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Epidemiology of Stroke in Denmark

Studies of occurrence and prognosis with an emphasis on younger adults

PhD Dissertation

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Nils Skajaa, September 2022

Studies

This dissertation is based on the following four original studies, which will be referred to in the following text by their roman numerals (I-IV).

I. **Skajaa N**, Adelborg K, Horváth-Puhó E, Rothman KJ, Henderson VW, Thygesen LC, Sørensen HT. Nationwide Trends in Incidence and Mortality of Stroke Among Younger and Older Adults in Denmark. *Neurology. 2021 Mar 30;96(13):e1711-23*

II. **Skajaa N**, Adelborg K, Horváth-Puhó E, Rothman KJ, Henderson VW, Thygesen LC, Sørensen HT. Risks of Stroke Recurrence and Mortality After First and Recurrent Strokes in Denmark: a Nationwide Registry Study. *Neurology. 2022 Jan 25;98(4):e329-42*

III. **Skajaa N**, Adelborg K, Horváth-Puhó E, Rothman KJ, Henderson VW, Thygesen LC, Sørensen HT. Stroke and Risk of Mental Disorders Compared With Matched General Population and Myocardial Infarction Comparators. *Stroke. 2022 Mar 23:STROKEAHA-121*.

IV. **Skajaa N**, Adelborg K, Horváth-Puhó E, Rothman KJ, Henderson VW, Thygesen LC, Sørensen HT. Labor Market Participation and Retirement After Stroke in Denmark [SUBMITTED].

Abbreviations

DREAM	The Danish Registry for Evaluation of Marginalization
CI	Confidence interval
AAPC	Average annual percent change
HR	Hazard ratio
SHR	Subdistribution hazard ratio
PS	Propensity score

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1. THESIS OUTLINE

Stroke constitutes a major global burden as the second-leading cause of death and the third-leading cause of death and disability combined.[1] According to estimates from the Global Burden of Disease Study, there were ~12.2 million incident cases, ~101 million prevalent cases, ~143 million disability-adjusted life years due to stroke, and ~6.6 million stroke deaths in 2019.[1] In Denmark, ~12.000 strokes occur each year, and stroke is the fourth leading cause of death.[1]

In most high-income countries, stroke incidence and mortality rates are currently declining.[1] However, worrying reports from the United States[2–4] and some European countries[5–10] suggest that these trends are heterogeneous by age, with flat or even increasing incidence rates among younger adults. Whether an increasing trend exists among younger adults in Denmark is poorly understood, and further research on this issue was recently called for.[11]

With the aging of populations and improving stroke survival, the absolute number of stroke survivors is increasing.[1] Between 1990 and 2019, the absolute number of patients with prevalent stroke (*i.e.,* those surviving at least 30 days) increased globally by 43%.[1] With more patients at risk of post-stroke outcomes, an updated and in-depth understanding of the stroke prognosis is warranted to inform patients, families, caregivers, and public health policymakers of prevention efforts.[12]

Thus, this dissertation aimed to describe 1) trends in the incidence and mortality of stroke among younger and older adults in Denmark (Study I) and 2) the prognosis of stroke in Denmark with regards to stroke recurrence (Study II), mental disorders (Study III), and labor market participation (Study IV).

This dissertation contains 11 chapters. The introduction outlines epidemiological aspects of stroke, including current treatment practices. This chapter also introduces prognostic studies, put in the context of stroke research. The chapter ends with a review of the existing literature pertaining to each study, with an outline of previous shortcomings and current knowledge gaps. The succeeding chapters describe the hypotheses and aims, the study methods, and the key results. Then, in the discussion chapter, the main findings are discussed in the context of the existing literature. This chapter also contains a discussion of key methodological aspects. The main conclusions and perspectives, summaries in English and Danish, references, and appendices with full versions of each study follow.

2. INTRODUCTION

2

2.1. Stroke definition

Despite its astounding health impact worldwide, stroke has historically lacked a consistent definition.[13] In the 1970s, the World Health Organization defined stroke as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin."[14] Due to its reliance on the clinical presentation and arbitrary focus on a 24-hour time period (*i.e.,* brain injury can occur much sooner), the American Heart Association/American Stroke Association now defines stroke more broadly as a "neurological deficit attributed to an acute focal injury of the central nervous system (*i.e.,* brain, retina, or spinal cord) by a vascular cause".[15] This definition also includes silent infarctions and hemorrhages. However, the World Health Organization definition is still frequently used.[1,16]

2.2. Stroke subtypes, risk factors, and etiologies

As is evident from the broad definition presented above, stroke is a heterogeneous disease, comprising distinct pathophysiologies.[17–20] In this dissertation, I consider three major pathological subtypes: ischemic stroke (*i.e.,* cerebral infarction), intracerebral hemorrhage, and subarachnoid hemorrhage. Ischemic stroke comprises the vast majority of all strokes (~80%), while intracerebral hemorrhage (~10-15%) and subarachnoid hemorrhage (~5-10%) are less frequent; however, the relative importance of each subtype varies according to geographical region, largely attributable to global differences in risk factor prevalences.[1] Ischemic stroke may occur as a result of embolism – either from the aortic arch, cervical arteries, or the heart – or *in situ* thrombosis, leading to arterial occlusion, with occlusion of the cerebral veins or venous sinuses much less frequent.[17] Spontaneous, non-traumatic, intracerebral hemorrhage is defined by brain injury as a result of blood extravasation into the brain parenchyma from a rupture of a cerebral blood vessel.[19,21] Subarachnoid hemorrhage occurs when blood is released into the subarachnoid space, surrounding the brain and spinal cord.[22]

The incidence rate of stroke increases steeply with advancing age; the median age of onset is ~72 years for ischemic stroke and intracerebral hemorrhage and ~57 years for subarachnoid hemorrhage.[23] Although stroke primarily affects the elderly population, ~10% of all strokes occur among younger adults (often defined as those aged 18–49 years).[24,25] The rate of ischemic stroke and intracerebral hemorrhage is slightly higher in men than in women, except in those aged younger than 30 years;[24] for subarachnoid hemorrhage, the rate is higher in women than in men.

The most important modifiable risk factors (*i.e.,* any exposure that increases the probability of an event[26]) for stroke resemble those for cardiovascular diseases such as myocardial infarction. The INTERSTROKE study, an international, 32-country, case-controls study, found that ten modifiable

risk factors were associated with ~90% of the population attributable risk (*i.e.,* the proportion of disease risk in a population attributable to one or more exposures[27]) of ischemic stroke and intracerebral hemorrhage collectively: hypertension, smoking, diabetes mellitus, physical inactivity, poor diet, abdominal obesity, alcohol consumption, cardiovascular disease (defined as atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valve), psychosocial factors (defined as home or work stress, life events, and depression), and apolipoproteins.[28] In that study, the relative importance of these varied somewhat according to the two subtypes included: for example, the importance of hypertension was greater for intracerebral hemorrhage, while that of smoking, diabetes, and cardiovascular disease was more important for ischemic stroke.[28] Atrial fibrillation remains the most important cardiovascular risk factor of ischemic stroke.[29] For subarachnoid hemorrhage, hypertension, smoking, and alcohol consumption appear to be the most important modifiable risk factors.[30,31]

A few words on causation: first, estimates of the population attributable risk are entirely contingent on the distributions of risk factors in the underlying population (*i.e.,* a given risk factor must exist in the underlying population to be considered).[26] Thus, estimates of the population attributable risk may differ between populations. Second, the onset of most diseases, particularly non-communicable diseases, is typically a product of a set of component causes that, for each individual case, is sufficient to cause disease.[32] Component causes can vary in strength (or importance) at the population level, but not at the individual level: for each individual case, a given set of component causes is necessary to cause disease, and, hence, each component cause is equally important.[32] Thus, when describing stroke risk factors, their relative importance only has meaning at the population level.

Yet, identifying the underlying disease mechanism (often, although unambiguously, termed etiology) for a given case is important for acute treatment and secondary prevention. To aid in this regard, the Trial of Org 10172 in Acute Stroke Treatment classification system divides ischemic stroke into five distinct etiologic subtypes: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-artery occlusion, 4) stroke of other determined etiology, and 5) stroke of undetermined etiology.[33] Although the relative proportions of these vary according to geographic region and age, large-artery atherosclerosis and small-artery occlusion are considered to be the underlying etiology in the majority of cases. Unlike ischemic stroke, no etiologic classification system exists for intracerebral hemorrhage; in fact, the underlying etiology of intracerebral hemorrhage is often unrecognized.[19] The two most common etiologies are 1) deep perforating vasculopathy or arteriolosclerosis (sometimes referred to as hypertensive intracerebral hemorrhage[34]) and 2) cerebral amyloid angiopathy.[19] As for intracerebral hemorrhage, no clear etiological classification system exists for subarachnoid hemorrhage, but a ruptured aneurysm is considered the primary mechanism in ~85% of all cases, while non-aneurysmal perimesencephalic hemorrhage accounts for ~10%.[20]

In younger adults, risk factors and etiologies are more varied than overall, and ~25% of ischemic strokes in this population are cryptogenic (*i.e.*, stroke of undetermined etiology).[24,25,35] Risk factors of particular importance in younger adults include, but are not limited to, oral contraceptives, pregnancy, migraine, illicit drug use, patent foramen ovale, inherited and acquired thrombophilias (*e.g.,* antiphospholipid syndrome), carotid or vertebral artery dissection (*e.g.,* from Ehlers-Danlos syndrome), as well as rare conditions, such as Fabry disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and Moyamoya.[24,25,35]

2.3. Stroke treatment

2.3.1 Acute treatment

One of the most important developments in acute stroke care, regardless of subtype, has been the development of specialized stroke units, in which patients are cared for by a multidisciplinary team with expertise in stroke treatment and rehabilitation.[36,37] Globally, Denmark has pioneered the organization of stroke care, with the establishment of stroke units already in the late 1990s, as well as an effective prehospital response.[38]

Reperfusion therapy is the cornerstone of acute ischemic stroke treatment, the development of which has transformed stroke from a largely untreatable disease.[39] Restoration of brain tissue perfusion can be achieved either medically with intravenous thrombolysis (*i.e.,* with alteplase, a tissue plasminogen activator) or with mechanical thrombectomy.[18,40] While the post-stroke disability and mortality benefits associated with these therapies are well-established,[18,40] strict eligibility criteria mean that only ~25% of all ischemic stroke patients are eligible for thrombolysis and ~10% for thrombectomy.[18] In Denmark, ~24% of patients with ischemic stroke receive either thrombolysis or thrombectomy,[41] a substantially higher proportion than elsewhere (*e.g.,* in the United States, ~11% receive thrombolysis and ~2% thrombectomy).[37,42] Regarding thrombolysis, only patients with disabling ischemic stroke symptoms and with presentation less than 4.5 hours since symptom onset should be considered for treatment.[18,40] Severity scales, such as the National Institutes of Health Stroke Scale or the Scandinavian Stroke Scale, can aid the clinical judgment of severity.[18] Thrombectomy is currently only indicated for large vessel occlusion; thus, the use of neuroimaging, *e.g.,* non-contrast computed tomography or magnetic resonance imaging, is necessary to rule out intracranial hemorrhage and establish the underlying etiology (*e.g.,* to establish large vessel occlusion).[18]

As most patients with intracerebral hemorrhage present with hypertension, which is associated with hematoma growth, acute blood pressure lowering (systolic target of 130 to 140 mm Hg) appears intuitive and is generally recommended; however, randomized trials did not show clear benefits in functional outcome with this approach.[19,21] Among the ~15% of patients with anticoagulation-related

intracerebral hemorrhage, reversal agents are generally recommended.[19,21] Other strategies include hemostatic drugs with recombinant factor VIIa, but the evidence of this approach is limited.[19,21] Lastly, craniotomy for the removal of the hematoma can be considered in selected patients.[19,21]

Acute subarachnoid hemorrhage treatment revolves around preventing early aneurism rebleeding, the occurrence of which is most frequent within six hours of onset.[43] Acute hypertension should be controlled until aneurysm obliteration; however, the magnitude of blood pressure control is not well-established. In patients with delayed obliteration, antifibrinolytic therapy can be considered. The ruptured aneurysm should be treated through surgical clipping or endovascular coiling.[43]

2.3.2 Secondary prevention

Following the terminology used in the American Heart Association/American Stroke Association guidelines, secondary prevention is here defined as "activities that prevent deterioration or reduce complications after disease", although this definition historically has been used for tertiary prevention.[26]

The key to effective secondary stroke prevention is knowledge of the underlying etiology.[44] For ischemic stroke, the Trial of Org 10172 in Acute Stroke Treatment classification scheme is commonly used to guide treatment decisions: broadly, antiplatelets should be given to all patients with non-cardioembolic strokes, while anticoagulants should be given to those with cardioembolic stroke (*e.g.,* in case of atrial fibrillation).[44] The choice of antithrombotic medication has varied over time: Aspirin and clopidogrel, alone or in combination, have been the mainstay of antiplatelet therapy.[44–46] Regarding anticoagulants, vitamin K antagonists (*e.g.,* warfarin) were recommended for cardioembolic strokes in the 2011 guidelines and before,[45] but non-vitamin K antagonists (*e.g.,* apixaban, dabigatran, edoxaban, or rivaroxaban) are now generally preferred.[44,46] In addition to antithrombotic therapy, management of vascular risk factors (*i.e.*, hypertension, lipid levels, diabetes, and tobacco smoking) and lifestyle factors (*i.e.*, diet and physical activity) remain essential. Except in the case of hypertension (*e.g.,* the MOSES[47] and PRoFESS[48] trials) and lipid levels (*e.g.,* the SPARCL[49] and TST[50] trials), randomized trial evidence regarding the benefit and safety of vascular risk factor management in pure stroke populations are generally lacking.

For both intracerebral and subarachnoid hemorrhage, blood pressure control is foundational for effective secondary prevention, although the optimal strategy is not clear and depends on the underlying etiology.[51,52] While it is generally recommended to delay starting or re-starting antithrombotic therapy in patients with intracerebral hemorrhage for up to four weeks, it is now well-established that intracerebral hemorrhage is associated with an increased risk of arterial events,[53,54] and restarting antiplatelets earlier rather than later may be beneficial;[55] regarding the

resumption of anticoagulants, the decision is challenging and should be individualized.[56] Similarly, the role of lipid-lowering drugs after intracerebral hemorrhage remains controversial,[57] as some evidence associates statins with a decreased risk of intracerebral hemorrhage,[58] while other studies did not find such an effect.[59]

Given the high prevalence of post-stroke depression (see Section 2.5.3), the routine use of pharmacologic interventions to reduce this risk has been debated for several years.[60,61] A 2020 Cochrane review concluded that there is low-certainty evidence that pharmacological interventions, particularly selective serotonin reuptake inhibitors, reduce depression risk.[62] Further, early evidence, including a Danish observational study, pointed to a benefit of selective serotonin reuptake inhibitors on functional status after stroke,[63] but newer trials did not find any such effect.[64,65] In Denmark, selective serotonin reuptake inhibitors have been frequently used after stroke.[66]

2.3.3 Rehabilitation

Rehabilitation, broadly referring to a targeted and defined process carried out by a multidisciplinary team of care professionals, is critical for effective stroke care.[67,68] Fundamental aspects of rehabilitation include 1) an assessment to understand the needs of the patient and relatives, 2) an outline of realistic goals, 3) interventions to achieve those goals, and 4) re-assessments to evaluate progress.[68] Rehabilitation generally takes a holistic approach, *i.e.*, both physical, psychological, and social consequences should be considered.[67] To aid in this regard, a wide panel of professionals is often needed. These include clinicians, nurses, physiotherapists, occupational therapists, neuropsychologists, and social workers, among others.[67] Rehabilitation interventions are patient-specific and highly heterogenous, and, therefore, their mention is beyond the scope of this section.

In Denmark, rehabilitation is broadly divided into three phases: 1) rehabilitation during the early, acute period (*i.e.*, acute treatment, as described in Section 2.3.2), 2) rehabilitation during the course of hospitalization, and 3) rehabilitation after hospital discharge. As noted in Section 2.3.2, rehabilitation during hospitalization (phase 2) is most often carried out in specialized stroke units. Rehabilitation after discharge is carried out under the auspices of the municipalities, and this transition away from hospital care is generally considered chaotic.[67] In fact, the newly published national action plan for stroke in Denmark stressed the need for an improved cross-sectional (*i.e.*, between hospitals and municipalities) collaboration, which is often characterized by poor communication and a lack of clarity regarding responsibilities.[69]

2.4. Prognostic studies and stroke outcomes

A fundamental aspect of clinical epidemiology is the study of disease prognosis.[70] Knowledge of prognosis is paramount for both patients and health care professionals and to guide clinical decisions.[12] I define here prognosis as the "probability or risk of an individual developing a particular health state (or outcome) over a specific time, based on his/her clinical profile".[71] When studying prognosis, one can differentiate between the "natural history" of a disease, *i.e.,* the prognosis in the absence of care, and the "clinical course", *i.e.,* the prognosis in the presence of care.[70] In routine clinical care settings, one is effectively studying the clinical course.[70]

Prognostic studies play a central role in this dissertation. Following the terminology used in Hemingway, *et al.*, Studies II-IV are placed within the realms of "fundamental prognostic research" and "prognostic factor research", two interrelated themes.[12] While fundamental prognostic research aims to describe prognosis under current diagnostic practices as well as the variation between patients with different clinical characteristics, prognostic factor research aims two identify factors, among people with a given disease, that are associated with a future outcome.[12,72] As Study I examines the trend in mortality after stroke, in addition to the trend in occurrence, this study also falls under fundamental prognostic research.[12]

The prognosis of stroke may be affected by a variety of factors. Adapted from Sackett, *et al.*, these factors may include 1) characteristics of the index disease itself (*e.g.,* stroke subtype, severity, location, and size), 2) the clinical profile of the patient (*e.g.,* age, sex, and comorbidities [*i.e.,* the presence of other diseases in addition to the index disease[73]], 3) the availability and accuracy of diagnostic tests (*e.g.,* computed tomography or magnetic resonance imaging scans), 4) acute treatment (*e.g.,* see Section 2.3.1) and secondary prevention (*e.g.,* see Section 2.3.2), 5) the clinical performance (*e.g.,* competence of clinician, admission to stroke unit), 6) and patient compliance (*e.g.,* compliance to secondary preventive drugs).[74] Because various factors affect prognosis, the average prognosis for a heterogeneous group of people may have little clinical relevance; instead, it remains important to disentangle and describe the heterogeneity in prognosis for different people.[12] For example, examining the potential age heterogeneity in trends (Study I) and prognoses (Studies II-IV) is central to this dissertation.

Fletcher argued that outcomes in prognostic research should be patient-centered, *i.e.,* outcomes that patients care about.[26] Outcomes can roughly be classified as either 1) hard outcomes (*e.g.,* mortality or stroke recurrence), 2) surrogate outcomes (*e.g.,* changes in blood pressure), 3) soft outcomes (*e.g.,* aphasia or fatigue), and composite outcomes (*e.g.,* the first occurrence of either stroke recurrence or mortality). In registry-based studies of routine clinical care settings, outcomes are often restricted to hard and composite outcomes,[75] although exceptions exist (*e.g.,* some clinical quality databases

include information on potential soft endpoints[16]). The potential research-worthy outcomes in prognostic studies of stroke are many, and an exhaustive list is beyond the scope of this section. Of note, however, information on many, softer outcomes (*e.g.*, post-stroke fatigue, falls, constipation, aphasia, cognitive decline), which carry great importance to stroke patients, is not routinely collected in clinical practice and is thus challenging to study using registries.[76] In this dissertation, I focused on the following hard outcomes: mortality (Study I), recurrence (Study II), mental disorders (Study III), and labor market participation (Study IV). Mental disorders may, however, also be considered a soft outcome (see Section 6.2.3.2).

2.5. Literature review

To review the literature relevant to this dissertation, I searched MEDLINE (PubMed) using the search builder with the Boolean operators AND/OR/NOT. When applicable, Medical Subject Headings terms were applied. Potential studies were initially screened for relevance based on 1) title and abstract and 2) full texts. Reference lists of identified studies from the search and suggested studies from MEDLINE were also screened. I also performed additional searches using CoCites, a citation-based search method, which more readily identifies the studies of greatest importance to a given topic.[77] Literature searches were conducted for each study separately. Tables 1-4 summarize the studies identified by the searches.

Table 1. Studies relevant for Study I.

Study I:				
Author, journal, year	**Design, setting, period**	**Study population (size, subtype, age group)**	**Measure**	**Main findings, comments**
George, et al.[2] Ann Neurol 2011	Cohort study Nationwide Inpatient Sample, US 1995-2008	n = not reported IS, ICH, SAH 5-14 y, 15-34 y, 35-44 y	Incidence	IS cases increased over years for all ages/sexes ICH cases decreased over years, except for 5-14 y SAH cases decreased over years, except for 5-14 y Hypertension, diabetes, obesity, lipid disorders, and tobacco increased in prevalence. Comment: No clear study size description.
Kissela, et al.[3] Neurology 2012	Cohort study The Greater Cincinatti/Northern Kentucky Stroke Study, US 1993-2005	n = 5,892 IS, ICH, SAH 20-44 y, 45-54 y, 55-64 y, 65-74 y, 75-84 y, 85+ y	Incidence	Mean age at stroke decreased from 71.2 y in 1994/1994 to 69.2 y in 2005. Proportion of strokes in adults < 55 y increased from 12.9% to 18.6%. Incidence increased in 20-54 y, most noticeably for IS, and decreased in older ages.
Rosengren, et al.[5] Stroke 2013	Cohort study Swedish Hospital Discharge Registry 1987-2010	n = 391,081 IS 18-44 y, 45-64 y, 65-84 y	Incidence, mortality	IS incidence in 18-44 y increased 1.3%/y for men and 1.6% for women; in 45-64 y, rate decreased 0.4%/y for men and 0.6% for women; in 65-84 y, rate decreased 3.7%/y for men and 5.1%/y for women (after 2005). Mortality declined continuously in all ages. Comment: Only IS-specific trends.
González-Pérez, et al.[78] Neurology 2013	Cohort study The Health Improvement Network Database, UK. 2000-2008	n = 1,102 ICH, SAH 20-49 y, 50-59 y, 60-69 y, 70-79 y, 80-89 y	Mortality	For ICH, 30-day mortality decreased over time overall (from 53% in 2000-2001 to 36% in 2006-2008) and across all ages. For SAH, 30-day mortality decreased over time overall (from 33% in 2000-2001 to 25% in 2006-2008) and across all ages, except in 20-49 y where an increase was seen.
Vaartjes, et al.[79] Stroke 2013	Cohort study Dutch Hospital Discharge Register and other registries 1997-2005	n = not reported IS 35-64 y, 65-74 y, 75-84 y, 85-94 y	Incidence, mortality	IS incidence rate increased in 35-64 for both sexes, while it was largely stationary in older ages. IS 30-day mortality clearly decreased over time in both sexes and across ages. Comment: Only IS-specific trends. No clear study size description.
Béjot, et al.[6] J Neurol Neurosurg Psychiatry 2014	Cohort study Dijon Stroke Registry, France 1985-2011	n = 4,506 IS, ICH <55 y, 55-64 y, 65-74 y, 75-84 y, 95+y	Incidence	Overall stroke in <55 y incidence from 11.6/100,000 PY in 1985-1993 to 20.2/100,000 PY in 2003-2011. Incidence increased slightly or remained stable in older age groups. Comment: Subtype-specific trends only reported for <55 y
Schmidt, et al.[80] Neurology 2014	Cohort study Danish National Patient Registry and other nationwide registries 1994-2011	n = 219,354 IS, ICH 15-49 y, 50-59 y, 60-69 y, 70-79 y, 80+ y	Mortality	Overall 30-day mortality after IS declined from 17% in 1994-1998 to 11% in 2009-2011; after ICH from 43% to 34%. These trends held within age groups.
Poisson, et al.[81] Neurology 2014	Cohort study National Center for Health Statistics, US 1989-2009	n = not reported IS, ICH, SAH 20-44 y, 45+ y	Mortality	Mortality per 100.000 person-years decreased over time for all subtypes and both age groups, except for IS in 20-44 y (11% increased mortality); in 45+ y, a 53% decline was observed. Comment: No clear study size description.

Tibæk, et al.[7] J Am Heart Assoc 2016	Cohort study Danish National Patient Registry and other nationwide registries 1994-2012	n = 4,156 IS, ICH, SAH, TIA 15-30 y	Incidence	Age-standardized rate for overall stroke increased from 12.0/100,000 PY in 1994 to 16.8/100.000 PY in 2012. The trend was driven by ischemic stroke; trends for ICH and SAH remained stable over time.
George, et al.[4] JAMA Neurol 2017	Cohort study Nationwide Inpatient Sample, US 1995-2012	n = not reported IS, ICH, SAH 18-34 y, 35-44 y, 45-54 y, 55-64 y	Incidence	IS incidence rate increased in 18-54 y for both sexes. Rates in 55-64 y were constant. ICH/SAH incidence rates were largely constant. Prevalence of multiple risk factors for IS nearly doubled. Comment: No clear study size description. Not individually-linked data regarding prevalence of risk factors.
Wafa, et al.[82] PLoS Med 2018	Cohort study South London Stroke Register 2000-2015	n = 3,088 IS only <55 y, 55+ y	Incidence	Age-standardized rate of IS decreased by 43% (from 137/100,000 PY) in 2000-2003 to 78/100,000 PY in 2012-2015. Rate decreased in both <55 y (33%) and 55+ y (43%). Most cardiovascular risk factors increased over time, except tobacco smoking and alcohol consumption.
Sipilä, et al.[83] PLoS One 2018	Cohort study Care Register for Health Care, Finland 2004-2014	n = 10,976 IS, ICH, SAH 18-34 y, 35-44 y, 45-54 y, 55-64 y	Incidence	In 18-64 y, the IS incidence rate decreased by 4% (from 60/100,000 PY in 2004-2005 to 57/100,000 PY in 2013-2014), but this was driven by the 55-64 y age group (-14%). The rate increased in 18-34 y (23%), in 35-44 y (33%), and remained largely unchanged in 45-54 y (-2%). ICH (-15%) and SAH (-27%) rates decreased over time.
Aparicio, et al.[84] Stroke 2019	Cohort study Framingham Study, US 1962-2005	n = 691 Overall stroke (IS+ICH) 35-54 y, 55+ y	Incidence	10-year risk of incident stroke declined over epochs in both age groups (for 35-54 y: from 2.4% in 1962-67 to 1.7% in 1998-2005; for 55+ y, from 11.7% to 10.6%. Prevalence of smoking, hypertension, cholesterol declined, but obesity increased, over epochs in both age groups. Comment: No subtype-specific trends.
Ekker, et al.[8] Neurology 2019	Cohort study Dutch Hospital Discharge Register and other registries 1998-2010	n = 15,257 IS, ICH 18-49 y, 50+ y	Incidence	For 18-49 y, rate of ischemic stroke increased by 46% from 7.4/100.000 PY in 1998 to 10.8/100.000 PY in 2010, driven by those 35+ y. Rate of ICH remained stable. For 50+ y, rate declined by 11% over time.
Seminog, et al.[9] BMJ 2019	Cohort study Health and Social Care Information Centre and Office for National Statistics, UK 2001-2010	n = 795,869 Overall stroke (IS+ICH) 20-34 y, 35-54 y, 55-64 y, 65-74 y, 75-84 y, 85+ y	Incidence, mortality	In all ages, incidence rate of overall stroke decreased by 1.3%/year for men (from 345/100.000 PY in 2001 to 284/100.000 PY in 2010) and by 2.1%/year for women (from 280/100.000 PY in 2001 to 234/100.000 PY in 2010). However, the rate increased slightly in ages 20-34 y and 35-54 y. 30-day mortality decreased across all ages and both sexes (by 4% to 5%/year). Comment: No subtype-specific trends.
Barra, et al.[85] J Neurol 2019	Cohort study Norwegian Patient Registry and other nationwide registries 2010-2015	n = 105,792 IS, ICH, TIA 15-24 y, 25-34 y, 35-44 y,	Incidence, mortality	Incidence of cerebrovascular events (IS, ICH, TIA) declined slightly over time, but driven by the 35-44 y group. In 15-24 y and 25-35 y age groups, trends were largely stationary. Mortality decreased over time. Comment: Main analysis was cerebrovascular event rates. No clear subtype-specific trends.
Ekker, et al.[86] JAMA 2019	Cohort study Dutch Hospital Discharge Register and other registries 1998-2010	n = 15,527 IS, ICH 18-49 y	Mortality	Overall 30-day mortality after IS decreased from 8%% in 1998 to 5% in 2010; after ICH, from 38% to 21%.

Yafasova, et al.[10] Neurology 2020	Cohort study Danish National Patient Registry and other nationwide registries 1996-2016	n = 224,617 IS 18-34 y, 35-44 y, 45-54 y, 55-64 y, 65-74 y, 75-84 y, 85+ y.	Incidence, mortality	Overall age-standardized rate decreased between 2002 (325/100.000 PY) and 2016 (1.99/100.000 PY). The youngest age groups (18-34, 35-44, 45-54) had a largely constant trend over time. 30-day mortality decreased from 17.1% in 1996 to 7.6% in 2016. Decreasing mortality trends were observed across all age groups.
Wafa, et al.[87] PLoS Med 2020	Cohort study South London Stroke Register 2000-2015	n = 3,128 IS <55 y, 55+ y	Mortality	Overall 30-day mortality decreased from 16% in 2000-2003 to 10% in 2012-2015; in <55 y, from 8% to 3%; in 55+ y, from 19% to 13%
Norman, et al.[88] Front Neurol 2022	Cohort study Swedish nationwide registries 2000-2018	n = 16,210 IS 18-54 y	Incidence	Rate of ischemic stroke remained largely stable between 2005 and 2018 in both men (31 per 100,000 PY) and women (19 per 100,000 PY).

Abbreviations. IS: ischemic stroke; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; TIA: transient ischemic attack; PY: person-years.

2.5.1 Trends in incidence and mortality of stroke (Study I)

Knowledge of temporal trends of disease occurrence and associated mortality is a cornerstone of public health, as it provides a foundation for effective prevention strategies, resource allocation, and research on risk factors and outcomes.

In the Global Burden of Disease Study, the age-standardized incidence and mortality rates decreased globally from 1990 to 2019 by 17% and 36%, respectively; however, among those younger than 70 years, the incidence rate increased by 15%.[1] The overall decline in incidence was more prominent for intracerebral hemorrhage (rate in 2019: 42 per 100,000 people; percentage change from 1990: -29%) than for ischemic stroke (rate in 2019: 95 per 100,000 people; percentage change from 1990: -10%) and subarachnoid hemorrhage (rate in 2019: 14 per 100,000 people; percentage change from 1990: -17%).[1] While the Global Burden of Disease Study provides an excellent overview, due to the large geographical variation in rates and the large variety in the quality of data sources used, studies from individual countries are needed to comprehensively understand current trends, particularly related to any potential age heterogeneity.

Despite overall declines in the age-standardized incidence rate in high-income countries,[1] a large body of literature from the United States[2–4] and some European countries[5–10] has reported increasing incidence rates among young adults (Table 1). For example, in a recent American study, leveraging data from the Nationwide Inpatient Sample, the rate of ischemic stroke increased between 2003-2004 and 2011-2012 by 27% in ages 18-34 years, by 36% in ages 35-44 years, and by 21% in ages 45-64 years. Most,[5–10] but not all,[82,83,85,88] European reports have reached similar conclusions. For example, in a large Swedish study using data from the Swedish Hospital Discharge Registry, the ischemic stroke rate increased between 1987-1992 and 2005-2010 by 33% (from 7.2 per 100,000 person-years to 9.6) in ages 18-44 years and by 20% (from 51 per 100,000 person-years to 61.4) in ages 45-54 years.[5] In a recent Dutch study pulling data from the Dutch Hospital Discharge Register, the ischemic stroke rate increased between 1998 and 2010 by 46% (from 7.4 per 100,000 person-years to 10.8) in ages 18-49 years, mainly driven by ages 35-49 years.[8] In contrast to these findings[5,8] and others,[6,7,9,10] studies from Finland,[83] the United Kingdom,[9] and Norway,[85] as well as a recent study from Sweden,[88] found slightly decreasing or stationary trends in younger adults. Although a few studies found stationary trends,[4,6] most studies reporting on rates in older adults found declining rates,[3,5,8–10,82,84] thus aligning with the findings from the Global Burden of Disease Study.[1]

The reasons for the apparent increase in incidence among younger persons in many geographical regions are not clearly understood. George, *et al.* hypothesized that the increasing occurrence of many vascular risk factors in the United States, such as hypertension, lipid disorders, and diabetes,

could be one explanation.[4] Rises in the occurrence of other risk factors, such as illicit drug use, which is more frequent in the younger population, could also play a role.[8]

Reports regarding trends in mortality rates have been less contradictory, with most previous studies reporting decreasing rates regardless of age.[5,9,10,79,80,85–87] Contrasting these findings, a study from the United States (1989-2009) found an increasing mortality rate after ischemic stroke for patients aged 20-44 years,[81] while a study from the United Kingdom (2000-2008) found an increasing rate after subarachnoid hemorrhage for patients aged 20-49 years.[78]

Collectively, studies on incidence and mortality trends in stroke were limited by their small or unreported study sizes (<5,000 patients or unreported study size),[2,4,6,7,78,79,81,82,84,87] lack of data on stroke severity, etiology, comorbidities, and drug use, and the fact they did not report rates in smaller age groups for both younger (<50 years) and older (50+ years) adults,[2,6–8,82,84,85,88] thereby not providing complete context to the issue. In addition, only a few studies reported separate trends for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage.[2–4,7,83]

Table 2. Studies relevant for Study II.

Study II:					
Author, journal, year	**Design, setting, period**	**Study population (size, subtype)**	**Recurrence definition**	**Analytic method**	**Main findings, comments**
Kolominsky-Rabas, et al.[89] Stroke 2001	Cohort study Erlangen Stroke Project 1994-1998	n = 583 IS	Any recurrence of new neurological deficit occurring ≥24 hours after initial event	KM	After IS, 2-y risk ranged from 10%-22%, depending on IS subtype. Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010).
Appelros, et al.[90] Stroke 2003	Cohort study "Hot pursuit" case ascertainment, Örebro, Sweden 1999-2000	n = 377 IS, ICH, UNS	Any recurrence occurring ≥28 days after initial event.	KM	After non-lacunar IS: 1-y risk: 10% After lacunar IS: 1-y risk: 3% After ICH: 1-y risk: 9% After UNS: 1-y risk: 29% Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010).
Modrego, et al.[91] J Neurol Sci 2004	Cohort study Public hospital, Alcañiz, Spain 1997-2001	n = 472 Overall stroke (IS, ICH combined)	Any recurrence of new neurological deficit with symptoms lasting ≥24 hours and occurring after initial event.	KM	After any stroke: 1-y risk: 9.5%; 5-y risk: 26% Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010). Only patients with complete follow-up analyzed.
Coull, et al.[92] BMJ 2004	Cohort study Oxford Vascular Study 2002-2003	n = 87 Overall stroke (subtypes not defined)	Not clearly defined	Not defined	After any stroke: 1-m y risk: 15%; 3-m risk: 19% Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010). Recurrence and analytic method not defined.
Coull, et al.[93] Stroke 2004	Cohort study Oxford Vascular Study and Oxfordshire Community Stroke Project, UK 1981-1986	n = 657 IS	3 definitions: a) Any recurrent stroke occurring ≥24 hours after incident event, irrespective of vascular territory. b) Any recurrent stroke occurring ≥24 hours after incident event in a different vascular territory *or* ≥21 days after incident event if in the same vascular territory. c) Any recurrent stroke ≥28 days after initial event.	KM	In OXVASC, 90-day risk: 18% (def. a), 7% (def. b), 6% (def. c) In OCSP, 90-day risk: 15% (def. a), 8% (def. b), 5% (def. c) Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010).
Hardie, et al.[94] Cerebrovasc Dis 2005	Cohort study The Perth Community Stroke Study, Australia 1989/1990 & 1995/1996	n = 464 Overall stroke (IS, ICH, SAH combined)	Any recurrent stroke occurring ≥24 hours after incident event in a different vascular territory *or* ≥21 days after incident event if in the same vascular territory.	KM	After any stroke in 1989-90: 1-y risk: 16%; 5-y risk: 32% After any stroke in 1995-96: 1-y risk: 9%; 5-y risk: 23% Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010).

Hata, et al.[95] J Neurol Neurosurg Psychiatry 2005	Cohort study Daily monitoring system, Hisayama, Japan 1961-1993	n = 1621 IS, ICH, SAH, UNS	Any recurrence occurring ≥21 days after initial event, or if earlier, clearly in a different vascular territory.	KM	After IS, 1-y risk: 10%; 5-y risk: 34%; 10-y risk: 50% After ICH, 1-y risk: 26%; 5-y risk: 35%; 10-y risk: 56% After SAH, 1-y risk: 33%; 5-y risk: 55%; 10-y risk: 70% Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010).
Dhamoon, et al.[96] Neurology 2006	Cohort study Northern Manhattan Study, US 1983-1988	n = 655 IS	Not defined	KM	After IS, 1-y risk: 8%; 5-y risk: 18% Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010). Recurrence not clearly defined.
Xu, et al.[97] Cerebrovasc Dis 2007	Cohort study Nanjing Stroke Registry Program 2003-2006	n = 1,432 IS	Not defined	KM	After IS, 1-y risk: 11%
Mohan, et al.[98] J Neurol Neurosurg Psychiatry 2009	Cohort study The South London Stroke Register, UK 1995-2004	n = 2,874 IS, ICH, SAH, UNS	Any recurrence occurring ≥21 days after initial event, or if earlier, clearly in a different vascular territory.	KM	After IS, 1-y risk: 7%; 5-y risk: 17%; 10-y risk: 26% After ICH, 1-y risk: 8%; 5-y risk: 17%; 10-y risk: 20% After SAH, 1-y risk: 5%; 5-y risk: 5%; 10-y risk: 8% After UNS, 1-y risk: 12%; 5-y risk: 22%; 10-y risk: 43% Comment: Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010).
Lewsey, et al.[99] BMC Med. 2010	Cohort study Scottish nationwide registries 1986-2001	n = 128,511 IS, ICH, SAH, UNS	New admission with a principal diagnosis of any stroke subsequent to the index event.	CIF	After any stroke: 5-y risk: 11%; comparing 2001 with 1986, risk decreased by 27%.
Mohan, et al.[100] Stroke 2011	Meta-analysis 13 individual studies 1950-2009	n = 9,115 Overall stroke (IS, ICH, SAH, UNS combined)	Any recurrence of new neurological deficit with symptoms lasting ≥24 hours and occurring after initial event.	As done in individual studies	After any stroke: 1-y risk: 11.1%; 5-y risk: 26.4%; 10-y risk: 39.2%. Comment: Wide variation in estimates across studies. Did not report estimates according to stroke subtype or patient subgroups Did not differentiate between ischemic and hemorrhagic recurrence Competing risk of death not accounted for in majority of studies. Older study period (< 2010)
Putaala, et al.[101] Ann Neurol 2013	Cohort study Helsinki Young Stroke Registry, Finland 1994-2004	n = 824 (age 18-50 y) IS	Not defined	KM	After IS, 1-y risk: 3%; 3-y risk: 7%; 5-y risk: 9% Comment: Only younger patients included. Outcome was non-fatal or fatal ischemic stroke recurrence. Competing risk of death was not accounted for. Small study size (n < 4,000), older study period (< 2010).
Rutten-Jacobs, et al.[102] Ann Neurol 2013	Cohort study FUTURE study, Netherlands 1980-2010	n = 724 (age 18-50 y) TIA, IS, ICH	Not defined	CIF	After IS, 20-y risk: 19%. Comment: Only younger patients included. Small study size (n < 4,000), older study period (< 2010).

Aarnio, et al.[103] Stroke 2014	Cohort study Helsinki Young Stroke Registry, Finland 1994-2007	n = 970 (age 15-49 y) IS	New persistent neurological deficit attributed to an obstruction in cerebral blood flow and intracerebral hemorrhage with no apparent nonvascular cause.	Cox	Among 30-d survivors, recurrence (time-dependent variable) was associated with increased mortality (HR: 17) Comment: Only younger patients included. Risks not reported, only HRs Small study size (n < 4,000), older study period (< 2010).
Pezzini, et al.[104] Circulation 2014	Cohort study Italian Project on Stroke in Young Adults, Italy 2000-2012	n = 1906 (age 18-45 y) IS	Similar to index event (WHO definition); only IS recurrences.	KM	After IS, 1-y risk: 3%; 5-y risk: 11%; 10-y risk: 14%. Comment: Only younger patients included. Competing risk of death was not accounted for. Small study size (n < 4,000).
Andersen, et al.[105] Stroke 2015	Cohort study Danish nationwide registries 2003-2012	n = 42,182 IS	New admission of ischemic stroke in the Danish Stroke Registry, occurring >14 days after discharge of initial event.	CIF, event rates	After IS, 1-y rate: 4 per 100 person-years; rate clearly increased with increasing Essen risk score, from 2 in those with a score of 0 to 5 in those with a score of ≥5. Comment: CIF estimates not reported, only illustrated.
Bergström, et al.[106] Stroke 2017	Cohort study Swedish nationwide registries 1998-2009	n = 196,765 IS	New admissions of ischemic stroke in the Swedish Stroke Register recorded from the day after discharge of index event.	KM	After IS; 1-y risk: 13%; the 1-y risk decreased from 15% in 1998-2000 to 12% in 2007-2009. Comment: Competing risk of death was not accounted for. Older study period (< 2010).
Khanevski, et al.[107] Acta Neurol Scand 2019	Cohort study Bergen Norstroke Registry 2007-2013	n = 1,988 IS, TIA	Similar to index event (WHO definition); only IS or TIA recurrences.	CIF, Cox	After IS or TIA, 1-y risk: 5%; 5-y risk: 11%; recurrence (time-dependent) was associated with increased mortality (HR: 2.6). Comment: Small study size (n < 4,000).
Flach, et al.[108] Stroke 2020	Cohort study South London Stroke Register 1995-2018	n = 6,052 IS, ICH, SAH	Any recurrence occurring ≥21 days after initial event, or if earlier, clearly in a different vascular territory.	KM, CIF	After IS, 1-y risk: 2.2%; 5-y risk: 12.6%; 10-y risk: 17.9% After ICH, 1-y risk: 4.8%; 5-y risk: 11.2%; 10-y risk: 18.7% After SAH, 1-y risk: 5.8%; 5-y risk: 5.8%; 10-y risk: 9.5% Comment: Competing risk of death was only accounted for in secondary analyses, but estimates not clearly reported.
Rücker, et al.[109] Stroke 2020	Cohort study Erlangen Stroke Project 1996-2015	n = 3,346 IS	Any recurrence of new neurological deficit occurring ≥24 hours after initial event.	KM, CIF	After IS, 1-y risk: 7.5%; 5-y risk: 20.1% Comment: Competing risk of death was only accounted for in secondary analyses, but estimates not clearly reported. Small study size (n < 4,000), older study period (< 2010).
Lin, et al.[110] Neurol Sci 2021	Meta-analysis 37 individual studies 2009-2019	n = 1,075,014 Overall stroke	Any recurrence of new neurological deficit with symptoms lasting ≥24 hours and occurring after initial event.	As done in individual studies	After any stroke: 3-m risk: 8%; 6-m risk: 10%; 1-y risk: 10%; 5-y risk: 15%; 10-y risk: 13%. Comment: Wide variation in estimates across studies. Did not report estimates according to stroke subtype or patient subgroups. Did not differentiate between ischemic and hemorrhagic recurrence. Competing risk of death not accounted for in majority of studies.

					Majority of studies from Asian countries.
Kolmos, et al.[111] J Stroke Cerebrovasc Dis 2021	Meta-analysis 26 individual studies 1997-2019	n = not reported IS	New neurological deficit presenting after a period of clinical stability, lasting for more than 24 hours and with attributable new ischemic or hemorrhagic lesions verified either by CT or MRI of the brain.	As done in individual studies	After IS, pooled risk was 12% (no time frame described) in studies using TOAST criteria and 14% (no time frame described) in studies using TOAST-like criteria.

Abbreviations. IS: ischemic stroke; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; UNS: unspecified stroke; TIA: transient ischemic attack; KM: Kaplan-Meier; CIF: cumulative incidence function (accounting for competing risks); HR: hazard ratio; TOAST: Trial of Org 10172 in Acute Stroke Treatment.

2.5.2 Risk of stroke recurrence and impact on mortality (Study II)

Despite the increasing number of stroke survivors worldwide,[1] recurrent stroke has received less research attention than incident strokes. Preventing recurrent stroke is of paramount importance and the primary aim of secondary stroke prevention.[44] A meta-analysis of randomized controlled trials of secondary stroke therapies showed that the annual recurrence risk has declined from 9% in the 1960s to 5% in the 2000s.[112] Because clinical trial populations often are selected, a detailed and in-depth understanding of absolute recurrence risks in an unselected and contemporary population is important.[113]

Several meta-analyses[100,110,111] and cohort studies[89–99,101,102,104–109] have assessed the risk of stroke recurrence in routine clinical settings, but results have varied considerably between studies (Table 2). In a meta-analysis of 13 studies, with study periods in the individual studies ranging from 1950 to 2009 and including a total of 9,115 patients with stroke, the estimated 1-year, 5-year, and 10-year risks of stroke recurrence were 11%, 26%, and 39%, respectively.[100] In newer meta-analyses, risk estimates were lower, but substantial heterogeneity between studies (*i.e.,* $I^2 > 98\%$) limited the interpretability.[110,111] Of particular importance, most individual studies did not consider the competing risk of death when estimating recurrence risks (*e.g.,* using the Kaplan-Meier estimator).[89–98,101,104,106] In settings where death is common, as is the case in stroke patients, and the outcome is a non-fatal event, failure to account for death as a competing event is known to inflate risk estimates;[114–117] thus, to date, most reported risk estimates on stroke recurrence may have been overestimated. However, a few newer studies have overcome this shortcoming. For example, in a large Scottish registry-based study of 128,511 strokes, identified between 1986 and 2001, the 5-year risk, after considering death as a competing event, was 11%.[99] Similarly, in a British study of 6,052 stroke patients from the South London Stroke Register between 2000 and 2018, the 5-year, and 10-year risk estimates, with competing risk adjustment, were 9% and 11% after ischemic stroke.[108]

In addition to the analytic limitations mentioned, studies reporting on stroke recurrence risks were limited by small study sizes (< 4,000 patients)[89–98,101,102,104,107,109] and older study periods (< 2010),[89–99,101,102,106] resulting in imprecise estimates not applicable in a contemporary setting. Further, studies have used a wide array of recurrence definitions, thereby challenging the comparability between findings.[89–99,101,102,104–109] In an older, smaller study, Coull *et al.* showed that 90-day recurrence risk estimates ranged from 6% to 18% depending on three commonly used recurrence definitions.[93] Only a few studies have reported risk estimates separately for ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage,[95,98,108] as well as in patient subgroups of potential importance for targeted preventive measures, *e.g.,* according to age, stroke severity, or comorbidity. For example, only a few studies have reported on risks specifically among younger adults.[101,102,104] One study reported that 1-year recurrence rates increased with increasing Essen risk score,[105] but this finding

remains to be replicated in a more contemporary setting. The Essen risk score is a clinical risk stratification score that predicts the 1-year risk of recurrent ischemic stroke and combined cardiovascular events on a 9-point scale,[118] but its utility in clinical practice remains poorly understood. Lastly, some evidence exists that recurrence risks have decreased over years,[99,106,119] but evidence on trends remains scarce.

Recurrent strokes are widely regarded as more often fatal and disabling than first-time events;[120] however, the strength of this association has only been scarcely investigated.[103,107]

Table 3. Studies relevant for Study III.

Study III:						
Author, journal, year	**Design, setting, period**	**Study population (size, subtype, prev. mental disorder)**	**Mental disorder**	**Analytic method**	**Comparison cohort**	**Main findings, comments**
Ayerbe, et al.[121] Stroke 2013	Cohort study South London Stroke Register 1995-2009	n = 4,022 Overall stroke No exclusions	Depression	Prevalence, annual risk	No	After any stroke, prevalence of depression was ~30% at any given time for up to 15 years. Annual risks were 15-20% the first 10 years. Comment: Single time-point assessments (annually) during follow-up.
Ayerbe, et al.[122] Br J Psychiatry 2013	Meta-analysis 43 individual studies 1983-2011	n = 20,293 Overall stroke No exclusions	Depression	Pooled prevalence	No	After any stroke, pooled prevalence of depression at any given time after diagnosis: 29%; in population-based studies: 22%; in hospital-based studies: 30%; in rehabilitation studies: 30%. Comment: Most individual studies had single time-point assessments during follow-up.
Hackett, et al.[123] Int J Stroke 2014	Meta-analysis 61 individual studies 2004-2013	n = 25,488 Overall stroke No exclusions	Depression	Pooled prevalence	No	After any stroke, pooled prevalence of depression at any given time up to five years after diagnosis: 31%. Comment: Most individual studies had single time-point assessments during follow-up.
Jørgensen, et al.[124] JAMA Psychiatry 2016	Cohort study Danish nationwide registries 2011-2011	n = 135,417 IS, ICH, UNS, TIA Prev. depression excluded	Depression	Event rates, Cox	Yes, GP	After any stroke, rate per 1,000 PY of depression within 2 years: 198 *vs.* 42 in GP; rate especially high within 3 months (602 *vs.* 66), HR = 8.99, declining to 1.9 after the first year.
Maymam, et al.[125] Neurology 2021	Cohort study Medicare claims, US. 2016-2017	n = 174,901 IS Prev. depression excluded	Depression	KM, Cox	Yes, MI	After IS, 1-y risk of depression was 16% *vs.* 10% in MI patients; HR = 1.6.
Pendlebury, et al.[126] Lancet Neurol 2009	Meta-analysis 27 individual studies 1950-2009	n = 7,511 Overall stroke Exclusions varied	Dementia	Pooled prevalence	No	Prevalence at 1 year after stroke differed markedly according to inclusion/exclusion criteria and study type: from 7% in population-based studies of first-ever stroke with prev. dementia excluded to 27% in hospital-based of any stroke without prev. dementia excluded.
Corraini, et al.[127] Stroke 2017	Cohort study Danish nationwide registries 1982-2013	n = 279,349 IS, ICH, SAH, UNS Prev. dementia excluded	Dementia	CIF, Cox	Yes, GP	The 10-y risk was 8% after IS, 9% after ICH, and 4% after SAH. The overall HR during 30 years of follow-up was 1.7 for IS, 2.7 for ICH, and 2.7 for SAH. In the first year of follow-up, the HRs were 2.3, 4.3, and 6.8, respectively.
Pendlebury, et al.[128] Lancet Neurol 2019	Cohort study Oxford Vascular Study 2002-2012	n = 1,982 IS, ICH, TIA Prev. dementia excluded	Dementia	KM, SMR	Yes, GP	After any stroke (IS, ICH), 1-y risk (KM) of dementia was 34% for severe stroke, 8% for minor stroke, and 5% for TIA. 51% of dementia cases within 5 y were diagnosed within 1 y. Compared with UK age- and sex-

						matched population, 1-y SMR of dementia was 47 for severe stroke, 6 for minor stroke, and 4 for TIA.
Koton, et al.[129] JAMA Neurol 2022	Cohort study The Atherosclerosis Risk in Communities Study 1987-2019	n = 1,378 IS Prev. dementia excluded	Dementia	KM, Cox	Yes, non-stroke	Risk of dementia (>1 year after stroke) was increased in stroke patients vs non-stroke: HR: 1.8 for minor/mild stroke, 3.5 for moderate/severe Comment: Single time-point assessments (mean 4.4 visits) during follow-up.
Ayerbe, et al.[130] Age Ageing 2014	Cohort study South London Stroke Register 1995-2009	n = 4,022 Overall stroke No exclusions	Anxiety	Prevalence, annual risk	No	After any stroke, prevalence of anxiety was 32-38% at any given time for up to 10 years. Annual risks were 17-24% the first 10 years. Comment: Single time-point assessments (annually) during follow-up.
Knapp, et al.[131] Int J Stroke 2020	Meta-analysis 97 individual studies 1984-2017	n = 26,262 Overall stroke No exclusions	Anxiety	Pooled prevalence	No	Pooled prevalence of anxiety within 1 m: 16%; 1-5 m: 21%; 6-12 m: 32%. Prevalence depended on measurement of anxiety: prevalences consistently higher when using rating scales *vs.* interviews.
Vyas, et al.[132] Stroke 2021	Meta-analysis 23 individual studies 2001-2020	n > 2 million Overall stroke No exclusions	Suicide or suicide attempt	Pooled risk ratio	Yes, non-stroke	Pooled risk ratio of suicide in stroke vs. non-stroke: 1.7.

Abbreviations. IS: ischemic stroke; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; UNS: unspecified stroke; TIA: transient ischemic attack; GP: general population; HR: hazard ratio; KM: Kaplan-Meier; MI: myocardial infarction; CIF: cumulative incidence functions; SMR: standardized morbidity ratio; NIHSS: National Institute of Health Stroke Scale; UK: United Kingdom.

2.5.3 Risk of mental disorders after stroke (Study III)

Neurologic and psychiatric sequelae of stroke have been recognized for decades,[133] and the issue has been discussed in several recent reviews.[134–137] Still, neurologic and psychiatric complications following stroke remain underdiagnosed and undertreated.[134] The United Kingdom Stroke Association recently listed mental and psychological complications following stroke as a research priority.[136]

Because the literature is copious, a focus is here placed on meta-analyses and major population-based cohort studies (Table 3). Most literature to date has focused on specific disorders, including depression,[121–125] dementia,[126–129] anxiety,[130,131] and suicide,[132] while other conditions such as substance abuse disorders have received less attention. Despite the abundance of available research on this topic, few individual studies were population-based of large size, *e.g.,* meta-analyses of depression,[122,123] dementia,[126] and anxiety[131] have each included a total of 20,000-25,000 patients. The study sizes have prevented a complete elucidation of risks according to stroke subtype and other patient characteristics. Importantly, only a few individual studies have included a general population comparison cohort.[124,127,128] For example, meta-analyses have almost unequivocally reported a post-stroke prevalence of depression of ~30% at any given time after stroke;[122,123] however, how post-stroke risks of depression and other mental disorders relate to risks expected in the general population remains less understood. In addition to a general population comparison cohort, a comparison patient cohort could aid in an enhanced understanding of the pathophysiology of post-stroke mental illness. The mechanism of post-stroke mental illness is not clearly understood, but it seems likely that both psychosocial and neurobiological components contribute.[60] A myocardial infarction comparison cohort could help disentangle the stroke-specific effect on mental illness from the effect of another acute medical event with a similar vascular risk factor profile; however, only one population-based study has used such a comparison cohort and that study only investigated post-stroke risks of depression.[125]

Thus, investigating post-stroke absolute and relative risks of a broad spectrum of mental disorders in a large population-based setting with relevant comparison cohorts is warranted.

Table 4. Studies relevant for Study IV.

Study IV:					
Author, journal, year	**Design, setting, period**	**Study population (size, subtype, age, employment)**	**Employment definition**	**Comparison cohort**	**Main findings, comments**
Glozier, et al.[138] Stroke 2008	Cohort study Auckland Regional Community Stroke Study, New Zealand 2002-2003	n = 210 Overall stroke (IS, ICH, SAH) No age restriction Employed at time of stroke diagnosis	Self-reported at 6 months	No	After any stroke, RTW probability at 6 m: 53% Psychiatric comorbidity strong predictor of RTW, OR: 0.42. Comment: Restricted to 6-m survivors
Busch, et al.[139] J Neurol Neurosurg Psychiatric 2009	Cohort study South London Stroke Register 1995-2004	n = 266 Overall stroke (IS, ICH, SAH) No age restriction Employed at time of stroke diagnosis	Self-reported at 1 year	No	After any stroke, RTW probability at 1 y: 37% Predictors of not RTW: older age, female sex, black ethnicity, diabetes, dependency, severity Comment: Restricted to 1-y survivors
Trygged, et al.[140] BMC Public Health 2011	Cohort study Swedish nationwide registries 1996-2000	n = 7,081 Overall stroke (IC, ICH, SAH, UNS) 40-59 y Employed at time of stroke diagnosis	Registry derived (minimum salary of €6,600)	No	After any stroke, RTW probability: 69% Predictors of RTW: higher education, higher income, male sex, IS/SAH,UNS vs. SAH, shorter hospital stay Comment: Time frame not reported.
Hannerz, et al.[141] BMJ Open 2011	Cohort study Danish nationwide registries 1996-2006	n = 19,903 Overall stroke (IC, ICH, SAH, UNS) 20-57 y Employed at time of stroke diagnosis	Registry derived (gainful occupation, *i.e.,* self-employed, assisting spouses, employees)	No	After any stroke, 2-y RTW probability: 62% Predictors of RTW: male sex, younger age, IS, not being self-employed, more skilled occupation
Hackett, et al.[142] PLoS One 2012	Cohort study Psychosocial Outcomes in Stroke study, Australia 2008-2010	n = 271 Overall stroke (IC, ICH, SAH, UNS) 18-64 y Employed at time of stroke diagnosis	Questionnaire derived at 6 months and 1 year	No	After any stroke, RTW probability after 1 y: 75% Predictors of RTW: male sex, younger age, independent in activities of daily living Comment: Restricted to 28-d survivors
Maaijwee, et al.[143] Neurology 2014	Cohort study FUTURE study, Netherlands 1980-2010	n = 694 IS, ICH, TIA 18-50 y No employment restriction	Registry derived (absence of disability payments)	Yes	At end of follow-up (mean 8 y), RTW probability was ~68% for IS, ~50% for ICH, and ~85% for TIA. Compared with Dutch general population, OR of not RTW was 2.3 for women and 3.2 for men. Predictors of severity, ICH
Westerlind, et al.[144] PLoS One 2017	Cohort study Sahlgrenska University Hospital, Sweden 2009-2010	n = 174 IS, ICH 18-63 y Employed at stroke diagnosis	Registry derived (absence of sickness payments)	No	After IS, 1-y RTW probability: ~50%; 2-y: 65% After ICH, 1-y RTW probability: ~37%; 2-y: 50% Predictors of RTW: severity
Glader, et al.[145] Acta Neurol Scand 2017	Cohort study Swedish nationwide registries 2008-2011	n = 2,539 IS, ICH, UNS 25-55 y Employed at time of stroke diagnosis	Self-reported at 1 year	No	After any stroke, RTW probability at 1 y: 74% Predictors of not RTW: low income, born outside Nordic countries, younger age Comment: Restricted to 1-y survivors

Aarnio, et al.[146] Neurology 2018	Cohort study Helsinki Young Stroke Registry 1994-2007	n = 769 IS 15-49 y Employed 1 year before stroke diagnosis	Registry derived (presence of pension payment)	No	After IS, 1-y RTW probability: 63%; 2-y: 58%; 5-y: 53% Predictors of not RTW: age, male sex, blue-collar worker, cardiovascular disease, smoking, diabetes, drinking, hypertension, severity
Tibæk, et al.[147] Front Neurol 2018	Cohort study Danish nationwide registries 1999-2015	n = 1,908 IS, ICH, SAH, UNS 19-30 y No employment restriction	Registry derived (self-support or absence of public transfer payments)	Yes	After IS/ICH/UNS: 1-y RTW probability: 82%; 2-y: 86%; 5-y: 91% After SAH: 1-y RTW probability: 86%; 2-y: 90%; 5-y: 94% Compared with Danish general population, OR of RTW was 0.20 for IS/ICH/UNS and 0.30 for SAH
Sen, et al.[148] Int J Stroke 2019	Cohort study South London Stroke Register 1995-2014	n = 940 Overall stroke (IS, ICH, SAH) No age restriction Employed at time of stroke diagnosis	Self-reported, annually	No	After any stroke, 1-y RTW probability: 18%; 5-y: 12% Predictors of RTW: functional independence, shorter hospital stay, younger age, non-manual occupation
Westerlind, et al.[149] Acta Neurol Scand 2020	Cohort study Swedish nationwide registries 2011	n = 1,695 Overall stroke (IS, ICH) 18-58 y Employed at stroke diagnosis	Registry derived (absence of sickness payments)	No	After any stroke, 1-y RTW probability: 72%; 2-y: 79% Predictors of RTW: male sex, younger age, IS, high education, lower stroke severity

Abbreviations. IS: ischemic stroke; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; UNS: unspecified stroke; RTW: return to work; OR: odds ratio.

2.5.4 Labor market participation and retirement after stroke (Study IV)

Among working-aged adults, returning to work after suffering a stroke is one of the most important aims of rehabilitation. Work resumption is important on a personal level for economic reasons, independence, and mental well-being.[150,151] For society, the economic burden of losing productive life years is substantial: A recent Danish study estimated that the cost attributable to loss of productivity due to illness after stroke exceeded €630 million per year in Denmark (~25% of the total annual stroke cost).[152] It remains important to quantify probabilities of work resumption after stroke according to subtype and patient characteristics. Detailed elucidation of this problem may enable a more targeted focus on patients with needs.

A 2018 systematic review, reporting on 29 individual studies, found that the median probability of work resumption was 41% at six months after stroke, 53% at one year, and 66% at two years.[153] However, the interpretability of the findings of this review and findings from individual studies[138–149] (Table 4) is challenged by a variety of reasons: studies generally had small study sizes (< 1,000 patients),[138,139,142–144,146,148] used a variety of outcome definitions (*e.g.,* self-reported or questionnaire information regarding employment),[138,139,142,145,148] did not disentangle the separate effects of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage,[138–146,148,149] and, importantly, did not contextualize findings to what is expected in the general population (*i.e.,* a general population comparison cohort).[138–142,144–146,148,149]

In one of only two studies that used a general population comparison cohort, the Dutch FUTURE study reported that, among 694 stroke patients identified between 1980 and 2010, the return to work probability after one year was ~68% after ischemic stroke and ~50% after intracerebral hemorrhage, corresponding to a 2.3-fold and 3.2-fold increased risk of unemployment for women and men, respectively, compared with the general population. In contrast, in the South London Stroke Register, among 1,695 patients with any stroke between 1995 and 2014, the return to work probability after one year was 18% and 12% after five years. Most previous studies assessed predictors of employment, *i.e.,* factors that predict work resumption within a stroke cohort.[138–146,148,149] Using a reference cohort, such as a general population cohort, to assess effect measure modification may be a better-suited analysis to identify patients of particular susceptibility specifically among stroke patients. However, this is an entirely unexplored area.

In addition to the limitations mentioned above, study settings have differed markedly between existing studies. Importantly, the Danish welfare system provides universal healthcare, unemployment benefits, and retirement benefits to all residents.[154] Such a system may result in higher probabilities of work resumption than in other countries. Thus, a detailed investigation of this issue in a Danish setting is warranted

3. Hypotheses and aims

Study I

Hypotheses: Overall stroke incidence and mortality, regardless of subtype, have decreased over time, but the incidence has increased in younger adults.

Aims: To examine nationwide trends in stroke incidence and mortality, separately by stroke subtype, in younger and older adults between 2005 and 2018 in Denmark, and to examine these trends according to smaller age groups, sex, severity, and etiology.

Study II

Hypotheses: Absolute stroke recurrence risks remain high, but risk estimates are lower than reported previously. Risks vary substantially according to patient characteristics. Stroke recurrence augments the risk of mortality.

Aims: 1) To examine absolute risks of stroke recurrence, separately by stroke subtype, and according to various patient subgroups; 2) to examine the impact of stroke recurrence on all-cause and stroke-specific mortality.

Study III

Hypotheses: Absolute and relative risks of mental disorders following stroke are higher compared with general population and myocardial infarction comparators. Risks vary substantially according to patient characteristics.

Aims: 1) To examine absolute and relative risks of a spectrum of mental disorders after stroke, separately by subtype, compared with matched general population and myocardial infarction comparators; 2) to explore whether these associations differ across various patient subgroups.

Study IV

Hypotheses: Stroke substantially impacts labor market participation, but more so after intracerebral and subarachnoid hemorrhage than ischemic stroke. Probabilities vary substantially according to patient characteristics.

Aims: 1) To examine labor market participation and retirement after stroke, separately by subtype, compared with matched general population comparators; 2) to explore whether these associations differ across various patient subgroups.

4. Methods

4

The following sections describe the methods used in Studies I-IV, and Table 5 provides a summary.

4.1. Setting

Denmark has a taxpayer-funded healthcare system that provides free access to health care for all residents.[154] In addition, Denmark provides public welfare benefits and other social services to all residents. A rich infrastructure of nationwide, population-based clinical and administrative registries has been created in the country.[154] All residents are assigned a civil registration number at birth or upon immigration, a unique 10-digit identification number that allows unambiguous linkage across registries at an individual level, as well as complete long-term follow-up.[155] Aside from being a key allowing deterministic linkage, the civil registration number holds information on the date of birth and sex for each person.

4.2. Data sources

The Danish Civil Registration System.[155] Initiated in 1968, this registry is updated daily concerning changes in vital status and migration for the entire Danish population, thereby ensuring virtually complete follow-up. From this registry, we used information on age and sex and vital status (*i.e.*, all-cause mortality) (Studies I-IV).

The Danish Stroke Registry.[16] This registry is a nationwide, clinical stroke registry initiated in 2003, but with complete coverage from May 2004. It was established as part of the Danish National Indicator Project, a nationwide quality improvement program started in 2000.[156] Reporting to this registry is mandatory for all Danish hospitals treating patients with acute stroke as defined by the World Health Organization. The registry includes patients with ischemic stroke, intracerebral hemorrhage, and unspecified stroke, but not patients with subarachnoid hemorrhage (this stroke subtype was included in 2017). The sensitivity and positive predictive value of the ischemic stroke and intracerebral hemorrhage diagnoses are estimated to exceed 90%.[157,158] Almost all (98% in our study) patients undergo computed tomography or magnetic resonance imaging scans during diagnostic workup. Several clinical variables are collected during admission, including the Scandinavian Stroke Scale, body mass index, smoking, alcohol intake, and in-hospital treatment such as thrombolysis and thrombectomy. We used this registry to define the study population (Studies I-IV), the outcomes (Study II), and various covariates, *e.g.*, stroke severity (Studies I-IV).

The Danish National Patient Registry.[159] This registry contains complete, nationwide information on hospital inpatient admissions since 1977 and hospital outpatient clinics and emergency contacts since 1995. Each hospital discharge or outpatient visit is recorded with one primary diagnosis

(required) and one or more secondary diagnoses (not required) coded according to the International Classification of Diseases, 8th Revision between 1977 and 1993 and 10th Revision thereafter. We used this registry to define the study population (Studies I-IV), the outcomes (Studies II and III), and various covariates, *e.g.,* comorbidity (Studies I-IV).

The Danish Psychiatric Central Research Registry.[160] This registry contains nationwide information on all psychiatric inpatient admissions in Denmark since 1970 and outpatient admissions since 1995. Diagnoses are coded according to the International Classification of Diseases, 8th Revision between 1977 and 1993 and 10th Revision thereafter. We used this registry to define the outcomes (Study III) and various covariates, *e.g.,* comorbidity (Studies I-IV).

Danish National Prescription Registry.[161] This registry contains data on all drug prescriptions redeemed in Danish community and outpatient pharmacies since 1 January 1995. For each redeemed prescription, the redemption date, the Anatomical Therapeutic Chemical Classification System code, type, and quantity of the drug are recorded. We used this registry to define the outcomes (Study III) and various covariates, *e.g.,* comorbidity (Studies I-IV).

The Danish Registry of Causes of Death.[162] This registry contains data on dates and causes of deaths in Denmark since 1943. It is currently complete until the end of 2016. Causes of deaths have been coded according to the International Classification of Diseases 10th Revision since 1994. Information on the cause of death includes the underlying cause of death, the immediate cause of death, contributory causes of death, and additional causes of death. We used this registry to define the outcomes (Studies II and III). Data were available until the end of 2016.

The Income Statistics Registry.[163] This registry, update yearly, contains data on income, entrepreneurial income, taxes, public transfer payments, public pensions, capital income, private pension contributions and payouts, home ownership, and fortunes since 1970. Data are primarily supplied by tax authorities. We used this registry to define the covariates (Studies III and IV).

The Integrated Database for Labor Market Research.[163] This registry, updated yearly, contains data on persons and workplaces on the individual level since 1981. Among other things, data are available regarding employment. We used this registry to define the covariates (Studies III and IV).

The Population Education Register.[163] This registry, updated yearly, contains data on the highest completed level of education and consists of data generated from administrative records of educational institutions and surveys since 1981. We used this registry to define the covariates (Studies III and IV).

The Danish Registry for Evaluation of Marginalization (DREAM).[164] This registry contains weekly information on residents receiving public transfer payments of any kind since 1991. If a person

receives any kind of transfer payment in a given week, the type of transfer payment is recorded with one of (at present) 134 codes. We used this registry to define the outcomes (Study IV).

StatBank Denmark.[165] This publicly available online resource, administered by Statistics Denmark, contains information on various aggregated population statistics. We used this registry to define the outcomes (Study I).

Table 5. Summary of methods for each study.

	Study I	**Study II**	**Study III**	**Study IV**
Design	Nationwide, population-based cohort study	Nationwide, population-based cohort study	Nationwide, population-based cohort study	Nationwide, population-based cohort study
Study period	January 2005–December 2018	May 2004–December 2018	May 2004–December 2018	May 2004–December 2018
Data sources	CRS, DSR, DNPR, DPCRR, NPR, StatBank Denmark	CRS, DSR, DNPR, DPCRR, NPR, DRCD	CRS, DSR, DNPR, DPCRR, NPR, DRCD, SDSR	CRS, DSR, DNPR, DPCRR, NPR, SDSR, DREAM
Study population	Patients (≥18 y) with first-time IS, ICH, or SAH (n = 123,243)	Patients (≥18 y) with first-time IS, ICH, or SAH (n = 128,331)	Patients (≥18 y) with first-time IS, ICH, or SAH (n = 92,968); matched individuals from the general population (n = 464,840); patients (≥18 y) with first-time MI (n = 92,968)	Patients (18-60 y) with first-time IS, ICH, or SAH (n = 22,907); matched individuals from the general population (n = 134,428)
Exclusion criteria	-	-	History of mental disorders	Non-participation in the labor market
Exposure	Calendar year	First-time stroke, recurrent stroke	First-time stroke	First-time stroke
Outcome	Stroke incidence, all-cause mortality	Recurrent stroke, all-cause mortality, stroke-specific mortality	Mood disorders, organic disorders, substance abuse disorders, neurotic disorders, attempted or completed suicide	Labor market participation, sick leave, disability pension, voluntary early retirement, state pension, all-cause mortality
Adjustment strategy	Direct standardization	Regression	Matching, regression	Matching, propensity score-weighting
Statistical analysis	Incidence rates, mortality risks, average annual percent change	Absolute risks and risk differences (Aalen-Johansen and Kaplan-Meier), subdistribution HRs (Fine-Gray), cause-specific HRs (Cox)	Absolute risks and risk differences (Aalen-Johansen), cause-specific HRs (stratified Cox)	Prevalences (log-linear Poisson), absolute probabilities (Aalen-Johansen)
Subgroup analyses	Stroke subtype, age, sex, stroke severity, stroke etiology	Stroke subtype, age, sex, stroke severity, body mass index, smoking, alcohol intake, Essen risk score, atrial	Stroke subtype, age, sex, stroke severity, calendar period, thrombolysis, income	Stroke subtype, age, sex, calendar period, labor market participation, income, education, somatic comorbidity, psychiatric

	Study I	Study II	Study III	Study IV
		fibrillation, calendar period		comorbidity, stroke severity, Essen risk score
Sensitivity analyses	1. Separate analyses of ischemic stroke and unspecified stroke 2. Altering the atrial fibrillation definition to those diagnosed during hospitalization or the following 180 days	1. Altering recurrence definition: only those >21 days after index event 2. Altering recurrence definition: only those of same subtype as index event 3. Kaplan-Meier estimator for absolute risks of recurrence 4. Multiple imputation with chained equations to handle missing data	1. Separate analysis among patients with prevalent mental disorders 2. Altering mood disorder definition: omitting prescriptions for antidepressants 3. Altering mood disorder definition: requiring only one antidepressant prescription 4. MICE to handle missing data 5. Omitting occupation and education as adjustment covariates to assess multicollinearity 6. Fine-Gray to account for competing risk of death	-

Abbreviations: CRS: Civil registration system; DSR: Danish Stroke Registry; DNPR: Danish National Patient Registry; DPCRR: Danish Psychiatric Central Research Registry; NPR: Danish National Prescription Registry; DRCD: Danish Registry of Causes of Death; SDSR: Statistics Denmark's social registries; DREAM: Danish Registry for Evaluation of Marginalization; IS: ischemic stroke; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; GP: general population; MI: myocardial infarction; HR: hazard ratio; MICE: multiple imputation with chained equations.

4.3. Study designs and populations

All four studies were nationwide, population-based cohort studies. Studies III and IV used a matched cohort design with general population (Studies III and IV) and myocardial infarction (Study III) comparison cohorts.

The study population in all four studies comprised patients with a first-time hospital-based diagnosis of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage, identified from the Danish Stroke Registry (ischemic stroke, intracerebral hemorrhage) and the Danish National Patient Registry (subarachnoid hemorrhage). For subarachnoid hemorrhage, only primary diagnoses were included to increase exposure specificity. To ensure capture of first-time events, we excluded patients with a previous diagnosis of stroke as registered in the Danish National Patient Registry going back to 1980. A patient could contribute to the analysis of only one stroke subtype. Because the positive predictive value of the subarachnoid hemorrhage diagnosis in the Danish National Patient Registry

is considered moderate (61%–67%),[166] we primarily focused the analyses and discussion on ischemic stroke and intracerebral hemorrhage. The study periods during which the study populations were identified were from 1 January 2005 to 31 December 2018 (Study I) and from 1 May 2004 to 31 December 2018 (Studies II-IV). Because Study I examined annual incidence rates, it was necessary to include years with complete data.

The general population comparison cohorts (Studies III and IV) were constructed using the Civil Registration System: we matched, with replacement (*i.e.,* one individual could act as a comparator for more than one stroke patient[167]), five persons from the general population to each stroke patient on birth year and sex, while requiring that comparators were alive on the stroke admission date of their matched patient (*i.e.,* the index date) and did not have a diagnosis of stroke before the index date. Similarly, the myocardial infarction comparison cohort (Study III) was constructed by identifying patients with a first-time diagnosis of myocardial infarction in the Patient Registry (using all available records) and matching stroke and myocardial infarction patients in a one-to-one ratio on age at diagnosis (five-year intervals), sex, and year of diagnosis (five-year intervals). For myocardial infarction comparators, the index date was set as the myocardial infarction admission date.

While no exclusion criteria were applied in Studies I and II, we excluded patients and comparators with a history of mental disorders in Study III and those not participating in the labor market four weeks before the index date in Study IV.

4.4. Exposures

In Study I, the exposure was calendar year, as the aim was to assess trends over time. In Studies II-IV, the exposure was first-time stroke (which also defined the study population), while recurrent stroke was a secondary exposure in Study II when examining the impact of recurrence on mortality.

4.5. Outcomes

4.5.1. Mortality (Studies I-IV)

All-cause mortality was a primary outcome in Study I, a secondary outcome in Study II, and a competing event in Studies III-IV. Information on the exact date of death was extracted from the Civil Registration System. We also examined cause-specific mortality in Studies II and III: in Study II, we considered stroke-specific mortality, while, in Study III, we considered completed suicide. We used both immediate and underlying causes of death. This information was obtained from the Registry of Causes of Death.

4.5.2. Recurrent stroke (Study II)

Recurrent stroke was the main outcome, as well as secondary exposure, in Study II. Following previous recommendations,[93] we defined recurrent stroke as any stroke subtype, occurring at least 24 hours after the onset of the first-time stroke, irrespective of vascular territory. As the Stroke Registry applies the World Health Organization stroke definition (*i.e.,* requiring at least 24 hours with stroke symptoms),[14] any subsequent entry in the Registry for a given patient was considered a recurrent event. We considered only the first recurrent event for each patient, *i.e.,* we ignored repeated recurrences. To capture subarachnoid hemorrhage recurrences, we used the Patient Registry, requiring at least one calendar day between the discharge date of the first-time event and the admission date of the recurrent event. We varied the recurrence definition in several sensitivity analyses (Table 5).

4.5.3. Mental disorders (Study III)

We considered a spectrum of common mental disorders as primary outcomes in Study III: mood disorders, organic brain disorders, substance abuse disorders, neurotic disorders, and attempted or completed suicide. We did not consider conditions most often diagnosed during childhood, adolescence, or early adulthood (*e.g.,* developmental disorders, intellectual disabilities). Mental disorders were identified from hospital-based diagnoses (any available records) registered in the Psychiatric Central Research Registry or the Patient Registry. Psychiatric diagnoses are given by hospital psychiatrists, reflecting routine secondary care. However, mild disease is often treated by general practitioners in primary care and thereby not captured by the registries. To circumvent this issue, specifically to capture mild depression (a mood disorder), we defined mood disorders as a hospital-based diagnosis or at least two redeemed prescriptions for an antidepressant, as recorded in the Prescription Registry. Attempted or completed suicide was defined based on hospital-based diagnoses or cause of death records in the Registry of Causes of Death.

4.5.4. Labor market participation (Study IV)

The primary outcome in Study IV was labor market participation, determined using data in the DREAM registry: patients and comparators were grouped, weekly, into seven mutually exclusive categories according to the type of transfer payment received: 1) labor market participation (*i.e.,* employed or receiving state educational grants, parental leave payments, or unemployment payments unrelated to health), 2) sick leave (*i.e.,* receipt of sick leave payments or other unemployment payments related to health, 3) disability pension, 4) voluntary early retirement, 5) state pension (received at retirement age), 6) death, or 7) emigration. If a person had no entry in the registry for a given week, he/she was considered to be self-supporting and participating in the labor market. In Denmark, sick leave payments are given for a limited period to persons unable to work

due to illness. Retirement entails several different pension schemes: disability pensions, available to individuals of any age with permanently reduced work capacity, voluntary early retirement, available in various forms for certain individuals at least 50 years of age, and state pension, available to individuals upon reaching the public retirement age (*i.e.,* 65–69 years, depending on birth year).

In an auxiliary time-to-event analysis, we defined labor market participation as four consecutive weeks with the classification "labor market participation." To capture the "return to labor market", this analysis was restricted to patients receiving sick leave payments within three weeks after stroke.

4.6. Covariates

In addition to the variables described above (study population, exposures, and outcomes), we compiled information on several additional covariates used to 1) describe cohorts, 2) examine risks across various subgroups and examine effect measure modification, and 3) control for imbalances between cohorts. Table 6 provides an overview of the use of covariates in Studies I-IV, focusing on those used for subgroup analyses and adjustment. While numerous covariates are presented, we define here two important covariates: the Scandinavian Stroke Scale, which measures stroke severity, is a validated neurological stroke scale with scores ranging from 0 (worst) to 58 (best) and is evaluated by the attending physician in the early admission phase.[168] The scale is conceptually similar to the more widely used National Institutes of Health Stroke Scale.[169] The Essen risk score is a risk stratification score that predicts the 1-year risk of recurrent ischemic stroke and combined cardiovascular events on a 9-point scale (1 point for age 65–75 years, 2 points for age >75 years, and 1 point for the occurrence of each of the following: hypertension, diabetes, myocardial infarction, other cardiovascular diseases, peripheral artery disease, smoking, transient ischemic attack).[118] Although the scoring system is not currently used in routine clinical practice in Denmark, its components are part of the combined risk assessment after a stroke undertaken by the treating clinician, and it is therefore easy to derive the combined score for each patient.

Table 6. Overview of covariates included in the studies.

	Study I	Study II	Study III	Study IV	Data source
Covariates used for subgroup analyses					
Age	✓	✓	✓	✓	CRS
Sex	✓	✓	✓	✓	CRS
Calendar year or period	✓	✓	✓	✓	DSR, DNPR
Stroke severity (Scandinavian Stroke Scale)	✓	✓	✓	✓	DSR
Stroke etiology	✓				DNPR, NPR
Body mass index		✓			DSR
Smoking		✓			DSR
Alcohol intake		✓			DSR
Essen risk score		✓		✓	DSR, DNPR, NPR
Atrial fibrillation		✓			DNPR
Calendar period		✓	✓	✓	DSR, DNPR
Thrombolysis			✓		DSR
Income			✓		SDSR
Education				✓	SDSR
Labor market participation				✓	DREAM
Somatic comorbidity*				✓	DNPR, NPR
Psychiatric comorbidity†				✓	DPCRR, DNPR, NPR
Covariates used for adjustment					
Age	✓	✓	✓	✓	CRS
Sex		✓	✓	✓	CRS
Calendar period		✓	✓	✓	DSR, DNPR
Income			✓	✓	SDSR
Occupation			✓		SDSR
Education			✓	✓	SDSR
Cardiovascular comorbidity‡			✓		DNPR, NPR
Non-cardiovascular comorbidity§			✓		DNPR, DPCRR, NPR
Somatic comorbidity				✓	DNPR, NPR
Psychiatric comorbidity				✓	DNPR, DPCRR, NPR

Abbreviations: CRS: Civil registration system; DSR: Danish Stroke Registry; DNPR: Danish National Patient Registry; DPCRR: Danish Psychiatric Central Research Registry; NPR: Danish National Prescription Registry; SDSR: Statistics Denmark's social registries; DREAM: Danish Registry for Evaluation of Marginalization

*Somatic comorbidities included: hypertension, dyslipidemia, ischemic heart disease, atrial fibrillation or flutter, valvular heart disease, heart failure, peripheral artery disease, venous thromboembolism, diabetes, thyroid disorder, gout, chronic pulmonary disease, allergy, ulcer/chronic gastritis, chronic liver disease, inflammatory bowel disease, diverticular disease of intestine, chronic kidney disease, prostate disorders, connective tissue disorders, osteoporosis, painful conditions, HIV/AIDS, anemias, cancers, vision problems, hearing problems, migraine, epilepsy, Parkinson disease, multiple sclerosis, and neuropathies

†Psychiatric comorbidities included: organic disorders, substance abuse, schizophrenia, mood disorders, neurotic disorders, eating disorders, personality disorders, intellectual disabilities, developmental disorders, and behavioral disorders

‡Cardiovascular comorbidities included: ischemic heart disease, atrial fibrillation/flutter, diabetes, heart failure, peripheral artery disease, valvular heart disease, hypertension, and endocarditis

§Non-cardiovascular comorbidities included: chronic pulmonary disease, cancer, thyroid disease, chronic kidney disease, and chronic liver disease

4.7. Statistical analyses

Data management, analyses, and visualizations for all studies were done in R, version 4.1.3 (The R Foundation for Statistical Computing, www.R-project.org). In Study IV, SAS, version 9.4 (SAS Institute) was also used.

In all studies, the covariates applicable to each study were tabulated across cohorts using counts and percentages for categorical variables and medians and interquartile ranges for continuous variables.

4.7.1. Trends in incidence rates and mortality risks (Study I)

The primary outcome in Study I was the annual incidence rate of first-time stroke as well as the 30-day and 1-year mortality risks, computed for each year in the study period, to assess changes over time. The incidence rate was computed as the number of first-time strokes divided by the underlying Danish midyear population. The used denominator functions as an approximation of follow-up time in person-years. Thus, following a cohort initially stroke-free for one year would yield approximately the same rate as found in our study. Similarly, mortality risks were computed as the number of deaths within 30 days or one year divided by the total number of first-time strokes. To account for variations in the age distribution over time, we age-standardized rates and mortality risks using direct standardization with the 2018 Danish population size as the standard.[170] Confidence intervals (CIs) around age-standardized estimates were computed with a Poisson approximation, while the delta method was used for age-specific estimates.[170,171]

To evaluate trends over time, we calculated the annual percent change, for which positive values indicate an upward trend and negative values a downward trend.[170] The annual percent change is derived from a transformation of the slope coefficient upon regressing the logarithm of the incidence rates or mortality risks on time assuming a linear slope.[170] Because the annual percent change implies a constant trend over the entire study period, which may not apply in all analyses, we also used joinpoint regression to compute the average annual percent change (AAPC), a weighted summary measure that incorporates segments in the data with distinct trends: if one breakpoint (sometimes referred to as joinpoint) exists, an annual percent change is derived for each of the two segments; the AAPC then represents a summary measure of the two annual percent changes, weighted according to the length of each segment.[172] If no breakpoints exist, the AAPC simply reduces to the annual percent change for the entire interval.[172] Permutation tests were used to determine the number of breakpoints best fitting the data.[173] CIs were based on a normal approximation.[172] To calculate annual percent changes and AAPCs, we used Joinpoint, a freely available software, developed by the United States National Cancer Institute.[174]

4.7.2. Cumulative incidence and competing risks (Studies II-IV)

To calculate the cumulative incidence (*i.e.,* the absolute risk) of outcomes in Studies II-IV, we used the Kaplan-Meier[175] and Aalen-Johansen[176] estimators. Both methods deal with time-to-event data (*i.e.,* survival data), for which censoring of follow-up time is possible. For example, if an individual emigrates during follow-up, his/her follow-up time is censored and the individual is no longer under

observation. A central assumption of censoring is that individuals remaining under observation have the same future risk of the event of interest as do censored individuals, *i.e.,* censoring is random or non-informative.[117] While that is probably a valid assumption in the case of emigration, it is not in the case of death: when an individual dies (for whatever reason), he/she is "prevented" from experiencing the event of interest when the event is not all-cause mortality. In other words, death is a competing event as it prevents the future occurrence of the event of interest. And because individuals dying do not have the same future risk of the event of interest as those still under observation, the non-informative assumption is violated. Crucially, the Kaplan-Meier estimator assumes that competing risks do not exist (*e.g.,* individuals are censored when dying, even when the event of interest is a non-fatal event). As a result, estimates from the Kaplan-Meier estimator pertain to a population in which individuals cannot die, a setting of questionable clinical relevance.[117] Further, it is now well-known that the Kaplan-Meier estimator overestimates the absolute risk in the presence of a competing risk, particularly if the magnitude of the competing risk is large.[114–117] Instead, the Aalen-Johansen estimator (or the cumulative incidence function) takes into account any competing events. For all practical purposes, the Aalen-Johansen estimator denotes the probability of experiencing the event of interest before a given time, *t*, and before the occurrence of the competing event (*e.g.,* death). Thus, when estimating absolute risks in Studies II-IV, we used the Kaplan-Meier estimator when the outcome was all-cause mortality and the Aalen-Johansen estimator when the outcome was cause-specific mortality or non-fatal events. The *mets* and *prodlim* packages in R were used.

4.7.3. Cox and Fine-Gray regression (Studies II and III)

While the Kaplan-Meier and Aalen-Johansen estimators provide measures of the absolute risk, Cox and Fine-Gray regression models provide measures of the relative rate, specifically hazard ratios (HR) and subdistribution HRs (SHRs).[177,178] In the absence of competing risks, a direct one-to-one correspondence exists between the Kaplan-Meier estimate and the HR (*i.e.,* between the survival and hazard functions); conversely, in the presence of competing risks, a one-to-one correspondence exists between the Aalen-Johansen estimate and the SHR.[117] Both models have the desirable ability to incorporate, and control for, additional covariates. A discrepancy in the literature exists regarding which model to employ when the study aim is etiological (*i.e.,* implying a causal question): some investigators advocate for the Cox model, even in the presence of competing risks (thereby yielding cause-specific HRs),[115,116] while other investigators argue that the Cox model should not be used for causal purposes due to its in-built selection bias.[179] When the study aim is descriptive or predictive, the Fine-Gray model is generally preferred, although the SHR has a challenging interpretation.[115,116] With these considerations in mind, the Fine-Gray was used in Study II as the study aim was primarily descriptive. In Study III, we attempted to isolate the stroke-specific effect on mental disorders using

both general population and myocardial infarction comparison cohorts. Thus, following recommendations,[115,116] we used the Cox model in primary analyses (although we also used the Fine-Gray model in sensitivity analyses). A challenge with this approach in the presence of competing risks is that a discrepancy between the Aalen-Johansen estimator (*i.e.,* the absolute risk) and the cause-specific HR (*i.e.,* the relative rate) may occur due to the loss of the one-to-one correspondence between the two quantities, especially if the magnitude of the competing risk is large.[114] For example, if a given covariate (*e.g.,* stroke severity) is strongly associated with mortality, it can appear protective on the relative scale (where the competing risk is unaccounted for) but harmful on the absolute scale (where the competing risk is accounted for). To mitigate this problem, we focused on 1-year risks, as the magnitude of the discrepancy grew with increasing follow-up time. Notwithstanding, in both Studies II and III, we prioritized the presentation and discussion of the absolute risk estimate (with competing risk adjustment), as this measure may be preferable for public health decisions. Model check of the Fine-Gray model was performed using cumulative sums of residuals and that of the Cox model was performed using log(-log[survival probability]) curves. We used the *survival* and *mets* packages in R.

4.7.4. Log-linear Poisson regression (Study IV)

In Study IV, we obtained exact prevalence estimates of the seven mutually exclusive categories of labor market participation (defined in Section 4.5.4) at four distinct time points for both stroke patients and comparators. Unlike in a time-to-event analysis, this approach allowed study members to move in and out of each category, which was deemed favorable when studying a dynamic concept such as labor market participation. To compare cohorts, we calculated prevalence differences and prevalence ratios using a log-linear Poisson model, with accompanying likelihood ratio-based CIs. To account for baseline differences between cohorts when estimating prevalence differences and ratios, propensity score (PS) weighting was employed (Section 4.7.5). The *PROC GENMOD* procedure in SAS was used for this analysis.

4.7.5. Propensity score weighting (Study IV)

In Study IV, we opted to use PS weighting to account for baseline differences between stroke patients and general population comparators due to the easier estimation of adjusted absolute probabilities using this approach rather than conventional regression methods (*e.g.,* Cox or Fine-Gray). Using a multivariable logistic regression model, we estimated the PS as the predicted probability of being diagnosed with stroke conditional on the covariates applicable to Study IV.[180] Stroke patients were then assigned a weight of one and comparators a weight equal to the odds of the PS (PS/1-PS).[180] This weighting approach, often termed standardized mortality ratio weighting, re-weights the comparator cohort so that its covariate distribution resembles that of the stroke cohort. The

estimand using this approach is the treatment effect in the treated population (*i.e.,* stroke patients). After the generation of weights, any model can subsequently be run (*e.g.,* the log-linear Poisson model in Study IV) with the weights included, thereby controlling for the measured covariates.[180] In subgroup analyses, the PS weights were re-calculated within each stratum, as recommended.[181] The *WeightIt* package in R was used.

4.7.6. Missing data (Studies II-IV)

Data were missing in varying degrees on variables from the Stroke Registry (*i.e.,* severity, body mass index, smoking, and alcohol intake) and data regarding socioeconomic position (*i.e.,* income, occupation, and education). In Studies II and III, we conducted sensitivity analyses using multiple imputation with chained equations to examine the potential impact of missing data.[182] In the imputation models, the covariates (including those with missing data), the outcome indicator, and the Nelson-Aalen cumulative hazard were included.[182] In Study II, 50 imputed datasets were created, while 10 were created in Study III. In both studies, we assumed that data were missing at random.[182] We used the *mice* package in R to conduct these analyses. In Study IV, in which propensity score analyses were conducted, we handled missing data on income and education in the propensity score estimation using a missing data indicator variable.[183]

4.8. Ethical considerations

In Denmark, ethical approval is not required for registry-based studies. All studies were registered with the Danish Data Protection Agency at Aarhus University (record no. 2016-051-000001-1502) and approved by the Danish Clinical Quality Program – National Clinical Registries. Data were pseudo-anonymized and securely stored on remote servers, hosted by Statistics Denmark.

5. Results

Sections 5.1-5.4 outline the main findings from Studies I-IV. Appendices I-IV provide detailed descriptions of the results for each study.

5.1. Trends in incidence and mortality of stroke (Study I)

Among younger adults (18-49 years), the age-standardized incidence rate per 100,000 person-years remained approximately stable between 2005 and 2018 for both ischemic stroke (from 20.8 in 2005 to 21.9 in 2018, AAPC: -0.6 [95% CI: -1.5, 0.3]) and intracerebral hemorrhage (from 2.2 in 2005 to 2.5 in 2018, AAPC: 0.6 [95% CI: -1.0, 2.3]), while a decreasing trend was observed for subarachnoid hemorrhage (from 9.9 in 2005 to 5.5 in 2018; AAPC: -4.6 [95% CI: -5.8, -3.3]). In smaller age groups, a slightly increasing trend was observed for ischemic stroke among those aged 18-29 years (AAPC: 1.7 [95% CI: -0.7, 4.1]) (Figure 1).

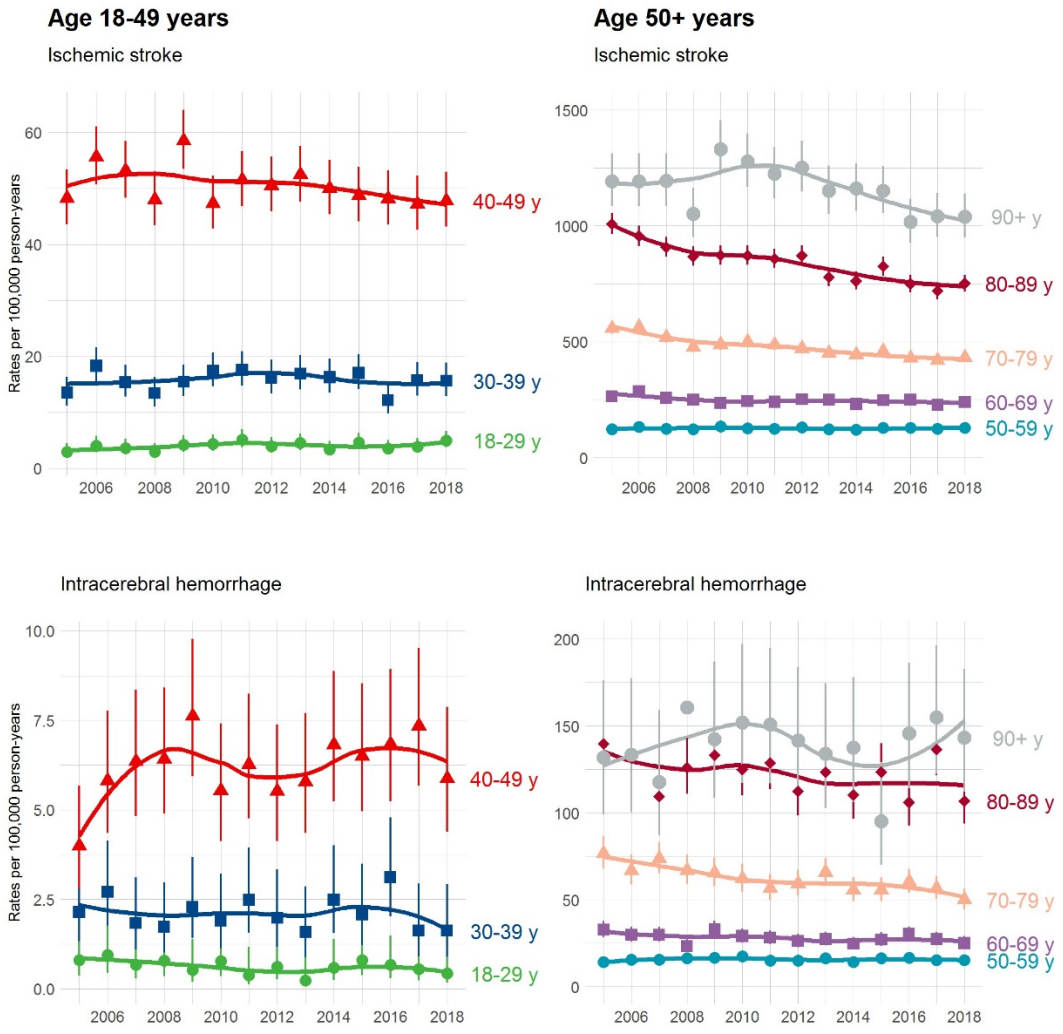

Figure 1. Age-specific incidence rates of a first-time ischemic stroke or intracerebral hemorrhage in younger and older adults, 2005 to 2018. Smoothed lines are made with a Loess smoother. From Skajaa, *et al.*[181]

Among older adults (≥50 years), the rate of ischemic stroke and intracerebral hemorrhage decreased over time, but most noticeably among adults older than 70 years. In fact, the trend was stable among those aged 50–59 years. For subarachnoid hemorrhage, the trend also declined, but less so than among younger adults (Figure 2).

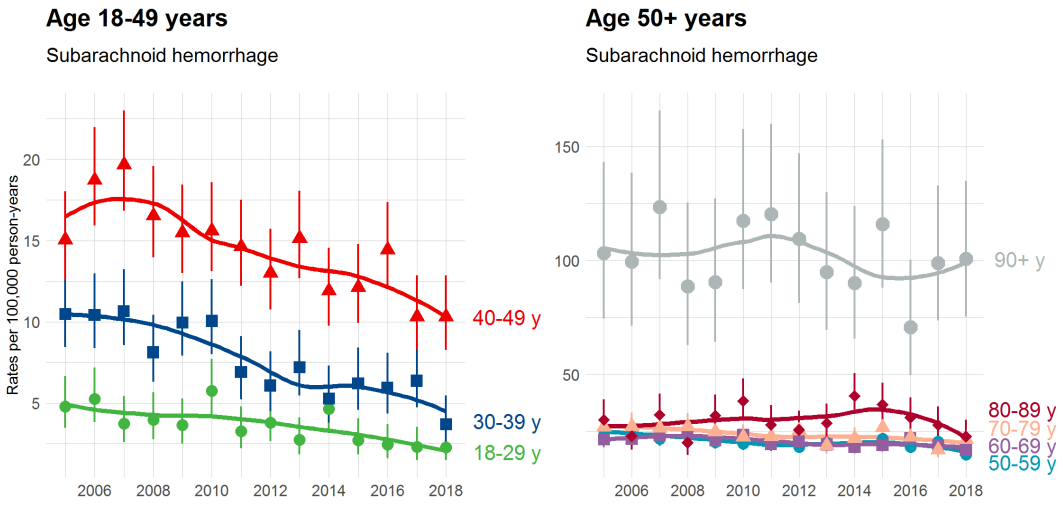

Figure 2. Age-specific incidence rates of a first-time subarachnoid hemorrhage in younger and older adults, 2005 to 2018. Smoothed lines are made with a Loess smoother. From Skajaa, *et al.*[181]

The rate was higher in men than in women (except among those 18-29 years), but the trends were broadly similar between sexes. The rate of mild stroke (ischemic stroke and intracerebral hemorrhage) increased over time in both younger and older adults, while that of severe stroke declined.

The 30-day mortality risk declined over time for all three subtypes and regardless of age. For example, the 30-day mortality after ischemic stroke declined from 2.3% in 2005 to 0.1% in 2018 (AAPC: -6.5 [95% CI: -12.5, -0.1]) among younger adults and from 8.2% to 6.0% (AAPC: -2.4 [95% CI: -3.4, -1.3]) among older adults. The overall declines were driven by declines in mortality after severe stroke. Similar trends were observed for 1-year mortality.

5.2. Risk of stroke recurrence and impact of recurrence on mortality (Study II)

The 1-, 5-, and 10-year risks of recurrence, after considering death a competing event, were 4%, 10%, and 13% after first-time ischemic stroke; 3%, 8%, and 12% after first-time intracerebral hemorrhage, and 15%, 18%, and 20% after first-time subarachnoid hemorrhage. The vast majority of recurrences after first-time ischemic stroke were ischemic strokes (89%), while only 47% of recurrences after first-time intracerebral hemorrhage were intracerebral hemorrhages (Table 7).

Table 7. Counts of recurrent strokes following first-time strokes according to stroke subtype.

First-time stroke, N	Recurrent stroke, N			Total
	Ischemic stroke	Intracerebral hemorrhage	Subarachnoid hemorrhage	
Ischemic stroke, N = 105,397	9,519 (89%)	918 (9%)	213 (2%)	10,650
Intracerebral hemorrhage, N = 13,387	534 (47%)	531 (47%)	68 (6%)	1,133
Subarachnoid hemorrhage, N = 9,584	213 (12%)	93 (5%)	1,459 (83%)	1,765

The risk differed in patient subgroups: For example, after first-time ischemic stroke, the risk increased with age, was higher for men than for women, was higher after mild than severe stroke, and increased sequentially with increasing Essen risk score (Figure 3). After first-time intracerebral hemorrhage or subarachnoid hemorrhage, the risk was similar between sexes and did not increase with Essen risk score. A decreasing recurrence risk over time was observed after first-time ischemic stroke (2016-2018 *vs.* 2004-2006, SHR: 0.75 [95% CI: 0.69, 0.80]), intracerebral hemorrhage (SHR: 0.59 [95% CI: 0.45-0.72]), but not subarachnoid hemorrhage (SHR: 1.30 [95% CI: 1.11-1.49]).

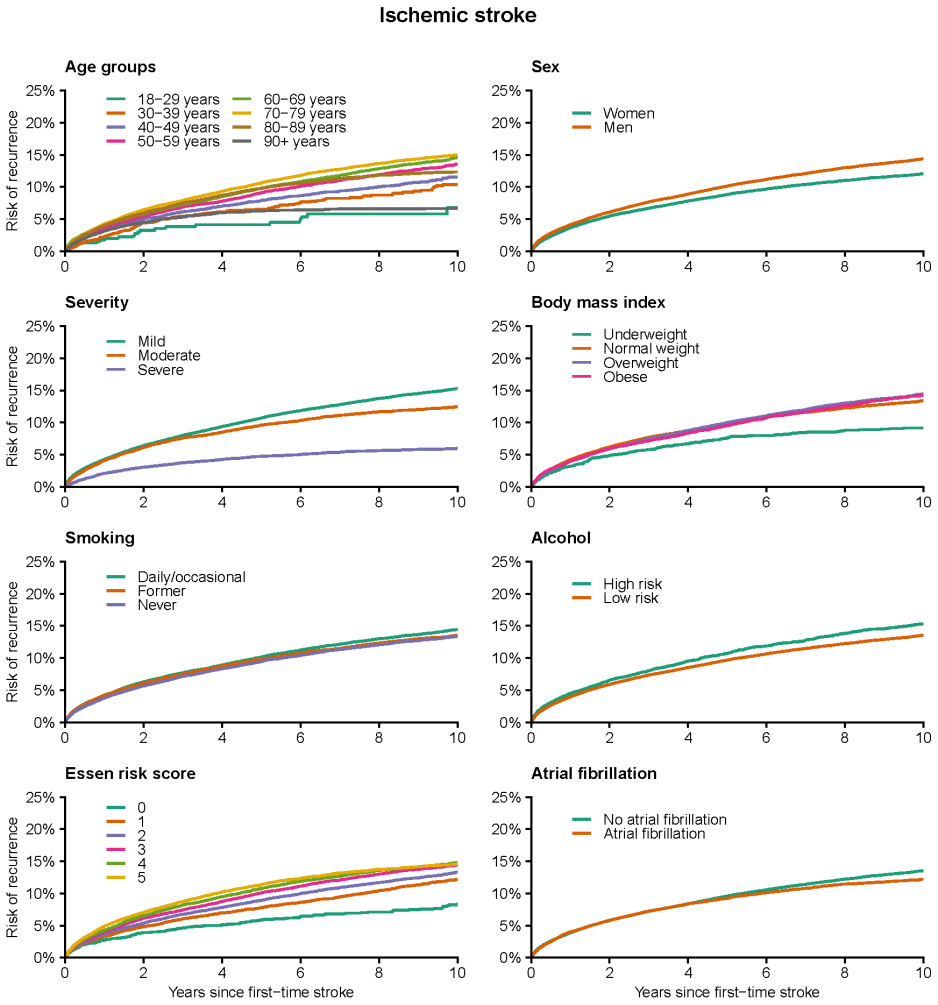

Figure 3. Risk of recurrence following ischemic stroke according to age groups, sex, severity, body mass index, smoking, alcohol, Essen risk score, and atrial fibrillation. From Skajaa, *et al.*[182]

The recurrence risk depended on the recurrence definition: when considering recurrent events of only the same subtype as the first-time event, risks were similar for ischemic stroke but lower for intracerebral hemorrhage. Using a Kaplan-Meier estimator, risks were markedly higher; for example, the 10-year risk after ischemic stroke increased from 13% in the main analysis to 19%.

Following ischemic stroke, the 10-year all-cause mortality risk was 56% after the first-time event and 70% after a recurrent event (HR comparing recurrent stroke with first-time stroke, adjusted for age, sex, and calendar period: 1.43 [95% CI: 1.39, 1.49]). In contrast, following intracerebral hemorrhage, 10-year all-cause mortality risks were 70% and 75% (HR: 0.88 [95% CI: 0.81, 0.96]); following subarachnoid hemorrhage, 10-year risks were 41% and 32% (HR: 0.57 [95% CI: 0.52, 0.63]). A similar pattern was observed for stroke-specific mortality.

5.3. Risk of mental disorders after stroke (Study III)

Risks of mental disorders were higher following stroke compared with general population and, albeit to a lesser degree, myocardial infarction comparators, particularly in the first year of follow-up. Following ischemic stroke, the 1-year risks, after considering death a competing event, were 15% for mood disorders, 2% for organic brain disorders, 1% for substance abuse disorders, 1% for neurotic disorders, 0% for attempted or completed suicide (Figure 4). The 1-year risk differences compared with general population comparators were 7.3% (95% CI: 7.0, 7.5) for mood disorders, 1.4% (95% CI: 1.3, 1.5) for organic brain disorders, 0.8% (95% CI: 0.7, 0.8) for substance abuse disorders, 0.5% (95% CI: 0.4, 0.5) for neurotic disorders, and near null for attempted or completed suicide. Adjusted HRs ranged from a 2- to 4-fold increased hazard in the first year of follow-up. Compared with myocardial infarction comparators, 1-year risk differences were 4.9% (95% CI: 4.6, 5.3) for mood disorders, 1.0% (95% CI: 0.8, 1.1) for organic brain disorders, 0.1% (95% CI: 0.0, 0.2) for substance abuse disorders, -0.2% (95% CI: -0.2, -0.1) for neurotic disorders, and near null for attempted or completed suicide. Adjusted HRs ranged from a 1.1 to 1.8-fold increased hazard in the first year of follow-up. A similar pattern was observed for intracerebral and subarachnoid hemorrhage.

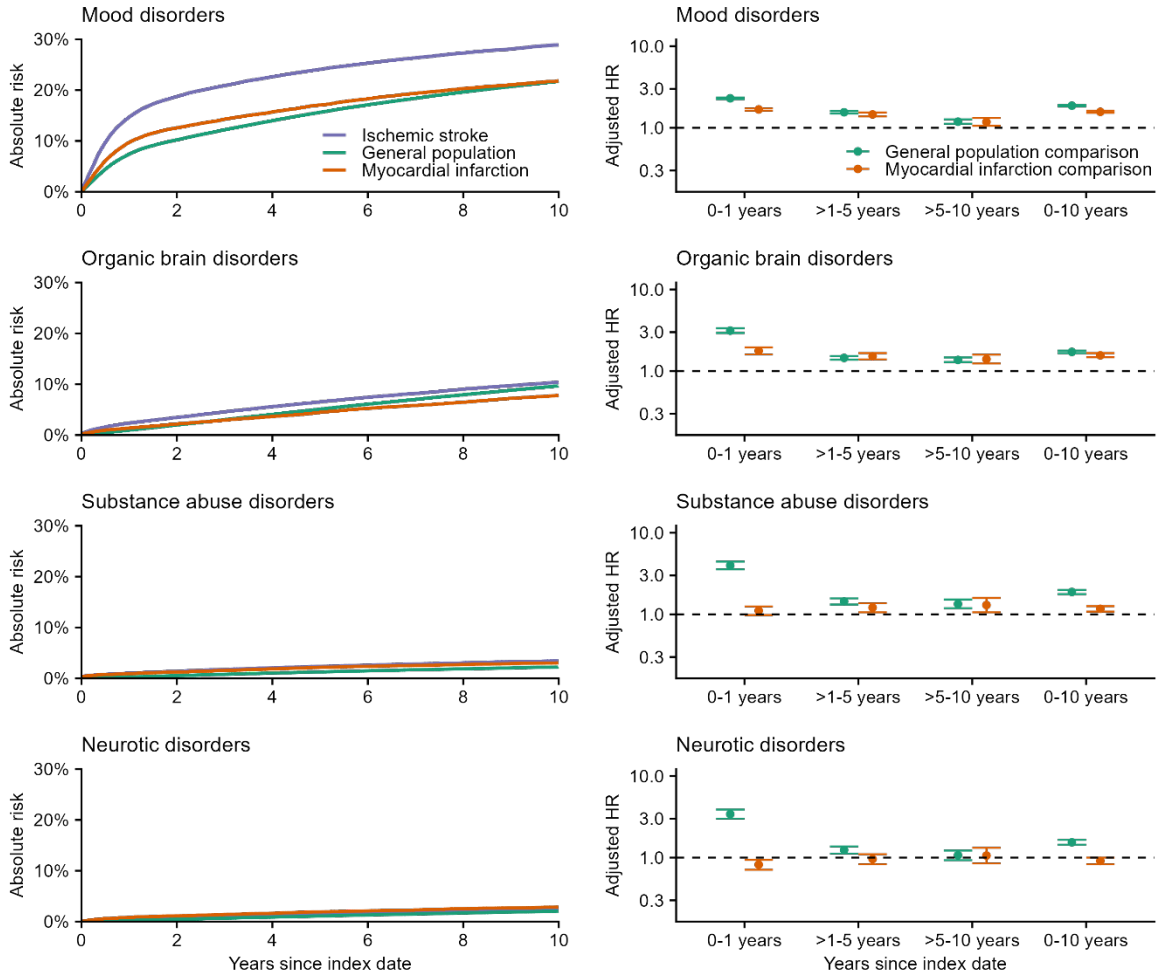

Figure 4. Absolute risks and adjusted hazard ratios of mood disorders, organic brain disorders, substance abuse disorders, and neurotic disorders for ischemic stroke compared with age, sex, and calendar year matched general population and myocardial infarction comparison cohorts. From Skajaa, *et al.*[183]

We observed some effect measure modification: the associations for mood disorder, the most common outcome, were more pronounced in men *vs.* women, after severe stroke *vs.* mild or moderate stroke, and for strokes diagnosed during 2004-2006 *vs.* 2016-2018. These effect measure modifications were largely consistent on both the absolute and relative scales.

5.4. Labor market participation and retirement after stroke (Study IV)

Expectedly, stroke had a profound impact on labor market participation among working-age adults (18-60 years). Most patients (62% of those with ischemic stroke, 69% of those with intracerebral hemorrhage, and 52% of those with subarachnoid hemorrhage) went on sick leave within three weeks following their diagnosis (Figure 5).

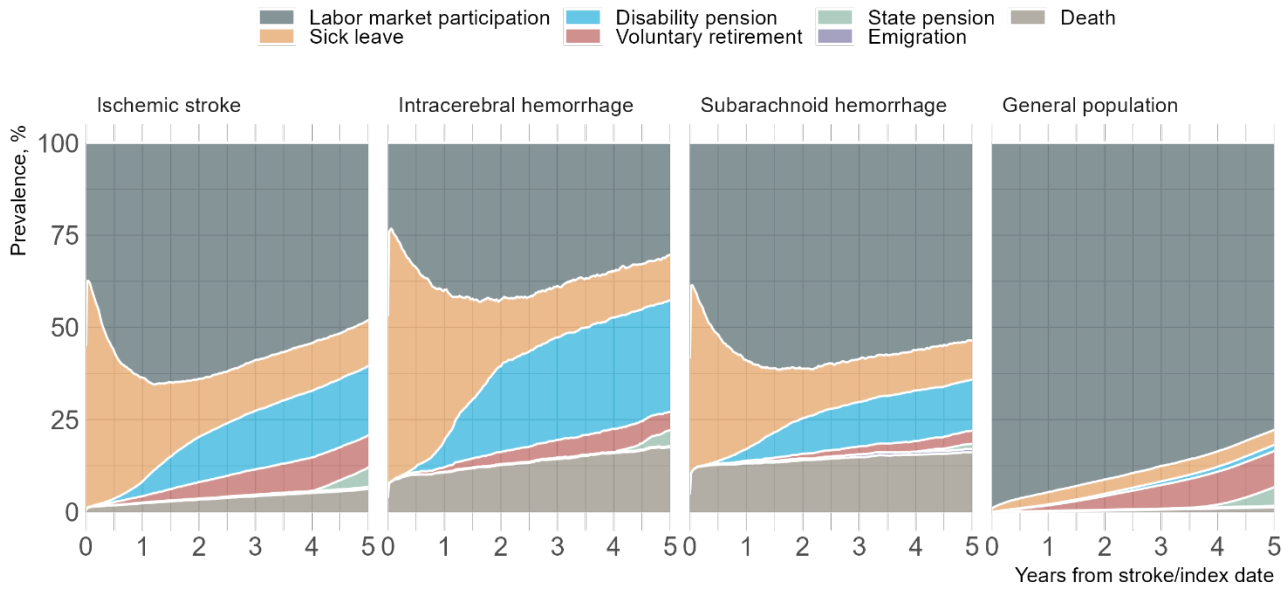

Figure 5. Weekly prevalences of labor market participation, sick leave, receipt of a disability pension, voluntary early retirement, receipt of a state pension, and death among patients with ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage and among age-, sex-, and calendar-year-matched individuals from the general population. From Skajaa, *et al.*[184]

The prevalence of labor market participation among patients with ischemic stroke was, at six months, 57% *vs*. 96% among matched individuals from the general population and, at two years, 64% *vs*. 91%. In PS-weighted analyses, accounting for comorbidity and socioeconomic differences between stroke patients and general population comparators, estimates changed only marginally. Patients with intracerebral hemorrhage had higher prevalences of sick leave and receipt of a disability pension and thus a lower prevalence of labor market participation, while prevalences for patients with subarachnoid hemorrhage were similar in magnitude to those for patients with ischemic stroke. In the auxiliary time-to-event analysis, the cumulative probability of return to labor market participation was, for ischemic stroke, 35% at 6 months and 71% at two years, after considering death and retirement as competing events.

In subgroup analyses, labor market participation was higher for younger *vs*. older patients, for patients with a stroke diagnosed during 2016-2018 *vs*. 2004-2006, for patients with high educational level vs. with educational level, and for patients with mild stroke *vs*. moderate or severe stroke.

6. Discussion

6.1. Summary of main findings

In contrast to incidence rates of first-time stroke in older adults, rates in younger adults (18-49 years) remained approximately constant between 2005 and 2018 in Denmark. Rates of mild stroke increased over time while rates of severe stroke decreased. Post-stroke mortality decreased continuously over time, regardless of age.

In a Danish, routine clinical setting, absolute risks of stroke recurrence were high, albeit lower than previously reported. Recurrence risks differed substantially according to patient characteristics, *e.g.,* according to Essen risk scores, an easy-to-compute clinical risk score. Mortality was higher after recurrent than first-time ischemic stroke, but not hemorrhagic strokes.

Risks of a range of mental disorders, but most prominently mood and organic brain disorders, were higher after stroke compared with the Danish general population and myocardial infarction patients. Risks were higher after intracerebral hemorrhage than ischemic stroke and after severe than mild stroke.

Among working-age adults (18-60 years), the majority of stroke patients went on sick leave immediately following diagnosis, but more than half of patients with ischemic stroke had returned to the labor market at six months following diagnosis; compared with the Danish general population, the probability of labor market participation was, at six months, approximately 40% reduced. The probability of labor market participation was lowest after intracerebral hemorrhage.

6.2. Comparison to the existing literature

6.2.1 Trends in incidence and mortality of stroke (Study I)

The main finding of a stationary incidence trend among younger adults (18-49 years) contradicts most previous reports, which found increasing trends.[2–10] However, a few European studies found decreasing or stationary trends, thus aligning with our findings.[82,83,85,88] The reasons for the discrepant trends are not entirely clear, but could relate to several factors: first, it is possible that changes in diagnostic practice, *e.g.,* increased use of brain imaging, such as diffusion-weighted imaging, have led to increased detection of mild stroke.[184,185] Along the same lines, diagnostic classifications may have changed in light of a new stroke definition (Section 2.1) that incorporates silent infarctions,[15] as well as a diagnostic drift between transient ischemic attack and stroke.[186] Strokes are, on average, milder in younger than older patients; thus, it is possible that rates in younger adults were overestimated in some settings and study periods where stroke ascertainment clearly improved. In this regard, our study extended previous research by investigating trends according to stroke severity. While the rate of mild stroke appeared to increase over time, it did so in

both younger and older adults. The rate increase of mild stroke in our study is likely explained by improvement over time in awareness of stroke symptoms in the general population, prehospital response leading to faster diagnostics, and more accessible neuroimaging techniques.[184,185] Second, a variety of age brackets have been used in the definition of younger adults (Table 1). For example, for ischemic stroke, we observed overall stable trends in younger adults (18-49 years), but a slightly increasing rate among those 18-29 years and a slightly decreasing rate among those 40-49 years. Of note, Tibæk, *et al.*, a previous Danish study, focused specifically on patients aged 15–30 years and reported an increasing trend.[7] Thus, the age group in focus has importance for the overall conclusions. Third, the rate of first-time stroke is influenced by primary prevention efforts and the prevalence of stroke risk factors in the general population. Risk factor prevalences likely differ across settings. For example, in George, *et al.*, the prevalences of hypertension and smoking increased between 2003–2004 and 2011–2012.[4] In contrast, although the prevalence of hypertension has increased slightly in the Danish general population overall (from 18% in 2010 to 21% in 2021), the prevalence has remained stable or even decreased among younger adults (*e.g.,* 7% in both 2010 and 2021 among those aged 34-44 years).[187] As well, the smoking prevalence has decreased continuously over time in the Danish general population across all ages.[187] These trends were mirrored in our study of stroke patients: the prevalence of hypertension was approximately constant among younger adults (23–26%), while that of daily/occasional smoking decreased from 51% to 41%. On the other hand, overweight and obesity have increased dramatically in Denmark; thus, the stationary incidence trends observed among younger adults in our study could be a result of such competing trends in risk factor prevalences.

Our finding of declining trends among older adults, regardless of stroke subtype, align with most previous work,[3,5,8–10,82,84] including the Global Burden of Disease Study.[1] The decline is considered attributable to improved control of hypertension, diabetes, and hyperlipidemia, a declining prevalence of smoking, as well as more aggressive treatment of atrial fibrillation with anticoagulants.[10,120,188]

Considering the evidence from this study and others,[2–10,82–85,88] it appears that considerable age heterogeneity exists in stroke incidence. Although we did not find an increasing rate, the lack of a downward trend among younger adults is worrying and highlights a need for an enhanced understanding of stroke prevention in this age group.[186]

In alignment with most studies,[5,9,10,79,80,85–87] we found that stroke mortality declined over time regardless of age. This encouraging finding could be explained by medical advancements in acute stroke care (*e.g.,* increased use of intravenous thrombolysis and mechanical thrombectomy), the

formation of specialized stroke units, and improved control of vascular risk factors in secondary stroke prevention.[9,16,80,120]

6.2.2. Risk of stroke recurrence and impact of recurrence on mortality (Study II)

Risk estimates of stroke recurrence were lower than those reported in most studies.[89–102,104–111] For example, the 1- and 10-year risks observed in our study were 4% and 13% following ischemic stroke and 3% and 12% following intracerebral hemorrhage; conversely, in a meta-analysis of 13 studies, the corresponding estimates were 11% and 39% following stroke of any subtype.[100] The discrepancy in absolute risk estimates is probably attributable to at least two explanations: first, we used the Aalen-Johansen estimator, which considers competing events, while most studies used the Kaplan-Meier estimator. As described in Section 4.7.2, the Kaplan-Meier estimator is known to inflate risk estimates, particularly when a competing event, such as death, is common.[114–117] To exemplify this issue, we re-estimated risks using the Kaplan-Meier estimator and found that the 10-year risk estimate of recurrence following ischemic stroke using this approach was 19%, an absolute risk difference compared with the Aalen-Johansen estimate of 6%. A second explanation could be that recurrence risks have decreased in magnitude over time, attributable to more effective secondary prevention, *e.g.,* lowered threshold for treatment with anticoagulation in patients with atrial fibrillation and a move towards non-vitamin K antagonists instead of warfarin.[44,46,188] We found decreasing recurrence risks over time following ischemic stroke and intracerebral hemorrhage, a finding in alignment with some previous reports.[99,106,119] Largely in alignment with our study, a South London Stroke Register study, with patients diagnosed between 1995 and 2018, reported a 10-year recurrence risk of 11% following ischemic stroke after considering death as a competing event.[108]

Our study also illustrated that the overall recurrence risk substantially differed across patient subgroups, thereby emphasizing the importance of investigating any potential heterogeneity in prognosis.[12] Perhaps most noticeably, the risk increased with increasing Essen risk score, although only following ischemic stroke. For example, the 10-year risk following ischemic stroke was 8% in those with an Essen risk score of 0 and 15% in those with a score of 5+. This finding aligns with a smaller Danish study also based on the Danish Stroke Registry.[105] Interestingly, the Essen risk score appeared to risk stratify recurrence risks even more clearly when restricting the population to younger adults less than 50 years. It remains unknown, however, whether focusing on patients with a score of 5+ regarding more intensified secondary prevention could have clinical utility. Further, an enhanced focus on younger adults regarding stroke recurrence and other vascular events has been argued previously,[101,102,104] and our results point in a similar direction: although recurrence risks increased with age, risks among younger adults were strikingly close in magnitude to those in older adults.

The somewhat unintuitive finding of lower recurrence risks with increasing stroke severity should be viewed in light of the higher mortality risks associated with increased stroke severity. Two studies did not find this pattern, but the disagreement can be explained by the use of the Kaplan-Meier estimator in those studies.[98,189]

Our study also confirms the wide belief that stroke recurrence is associated with increased mortality compared with first-time stroke, but only following ischemic stroke. This finding aligns with two previous reports,[103,107] although the magnitude of the association was slimmer in our study. The additional neurological deficit associated with recurrence could lower the threshold for complications, such as infections, and thereby explain the excess mortality.[107]

6.2.3. Risk of mental disorders after stroke (Study III)

Previous studies of post-stroke mental illness focused on specific disorders, most prominently depression,[121–125] dementia,[126–129] anxiety,[130,131] and suicide[132] (Table 3). Direct comparison with these studies is, however, challenging due to variations in the patient inclusion and exclusion criteria (*e.g.,* some studies excluded patients with a history of the examined outcome,[124–129] while others did not[121–123,130–132]) and in the analytic method (*e.g.,* several studies reported prevalences of the examined outcome at specific time points,[121–123,130,131] while others estimated the cumulative incidence using the Kaplan-Meier estimator[125,126,129]). As well, only a few studies used a comparison cohort to contextualize risk estimates to those expected in the general population[124,127,128] or to other patient populations, *e.g.,* myocardial infarction patients.[125]

A novel aspect of our study is the use of a myocardial infarction comparison cohort. In agreement with our findings that mental disorders, albeit most noticeably mood disorders, were higher after stroke than myocardial infarction patients, a study from the United States found a 1.5-fold increased risk of depression after stroke compared with myocardial infarction patients.[125] The increased risks after stroke compared with myocardial infarction patients are suggestive of a neurobiological pathogenesis for some forms of post-stroke mental illness, although the exact mechanisms are still poorly understood.[60] Causes of post-stroke mental illness are likely multifactorial including both psychosocial (*e.g.,* coping with new disability) and biological components.[60] Post-stroke mental illness resulting from biological causes may respond better to treatment,[60] but identifying such cases is challenging. Agreeing with other studies,[121,124,128,129] stroke severity appeared to modify the effect of stroke on mood and organic brain disorders. On one hand, the increased neurological damage associated with increased stroke severity could lower the threshold for mental illness development; on the other hand, increased neurological damage is also associated with increased disability such as aphasia and paresis, complications much more frequent after stroke than myocardial infarction,[190] which could mediate part of the effect. The fact that associations generally were more pronounced

for intracerebral hemorrhage than ischemic stroke aligns with the finding for severity, as the former subtype is associated with increased severity and disability.[191] We note, however, that risks were increased even for patients suffering mild strokes, the vast majority of strokes, suggesting that mental health evaluation after stroke is important for all patients.[192]

We observed the largest effect for mood disorders, mainly depression, which aligns with the current understanding of post-stroke neurologic and psychiatric sequelae of stroke.[134–137] In alignment with only one study that used a general population comparison cohort,[124] the effect was largest in the first year of follow-up, declining thereafter, although the effect size was smaller in our study (*e.g.,* in that study, the HR was 8.9 during 0-3 months, declining in the second and subsequent years[124]). The large effect immediately following diagnosis could partly be explained by the initiation of antidepressants for indications other than clinical depression, *e.g.,* pathological crying or anxiety.[66] The fact that we used prescriptions for antidepressants in the mood disorder definition and not in the anxiety definition could explain the lower risks of neurotic disorders in our study than what has been reported previously (*e.g.,* Ayerbe, *et al.* found that the prevalence of anxiety was 32%-38% at any given time for up to 10 years).[130,131] Our results regarding organic brain disorders (mainly dementia) align with previous studies from Denmark,[127] the United Kingdom,[128] and the United States,[129] although risk estimates tended to be higher than in our study (*e.g.,* in the Oxford Vascular Study, the 1-year risk ratio, compared with the British general population, was 47 for severe stroke, six for minor stroke, and four for transient ischemic attack[128]).

Aside from stroke severity, we examined the associations in a range of patient subgroups. Of note, the associations with mood and organic brain disorders appeared to decline over time. This encouraging trend could stem from an increased focus on post-stroke mental illness over time.

6.2.4. Labor market participation and retirement after stroke (Study IV)

Probability estimates of labor market participation in our study broadly align with those reported in a 2018 systematic review.[153] For example, in our study, the prevalence estimate of labor market participation was, for ischemic stroke, 57% at six months and 64% at two years, while corresponding estimates from the systematic review were 41% and 66%.[153] However, as noted in Section 2.5.4, the direct comparison between individual studies is challenging. Most critically, only two previous studies used a comparison cohort in their design. For example, the Dutch FUTURE study focused on the relative contrast and found a 2 to 3-fold increased risk of unemployment compared with the general population during a mean follow-up of eight years. Our findings align reasonably well with this finding, although we focused on a shorter period after diagnosis, during which the magnitude of the contrast was greater.

Our study contributes to the existing literature in various ways. We highlight here three aspects: first, the DREAM registry allowed us to study labor market participation dynamically, *i.e.,* patients were allowed to move in and out of each category (Section 4.5.4) during follow-up. For example, we found that labor market participation peaked at around two years, after which rises in prevalences of disability pensions and other pensions resulted in an overall decline in labor market participation. Second, although labor market participation was clearly lower in stroke patients than in the general population, it is promising that the majority of patients with ischemic stroke participated in the labor market just six months after diagnosis. It is also encouraging that labor market participation appeared to increase with successive calendar periods of diagnosis. As labor market participation was slightly higher for patients with mild *vs.* severe stroke, the increasing rate of mild stroke during the study period (Study I) could explain this reassuring finding.[193] Yet, with the implementation of a national action plan for stroke in Denmark, which called for greater focus on both physical and cognitive rehabilitation after stroke,[69] labor market participation after stroke could improve in the future. Third, unlike previous reports,[138–146,148,149] we disentangled the separate effects of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage on labor market participation. It is noteworthy in this regard that, although subarachnoid hemorrhage is associated with high short-term mortality (*e.g.,* the 6-month mortality was 13% in our study), prevalences of labor market participation for this subtype were similar to those found for ischemic stroke. Thus, early survivors of subarachnoid hemorrhage appear to have a favorable prognosis, a finding also evident regarding recurrence (Study II).[194]

6.3. Methodological considerations

The studies presented in this dissertation were based on large-scale nationwide registry data. As such, Studies I-IV relied on secondary data, *i.e.,* data collected for purposes other than these studies.[195] Still, all four studies were based on prospectively collected data, as the information on exposures and covariates in the registries were recorded before the information on the outcomes.[195] In the following, the internal and external validity of Studies I-IV are discussed. First, I briefly discuss random error, before focusing on systematic errors, specifically the three main sources of bias encountered in epidemiologic studies: selection bias, information bias, and confounding bias. Lastly, I touch on the generalizability and transportability of the study findings.

6.3.1. Random error

Random error (or variation) is ubiquitous in nature as well as in epidemiologic studies.[196] A main source of random error arises from the process of sampling the study population (*i.e.,* sampling variation).[196] Even when sampling from an entire nation, as was the case in Studies I-IV, the included participants could be considered a sample of a larger super-population, not bound by borders.[196]

Another source of random error is the random variation in disease occurrence.[196] One approach to decrease the variance (or increase the precision, the opposite) is to increase the study size.[196] Thus, holding all else equal, the precision of estimates will increase with an increasing study size.[196] In all four studies, we measured the magnitude of random error using statistical estimation.[196] In alignment with reporting guidelines for observational studies and modern thinking within epidemiology,[196–199] we refrained from conducting significance or hypothesis testing. Instead, we relied on CIs which encapsulate both the effect size and the precision as two separate quantities, unlike the *P*-value which blends these quantities.[198]

6.3.2. Selection bias

Selection bias occurs when a study population differs from the population of interest (*i.e.,* the target population).[200] Given this definition, selection bias likely did not pose a major threat to the findings of Studies I-IV: all four studies had nationwide, population-based designs, were conducted within a universal healthcare system, and data sources were deterministically linked at the individual level ensuring virtually no loss to follow-up.[154] These design strengths reduced the risk of selective inclusion of specific hospitals or groups of individuals, *e.g.,* according to health insurance, ethnicity, or socioeconomic position.[154] The study populations in all four studies were restricted to stroke patients admitted to a hospital; as a result, we did not capture a small proportion of patients who died at home or on the way to the hospital and thus were not registered. However, as the sensitivity of the stroke diagnosis in the Danish Stroke Registry exceeds 90%, this issue is minor (see also Section 6.2.3.1).[16]

Other types of selection mechanisms need to be mentioned. In Study II, we studied the risk of stroke recurrence within strata of various patient characteristics. Because only first-time stroke patients are at risk of stroke recurrence (*i.e.,* a second stroke), we did not include a comparison cohort for this study. Instead, risks were compared within strata with an arbitrarily chosen reference (*e.g.,* normal weight was chosen as a reference within strata of body mass index levels). Overweight/obesity is a well-established risk factor for first-time stroke,[201] but, paradoxically, an apparent protective factor for stroke recurrence and post-stroke mortality[202] – a finding also present in our study. As noted previously,[203] this phenomenon could be explained by collider stratification bias: by restricting the study population (*i.e.,* a sampling mechanism) to stroke patients, a spurious association may appear between overweight/obesity (which is known to be associated with first-time stroke) and stroke recurrence (which is also associated with first-time stroke) by opening a back-door path between overweight/obesity and other, unmeasured risk factors associated with both first-time stroke and stroke recurrence (Figure 6, A). Notwithstanding, we hesitate to refer to this selection mechanism as bias, as that implies error: our study question was not causal; rather, the objective of Study II was to

describe absolute risks according to a variety of patient characteristics, *i.e.,* to describe the clinical course with a focus on the prognostic heterogeneity.

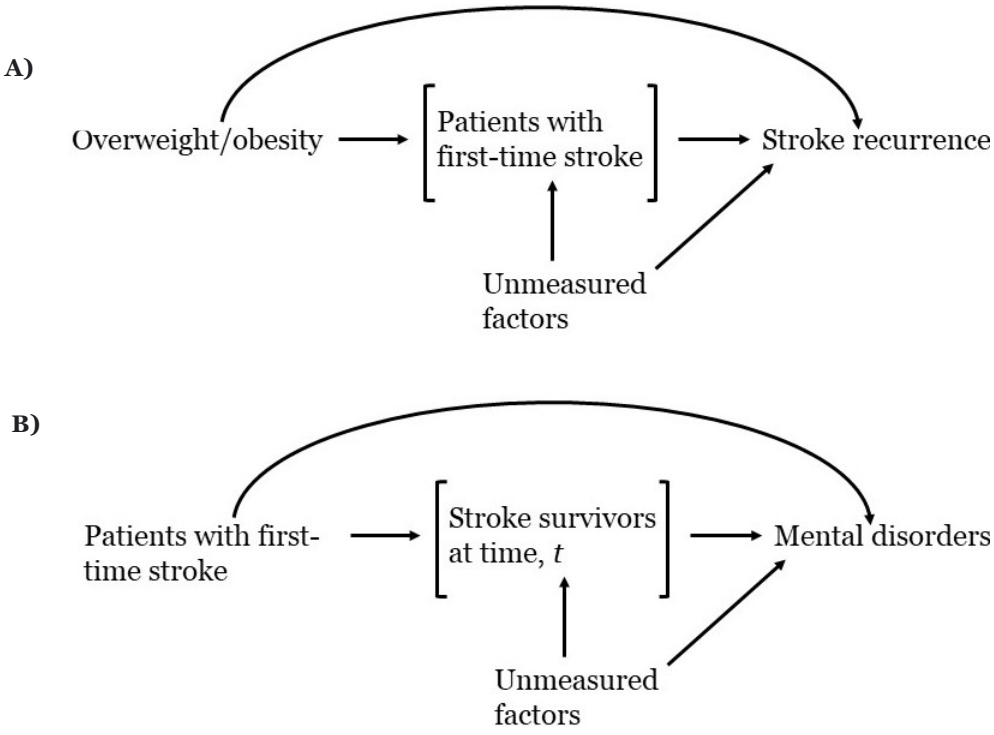

Figure 6. Directed acyclic graphs depicting the potential collider stratification bias in Study II (A) and the in-built selection bias in period-specific hazard ratios in Study III (B). Brackets denote conditioning/restriction.

Another, yet conceptually similar, selection mechanism of potential concern involves the phenomenon of "survivor bias", present when calculating period-specific HRs (Study III).[179] For example, when estimating the >1-5-year HR of mental disorders in Study III, the study population was restricted to those surviving (and remaining free of mental disorders) for at least one year (Figure 6, B). Although we wished to examine any potential time-varying effects (the rationale for calculating period-specific HRs) in Study III, we focused primarily on 1-year absolute risks and HRs, which both eliminated the issue surrounding the in-built survivor bias of HRs and, at the same time, mitigated the potential issue surrounding the loss of the one-to-one correspondence between the absolute risk (with competing risk adjustment) and the HR (without competing risk adjustment), as described in Section 4.7.3.

A last selection mechanism worth discussing is referred to as "depletion of susceptibles", a type of selection mechanism occurring during follow-up. An example of this phenomenon is the unintuitive finding of lower absolute recurrence risks with increasing stroke severity, after considering death as a competing event (Study II). As described in Section 4.7.2, the absolute risk estimate with competing event adjustment should be interpreted as the probability of experiencing the event of interest (here

stroke recurrence) before a given time, *t*, and before the occurrence of the competing event (here death). Because stroke severity is highly associated with mortality, which prevents the occurrence of recurrence, patients with severe stroke are less likely than patients with mild stroke to suffer recurrence.

6.3.3. Information bias

Measurement error (or misclassification) is common in epidemiologic research. All types of study variables (*e.g.,* exposure, covariate, or outcome data) are susceptible to measurement error, and it is paramount to consider the extent measurement error of any study variable may affect study results.[204] Broadly, measurement error can be considered differential (*i.e.,* the extent of measurement error depends on other study variables) and non-differential (*i.e.,* the extent of measurement error does not depend on other study variables).[204] The direction of bias in the case of differential measurement error is irregular; it may lead to over- or underestimation.[204] Conversely, in the case of non-differential measurement error, the direction of bias is often towards the null (*e.g.,* non-differential measurement error of a binary exposure), although exceptions to this rule-of-thumb exist (*e.g.,* if the exposure has more than two levels).[205]

6.3.3.1 Stroke measurement

The sensitivity (*i.e.,* the probability that a diseased individual is correctly classified as such[205]) and positive predictive value (i.e. the probability that a disease-classified individual truly is diseased[205]) of the ischemic stroke and intracerebral hemorrhage diagnoses in the Danish Stroke Registry are estimated to be high, both exceeding 90%.[157,158] In Study I, it is probable that the absolute rates of first-time ischemic stroke and intracerebral hemorrhage were slightly underestimated, due to the small proportion of patients not captured by the Stroke Registry (see also Section 6.2.2). At the same time, it is conceivable that rates would artificially increase over time given improvements in stroke diagnostics over time, resulting in a possible upward bias in the trend, particularly among younger adults, for whom strokes are on average milder. However, rates of mild stroke increased over time regardless of age, indicating that this issue likely did not pose a major threat to the findings of Study I. Similarly, in Studies II-IV, the impact of ischemic stroke and intracerebral hemorrhage measurement error was likely trivial due to the high positive predictive values.

In all four studies, findings for subarachnoid hemorrhage should be considered with caution considering the moderate positive predictive value (61%–67%)[166] and unknown sensitivity in the Danish National Patient Registry. In a previous validation study of spontaneous, non-traumatic subarachnoid hemorrhage in the Danish National Patient Registry, the diagnosis was confirmed in 64% (95% CI: 61%, 67%) of cases; among cases unconfirmed, 40% were traumatic subarachnoid

hemorrhage, 15% were parenchymal hemorrhage, and 19% were suspected with spontaneous, non-traumatic subarachnoid hemorrhage but dismissed during admission.

6.3.3.2 Outcome measurement

Mortality. The Danish Civil Registration System is updated daily regarding changes in vital status, ensuring virtually complete follow-up regarding all-cause mortality;[155] thus, measurement error regarding all-cause mortality was unlikely in all four studies. In Studies II and III, data on cause-specific mortality, extracted from the Danish Registry of Causes of Death, are prone to measurement error.[162] In Study II, we considered stroke-specific mortality, using similar codes as previous reports.[206] Although no validation studies exist regarding stroke-specific mortality, it is conceivable that the sensitivity of these codes is moderate (*i.e.,* we missed some patients who truly died of stroke, leading to potential underestimation of absolute cause-specific mortality risks), while the positive predictive value is fairly high. Regarding completed suicide (Study III), a validation study found a positive predictive value of 90%,[207] suggesting that risk contrasts for this outcome between the stroke and comparison cohorts were not severely affected, assuming a similar sensitivity between cohorts.

Stroke recurrence. A limitation of Study II is the lack of comprehensive validation of the stroke recurrence measurement in the Danish registries. One study assessed the validity of intracerebral hemorrhage recurrence in the Danish Stroke Registry (considering only within-subtype recurrence) and found a positive predictive value of 90% and a sensitivity of 76% when using a blanking period of 30 days (*i.e.,* a period immediately subsequent to the index event where recurrences are ignored).[208] We did not use a blanking period in primary analyses; instead, we considered repeated entries in the Stroke Registry as separate events: considering the inclusion criteria in the Registry (*i.e.,* acute strokes meeting the World Health Organization stroke definition),[16] we deemed this approach reasonable. Notwithstanding, in sensitivity analyses, we altered the recurrence definition. For example, using a 21-day blanking period, risk estimates changed only marginally (*e.g.,* for ischemic stroke, the 1-year risk was 3.9% in primary analyses and 3.4% using the 21-day blanking period; for intracerebral hemorrhage, the corresponding estimates were 3.3% and 3.0%).

Mental disorders. As noted in Section 4.5.3, data on mental disorders were primarily collected from hospital-based registries (Study III). The validity of hospital-based psychiatric diagnoses was previously found to be acceptable for research purposes.[160,209–213] Importantly, however, hospital-based registries likely have a high sensitivity to severe mental illness, but as mild mental illness often is treated in primary care, the sensitivity to these cases is probably low to moderate.[160] Except for mood disorders for which we also used redeemed antidepressant prescriptions, thereby capturing cases treated in primary care,[124] absolute risks of mental disorders were likely underestimated. For mood disorders, although the sensitivity was increased by using antidepressants in the outcome

definition, the specificity likely decreased, as antidepressants have indications other than clinical depression (see also Section 6.1.3).

Another concern is the potential for differential measurement error of mental disorders, induced by increased surveillance of stroke patients (*i.e.,* surveillance bias): the stroke hospitalization itself and subsequent follow-up visits in outpatient clinics may lead to an increased probability of being diagnosed with a mental disorder compared with compared general population comparators that, on average, are less attached to the healthcare system. For myocardial infarction comparators, this issue is less of a concern, which partly could explain the less pronounced associations for this comparison. Lastly, although we excluded patients with prevalent mental disorders, we cannot completely disregard the possibility that some mental disorders were erroneously recorded as incident cases during follow-up due to the insidious onset of these conditions (*e.g.,* dementia), which may have led to some degree of reverse causation.

Labor market participation. A primary concern in Study IV is that the DREAM registry (from which we collected data on labor market participation) does not capture short-term sick leave.[164] DREAM captures all public transfer payments, including sick leave benefits; however, according to Danish legislature, employers are required to pay out either normal salary or sick leave benefits to individuals on sick leave for the first 30 days (this period varied from 14 days to 30 days during the study period). Thereafter, employers are eligible for municipal reimbursement at which point the sick leave period is captured in DREAM. Importantly, once registered in DREAM, the sick leave period is registered from the first day of leave. Consequently, some patients on short-term sick leave may erroneously have been classified as having never left the labor market after stroke. Thus, we may have underestimated the proportion of stroke patients going on sick leave immediately following diagnosis; however, the impact of this source of measurement error on prevalence estimates at six months or later is likely minor.

6.3.3.3 Covariate measurement

An important aspect of this thesis was to describe and illuminate the heterogeneity in occurrence trends (Study I) and prognoses (Studies II-IV); as such, we performed stratified analyses in all four studies. Variables from the Danish Stroke Registry (*e.g.,* severity, body mass index, smoking, and alcohol intake) are collected by hospital staff members; thus, measurement error is possible. No validation study exists regarding these data, but yearly audits are conducted, suggesting that data quality likely is high.[16] Still, data on these variables were missing in varying degrees (see also Section 4.7.6). In Study II, we used multiple imputation with chained equations to assess the impact of missingness, but the results did not change materially. A similar finding was found after imputing data on income, occupation, and education (Study III). We also collected data on a range of

comorbidities (used for both stratification and adjustment, see Table 6) based on hospital-based diagnoses and redeemed prescriptions. Some degree of measurement of error of these data is inevitable, but we see no reason it should be differential with respect to stroke. The validity of many relevant hospital-based diagnoses, *e.g.,* cardiovascular diagnoses, has previously been found to be high.[154,159,214]

6.3.4. Confounding bias

In non-randomized studies of cause and effect, confounding bias is a chief concern. The issue revolves around the common situation in non-randomized studies that the exposed and unexposed individuals differ concerning other factors that also affect the outcome.[215] Thus, if such other factors are left uncontrolled, the exposure-outcome association may be estimated with error if the study aim is causal.

The overarching aim of this dissertation was to extend the knowledge of epidemiologic aspects of stroke, with an emphasis on description rather than causation.[216] Although covariate adjustment played a role in all four studies, a common theme throughout all studies was the focus on unadjusted absolute estimates (*e.g.,* the age-specific trends in Study I). In Studies I and II, control of covariates were kept at a minimum, while Studies III and IV, which included comparison cohorts, incorporated a more comprehensive set of covariates (see Table 6). Covariates for Studies III and IV were chosen based on the disjunctive cause criterion, *i.e.,* chosen covariates are considered a cause of either the exposure, the outcome, or both.[215] The more comprehensive adjustment sets in included in Studies III and IV were chosen to more strictly isolate the effect of stroke. In these two studies, unadjusted and adjusted estimates differed very little after matching on age, sex, and calendar period (*e.g.,* in Study III, the 1-year unadjusted HR of mood disorders was 1.58 and the adjusted HR was 1.68 when compared with myocardial infarction patients). Although we cannot exclude the possibility of unknown or residual confounding bias (*e.g.,* we probably only partly captured the confounding effect of smoking by using chronic pulmonary disease as a proxy in Study III), the slight differences between unadjusted and adjusted estimates do not suggest that confounding bias played a major role.

6.3.5. Generalizability and transportability

Generalizability refers to the extent to which a study's findings apply to the target population, while transportability refers to the extent to which a study's findings apply to other populations.[200,217] Assuming high interval validity (discussed in the preceding sections), our findings are likely generalizable to all Danish stroke patients. The transportability of our findings to other populations needs discussing. For example, in Study I, the divergent trends over time in stroke incidence in

different geographical settings could be explained by a variety of factors (Section 6.1.1), including differential changes in diagnostic practice and differences in risk factor prevalences in the general population. Further, given the fairly homogenous Danish population, it is possible that our findings are not readily transportable to settings more heterogeneous regarding ethnicity. For example, evidence suggests that stroke etiology, on average, differ between black and white patients[218] and that black patients are less likely than white patients to receive evidence-based acute stroke treatment.[219]

7. Conclusions and perspectives

The studies included in this dissertation have added to our collective understanding of stroke epidemiology.

Despite evidence pointing to an increasing incidence rate of stroke among younger adults (18-49 years) in many countries, a stationary trend existed in Denmark (Study I). On one hand, the absence of an increasing rate in Denmark is encouraging; on the other hand, bearing in mind the declining incidence rate of stroke when considering all ages, an enhanced focus on the primary prevention of stroke among younger adults seems warranted. The findings from Study I may provide foundational evidence regarding future primary prevention interventions specifically among younger adults.

Study II showed that absolute risks of recurrence were high in a contemporary, routine clinical setting in Denmark, even after correcting for the competing risk of death. While high on average, recurrence risks depended on patient characteristics. Another important finding was that stroke recurrence augmented the already high risk of mortality. These findings underscore the importance of 1) preventing recurrence, 2) investigating the heterogeneity in prognoses, and 3) considering death as a competing event to avoid overestimation of absolute risks. Although the risk of recurrence clearly depended on the Essen risk score, the potential utility of this risk score in clinical practice, particularly among younger adults, remains poorly understood.

Study III added to a large body of evidence showing that mental illness, particularly mood and organic brain disorders, is common after stroke. A novel finding was that the risks of most mental disorders were higher after stroke than after myocardial infarction, a disease with a similar vascular risk factor profile. This finding may suggest a neurobiological pathogenesis for some forms of post-stroke mental illness, although the exact mechanisms are still poorly understood. Another important finding was that, although stroke severity modified the effect, risks were higher even for patients suffering mild strokes, the vast majority of strokes, suggesting that mental health evaluation after stroke is important for all patients.

Study IV provided a detailed examination of labor market participation and retirement after stroke among working-age adults (18-60 years). Expectedly, stroke clearly impacted labor market participation when compared with the Danish general population, but, encouragingly, more than half of patients with ischemic stroke had returned to the labor market just six months following diagnosis. The absolute and relative probabilities of labor market participation reported in this study may serve as a scientific basis when designing and implementing stroke rehabilitation programs and intervention studies.

8. Summary

8

Stroke constitutes a major global burden as the second-leading cause of death and the third-leading cause of death and disability combined. The incidence and mortality rates of stroke are currently declining in most high-income countries. However, several studies have reported flat or even increasing incidence rates among younger adults (18-49 years), suggesting an age-heterogeneous trend. Whether an increasing trend exists among younger adults in Denmark is poorly understood.

With the aging of populations and improving stroke survival, the absolute number of stroke survivors is increasing. Consequently, with more patients at risk of post-stroke outcomes, an updated and in-depth understanding of the stroke prognosis is warranted.

Using large-scale, nationwide, Danish registry data, this dissertation aimed to describe 1) trends in the incidence and mortality of stroke among younger and older adults (Study I) and 2) the prognosis of stroke with regards to stroke recurrence (Study II), mental disorders (Study III), and labor market participation (Study IV).

In Study I, we found that the stroke incidence rate remained approximately stable from 2005 to 2018 among younger adults for both ischemic stroke and intracerebral hemorrhage, while a decreasing trend was observed for subarachnoid hemorrhage. Among older adults, the rate declined over time regardless of subtype, but most noticeably among adults older than 70 years. The 30-day mortality risk declined over time for all three subtypes, regardless of age.

In Study II, we corrected previous shortcomings by taking into account the competing risk of death to avoid overestimating absolute stroke recurrence risks. Still, the recurrence risk was high overall (10-year risk: 13% after ischemic stroke), although it differed substantially according to patient characteristics. For example, following ischemic stroke, the risk of recurrence increased sequentially with an increasing Essen risk score.

In Study III, we found that risks of a range of mental disorders, but most prominently mood and organic brain disorders, were higher after stroke compared with the Danish general population and myocardial infarction patients. The higher risks after stroke than myocardial infarction patients may suggest a neurobiological pathogenesis of post-stroke mental illness.

In Study IV, we found that stroke had a clear impact on labor market participation among working-age adults (18-60 years). Encouragingly, more than half of patients with ischemic stroke had returned to the labor market at six months following diagnosis. In reference to the Danish general population, the probability of labor market participation was, at six months, approximately 40% reduced.

9. Dansk resumé (Danish summary)

Stroke, bestående af iskæmisk apopleksi, intracerebral blødning og subaraknoidalblødning, er på verdensplan den næst hyppigste dødsårsag og den tredje hyppigste årsag til død og handicap tilsammen. I højindkomstlande er både forekomsten af stroke samt den efterfølgende dødelighed faldende. Flere undersøgelser har dog rapporteret en statisk eller endda stigende forekomst blandt yngre voksne (18-49 år), hvilket kunne tyde på en aldersheterogen tendens. Der mangler viden om hvorvidt en stigende tendens eksisterer blandt yngre voksne i Danmark.

I takt med den globale befolkningsaldring og forbedrende overlevelse efter stroke er det absolutte antal stroke-overlevere, som dermed er i risiko for efterfølgende konsekvenser, stigende. Som følge heraf er en opdateret og dybdegående forståelse af prognosen for stroke berettiget.

Med brug af landsdækkende, danske registerdata havde denne afhandling til formål at beskrive 1) tendensen i forekomsten og dødeligheden af stroke blandt yngre og ældre voksne (Studie I) og 2) prognosen for stroke med fokus på recidiv (Studie II), neurologiske og psykiatriske sygdom (Studie III) og arbejdsmarkedstilknytning (Studie IV).

I Studie I fandt vi at forekomsten af både iskæmisk apopleksi og intracerebral blødning blandt yngre voksne forblev omtrent uændret fra 2005 til 2018, hvorimod forekomsten af subaraknoidalblødning faldt. Blandt ældre voksne faldt forekomsten over tid uanset stroke subtype, men mest mærkbart blandt personer over 70 år. 30-dages dødeligheden faldt over tid for alle tre subtyper og uanset alder.

I Studie II korrigerede vi tidligere studiers metodiske svagheder ved at tage højde for død som en konkurrerende risiko for at undgå at overvurdere den absolutte risiko for recidiv. På trods af dette fandt vi en høj overordnet risiko for recidiv (10-års risiko: 13% efter iskæmisk apopleksi), men prognosen afhang mærkbart af patientkarakteristika. For eksempel steg risikoen for recidiv efter iskæmisk apopleksi sekventielt med stigende Essen risikoscore.

I Studie III fandt vi en øget risiko for en række neurologiske og psykiatriske sygdomme, dog mest udtalt for affektive og organiske lidelser, efter stroke sammenlignet med den danske baggrundsbefolkning og patienter med myokardieinfarkt. De højere risici efter stroke sammenlignet med myokardieinfarkt kan tyde på en neurobiologisk patogenese af neurologisk og psykiatrisk sygdom efter stroke.

I Studie IV fandt vi at stroke havde en markant indvirkning på arbejdsmarkedstilknytningen blandt voksne i den arbejdsdygtige alder (18-60 år). Et opmuntrende fund var dog, at mere end halvdelen af patienterne med iskæmisk apopleksi havde vendt tilbage til arbejdsmarkedet seks måneder efter diagnosen. Sammenlignet med den danske baggrundsbefolkning var sandsynligheden for arbejdsmarkedstilknytning efter seks måneder omtrent 40% reduceret.

10. References

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795-820. doi:10.1016/S1474-4422(21)00252-0

2. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Ann Neurol*. 2011;70(5):713-721. doi:10.1002/ana.22539

3. Kissela BM, Khoury JC, Alwell K, et al. Age at stroke: temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79(17):1781-1787. doi:10.1212/WNL.0b013e318270401d

4. George MG, Tong X, Bowman BA. Prevalence of Cardiovascular Risk Factors and Strokes in Younger Adults. *JAMA Neurol*. 2017;74(6):695-703. doi:10.1001/jamaneurol.2017.0020

5. Rosengren A, Giang KW, Lappas G, Jern C, Torén K, Björck L. Twenty-four-year trends in the incidence of ischemic stroke in Sweden from 1987 to 2010. *Stroke*. 2013;44(9):2388-2393. doi:10.1161/STROKEAHA.113.001170

6. Béjot Y, Daubail B, Jacquin A, et al. Trends in the incidence of ischaemic stroke in young adults between 1985 and 2011: the Dijon Stroke Registry. *J Neurol Neurosurg Psychiatry*. 2014;85(5):509-513. doi:10.1136/jnnp-2013-306203

7. Tibæk M, Dehlendorff C, Jørgensen HS, Forchhammer HB, Johnsen SP, Kammersgaard LP. Increasing Incidence of Hospitalization for Stroke and Transient Ischemic Attack in Young Adults: A Registry-Based Study. *J Am Heart Assoc*. 2016;5(5). doi:10.1161/JAHA.115.003158

8. Ekker MS, Verhoeven JI, Vaartjes I, van Nieuwenhuizen KM, Klijn CJM, de Leeuw FE. Stroke incidence in young adults according to age, subtype, sex, and time trends. *Neurology*. 2019;92(21):e2444-e2454. doi:10.1212/WNL.0000000000007533

9. Seminog OO, Scarborough P, Wright FL, Rayner M, Goldacre MJ. Determinants of the decline in mortality from acute stroke in England: linked national database study of 795 869 adults. *BMJ*. 2019;365:l1778. doi:10.1136/bmj.l1778

10. Yafasova A, Fosbøl EL, Christiansen MN, et al. Time trends in incidence, comorbidity, and mortality of ischemic stroke in Denmark (1996-2016). *Neurology*. 2020;95(17):e2343-e2353. doi:10.1212/WNL.0000000000010647

11. Béjot Y, Delpont B, Giroud M. Rising Stroke Incidence in Young Adults: More Epidemiological Evidence, More Questions to Be Answered. *J Am Heart Assoc*. 2016;5(5):e003661. doi:10.1161/JAHA.116.003661

12. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ*. 2013;346:e5595. doi:10.1136/bmj.e5595

13. Coupland AP, Thapar A, Qureshi MI, Jenkins H, Davies AH. The definition of stroke. *J R Soc Med*. 2017;110(1):9-12. doi:10.1177/0141076816680121

14. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. *Bull World Health Organ*. 1980;58(1):113-130.

15. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44(7):2064-2089. doi:10.1161/STR.0b013e318296aeca

16. Johnsen SP, Ingeman A, Hundborg HH, Schaarup SZ, Gyllenborg J. The Danish Stroke Registry. *Clin Epidemiol*. 2016;8:697-702. doi:10.2147/CLEP.S103662

17. Campbell BCV, Khatri P. Stroke. *The Lancet*. 2020;396(10244):129-142. doi:10.1016/S0140-6736(20)31179-X

18. Zerna C, Thomalla G, Campbell BCV, Rha JH, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischaemic stroke. *Lancet*. 2018;392(10154):1247-1256. doi:10.1016/S0140-6736(18)31874-9

19. Cordonnier C, Demchuk A, Ziai W, Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet*. 2018;392(10154):1257-1268. doi:10.1016/S0140-6736(18)31878-6

20. van Gijn J, Kerr RS, Rinkel GJE. Subarachnoid haemorrhage. *Lancet*. 2007;369(9558):306-318. doi:10.1016/S0140-6736(07)60153-6

21. Greenberg SM, Ziai WC, Cordonnier C, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2022;53(7):e282-e361. doi:10.1161/STR.0000000000000407

22. Welty TE, Horner TG. Pathophysiology and treatment of subarachnoid hemorrhage. *Clin Pharm*. 1990;9(1):35-39.

23. Plana-Ripoll O, Dreier JW, Momen NC, et al. Analysis of mortality metrics associated with a comprehensive range of disorders in Denmark, 2000 to 2018: A population-based cohort study. *PLoS Med*. 2022;19(6):e1004023. doi:10.1371/journal.pmed.1004023

24. Ekker MS, Boot EM, Singhal AB, et al. Epidemiology, aetiology, and management of ischaemic stroke in young adults. *The Lancet Neurology*. 2018;17(9):790-801. doi:10.1016/S1474-4422(18)30233-3

25. George Mary G. Risk Factors for Ischemic Stroke in Younger Adults. *Stroke*. 2020;51(3):729-735. doi:10.1161/STROKEAHA.119.024156

26. Fletcher RH, Fletcher SW, Fletcher GS. *Clinical Epidemiology - The Essentials*. Fifth. Lippincott Williams & Wilkins; 2016.

27. Benichou J, Gail MH. Variance calculations and confidence intervals for estimates of the attributable risk based on logistic models. *Biometrics*. 1990;46(4):991-1003.

28. O'Donnell MJ, Chin SL, Rangarajan S, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. *Lancet*. 2016;388(10046):761-775. doi:10.1016/S0140-6736(16)30506-2

29. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988. doi:10.1161/01.str.22.8.983

30. Feigin VL, Rinkel GJE, Lawes CMM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. *Stroke*. 2005;36(12):2773-2780. doi:10.1161/01.STR.0000190838.02954.e8

31. Andreasen TH, Bartek J, Andresen M, Springborg JB, Romner B. Modifiable risk factors for aneurysmal subarachnoid hemorrhage. *Stroke*. 2013;44(12):3607-3612. doi:10.1161/STROKEAHA.113.001575

32. Rothman KJ. *Epidemiology - An Introduction*. 2nd ed. Oxford University Press; 2012.

33. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35-41. doi:10.1161/01.str.24.1.35

34. Magid-Bernstein J, Girard R, Polster S, et al. Cerebral Hemorrhage: Pathophysiology, Treatment, and Future Directions. *Circ Res*. 2022;130(8):1204-1229. doi:10.1161/CIRCRESAHA.121.319949

35. Jacob MA, Ekker MS, Allach Y, et al. Global Differences in Risk Factors, Etiology, and Outcome of Ischemic Stroke in Young Adults-A Worldwide Meta-analysis: The GOAL Initiative. *Neurology*. 2022;98(6):e573-e588. doi:10.1212/WNL.0000000000013195

36. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2013;(9):CD000197. doi:10.1002/14651858.CD000197.pub3

37. Aguiar de Sousa D, von Martial R, Abilleira S, et al. Access to and delivery of acute ischaemic stroke treatments: A survey of national scientific societies and stroke experts in 44 European countries. *Eur Stroke J*. 2019;4(1):13-28. doi:10.1177/2396987318786023

38. Andersen G, Damgaard D, Forchhammer HB, Iversen HK. Organisation. In: *Apopleksi - Sygdom, Behandling Og Organisation*. 1. edition. Munksgaard; 2016.

39. The Lancet null. 21st century management and prevention of stroke. *Lancet*. 2018;392(10154):1167. doi:10.1016/S0140-6736(18)32358-4

40. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/STR.0000000000000211

41. The Danish Clinical Quality Program - National Clinical Registries. *Danish Stroke Registry - Annual Report 2020.*; 2021.

42. Saini V, Guada L, Yavagal DR. Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. *Neurology*. 2021;97(20 Suppl 2):S6-S16. doi:10.1212/WNL.0000000000012781

43. Connolly ES, Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. *Stroke*. 2012;43(6):1711-1737. doi:10.1161/STR.0b013e3182587839

44. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2021;52(7):e364-e467. doi:10.1161/STR.0000000000000375

45. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke*. 2011;42(1):227-276. doi:10.1161/STR.0b013e3181f7d043

46. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160-2236. doi:10.1161/STR.0000000000000024

47. Schrader J, Lüders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005;36(6):1218-1226. doi:10.1161/01.STR.0000166048.35740.a9

48. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med*. 2008;359(12):1225-1237. doi:10.1056/NEJMoa0804593

49. Amarenco P, Bogousslavsky J, Callahan A, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355(6):549-559. doi:10.1056/NEJMoa061894

50. Amarenco P, Kim JS, Labreuche J, et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. *N Engl J Med*. 2020;382(1):9. doi:10.1056/NEJMoa1910355

51. Sheth KN, Selim M. Focused Update on Vascular Risk and Secondary Prevention in Survivors of Intracerebral Hemorrhage. *Stroke*. 2022;53(7):2128-2130. doi:10.1161/STROKEAHA.122.039819

52. Minhas JS, Moullaali TJ, Rinkel GJE, Anderson CS. Blood Pressure Management After Intracerebral and Subarachnoid Hemorrhage: The Knowns and Known Unknowns. *Stroke*. 2022;53(4):1065-1073. doi:10.1161/STROKEAHA.121.036139

53. Murthy SB, Zhang C, Diaz I, et al. Association Between Intracerebral Hemorrhage and Subsequent Arterial Ischemic Events in Participants From 4 Population-Based Cohort Studies. *JAMA Neurol*. 2021;78(7):809-816. doi:10.1001/jamaneurol.2021.0925

54. Gaist D, González-Pérez A, Hald SM, García Rodríguez LA. Higher Risk of Ischemic Stroke After an Intracerebral Hemorrhage Than in General Population: A Cohort Study From the United Kingdom. *Stroke*. 2022;53(2):e50-e52. doi:10.1161/STROKEAHA.121.037633

55. Al-Shahi Salman R, Minks DP, Mitra D, et al. Effects of antiplatelet therapy on stroke risk by brain imaging features of intracerebral haemorrhage and cerebral small vessel diseases: subgroup analyses of the RESTART randomised, open-label trial. *Lancet Neurol*. 2019;18(7):643-652. doi:10.1016/S1474-4422(19)30184-X

56. Puy L, Forman R, Cordonnier C, Sheth KN. Protecting the Brain, From the Heart: Safely Mitigating the Consequences of Thrombosis in Intracerebral Hemorrhage Survivors With Atrial Fibrillation. *Stroke*. 2022;53(7):2152-2160. doi:10.1161/STROKEAHA.122.036888

57. Shoamanesh A, Selim M. Use of Lipid-Lowering Drugs After Intracerebral Hemorrhage. *Stroke*. 2022;53(7):2161-2170. doi:10.1161/STROKEAHA.122.036889

58. Rudolph DA, Hald SM, García Rodríguez LA, et al. Association of Long-term Statin Use With the Risk of Intracerebral Hemorrhage: A Danish Nationwide Case-Control Study. *Neurology*. Published online May 16, 2022:10.1212/WNL.0000000000200713. doi:10.1212/WNL.0000000000200713

59. Sanz-Cuesta BE, Saver JL. Lipid-Lowering Therapy and Hemorrhagic Stroke Risk: Comparative Meta-Analysis of Statins and PCSK9 Inhibitors. *Stroke*. 2021;52(10):3142-3150. doi:10.1161/STROKEAHA.121.034576

60. Towfighi A, Ovbiagele B, El Husseini N, et al. Poststroke Depression: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2017;48(2):e30-e43. doi:10.1161/STR.0000000000000113

61. Mortensen JK, Andersen G. Pharmacological management of post-stroke depression: an update of the evidence and clinical guidance. *Expert Opin Pharmacother*. 2021;22(9):1157-1166. doi:10.1080/14656566.2021.1880566

62. Allida S, Cox KL, Hsieh CF, House A, Hackett ML. Pharmacological, psychological and non-invasive brain stimulation interventions for preventing depression after stroke. *Cochrane Database Syst Rev*. 2020;5:CD003689. doi:10.1002/14651858.CD003689.pub4

63. Mortensen JK, Larsson H, Johnsen SP, Andersen G. Post stroke use of selective serotonin reuptake inhibitors and clinical outcome among patients with ischemic stroke: a nationwide propensity score-matched follow-up study. *Stroke*. 2013;44(2):420-426. doi:10.1161/STROKEAHA.112.674242

64. FOCUS Trial Collaboration. Effects of fluoxetine on functional outcomes after acute stroke (FOCUS): a pragmatic, double-blind, randomised, controlled trial. *Lancet*. 2019;393(10168):265-274. doi:10.1016/S0140-6736(18)32823-X

65. AFFINITY Trial Collaboration. Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2020;19(8):651-660. doi:10.1016/S1474-4422(20)30207-6

66. Mortensen JK, Johnsen SP, Andersen G. Prescription and predictors of post-stroke antidepressant treatment: A population-based study. *Acta Neurol Scand*. 2018;138(3):235-244. doi:10.1111/ane.12947

67. Forchhammer HB. Rehabilitering. In: *Apopleksi - Sygdom, Behandling Og Organisation*. 1. edition. Munksgaard; 2016.

68. Langhorne P, Bernhardt J, Kwakkel G. Stroke rehabilitation. *Lancet*. 2011;377(9778):1693-1702. doi:10.1016/S0140-6736(11)60325-5

69. The Danish Stroke Association. *Action Plan for Stroke*.; 2022. https://www.hjernesagen.dk/wp-content/uploads/2022/02/ENDELIG_handleplan-for-stroke-2022-enkeltsider_med-links.pdf

70. Vandenbroucke JP, Sørensen HT. Clinical Epidemiology. In: *Modern Epidemiology*. 4th ed. Lippincott Williams & Wilkins; 2021:895-933.

71. Moons KGM, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? *BMJ*. 2009;338:b375. doi:10.1136/bmj.b375

72. Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med*. 2013;10(2):e1001380. doi:10.1371/journal.pmed.1001380

73. Ording AG, Sørensen HT. Concepts of comorbidities, multiple morbidities, complications, and their clinical epidemiologic analogs. *Clin Epidemiol*. 2013;5:199-203. doi:10.2147/CLEP.S45305

74. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical Epidemiology - a Basic Science for Clinical Medicine*. 2nd edition. Little Brown & Co; 1991.

75. Ording AG, Cronin-Fenton D, Ehrenstein V, et al. Challenges in translating endpoints from trials to observational cohort studies in oncology. *Clin Epidemiol*. 2016;8:195-200. doi:10.2147/CLEP.S97874

76. Ingeman A, Andersen G, Hundborg HH, Johnsen SP. Medical complications in patients with stroke: data validity in a stroke registry and a hospital discharge registry. *Clin Epidemiol*. 2010;2:5-13. doi:10.2147/clep.s8908

77. Janssens ACJW, Gwinn M, Brockman JE, Powell K, Goodman M. Novel citation-based search method for scientific literature: a validation study. *BMC Medical Research Methodology*. 2020;20(1):25. doi:10.1186/s12874-020-0907-5

78. González-Pérez A, Gaist D, Wallander MA, McFeat G, García-Rodríguez LA. Mortality after hemorrhagic stroke: data from general practice (The Health Improvement Network). *Neurology*. 2013;81(6):559-565. doi:10.1212/WNL.0b013e31829e6eff

79. Vaartjes I, O'Flaherty M, Capewell S, Kappelle J, Bots M. Remarkable decline in ischemic stroke mortality is not matched by changes in incidence. *Stroke*. 2013;44(3):591-597. doi:10.1161/STROKEAHA.112.677724

80. Schmidt M, Jacobsen JB, Johnsen SP, Bøtker HE, Sørensen HT. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. *Neurology*. 2014;82(4):340-350. doi:10.1212/WNL.0000000000000062

81. Poisson SN, Glidden D, Johnston SC, Fullerton HJ. Deaths from stroke in US young adults, 1989-2009. *Neurology*. 2014;83(23):2110-2115. doi:10.1212/WNL.0000000000001042

82. Wafa HA, Wolfe CDA, Rudd A, Wang Y. Long-term trends in incidence and risk factors for ischaemic stroke subtypes: Prospective population study of the South London Stroke Register. *PLoS Med*. 2018;15(10):e1002669. doi:10.1371/journal.pmed.1002669

83. Sipilä JOT, Posti JP, Ruuskanen JO, Rautava P, Kytö V. Stroke hospitalization trends of the working-aged in Finland. *PLOS ONE*. 2018;13(8):e0201633. doi:10.1371/journal.pone.0201633

84. Aparicio HJ, Himali JJ, Satizabal CL, et al. Temporal Trends in Ischemic Stroke Incidence in Younger Adults in the Framingham Study. *Stroke*. 2019;50(6):1558-1560. doi:10.1161/STROKEAHA.119.025171

85. Barra M, Labberton AS, Faiz KW, et al. Stroke incidence in the young: evidence from a Norwegian register study. *J Neurol*. 2019;266(1):68-84. doi:10.1007/s00415-018-9102-6

86. Ekker MS, Verhoeven JI, Vaartjes I, Jolink WMT, Klijn CJM, Leeuw FE de. Association of Stroke Among Adults Aged 18 to 49 Years With Long-term Mortality. *JAMA*. 2019;321(21):2113-2123. doi:10.1001/jama.2019.6560

87. Wafa HA, Wolfe CDA, Bhalla A, Wang Y. Long-term trends in death and dependence after ischaemic strokes: A retrospective cohort study using the South London Stroke Register (SLSR). *PLoS Med*. 2020;17(3):e1003048. doi:10.1371/journal.pmed.1003048

88. Norman K, Eriksson M, von Euler M. Sex Differences in Ischemic Stroke Within the Younger Age Group: A Register-Based Study. *Front Neurol*. 2022;13:793181. doi:10.3389/fneur.2022.793181

89. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*. 2001;32(12):2735-2740. doi:10.1161/hs1201.100209

90. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. *Stroke*. 2003;34(1):122-126. doi:10.1161/01.str.0000047852.05842.3c

91. Modrego PJ, Mainar R, Turull L. Recurrence and survival after first-ever stroke in the area of Bajo Aragon, Spain. A prospective cohort study. *J Neurol Sci*. 2004;224(1-2):49-55. doi:10.1016/j.jns.2004.06.002

92. Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ*. 2004;328(7435):326. doi:10.1136/bmj.37991.635266.44

93. Coull AJ, Rothwell PM. Underestimation of the Early Risk of Recurrent Stroke: Evidence of the Need for a Standard Definition. *Stroke*. 2004;35(8):1925-1929. doi:10.1161/01.STR.0000133129.58126.67

94. Hardie K, Jamrozik K, Hankey GJ, Broadhurst RJ, Anderson C. Trends in five-year survival and risk of recurrent stroke after first-ever stroke in the Perth Community Stroke Study. *Cerebrovasc Dis*. 2005;19(3):179-185. doi:10.1159/000083253

95. Hata J, Tanizaki Y, Kiyohara Y, et al. Ten year recurrence after first ever stroke in a Japanese community: the Hisayama study. *J Neurol Neurosurg Psychiatry*. 2005;76(3):368-372. doi:10.1136/jnnp.2004.038166

96. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MSV. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. *Neurology*. 2006;66(5):641-646. doi:10.1212/01.wnl.0000201253.93811.f6

97. Xu G, Liu X, Wu W, Zhang R, Yin Q. Recurrence after ischemic stroke in chinese patients: impact of uncontrolled modifiable risk factors. *Cerebrovasc Dis*. 2007;23(2-3):117-120. doi:10.1159/000097047

98. Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CDA, Heuschmann PU. Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke

Register. *J Neurol Neurosurg Psychiatry*. 2009;80(9):1012-1018. doi:10.1136/jnnp.2008.170456

99. Lewsey J, Jhund PS, Gillies M, et al. Temporal trends in hospitalisation for stroke recurrence following incident hospitalisation for stroke in Scotland. *BMC Med*. 2010;8:23. doi:10.1186/1741-7015-8-23

100. Mohan KM, Wolfe CDA, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. *Stroke*. 2011;42(5):1489-1494. doi:10.1161/STROKEAHA.110.602615

101. Putaala J, Haapaniemi E, Metso AJ, et al. Recurrent ischemic events in young adults after first-ever ischemic stroke. *Ann Neurol*. 2010;68(5):661-671. doi:10.1002/ana.22091

102. Rutten-Jacobs LCA, Maaijwee NAM, Arntz RM, et al. Long-term risk of recurrent vascular events after young stroke: The FUTURE study. *Ann Neurol*. 2013;74(4):592-601. doi:10.1002/ana.23953

103. Aarnio K, Haapaniemi E, Melkas S, Kaste M, Tatlisumak T, Putaala J. Long-term mortality after first-ever and recurrent stroke in young adults. *Stroke*. 2014;45(9):2670-2676. doi:10.1161/STROKEAHA.114.005648

104. Pezzini A, Grassi M, Lodigiani C, et al. Predictors of long-term recurrent vascular events after ischemic stroke at young age: the Italian Project on Stroke in Young Adults. *Circulation*. 2014;129(16):1668-1676. doi:10.1161/CIRCULATIONAHA.113.005663

105. Andersen SD, Gorst-Rasmussen A, Lip GYH, Bach FW, Larsen TB. Recurrent Stroke: The Value of the CHA2DS2VASc Score and the Essen Stroke Risk Score in a Nationwide Stroke Cohort. *Stroke*. 2015;46(9):2491-2497. doi:10.1161/STROKEAHA.115.009912

106. Bergström L, Irewall AL, Söderström L, Ögren J, Laurell K, Mooe T. One-Year Incidence, Time Trends, and Predictors of Recurrent Ischemic Stroke in Sweden From 1998 to 2010: An Observational Study. *Stroke*. 2017;48(8):2046-2051. doi:10.1161/STROKEAHA.117.016815

107. Khanevski AN, Bjerkreim AT, Novotny V, et al. Recurrent ischemic stroke: Incidence, predictors, and impact on mortality. *Acta Neurol Scand*. 2019;140(1):3-8. doi:10.1111/ane.13093

108. Flach C, Muruet W, Wolfe CDA, Bhalla A, Douiri A. Risk and Secondary Prevention of Stroke Recurrence: A Population-Base Cohort Study. *Stroke*. 2020;51(8):2435-2444. doi:10.1161/STROKEAHA.120.028992

109. Rücker V, Heuschmann PU, O'Flaherty M, et al. Twenty-Year Time Trends in Long-Term Case-Fatality and Recurrence Rates After Ischemic Stroke Stratified by Etiology. *Stroke*. 2020;51(9):2778-2785. doi:10.1161/STROKEAHA.120.029972

110. Lin B, Zhang Z, Mei Y, et al. Cumulative risk of stroke recurrence over the last 10 years: a systematic review and meta-analysis. *Neurol Sci*. 2021;42(1):61-71. doi:10.1007/s10072-020-04797-5

111. Kolmos M, Christoffersen L, Kruuse C. Recurrent Ischemic Stroke - A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis*. 2021;30(8):105935. doi:10.1016/j.jstrokecerebrovasdis.2021.105935

112. Hong KS, Yegiaian S, Lee M, Lee J, Saver JL. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. *Circulation*. 2011;123(19):2111-2119. doi:10.1161/CIRCULATIONAHA.109.934786

113. Nohr EA, Olsen J. Commentary: Epidemiologists have debated representativeness for more than 40 years--has the time come to move on? *Int J Epidemiol*. 2013;42(4):1016-1017. doi:10.1093/ije/dyt102

114. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012;41(3):861-870. doi:10.1093/ije/dyr213

115. Austin Peter C., Lee Douglas S., Fine Jason P. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation*. 2016;133(6):601-609. doi:10.1161/CIRCULATIONAHA.115.017719

116. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol*. 2009;170(2):244-256. doi:10.1093/aje/kwp107

117. Haneuse S. Time-To-Event Analysis. In: *Modern Epidemiology*. 4th ed. Lippincott Williams & Wilkins; 2021:551-556.

118. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348(9038):1329-1339. doi:10.1016/s0140-6736(96)09457-3

119. Modig K, Talbäck M, Ziegler L, Ahlbom A. Temporal trends in incidence, recurrence and prevalence of stroke in an era of ageing populations, a longitudinal study of the total Swedish population. *BMC Geriatrics*. 2019;19(1):31. doi:10.1186/s12877-019-1050-1

120. Lackland DT, Roccella EJ, Deutsch AF, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(1):315-353. doi:10.1161/01.str.0000437068.30550.cf

121. Ayerbe L, Ayis S, Crichton S, Wolfe CDA, Rudd AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. *Stroke*. 2013;44(4):1105-1110. doi:10.1161/STROKEAHA.111.679340

122. Ayerbe L, Ayis S, Wolfe CDA, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. *Br J Psychiatry*. 2013;202(1):14-21. doi:10.1192/bjp.bp.111.107664

123. Hackett ML, Pickles K. Part I: frequency of depression after stroke: an updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2014;9(8):1017-1025. doi:10.1111/ijs.12357

124. Jørgensen TSH, Wium-Andersen IK, Wium-Andersen MK, et al. Incidence of Depression After Stroke, and Associated Risk Factors and Mortality Outcomes, in a Large Cohort of Danish Patients. *JAMA Psychiatry*. 2016;73(10):1032-1040. doi:10.1001/jamapsychiatry.2016.1932

125. Mayman N, Stein LK, Erdman J, et al. Risk and Predictors of Depression Following Acute Ischemic Stroke in the Elderly. *Neurology*. 2021;96(17):e2184-e2191. doi:10.1212/WNL.0000000000011828

126. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol*. 2009;8(11):1006-1018. doi:10.1016/S1474-4422(09)70236-4

127. Corraini P, Henderson VW, Ording AG, Pedersen L, Horváth-Puhó E, Sørensen HT. Long-Term Risk of Dementia Among Survivors of Ischemic or Hemorrhagic Stroke. *Stroke*. 2017;48(1):180-186. doi:10.1161/STROKEAHA.116.015242

128. Pendlebury ST, Rothwell PM. Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. *Lancet Neurol*. 2019;18(3):248-258. doi:10.1016/S1474-4422(18)30442-3

129. Koton S, Pike JR, Johansen M, et al. Association of Ischemic Stroke Incidence, Severity, and Recurrence With Dementia in the Atherosclerosis Risk in Communities Cohort Study. *JAMA Neurol*. 2022;79(3):271-280. doi:10.1001/jamaneurol.2021.5080

130. Ayerbe L, Ayis SA, Crichton S, Wolfe CDA, Rudd AG. Natural history, predictors and associated outcomes of anxiety up to 10 years after stroke: the South London Stroke Register. *Age Ageing*. 2014;43(4):542-547. doi:10.1093/ageing/aft208

131. Knapp P, Dunn-Roberts A, Sahib N, et al. Frequency of anxiety after stroke: An updated systematic review and meta-analysis of observational studies. *Int J Stroke*. 2020;15(3):244-255. doi:10.1177/1747493019896958

132. Vyas MV, Wang JZ, Gao MM, Hackam DG. Association Between Stroke and Subsequent Risk of Suicide: A Systematic Review and Meta-Analysis. *Stroke*. 2021;52(4):1460-1464. doi:10.1161/STROKEAHA.120.032692

133. Robinson RG, Price TR. Post-stroke depressive disorders: a follow-up study of 103 patients. *Stroke*. 1982;13(5):635-641. doi:10.1161/01.str.13.5.635

134. Ferro JM, Caeiro L, Figueira ML. Neuropsychiatric sequelae of stroke. *Nat Rev Neurol*. 2016;12(5):269-280. doi:10.1038/nrneurol.2016.46

135. Hackett ML, Köhler S, O'Brien JT, Mead GE. Neuropsychiatric outcomes of stroke. *Lancet Neurol*. 2014;13(5):525-534. doi:10.1016/S1474-4422(14)70016-X

136. Chun HYY, Ford A, Kutlubaev MA, Almeida OP, Mead GE. Depression, Anxiety, and Suicide After Stroke: A Narrative Review of the Best Available Evidence. *Stroke*. 2022;53(4):1402-1410. doi:10.1161/STROKEAHA.121.035499

137. Rost NS, Brodtmann A, Pase MP, et al. Post-Stroke Cognitive Impairment and Dementia. *Circ Res*. 2022;130(8):1252-1271. doi:10.1161/CIRCRESAHA.122.319951

138. Glozier N, Hackett ML, Parag V, Anderson CS. The influence of psychiatric morbidity on return to paid work after stroke in younger adults: the Auckland Regional Community Stroke (ARCOS) Study, 2002 to 2003. *Stroke*. 2008;39(5):1526-1532. doi:10.1161/STROKEAHA.107.503219

139. Busch MA, Coshall C, Heuschmann PU, McKevitt C, Wolfe CDA. Sociodemographic differences in return to work after stroke: the South London Stroke Register (SLSR). *J Neurol Neurosurg Psychiatry*. 2009;80(8):888-893. doi:10.1136/jnnp.2008.163295

140. Trygged S, Ahacic K, Kåreholt I. Income and education as predictors of return to working life among younger stroke patients. *BMC Public Health*. 2011;11:742. doi:10.1186/1471-2458-11-742

141. Hannerz H, Holbæk Pedersen B, Poulsen OM, Humle F, Andersen LL. A nationwide prospective cohort study on return to gainful occupation after stroke in Denmark 1996-2006. *BMJ Open*. 2011;1(2):e000180. doi:10.1136/bmjopen-2011-000180

142. Hackett ML, Glozier N, Jan S, Lindley R. Returning to paid employment after stroke: the Psychosocial Outcomes In StrokE (POISE) cohort study. *PLoS One*. 2012;7(7):e41795. doi:10.1371/journal.pone.0041795

143. Maaijwee NAMM, Rutten-Jacobs LCA, Arntz RM, et al. Long-term increased risk of unemployment after young stroke: a long-term follow-up study. *Neurology*. 2014;83(13):1132-1138. doi:10.1212/WNL.0000000000000817

144. Westerlind E, Persson HC, Sunnerhagen KS. Return to Work after a Stroke in Working Age Persons; A Six-Year Follow Up. *PLoS One*. 2017;12(1):e0169759. doi:10.1371/journal.pone.0169759

145. Glader EL, Jonsson B, Norrving B, Eriksson M. Socioeconomic factors' effect on return to work after first stroke. *Acta Neurol Scand*. 2017;135(6):608-613. doi:10.1111/ane.12639

146. Aarnio K, Rodríguez-Pardo J, Siegerink B, et al. Return to work after ischemic stroke in young adults: A registry-based follow-up study. *Neurology*. 2018;91(20):e1909-e1917. doi:10.1212/WNL.0000000000006510

147. Tibæk M, Kammersgaard LP, Johnsen SP, Dehlendorff C, Forchhammer HB. Long-Term Return to Work After Acquired Brain Injury in Young Danish Adults: A Nation-Wide Registry-Based Cohort Study. *Front Neurol*. 2018;9:1180. doi:10.3389/fneur.2018.01180

148. Sen A, Bisquera A, Wang Y, et al. Factors, trends, and long-term outcomes for stroke patients returning to work: The South London Stroke Register. *Int J Stroke*. 2019;14(7):696-705. doi:10.1177/1747493019832997

149. Westerlind E, Persson HC, Eriksson M, Norrving B, Sunnerhagen KS. Return to work after stroke: A Swedish nationwide registry-based study. *Acta Neurol Scand*. 2020;141(1):56-64. doi:10.1111/ane.13180

150. Vestling M, Tufvesson B, Iwarsson S. Indicators for return to work after stroke and the importance of work for subjective well-being and life satisfaction. *J Rehabil Med*. 2003;35(3):127-131. doi:10.1080/16501970310010475

151. Röding J, Glader EL, Malm J, Lindström B. Life satisfaction in younger individuals after stroke: different predisposing factors among men and women. *J Rehabil Med*. 2010;42(2):155-161. doi:10.2340/16501977-0497

152. Vestergaard SV, Rasmussen TB, Stallknecht S, et al. Occurrence, mortality and cost of brain disorders in Denmark: a population-based cohort study. *BMJ Open*. 2020;10(11):e037564. doi:10.1136/bmjopen-2020-037564

153. Edwards JD, Kapoor A, Linkewich E, Swartz RH. Return to work after young stroke: A systematic review. *Int J Stroke*. 2018;13(3):243-256. doi:10.1177/1747493017743059

154. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591. doi:10.2147/CLEP.S179083

155. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3

156. Mainz J, Krog BR, Bjørnshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. *Int J Qual Health Care*. 2004;16 Suppl 1:i45-50. doi:10.1093/intqhc/mzh031

157. Wildenschild C, Mehnert F, Thomsen RW, et al. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. *Clin Epidemiol*. 2013;6:27-36. doi:10.2147/CLEP.S50449

158. Hald SM, Kring Sloth C, Hey SM, et al. Intracerebral hemorrhage: positive predictive value of diagnosis codes in two nationwide Danish registries. *Clin Epidemiol*. 2018;10:941-948. doi:10.2147/CLEP.S167576

159. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

160. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(7 Suppl):54-57. doi:10.1177/1403494810395825

161. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f. doi:10.1093/ije/dyw213

162. Helweg-Larsen K. The Danish Register of Causes of Death. *Scand J Public Health*. 2011;39(7 Suppl):26-29. doi:10.1177/1403494811399958

163. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7 Suppl):12-16. doi:10.1177/1403494811399956

164. Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. *Scand J Public Health*. 2007;35(5):497-502. doi:10.1080/14034940701271882

165. Statistics Denmark. StatBank Denmark. https://www.statbank.dk/statbank5a/default.asp?w=1920

166. Sonne A, Andersen JB, Rasmussen LS. The positive predictive value of spontaneous subarachnoid hemorrhage diagnoses in the Danish National Patient Register. *Clin Epidemiol*. 2019;11:323-331. doi:10.2147/CLEP.S197251

167. Heide-Jørgensen U, Adelborg K, Kahlert J, Sørensen HT, Pedersen L. Sampling strategies for selecting general population comparison cohorts. *Clin Epidemiol*. 2018;10:1325-1337. doi:10.2147/CLEP.S164456

168. Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. *Stroke*. 1985;16(5):885-890. doi:10.1161/01.STR.16.5.885

169. Gray LJ, Ali M, Lyden PD, Bath PMW, Virtual International Stroke Trials Archive Collaboration. Interconversion of the National Institutes of Health Stroke Scale and Scandinavian Stroke Scale in acute stroke. *J Stroke Cerebrovasc Dis*. 2009;18(6):466-468. doi:10.1016/j.jstrokecerebrovasdis.2009.02.003

170. Boyle P, Parkin DM. Cancer registration: principles and methods. Statistical methods for registries. *IARC Sci Publ*. 1991;(95):126-158.

171. Stern J, Kirkwood BR. *Essential Medical Statistics*. 2nd ed. John Wiley And Sons Ltd

172. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med*. 2009;28(29):3670-3682. doi:10.1002/sim.3733

173. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19(3):335-351. doi:10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z

174. Statistical Research and Applications Branch, National Cancer Institute. Joinpoint Regression Program. Published online February 2019.

175. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association*. 1958;53(282):457-481.

176. Aalen OO, Johansen S. An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. *Scandinavian Journal of Statistics*. 1978;5:141-150.

177. Cox DR. Regression Models and Life-Tables. *Journal of the Royal Statistical Society*. 1972;34(2):187-202.

178. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association*. 1999;94(446):496-509.

179. Hernán MA. The Hazards of Hazard Ratios. *Epidemiology*. 2010;21(1):13-15. doi:10.1097/EDE.0b013e3181c1ea43

180. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ*. 2019;367:l5657. doi:10.1136/bmj.l5657

181. Izem R, Liao J, Hu M, et al. Comparison of propensity score methods for pre-specified subgroup analysis with survival data. *J Biopharm Stat*. 2020;30(4):734-751. doi:10.1080/10543406.2020.1730868

182. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/bmj.b2393

183. Choi J, Dekkers OM, le Cessie S. A comparison of different methods to handle missing data in the context of propensity score analysis. *Eur J Epidemiol*. 2019;34(1):23-36. doi:10.1007/s10654-018-0447-z

184. Burke JF, Skolarus LE. Are More Young People Having Strokes?-A Simple Question With an Uncertain Answer. *JAMA Neurol*. 2017;74(6):639-641. doi:10.1001/jamaneurol.2017.0161

185. Li L, Binney LE, Luengo-Fernandez R, Silver LE, Rothwell PM. Temporal trends in the accuracy of hospital diagnostic coding for identifying acute stroke: A population-based study. *Eur Stroke J*. 2020;5(1):26-35. doi:10.1177/2396987319881017

186. Scott CA, Li L, Rothwell PM. Diverging Temporal Trends in Stroke Incidence in Younger vs Older People: A Systematic Review and Meta-analysis. *JAMA Neurol*. Published online August 9, 2022. doi:10.1001/jamaneurol.2022.1520

187. Danish Health Authority. *Danskernes Sundhed - Den Nationale Sundhedsprofil 2021*. https://www.sst.dk/-/media/Udgivelser/2022/Sundhedsprofil/Sundhedsprofilen.ashx

188. Adelborg K, Grove EL, Sundbøll J, Laursen M, Schmidt M. Sixteen-year nationwide trends in antithrombotic drug use in Denmark and its correlation with landmark studies. *Heart*. 2016;102(23):1883-1889. doi:10.1136/heartjnl-2016-309402

189. Hsieh CY, Lin HJ, Hu YH, Sung SF. Stroke severity may predict causes of readmission within one year in patients with first ischemic stroke event. *Journal of the Neurological Sciences*. 2017;372:21-27. doi:10.1016/j.jns.2016.11.026

190. Dhamoon MS, Longstreth WT, Bartz TM, Kaplan RC, Elkind MSV. Disability Trajectories Before and After Stroke and Myocardial Infarction: The Cardiovascular Health Study. *JAMA Neurol*. 2017;74(12):1439-1445. doi:10.1001/jamaneurol.2017.2802

191. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. *Stroke*. 2009;40(6):2068-2072. doi:10.1161/STROKEAHA.108.540112

192. Terrill AL, Schwartz JK, Belagaje SR. Best Practices for The Interdisciplinary Rehabilitation Team: A Review of Mental Health Issues in Mild Stroke Survivors. *Stroke Res Treat*. 2018;2018. doi:10.1155/2018/6187328

193. Skajaa N, Adelborg K, Horváth-Puhó E, et al. Nationwide Trends in Incidence and Mortality of Stroke Among Younger and Older Adults in Denmark. *Neurology*. 2021;96(13):e1711-e1723. doi:10.1212/WNL.0000000000011636

194. Skajaa N, Adelborg K, Horváth-Puhó E, et al. Risks of Stroke Recurrence and Mortality After First and Recurrent Strokes in Denmark: A Nationwide Registry Study. *Neurology*. Published online November 29, 2021:10.1212/WNL.0000000000013118. doi:10.1212/WNL.0000000000013118

195. Huybrechts KF, Schneeweiss S. Studies Relying on Secondary Data. In: *Modern Epidemiology*. 4th ed. Lippincott Williams & Wilkins; 2021:247-262.

196. Rothman KJ, Lash TL. Precision and Study Size. In: *Modern Epidemiology*. 4th ed. Lippincott Williams & Wilkins; 2021:333-364.

197. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Bull World Health Organ*. 2007;85(11):867-872. doi:10.2471/blt.07.045120

198. Rothman KJ. Six persistent research misconceptions. *J Gen Intern Med*. 2014;29(7):1060-1064. doi:10.1007/s11606-013-2755-z

199. Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature*. 2019;567(7748):305-307. doi:10.1038/d41586-019-00857-9

200. Rothman KJ, Lash TL. Selection Bias and Generalizability. In: *Modern Epidemiology*. 4th ed. Lippincott Williams & Wilkins; 2021:315-331.

201. Kurth T, Gaziano JM, Berger K, et al. Body mass index and the risk of stroke in men. *Arch Intern Med*. 2002;162(22):2557-2562. doi:10.1001/archinte.162.22.2557

202. Andersen KK, Olsen TS. The Obesity Paradox in Stroke: Lower Mortality and Lower Risk of Readmission for Recurrent Stroke in Obese Stroke Patients. *International Journal of Stroke*. 2015;10(1):99-104. doi:10.1111/ijs.12016

203. Banack HR, Kaufman JS. The "obesity paradox" explained. *Epidemiology*. 2013;24(3):461-462. doi:10.1097/EDE.0b013e31828c776c

204. Lash TL, VanderWeele TJ, Rothman KJ. Measurement and Measurement Error. In: *Modern Epidemiology*. 4th ed. Lippincott Williams & Wilkins; 2021:287-314.

205. Yland JJ, Wesselink AK, Lash TL, Fox MP. Misconceptions About the Direction of Bias From Nondifferential Misclassification. *Am J Epidemiol*. 2022;191(8):1485-1495. doi:10.1093/aje/kwac035

206. Andersen KK, Olsen TS. Social Inequality by Income in Short- and Long-Term Cause-Specific Mortality after Stroke. *J Stroke Cerebrovasc Dis*. 2019;28(6):1529-1536. doi:10.1016/j.jstrokecerebrovasdis.2019.03.013

207. Tøllefsen IM, Helweg-Larsen K, Thiblin I, et al. Are suicide deaths under-reported? Nationwide re-evaluations of 1800 deaths in Scandinavia. *BMJ Open*. 2015;5(11). doi:10.1136/bmjopen-2015-009120

208. Jensen MM, Hald SM, Kristensen LMB, Boe NJ, Harbo FSG, Gaist D. Validity of Simple Algorithms to Identify Recurrence of Intracerebral Hemorrhage in Two Danish Nationwide Registries. *Clin Epidemiol*. 2021;13:949-958. doi:10.2147/CLEP.S333624

209. Munk-Jørgensen P, Østergaard SD. Register-based studies of mental disorders. *Scand J Public Health*. 2011;39(7 Suppl):170-174. doi:10.1177/1403494810390728

210. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. *Clin Pract Epidemiol Ment Health*. 2009;5:4. doi:10.1186/1745-0179-5-4

211. Phung TKT, Andersen BB, Høgh P, Kessing LV, Mortensen PB, Waldemar G. Validity of dementia diagnoses in the Danish hospital registers. *Dement Geriatr Cogn Disord*. 2007;24(3):220-228. doi:10.1159/000107084

212. Osler M, Rozing MP, Wium-Andersen IK, et al. Use of register- and survey-based measures of anxiety in a population-based Danish cohort. *Acta Psychiatr Scand*. Published online June 17, 2021. doi:10.1111/acps.13339

213. Gasse C, Danielsen AA, Pedersen MG, Pedersen CB, Mors O, Christensen J. Positive predictive value of a register-based algorithm using the Danish National Registries to identify suicidal events. *Pharmacoepidemiol Drug Saf*. 2018;27(10):1131-1138. doi:10.1002/pds.4433

214. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6(11). doi:10.1136/bmjopen-2016-012832

215. VanderWeele TJ, Rothman KJ, Lash TL. Confounding and Confounders. In: *Modern Epidemiology*. 4th ed. Lippincott Williams & Wilkins; 2021:263-286.

216. Fox MP, Murray EJ, Lesko CR, Sealy-Jefferson S. On the Need to Revitalize Descriptive Epidemiology. *Am J Epidemiol*. Published online March 22, 2022:kwac056. doi:10.1093/aje/kwac056

217. Lesko CR, Buchanan AL, Westreich D, Edwards JK, Hudgens MG, Cole SR. Generalizing study results: a potential outcomes perspective. *Epidemiology*. 2017;28(4):553-561. doi:10.1097/EDE.0000000000000664

218. Markus HS, Khan U, Birns J, et al. Differences in stroke subtypes between black and white patients with stroke: the South London Ethnicity and Stroke Study. *Circulation*. 2007;116(19):2157-2164. doi:10.1161/CIRCULATIONAHA.107.699785

219. Schwamm LH, Reeves MJ, Pan W, et al. Race/ethnicity, quality of care, and outcomes in ischemic stroke. *Circulation*. 2010;121(13):1492-1501. doi:10.1161/CIRCULATIONAHA.109.881490

11. Appendices

Full versions of Studies I-IV including supplemental materials.

The papers have been removed from the file due to copyright issues