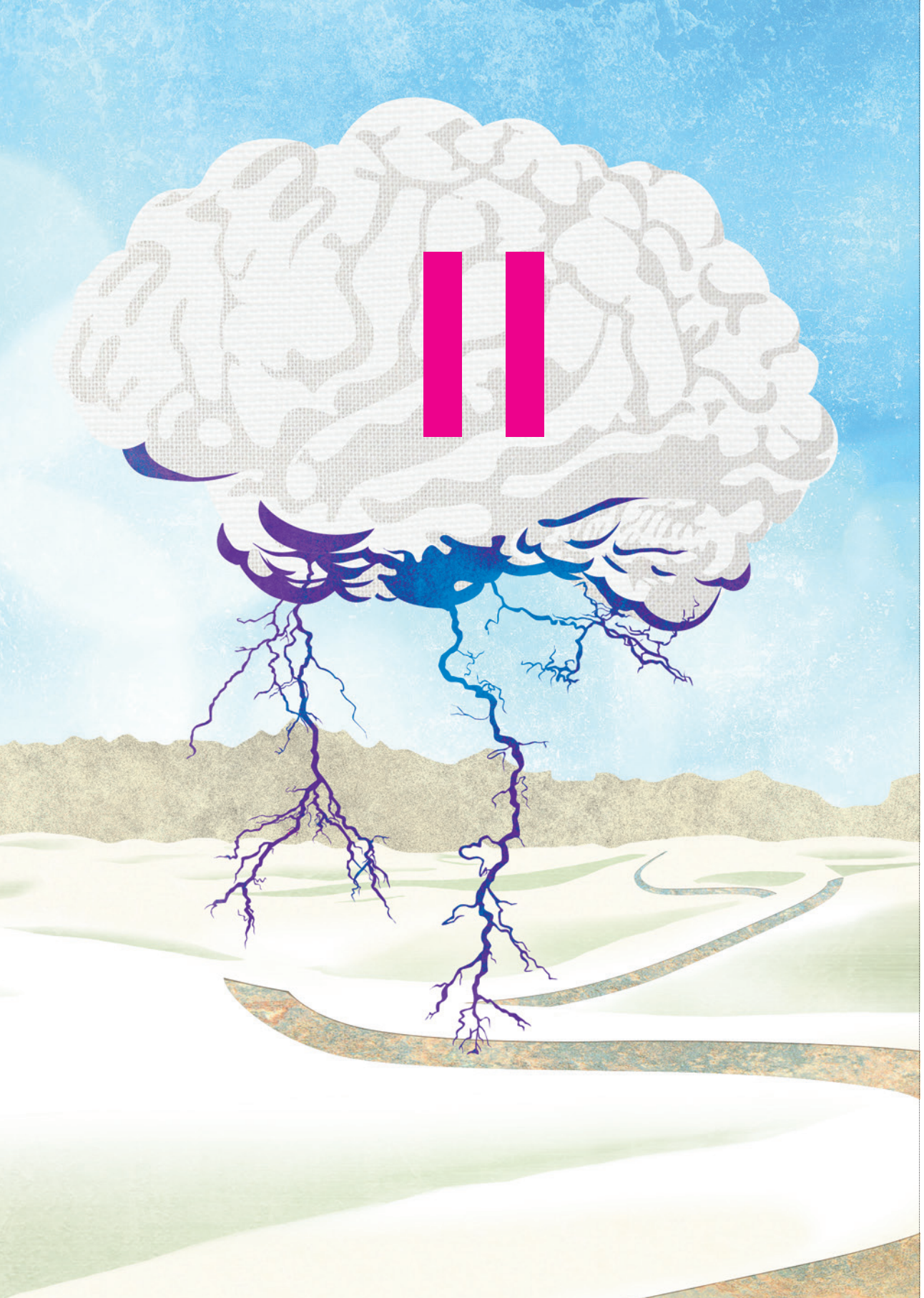
No significant differences were found between patients and controls with respect to the presence of depressive symptoms and anxiety.

In **chapter 9,** we report on the proportion of unemployment in all consecutive patients with a first-ever TIA, ischaemic stroke or intracerebral haemorrhage, defined as the proportion of patients receiving a disability benefit. Between 25.9% and 43.9% of patients between 35 and 65 years of age were unemployed after a mean follow-up of 8.1 (SD 7.7) years. Overall, patients had a higher risk of being unemployed than their peers in the Dutch population of vocational age (women: OR 2.3, 95%-CI 1.8-2.9, men: OR 3.2, 95%-CI 2.5-4.0). A more severe stroke and longer follow-up duration were associated with a higher risk of unemployment. The patients of 35-44 years of age had the highest risk of being unemployed (women: OR 4.7, 95%-CI 3.0-7.0, men: OR 9.4, 95%-CI 5.6-15.3).

Conclusion

The studies in this thesis describe that in patients who suffer from a stroke at young age (18 through 50 years), neuropsychological and social problems are very common, even up to a decade after the young stroke. This is in contrast with the general feeling of a rather favourable prognosis. Since these symptoms are associated with functional dependence and a high risk of not returning to pre-stroke activities, for example return to work, they lead to a significant individual loss for the patient, but also to a burden for society as a whole.

The results from the studies in this thesis enable physicians and other stroke caregivers to better inform patients on these possible long-term consequences they can be confronted with in the future. More studies are needed to further unravel the underlying pathophysiological mechanisms and develop treatment strategies.



II

General discussion and future perspectives

General discussion and future perspectives

Long-term prognosis after a stroke in young adults is not only determined by the presence of focal, visible neurological deficits, such as a hemiparesis, but even more by non-visible symptoms, such as subjective cognitive complaints or even cognitive impairment or mood disorders, and also social consequences.[275] However, to date, only few studies exist that evaluated the presence and magnitude of these non-visible symptoms after a stroke at young age.

Therefore, we wanted to investigate long-term neuropsychological and social consequences after a stroke at young age. Our general aim was to provide reliable information on the occurrence of these long-term sequelae, both for survivors of a stroke at young age as well as their caregivers and treating physicians. Furthermore, the association of these symptoms with a poor functional outcome was determined.

The studies described in this thesis are based on data from the FUTURE study, a prospective cohort study, including all consecutive patients with a TIA, ischaemic, and haemorrhagic stroke aged 18-50 years between 1980-2011. All patients visited the department of neurology of the Radboud University Nijmegen Medical Centre, the Netherlands.

In this chapter, the most important methodological features of the studies in this thesis will be discussed first. Next, possible explanations for our main findings will be explored. Subsequently, we will discuss the challenges our findings may create for current daily practice, and formulate future research questions that need to be answered.

Methodological considerations

Study design

We collected follow-up data from a cohort of all consecutive patients (n=1 005) with a stroke between 18 and 50 years, admitted to the Radboud University Nijmegen Medical Centre since 1980. The cohort was identified, based on a prospective registry of stroke in young adults that has been kept at our neurology department since the late 1970-ies. The general objective of the FUTURE study was to investigate aetiology and long-term prognosis after stroke at young age. For the studies in this thesis, outcomes (cognitive performance, presence of subjective cognitive complaints, depressive symptoms, anxiety, fatigue, and unemployment) were measured at 1 time-point during this observation period. This resulted in a variable length of follow-up for each individual patient, ranging from 0.5-31.0 years.

This very long maximum length of observation is a unique strength of this study and provides valuable information on long-term psychosocial consequences that patients with stroke at young age may encounter. Since we assessed outcome measures at only 1 time-point during follow-up, we were not able to accurately assess the fluctuation over time of these consequences. However, the large variation in observation length allowed us to compare prevalence of outcomes between different observation lengths, which gives us some insight into variation in frequencies of outcomes over time.
Another strength of the studies in this thesis is the inclusion of a stroke-free age-matched and sex-matched control cohort, for comparison of prevalence of outcome measures. Some outcome measures are known to be quite prevalent in the general population.[276-278] Therefore, the comparison with stroke-free controls is important, to assess the excess influence of the stroke at young age on the frequency of these symptoms.

Internal validity

The internal validity of a study reflects the reliability of the conclusions than can be drawn, based on the data collected. Results based on these data are always in a more or less extent vulnerable to bias. Three forms of bias can be distinguished: selection bias, information bias, and confounding.
Selection bias occurs when the association between a certain determinant and outcome is different in the population under study, than in the population from which these participants were drawn. Selection bias may occur when selection for participation in a study is dependent on the outcome, and not random.[279] In our study, selection bias may have occurred, because the presence of neuropsychological complaints or employment status might have been related to participation. Obviously, outcome was only to be assessed in the patients alive at the time of follow-up, but also solely among participants. This might have led to an underestimation of the prevalence of psychosocial consequences of a stroke at young age, since the deceased patients probably had a more severe stroke, most likely leading to more post-stroke disabilities and psychosocial issues. The same may hold true for patients that refused to participate. Including these patients would have then increased the differences we found between patients and controls, but most likely would not have altered our conclusions. On the other hand, patients that refused to participate might also have recovered without any residual symptoms, not giving priority to participate in this study. In this case, our current results would be an overestimation of the prevalence of outcomes. Probably, both explanations will have influenced participation in our study and it is therefore unlikely that this selection bias largely influences our results. However, we do not have any

formal data on this issue.
Information bias arises when an error occurs in the measurement of a variable. For example, this form of bias may be introduced when outcome measures are not clearly defined or cannot be measured objectively, which may lead to misclassification.[279] Some of our outcome measures (subjective memory complaints, depressive symptoms, anxiety, and fatigue) were based on self-questionnaires and are therefore subjective. Some misclassification may have occurred due to the use of these subjective measures, which are more prone to misclassification than objective outcomes, such as mortality. However, all the questionnaires are well-validated, thereby limiting misclassification when previously defined cut-off values from these validation studies are used.[183, 233, 241] For the measurement of unemployment, data from the Central Bureau of Statistics were used, which are objective data on whether a patient is receiving an unemployment benefit or not. Therefore, misclassification is not an issue in this study.
Another source of information bias could arise due to the fact that researchers were not blinded for a participant being a patient or a control, for example, due to visible physical post-stroke disabilities. However, all researchers were well-trained to use the structured questionnaires and tests in a pre-defined order, so these data were collected uniformly in all participants.
Recall bias is another form of information bias that might have been introduced by the use of questionnaires. However, most outcomes are on psychosocial complaints in the past week or month, reducing the chance of recall bias.
Finally, *confounding* is an important form of bias to consider. A confounder is a factor that is related to both the determinant and the outcome, without being part of the causal chain between determinant and outcome.[279] In our studies, age, sex, educational level, and socio-economic status may be important confounders. They are related to the risk of stroke at young age as well as cognitive impairment, depressive symptoms, or unemployment, etcetera. We tried to overcome confounding bias by adjusting for these confounding factor in the analyses. Moreover, patients and controls were matched for age and sex and controls were recruited from the same environment as the patients. Therefore, it is likely that socio-economic status between patients and controls is comparable.

Precision

Precision indicates to what extent the findings deviate from the true value, due to random (unknown) error.[279] In the studies in this thesis, random error may have occurred, due to the fact that outcome measures, such as cognitive performance or the presence

of depressive symptoms may fluctuate over days. A patients' performance during an extensive neuropsychological examination or answers on questions about feelings of depression probably depend on the presence of other variables, such as the quality of last night sleep or complaints from co morbidities. We tried to minimise the chance of this error, by including a large number of patients with a TIA (range between 160 and 215 participants) and ischaemic stroke (range between 277 and 425 participants). However, we assessed neuropsychological symptoms in only 45 patients with an intracerebral haemorrhage, which may have resulted in diminished precision. Therefore, studies with larger sample sizes are needed to confirm findings from this particular study.

External validity

The extent to which results from the study sample can be generalised to patients outside the study sample is called *external validity*. Our study cohort is comparable to other young stroke cohorts with respect to mean age of approximately 40 years at the time of the event, but our study cohort has a lower proportion (<50%) of men than other young stroke cohorts (>55%).[26, 43, 44] However, concordant with epidemiological data on stroke at young age, the higher proportion of women in our cohort probably reflects a true young stroke population.[280]

With respect to stroke severity, our cohort consisted of patients who suffered from relatively mild strokes, with a median NIHSS-score on admission of 4, which seems somewhat less severe compared to 1 other study (mean NIHSS-score of 7.7, median not reported).[131] However, another study reported a more or less comparable NIHSS-score on admission with our study with a median of 3,[109] and other studies also described that neurological deficits on admission were minor to moderate in the majority of patients.[203, 281] Therefore, with respect to stroke severity, our cohort seems comparable to other young stroke populations.

Our academic hospital serves as a tertiary referral centre for a large area in the eastern part of the Netherlands. Since most patients with a stroke at young age usually are referred to a university medical centre somewhere along the course of the disease, we most likely included the majority of patients in our catchment area.

To conclude, our study cohort has demographic and stroke characteristics, comparable to other young stroke cohorts. Moreover, our study cohort probably is a representative sample of all young strokes in our catchment area, despite being hospital-based instead of population-based. Therefore, we believe results from our studies can be generalised to other Dutch patients with a stroke at young age as well as to patients with a stroke at young age in other Western societies.

General discussion of main findings

To date, a survivor of a stroke at young age was generally expected to regain pre-stroke activities in most cases. This expectation was based on previous studies, that found a relatively good motor recovery after a stroke under 50 years of age.[118, 129] However, independent functioning in daily life requires more than only good motor recovery, for example adequate cognitive performance. The studies in this thesis show that impaired cognitive performance, and also other neuropsychological complaints were very common after very long-term follow-up after a stroke at young age. Subjective and objective cognitive impairment, depressive symptoms, anxiety, and fatigue were far more prevalent among survivors of a stroke at young age than among their peers in the control group. Moreover, we found that depressive symptoms, anxiety, and fatigue were associated with a poor functional outcome. This functional outcome was assessed with the mRS, mainly a motor score, but also the with the IADL, which assesses more complex tasks in daily life functioning. Furthermore, fatigue was also associated with cognitive impairment on the domains of information processing speed and working memory.

The recognition of long-term persistent 'non-visible' symptoms is one of the new insights provided by our studies due to the very long-term follow-up, since this was usually limited in previous studies that investigated neuropsychological outcomes.[28-31, 34] The relation of these symptoms with a poor functional outcome stresses the importance of the recognition (and eventually treatment) of these symptoms in post-stroke care.

The negative influence of depressive symptoms, anxiety, and fatigue not only affects the individual patient and his or her direct social environment, but also places a burden to society as a whole. This is shown by our study on unemployment, in which we found a 2- to 3-fold increased risk of unemployment after a stroke at young age, compared to the general Dutch population. The highest risk was found in the population between 35 and 44 years, which causes a major loss of years of productivity.

The high prevalence of long-term depressive symptoms, fatigue, and anxiety poses the question on which pathophysiological mechanisms underlie the occurrence and long-term persistence of these symptoms, even for decades after the initial stroke. Possible underlying mechanisms will now be discussed.

First, a direct causal relationship between the stroke at young age and the long-term neuropsychological symptoms may exist. To increase the probability of a causal relationship between 2 variables, a study needs to show that the risk factor is time- an dose-dependent, among other criteria.[98] This requires a large, prospective cohort study. In our study, patients were divided into 3 groups, categorised by tertiles of length of

follow-up. We found that a stroke at young age was not related with psychological outcomes in a length of observation-dependent way. Depressive symptoms, anxiety, and fatigue were actually somewhat less prevalent or did not differ between the group with shortest length of follow-up (eg., first tertile of length of follow-up) and the group with the longest length of follow-up (eg., third tertile of length of follow-up), rather than being more prevalent. On the other hand, longer follow-up was associated with more cognitive impairment. It may be that the acute damage to the brain parenchyma causes neuropsychological symptoms on the short-term, whereas on the long-term other pathophysiological mechanisms come into play, such as accumulating neurodegenerative pathology in an ageing brain.

According to the dose-dependent criterium (the more strokes, the more neuropsychological sequelae), recurrent strokes would lead to a higher prevalence of neuropsychological symptoms over time. This is indeed suggested by our finding that recurrent cerebrovascular events were related to the presence of fatigue in young ischemic stroke patients. However, recurrent strokes were not significantly related to depressive symptoms or anxiety.

A direct causal relationship between the stroke and long-term neuropsychological symptoms may be suggested (although not proven), when symptoms only occur after lesions in specific parts of the brain. In the case of cognitive impairment, we found that cognitive performance was more affected by a left hemispheric strokes than a right hemispheric stroke, suggesting that lesion localisation may, at least partly, determine the extent of cognitive impairment. However, in the case of depressive symptoms, anxiety, and fatigue, we found no differences in prevalence by stroke localisation.

Findings from our studies clearly not uniformly point to a direct causal relationship between stroke and long-term neuropsychological symptoms, suggesting that there should be another explanation. We found that depressive symptoms, anxiety, and fatigue were all related to a poor functional outcome in survivors of a stroke at young age. These young patients are in a demanding phase of life, with a young family and a career, and are suddenly confronted with a serious and often unexpected disease. Insufficient coping strategies may lead to an imbalance between physical and mental disabilities and high demands from the social environment. Most likely, patients become trapped in a downwards helix of ever increasing neuropsychological symptoms, followed by more impairments in daily life, and vice versa.

Clinical relevance

Neuropsychological and social problems after a stroke at young age have received little attention in post-stroke care so far, reflected in scarce literature on the subject. Meanwhile, patients rate these topics among the top 10 list of research priority.[48] An explanation may be that in the (sub)acute post-stroke care, the visible motor deficits probably attract more attention and these symptoms generally ameliorate in the first weeks or during the rehabilitation period. After the subacute and first rehabilitation phase, post-stroke care usually stops. However, it is only after this period that patients are being confronted with regular daily life, and only then the less visible psychosocial issues come into play.

Moreover, the importance of providing information to survivors of a stroke at young age on long-term prognosis lies in the fact that these young patients usually have a long life expectancy. These patients are often in the midst of an active social life, forming new families and planning important career steps. The major impact of psychosocial problems on daily life functioning is underlined by our finding that depressive symptoms, anxiety, and fatigue were associated with a poor functional outcome.

Current practice may therefore need to change, with a longer follow-up of patients, ideally in a multidisciplinary team, to evaluate both the important medical status, but also the equally relevant psychosocial issues. In our hospital, this multidisciplinary team is being formed currently for young patients with cerebrovascular disease. This teams actually consists of 2 subteams. One team contains a neurologist, cardiologist, vascular internal specialist, and a vascular surgeon, aiming to evaluate risk factors for the stroke and start secondary prevention. The other team consists of a medical psychologist, a nurse practitioner, and a social worker. They will offer the patient a 'menu' with possible neuropsychological or social difficulties. The young patient can then choose which topics need special attention in his or her individual situation, in order to regain pre-stroke activities as much as possible. Examples include 'fatigue', 'return to work', and 'social interactions'.

Education of the patient and his social environment, for example employers and colleagues, and thereby creating more understanding of difficulties a patient encounters, may be another method to alleviate psychosocial problems in patients.

We believe that recognition of these symptoms by clinicians, patients, and society may be the first step in initialising treatment.

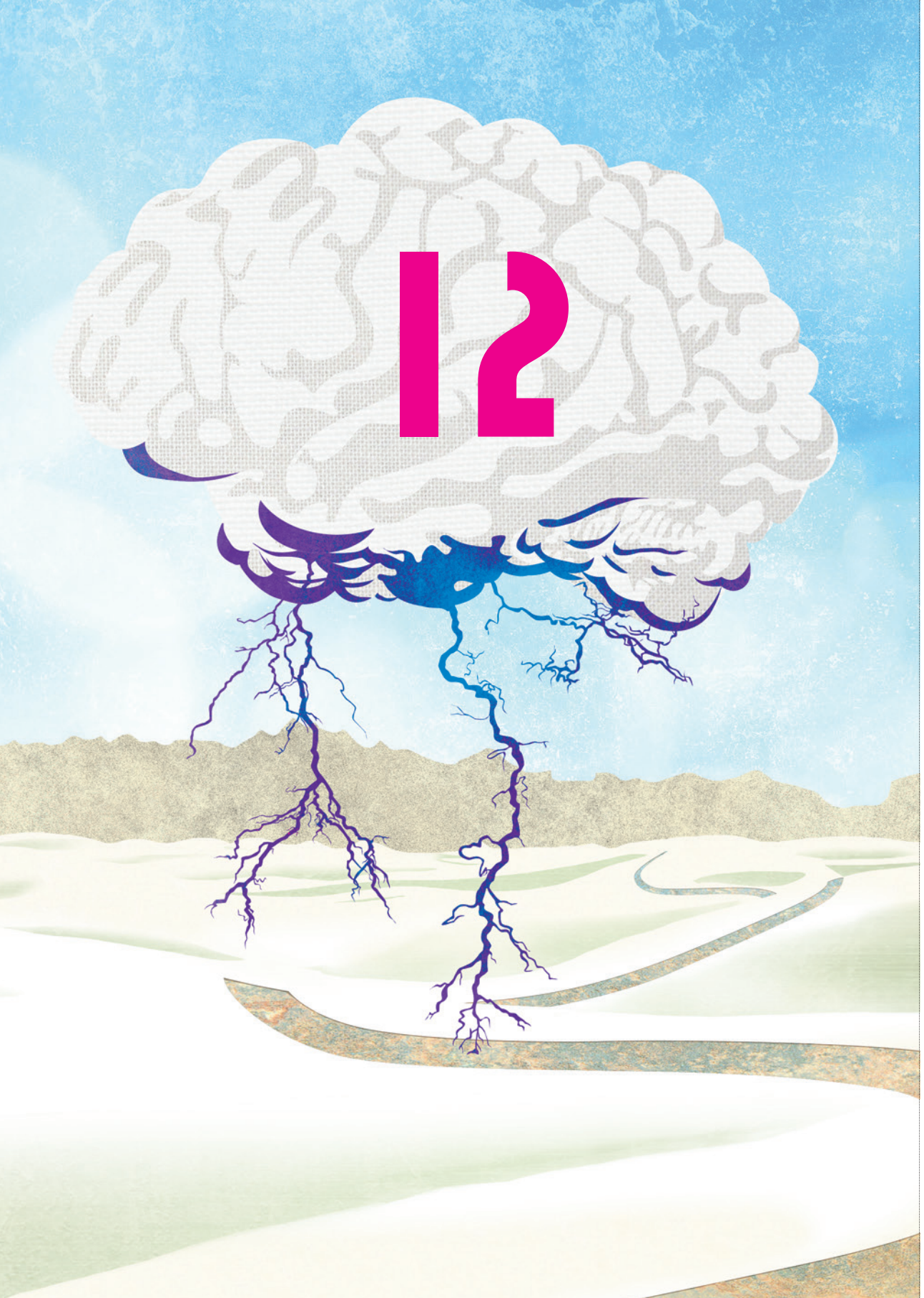
Future directions

The combination of a rising incidence of stroke in young adults[6] and the high prevalence of psychosocial consequences results in a considerable burden for patients and their direct social environment as well as for society as a whole. With results from the studies in this thesis, stroke physicians will now be able to better inform patients with a stroke at young age on long-term prognosis, and create more awareness for the recognition of these symptoms.

Although the recognition of problems in the neuropsychological and social domain in patients after a stroke at young age is the essential first step in treatment of these problems, an actual optimal treatment strategy is not available.[160, 161] Clinical trials with medications, psychological interventions, and occupational therapy are needed to evaluate which treatment strategies can alleviate symptoms. To develop these treatment strategies however, we first need to learn more about the origin of these complaints. For example, are structural damage to brain networks or altered brain function causing these symptoms or are inadequate coping strategies or insufficient guidance from a social environment playing a role?

Furthermore, trials should reveal whether there are certain high risk groups, for example on the basis of medical or psychiatric history, stroke severity or subtype (including intracerebral haemorrhage) or recovery patterns, that would benefit from earlier, more intensive or different treatments than other patients.

This optimalisation of treatments and their adjustment to individual patients, based on their individual clinical characteristics may result in more cost-effective use of scarce health care budgets, with advantages for the individual patient and society as a whole.



Dutch summary / Nederlandse samenvatting

Nederlandse samenvatting

Een beroerte is wereldwijd een van de belangrijkste oorzaken van overlijden en handicap. Beroerte wordt voornamelijk gezien als een ziekte van oudere mensen, maar ongeveer 10% van alle beroertes betreft jonge volwassenen, onder de leeftijd van 50 jaar. Ondanks dit aanzienlijke percentage, is er maar weinig literatuur te vinden over deze jonge patiënten, zeker als het gaat om lange-termijn prognose. Voor hen is juist deze lange-termijn prognose van belang, omdat zij in het algemeen een lange levensverwachting hebben en omdat zij zich in een veeleisende fase van hun leven bevinden, waarin belangrijke beslissingen moeten worden genomen over bijvoorbeeld een carrière of het stichten van een eigen gezin.

In **deel 1, hoofdstuk 2** van dit proefschrift geven wij een kritisch overzicht van de literatuur over oorzaken en gevolgen van een herseninfarct bij jonge volwassenen. In de bestaande literatuur tot nu toe ging de aandacht met name uit naar zeldzame risicofactoren of onderliggende aandoeningen die een herseninfarct kunnen veroorzaken. Echter, de bewijslast hiervoor is relatief beperkt. Er wordt steeds vaker beschreven dat de traditionele cardiovasculaire risicofactoren frequent voorkomen bij deze jonge patiënten. De vraag is nu of de ziekte 'herseninfarct bij jonge volwassenen' als aparte ziekte-entiteit bestaat, los van een 'herseninfarct op oudere leeftijd'. In dit hoofdstuk beschrijven wij dat, met betrekking tot de onderliggende oorzaak van een herseninfarct op jonge leeftijd, er eigenlijk meer sprake is van een heterogene aandoening. Er bestaat inderdaad een subgroep van hele jonge volwassenen (<35 jaar) die een zeldzame onderliggende aandoening heeft als oorzaak voor de beroerte, maar daarnaast ook een iets oudere subgroep (35-50 jaar) bij wie de cardiovasculaire risicofactoren een grote rol spelen in het ontstaan van de beroerte, zoals ook bij de oudere patiënten het geval is. Tot slot is er een subgroep van patiënten bij wie geen enkele oorzaak kan worden gevonden voor de beroerte.

De lange-termijn prognose wat betreft mortaliteit en cardiovasculaire comorbiditeit van patiënten die op jonge leeftijd een herseninfarct hebben gehad is slechter dan voorheen altijd werd gedacht. De mortaliteit is weliswaar lager dan bij oudere patiënten met een beroerte, maar de cumulatieve mortaliteit ligt 2 tot 4 keer hoger dan bij volwassenen van gelijk geslacht en gelijke leeftijd, die géén beroerte hebben gehad. Het lange-termijn risico op het krijgen van cardiovasculaire aandoeningen was eveneens hoog.

Cognitieve beperkingen, depressieve symptomen, angst en vermoeidheid lijken na een beroerte op jonge leeftijd veel voor te komen. Echter, tot op heden zijn er maar weinig studies die deze uitkomsten onderzochten in deze populatie. Bovendien waren

de verrichte studies beperkt met betrekking tot duur van de follow-up periode of met betrekking tot het aantal geïncludeerde patiënten. Voorts zijn er nauwelijks gegevens over de invloed van deze symptomen op het algemeen dagelijks functioneren.
Daarom werd de FUTURE studie uitgevoerd. In **deel 2, hoofdstuk 3** beschrijven we de achtergrond en de opbouw van de FUTURE studie; een prospectieve cohortstudie, opgezet om de etiologie en lange- termijn gevolgen van een TIA, herseninfarct, of hersenbloeding op de leeftijd van 18 t/m 50 jaar te onderzoeken in 1 005 volwassenen die vanaf 1 januari 1980 tot 1 november 2010 patiënt onder behandeling zijn geweest in het Radboudumc te Nijmegen.
De studies in dit proefschrift beschrijven de neuropsychologische en sociale gevolgen op lange termijn van een beroerte op jonge leeftijd en de invloed van deze symptomen op de functionele uitkomst.

Neuropsychologische en sociale gevolgen op lange termijn na een beroerte op jonge leeftijd

In **deel III, hoofdstuk 4**, beschrijven we de cognitieve functies van patiënten met een herseninfarct. De patiënten presteerden slechter op de meeste cognitieve domeinen in vergelijking met 146 op leeftijd en geslacht gematchte controles zonder een beroerte. Na een gemiddelde follow-up duur van 11.0 (SD 8.2) jaar had zelfs de helft van de patiënten op sommige domeinen een benedengemiddelde score of cognitieve beperking. Een langere follow-up duur was geassocieerd met lagere testscores op de domeinen 'korte-termijn geheugen', 'lange-termijn geheugen' en 'executieve taken'. De meeste afwijkingen werden gevonden in de cognitieve domeinen 'snelheid van informatieverwerking', 'werkgeheugen' en 'aandacht'. Patiënten met een beroerte in de linkerhemisfeer van de hersenen presteerden het slechtst. In **hoofdstuk 5** rapporteren we dat subjectieve geheugenklachten en subjectieve executieve stoornissen vaker vóórkomen bij patiënten met een TIA of herseninfarct dan bij de controlegroep (86.4% versus 67.7% en 67.4% versus 41.4%). Deze subjectieve klachten bleken niet sterk gerelateerd aan het daadwerkelijk vóórkomen van objectieve cognitieve stoornissen, wanneer deze werden getest tijdens een uitgebreid neuropsychologisch onderzoek. Bij patiënten en controles bleken de subjectieve cognitieve klachten wel geassocieerd met vermoeidheid. Deze vermoeidheid werd gemeten met de Checklist of Individual Strength vragenlijst. Deze vragenlijst bestaat uit items over zowel fysieke als mentale vermoeidheid.
Vervolgens onderzochten wij de lange-termijn prevalentie van depressieve symptomen

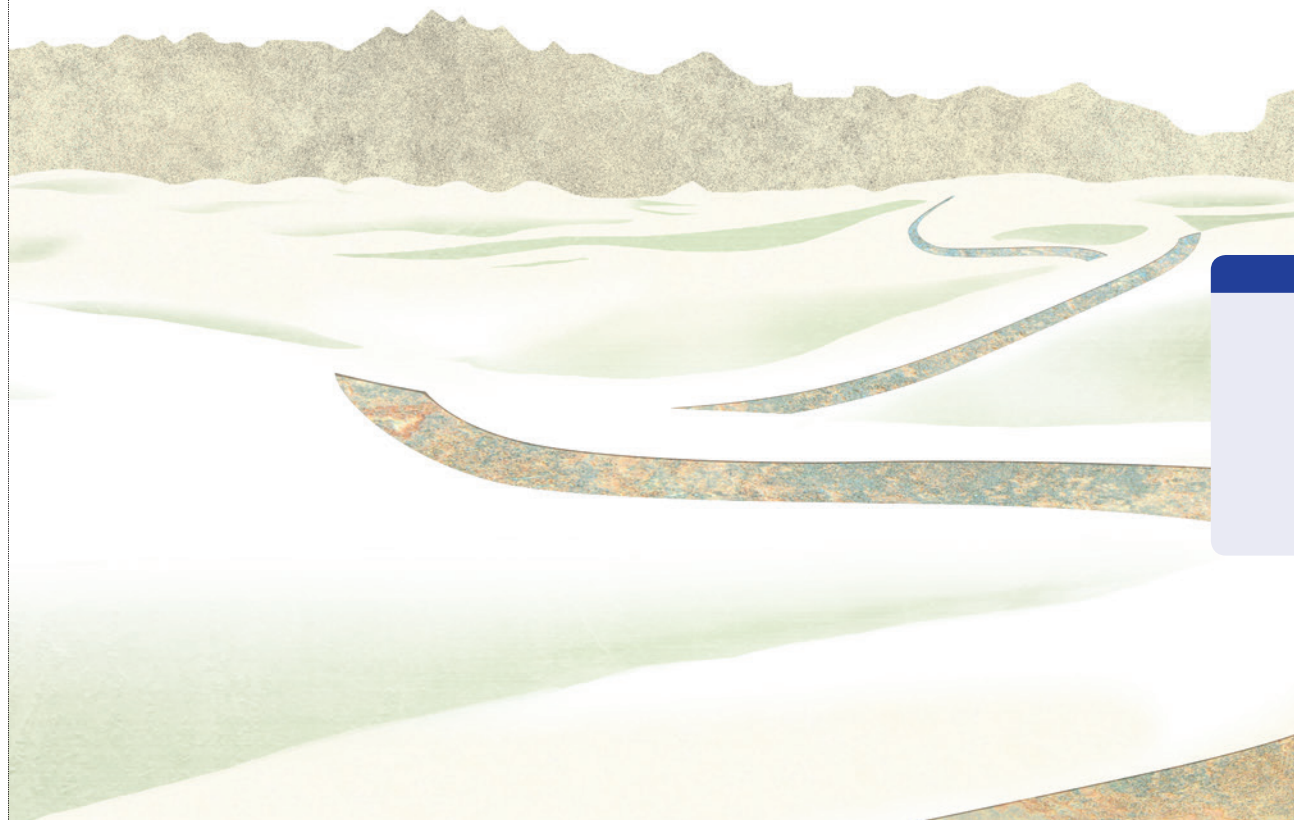
en angst (**hoofdstuk 6**) en vermoeidheid (**hoofdstuk 7**). Al deze symptomen kwamen vaker voor bij patiënten (depressieve symptomen: 16.8%, angst: 23.0%, vermoeidheid: 41.0%) dan bij controle-proefpersonen. De prevalentie van deze symptomen verschilde niet tussen de verschillende lokalisaties van de beroerte (links of rechts supratentorieel, of infratentorieel). Na een langere follow-up duur waren depressieve symptomen en angst wat minder prevalent dan in de eerste jaren na de beroerte. De prevalentie van vermoeidheid toonde eenzelfde trend, maar verschillen tussen korte- en lange-termijn follow-up waren niet statistisch significant na adjusteren voor leeftijd, geslacht, opleidingsniveau, ernst van de beroerte en depressie in de voorgeschiedenis. Bij patiënten met een herseninfarct waren depressieve symptomen, angst en vermoeidheid allen geassocieerd met een slechte functionele uitkomst, gemeten met de modified Rankin Scale (mRS) en de Instrumental Activities of Daily Living-vragenlijst (IADL). Vermoeidheid was tevens geassocieerd met beperkingen in het cognitief functioneren op de domeinen 'snelheid van informatieverwerking' en 'werkgeheugen'.
In **hoofdstuk 8** onderzochten we de prevalentie van cognitieve beperkingen, depressieve symptomen, angst en vermoeidheid na een follow-up periode van 9.8 (SD 8.0) jaar bij 45 patiënten met een hersenbloeding en vergeleken dit met 45 op geslacht, leeftijd en opleidingsniveau gematchte controles. Subjectieve cognitieve klachten hadden een hogere prevalentie in patiënten dan in controles (93.9% versus 73.0%, p=0.02), evenals cognitieve beperkingen op de volgende domeinen: 'Snelheid van informatieverwerking' (33.3% versus 5.4%, p=0.003), 'werkgeheugen' (29.4% versus 10.8%, p=0.049), 'korte-termijn geheugen' (26.5% versus 8.1%, p=0.04), and 'lange-termijn geheugen' (20.6% versus 2.7%, p=0.02). Er was een trend wat betreft vóórkomen van vermoeidheid (40.5% versus 22.2%, p=0.07). Er werden geen significante verschillen gevonden tussen patiënten en controles wat betreft de prevalentie van depressieve symptomen en angst.
Tot slot rapporteert **hoofdstuk 9** over het percentage werkloosheid onder patiënten met een TIA, herseninfarct of hersenbloeding, gedefinieerd als het aantal mensen die een arbeidsongeschiktheidsuitkering ontvingen. Na een follow-up periode van gemiddeld 8.1 (SD 7.7) jaar was 25.9%-43.9% van de patiënten tussen de 35 en 65 jaar werkloos. Patiënten hadden een hogere kans om werkloos te zijn dan de rest van de Nederlandse beroepsbevolking (vrouwen: OR 2.3, 95%-CI 1.8-2.9, mannen: OR 3.2, 95%-CI 2.5-4.0). Een ernstigere beroerte en een langere follow-up duur waren geassocieerd met een hoger risico op werkloosheid. De patiënten in de leeftijdscategorie 35-44 jaar hadden het hoogste risico op werkloosheid (vrouwen: OR 4.7, 95%-CI 3.0-7.0, mannen: OR 9.4, 95%-CI 5.6-15.3).

Conclusie

De studies in dit proefschrift beschrijven dat patiënten die op jonge leeftijd (18 t/m 50 jaar) een beroerte doormaken vaak worden geconfronteerd met problemen op neuropsychologisch en sociaal vlak, zelfs na ongeveer 10 jaar follow-up. Dit spreekt de algemene gedachte onder neurologen en andere behandelaren tegen, dat de prognose na een beroerte op jonge leeftijd relatief gunstig zou zijn. Deze klachten hebben gevolgen voor de patiënt zelf, maar ook voor zijn directe omgeving en de maatschappij, gezien het feit dat deze neuropsychologische en sociale problemen gerelateerd bleken aan functionele afhankelijkheid en een kleinere kans om voormalige dagelijkse activiteiten, bijvoorbeeld werk, weer op te pakken.

De resultaten uit dit onderzoek maken het mogelijk voor artsen en andere beroepsgroepen die betrokken zijn bij de zorg voor deze patiënten om betere informatie te kunnen geven over de mogelijke lange-termijn gevolgen die een beroerte op jonge leeftijd met zich mee kan brengen. In de toekomst is verder onderzoek nodig om de onderliggende pathofysiologische mechanismen verder te ontrafelen en behandelingsstrategieën te ontwikkelen.

PART V
Appendices



Appendices

List of abbreviations

BI	Barthel Index
BMI	Body Mass Index
CBS	Central Bureau of Statistics
CFQ	Cognitive Failures Questionnaire
CIS	Checklist of Individual Strength questionnaire
FUTURE Study	Follow-up of Transient ischaemic attack and stroke patients and Unelucidated Risk factor Evaluation Study
HADS-a	Hospital Anxiety and Depression Scale, items on anxiety
HADS-d	Hospital Anxiety and Depression Scale, items on depressive symptoms
IADL	Instrumental Activities of Daily Living
ICH	Intracerebral haemorrhage
ILO	International Labour Organisation
IS	Ischaemic stroke
MMSE	Mini Mental State Examination
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PPMST	Paper and Pencil Memory Scanning Test
RAVLT	Rey Auditory Verbal Learning Test
ROCF	Rey-Osterrieth Complex Figure
SDMT	Symbol-Digit Modalities test
TIA	Transient Ischaemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VSAT	Verbal Series Attention Test

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Curriculum Vitae

Noortje Maaijwee was born on April 27th, 1983 in Waalwijk, The Netherlands.
She attended the gymnasium at the Dr. Mollercollege in Waalwijk and graduated cum laude in 2001. That year she started medical school at the Radboud University of Nijmegen. She did a research internship at the department of Psychiatry of the Radboud University Nijmegen Medical Centre on 'Genetic predictors of relapse after detoxification of alcohol addiction'.

After a senior internship at the department of Neurology at the Rijnstate hospital in Arnhem, she started there as a resident in neurology from October 2007 until March 2008.
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In 2009, she started the PhD-project, resulting in this thesis, together with Loes Rutten-Jacobs, under supervision of Dr. Frank-Erik de Leeuw.
She hopes to finish her specialisation in 2016.

List of publications

Schaapsmeerders P, van Uden IW, Tuladhar AM, **Maaijwee NA**, van Dijk EJ, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, Dorresteijn LD, de Leeuw FE, Kessels RP. Ipsilateral hippocampal atrophy is associated with long-term memory dysfunction after ischemic stroke in young adults. *Hum Brain Mapp.* 2015 Mar 10; doi: 10.1002/hbm.22782. [Epub ahead of print]

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