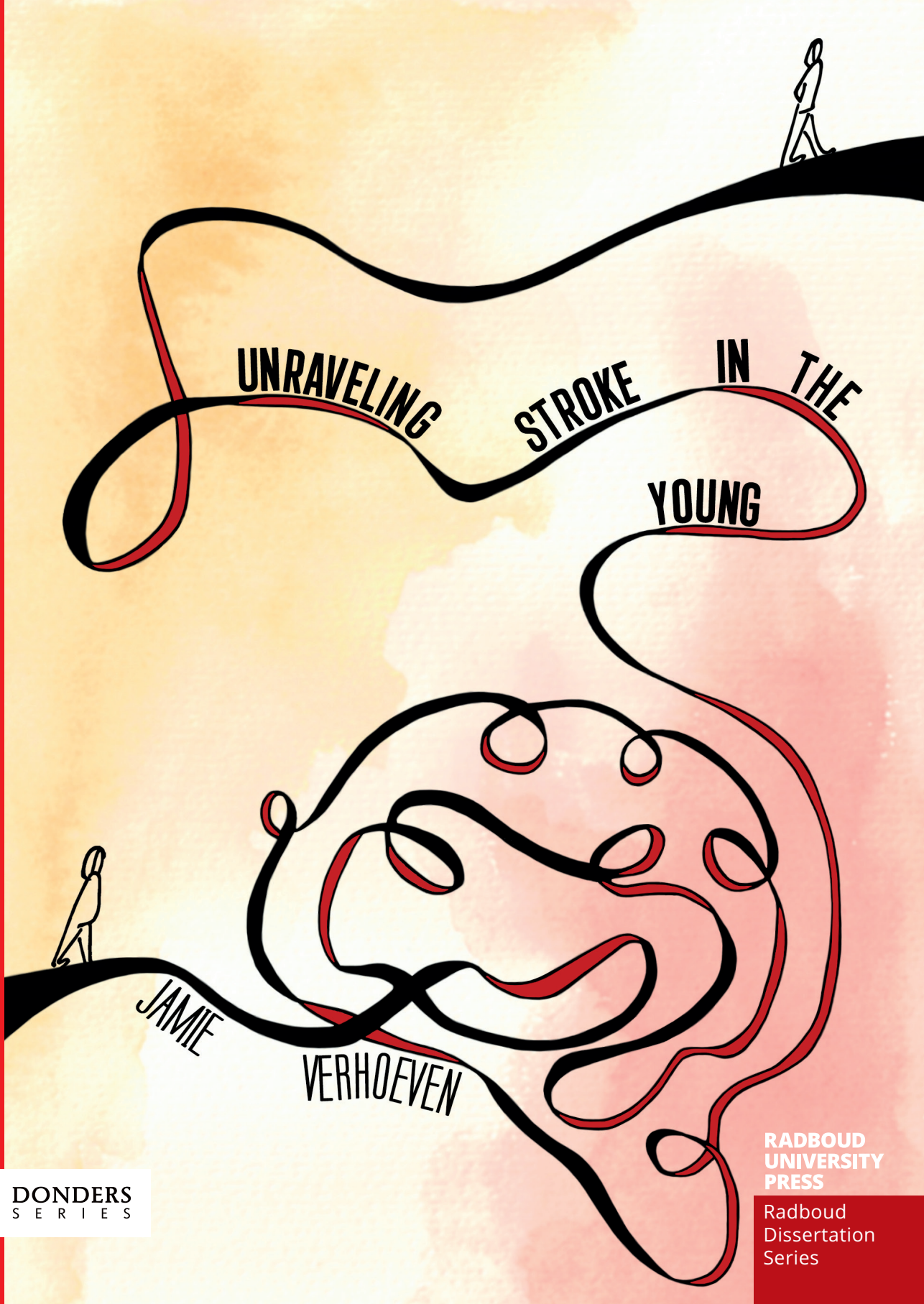


DONDERS SERIES

RADBOUD UNIVERSITY PRESS

Radboud Dissertation Series

UNRAVELING STROKE IN THE YOUNG

Jamie Inge Verhoeven

Author: Jamie Inge Verhoeven
Title: Unraveling Stroke in the Young

Radboud Dissertation Series
ISSN: 2950-2772 (Online); 2950-2780 (Print)

Published by RADBOUD UNIVERSITY PRESS
Postbus 9100, 6500 HA Nijmegen, The Netherlands
www.radbouduniversitypress.nl

Design: Proefschrift AIO | Guus Gijben
Cover: Jamie Verhoeven & Sophie Pouwels
Printing: DPN Rikken/Pumbo

ISBN: 9789465150376
DOI: 10.54195/9789465150376
Free download at: https://doi.org/10.54195/9789465150376

RADBOUD
UNIVERSITY
PRESS

Unraveling Stroke in the Young

Proefschrift ter verkrijging van de graad van doctor

aan de Radboud Universiteit Nijmegen

op gezag van de rector magnificus prof. dr. J.M. Sanders,

volgens besluit van het college voor promoties

in het openbaar te verdedigen op

donderdag 20 maart 2025

om 12.30 uur precies

door

Jamie Inge Verhoeven

geboren op 20 juli 1994

te Nijmegen

Promotoren:
Prof. dr. H.F. de Leeuw
Prof. dr. C.J.M. Klijn
Prof. dr. M.J.M. Broeders

Copromotor:
Dr. C.M.L. Driessen

Manuscriptcommissie:
Prof. dr. S. Middeldorp
Prof. dr. C.M.L. van Herpen
Dr. J.M. Coutinho (AmsterdamUMC)

Table of contents

Part Five: Summary and general discussion

Part Six: Appendices

PART ONE

INTRODUCTION

Chapter I

General introduction, aims and outline

General introduction

Stroke is defined as an acute neurological deficit, caused by a sudden occlusion of a cerebral artery (ischemic stroke or transient ischemic attack [TIA]), or spontaneous rupture of a cerebral artery (intracerebral hemorrhage [ICH]). The distinction between ischemic stroke and TIA is historically based on the duration of symptoms; with symptoms present for less than 24 hours (TIA) or more than 24 hours (ischemic stroke).[1] In recent years an imaging proven TIA is often classified as an ischemic stroke.[2]

Currently, 10-15% of all first-ever strokes occur in young adults aged 18 to 49 years old. This amounts to around 3000 patients in the Netherlands every year, and over 2 million worldwide.[3] Furthermore, the stroke burden of these young patients is huge compared to older patients, as they very often still have decades to live. The consequences of a stroke at young age are often life-long and impact these patients in demanding periods of their lives, with young families, budding careers and busy social lives. To provide optimal treatment and care for these young patients with ischemic stroke, TIA or ICH, we need to unravel the still unknown mechanisms behind stroke occurring at young age, as well as the long-term implications of stroke in the young, regarding long-term risk of recurrence, possible adverse effects of treatment, risk of death, but also the socioeconomic sequela.

Epidemiology of stroke in the young

Despite serious improvements in stroke diagnostics and acute treatment, as well as improved primary and secondary prevention over the last decades, stroke remains the leading cause of disability worldwide.[4] And although in recent years we have seen a decline of stroke incidence in the elderly, the incidence of stroke in young adults has continued to increase.[5] This may be partially explained by improved stroke detection because of more advanced neuro-imaging. In addition, the rapidly increasing prevalence of classic cardiovascular risk-factors like diabetes and hypertension, even already during childhood and early adolescence and other newly identified risk-factors like illicit drug use and air pollution may contribute as well.[6-8] Detailed analysis of time trends in stroke incidence of different subgroups in stroke subtype, age and sex, will provide more insight in the mechanisms behind this overall increase.

The nature and implications of stroke at young age are very different from older patients and therefore knowledge gained in the elderly stroke population cannot simply be extrapolated to the young. This is illustrated by the fact that despite an extensive routine diagnostic work-up, in 30% of patients aged 18-49 years old no cause of stroke can be identified.[9] The current classification system used for ischemic stroke and TIA (Trial of Org 10172 in Acute Stroke Treatment [TOAST]) has been validated in the elderly stroke population and largely relies on atherosclerosis-related stroke and cardiac causes, like atrial fibrillation.[10] These causes are highly prevalent in the older stroke population, but rare in young adults. The high number of strokes of *undetermined cause* (cryptogenic) is likely partially explained by the fact that the TOAST classification focuses on common causes of stroke and does not recognize any age-specific risk-factors. In children and adolescents the *International Pediatric Stroke Study* classification (IPSS) is used, which is an extensive risk factor based classification system.[11,12] Investigating (clusters of) more age specific and newly identified risk-factors in young adults with ischemic stroke may provide insight in still unelucidated pathophysiological mechanisms.

Recently, there has been more attention for environmental risk-factors like air pollution, which may also play a role in stroke manifesting at a younger age.[13] According to the global burden of disease study, air pollution is the most important environmental risk factor and contributes to 16% of the global stroke burden. Although both short-term fluctuations and long-term exposure have been shown to be associated with an increased incidence of ischemic stroke, and to a lesser degree with intracerebral hemorrhage, currently over 90% of people live in areas that exceed the air pollution regulations set by the World Health Organization.[7,14,15] Despite that many of the previously performed epidemiological studies having significant methodological limitations and the fact that the exact pathophysiological mechanisms behind pollution related stroke remain uncertain, the association between air pollution and cardiovascular disease is widely accepted.[16] To translate these findings into clinical practice, we need to know on an individual patient level, which patients are most at risk of pollution-related stroke, and how air pollutants interact with other risk-factors.

Stroke in the young: Cancer in disguise?

Stroke and cancer can be intimately related, as stroke may be a first manifestation of an occult cancer. Patients with an active cancer are at increased risk of mainly ischemic stroke because of direct tumor effects, prothrombotic effects, and

treatment effects. In addition, ischemic stroke and most cancers have joint risk-factors, like smoking and obesity.[17,18] Previous hospital-based studies have shown that approximately 2-5% of all patients with an ischemic stroke, receive a new cancer diagnosis in the first year after stroke.[19,20] In hindsight, this newly diagnosed cancer can be considered as occult, yet already active at the time of the stroke, and may have played a role in causing the stroke. The percentage of patients with occult cancer at the time of stroke has been reported to be highest in patients with a cryptogenic stroke.[20] Therefore, the association between stroke and cancer may be most pronounced in young adults, and may explain some of the 30% cryptogenic strokes in young adults.[9] As of yet, there is scarce literature available on this association between stroke and cancer at young age for both ischemic stroke and intracerebral hemorrhage.

In the last decades cancer treatment has dramatically improved, making earlier diagnosis more and more important to ensure a good outcome. Thus, identifying patients with ischemic stroke or intracerebral hemorrhage at high risk of an underlying occult malignancy (as cause of their stroke) may contribute to earlier diagnosis and ergo earlier treatment. Previous studies have suggested some clinical risk-factors for an occult cancer in ischemic stroke patients: age, smoking, inflammatory markers, d-dimer, and multiple vascular territories involved (three territory sign) on neuro-imaging.[18,19,21] However, these risk-factors have not been studied in young adults, who not only differ from older adults in risk-factors, but also in cancer incidence.

Long-term prognosis of stroke in young adults

Despite the long-lasting sequelae and therefore high burden of stroke in young adults, literature on long-term mortality and consequences of both ischemic stroke and especially of ICH at young age is limited. Long-term mortality, its predictors, but also causes of death may be very different for young patients with ischemic stroke or ICH compared to older patients.[22,23] In addition, it is important to study more recent data and investigate time trends in long-term outcomes, as stroke care regarding acute interventions and secondary prevention has changed considerably in the last decades.

To prevent recurrent ischemic stroke or TIA in these young patients, generally life-long antiplatelet therapy is prescribed. The evidence for this treatment is based on randomized clinical trials in which young patients were highly underrepresented

and with a limited follow-up of only a few years.[24,25] This one-size fits all approach based on the older stroke population may not be appropriate for young patients as their long-term prognosis is much more heterogenous and their life expectancy is much longer. Long-term treatment with antiplatelet therapy also carries a risk of bleeding complications, and although young patients remain at risk of complications for many more years compared to older patients, these complications have only very sparsely been investigated.[25-27]

Aim of this thesis and study design

The aim of this thesis was to investigate the incidence, risk-factors and etiology, as well as the long-term prognosis of both ischemic stroke and ICH in young adults aged 18 – 49 years old.

The original research studies included in this thesis are based on registry-based datasets from Statistics Netherlands (CBS) and the Comprehensive Dutch Cancer Organization (IKNL), as well as three observational cohort studies; the Observational Dutch Young Symptomatic StrokE study (ODYSSEY), the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study, and the Prognosis of InTra-Cerebral Hemorrhage (PITCH) cohort. The cohort and registry characteristics are listed in table 1 and 2.

Table 1: Characteristics of Cohort studies used in this thesis

	Observational Dutch Young Symptomatic StrokE studY	**Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation study**	**Prognosis of Intracerebral Hemorrhage Cohort**
Acronym	**ODYSSEY**	**FUTURE**	**PITCH**
Chapters	IV, VI, VI	VI, IX	VIII
Study design	Multicenter prospective observational cohort study	Single center prospective observational cohort study	Single center prospective observational cohort study
Protocol paper	Arntz, et al (2014) [28]	Rutten-Jacobs, et al (2010) [29]	Cordonnier, et al (2009) [30]
Stroke subtypes	Ischemic stroke, ICH	Ischemic stroke, TIA and ICH	ICH
Diagnosis	Imaging-proven	Clinical diagnosis	Imaging-proven
Inclusion site(s)	17 centers across the Netherlands	Radboud University medical center	Lille University hospital
Inclusion period	2013 – 2021	1980 – 2010	2004 – 2007
Number of patients	1492	1005	373
Median age at stroke, (IQR)	44.1 (9.4)	42.0 (11.4)	70 (11.5)
Women, n (%)	695 (46.5)	661 (52.5)	198 (53.0)

Table 2: Characteristics of Nationwide Registries used in this thesis

	Dutch hospital discharge registry	**Dutch Cancer Registry**
Data owned by	Statistics Netherlands (CBS)	Dutch Comprehensive Cancer Organization (IKNL)
Years of availability	1998 – 2018	1989 – 2021
Linkage procedures	linkage key of date of birth, sex and numeric part of postal code	linkage key of date of birth, sex, initials, surname and postal code
Chapters	II, V, VII	V, VI
Unique Linkage to study population (estimated)	85-100% [31]	98% [32]
Linkage performed in this thesis	Population Register and national Cause of Death register	ODYSSEY and FUTURE study

Outline of this thesis

Chapter II describes the time trends, and sex- and age-differences in both ischemic stroke and intracerebral hemorrhage incidence in young adults in the Netherlands between 1998 and 2010, using administrative data from Statistics Netherlands.

In part two, chapter III, I investigated risk-factors and causes of ischemic stroke in young adults in the Netherlands, who took part in the ODYSSEY. In this study, we classified patients according to both the TOAST and IPSS criteria and focused on the prevalence of different risk-factors in patients with a cryptogenic stroke. **Chapter IV** is a narrative review on the association between short-term and long-term exposure to ambient air pollution and the incidence of both ischemic stroke and intracerebral hemorrhage. This review provides a detailed outlook on the available evidence focusing on individual patient characteristics associated with air pollutant-related stroke, methodological limitations and future perspectives.

In the **third part** of this thesis, I investigated whether the risk of a new cancer diagnosis in the first years after stroke in young adults and older adults is increased, compared to peers from the population, again with nationwide data from Statistics Netherlands, and data from IKNL (**chapter V**). In **chapter VI**, I studied the patient- and stroke-characteristics associated with underlying cancer in the participants of the ODYSSEY and FUTURE study after linkage with the Dutch Cancer Registry of the IKNL.

In **part four**, I focused on the long-term outcomes in young adults with ischemic stroke and intracerebral hemorrhage. In **chapter VII**, I studied the long-term risk of mortality in both young patients with ischemic stroke and intracerebral hemorrhage in the Netherlands, as well as time trends in long-term mortality between 1998 and 2018, and causes of death. **Chapter VIII** reports the long-term mortality risk, with clinical-, as well as imaging-related predictors of long-term mortality, in a small but unique French population of young adults with spontaneous ICH. In **chapter IX**, I combined prospectively and retrospectively collected data to study the long-term risk of bleeding events versus recurrent ischemic events in young patients with ischemic stroke from the FUTURE study.

The final part of this thesis (**Part five**) includes a summary (**chapter X** in English; **chapter XII** in Dutch) and general discussion of the main results with implications and recommendations for future research and clinical practice (**chapter XI**).

Chapter II

Stroke incidence in young adults according to age, subtype, sex, and time trends

Published as: 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 May 21;92(21):e2444-e2454. Epub 2019 Apr 24.

** Shared first authorship*

Abstract

Objective: To investigate incidence of stroke and its subtypes in young adults, according to sex and age, and to study trends over time.

Methods: We established a nationwide cohort through linkage of national registries (hospital discharge-, cause of death-, and population-register) with patients aged 18-50 years and those ≥ 50 with first-ever ischemic stroke, intracerebral hemorrhage or unspecified stroke, using ICD-9/-10 codes between 1998 and 2010 in the Netherlands. Outcomes were yearly incidence of stroke stratified by age-, sex-, stroke-subtype, its changes over time, and comparison of incidence in patients 18-50 to patients ≥ 50.

Results: We identified 15,257 patients (53% women; mean age 41.8). Incidence increased exponentially with age (R2=0.99) and was higher for women than men, most prominently in the youngest patients (18-44). The relative proportion of ischemic stroke increased with age (18-24: 38.3%; 44-49: 56.5%), whereas the relative proportion of intracerebral hemorrhage decreased (18-24: 34.0%; 44-49: 18.3%). Incidence of any stroke in young adults increased (1998: 14.0/ 100,000 person-years: 2010: 17.2; +23%; p <0.001), driven by an increase in those aged over 35 and ischemic stroke incidence (46%), whereas incidence decreased in those ≥ 50 (329.1 to 292.2; -11%; p = 0.009).

Conclusions: Incidence of any stroke in the young increases with age in patients over 35, is higher in women than men aged 18-44 and has increased by 23% in one decade, through an increase in ischemic stroke. Incidence of intracerebral hemorrhage is comparable for women and men and remained stable over time.

Introduction

An estimated 10-15% of all first-ever strokes occur in people aged 18 to 50 years.[3,6] With a yearly stroke incidence of 15 million people worldwide, at least 1.5 million young adults are affected every year.[33] The consequences of stroke in the young are substantial and, due to their long survival after stroke, long-lasting. Sequelae of stroke in the young have specific implications in relation to their age, as young patients are often at cross-roads in their lives with young families, demanding careers, and social interactions that may remain impaired for decades to come. In addition, the social-economic burden of stroke in the young is high, considering the number of productive life years lost.[34,35]

Despite improvement in the prevention and treatment of cardiovascular disease, recent studies have suggested an increase in the incidence of stroke in young adults, which is in contrast with the decrease in incidence observed in the elderly.[6,9,36-41] However, there are still several uncertainties. Due to low patient numbers it is unknown whether the suggested increase in incidence is present across all age strata for both men and women. In addition, most previous studies were (single) hospital based (with the possibility of selection bias) or occurred in countries where not all patients with stroke were likely to be seen by a neurologist, were limited to either ischemic stroke, intracerebral hemorrhage, or did not specify a stroke subtype, and included also subarachnoid hemorrhage. The studies also had varying lower and upper age limits to define young adults, did not always adjust for the total number of individuals within the general population when reporting the (change of) incidence and did not compare results with time-trend in incidence of stroke in patients over 50 years of age to determine whether observed time-trends were age-specific.

We therefore investigated age- and sex-specific incidence, and incidence trends over time of first-ever ischemic stroke and intracerebral hemorrhage among young adults in the Netherlands.

Methods

Patients

Through linkage of the Dutch Hospital Discharge Register (HDR) and Population Register all Dutch patients with a hospitalization for first-ever stroke (either ischemic stroke, intracerebral hemorrhage or stroke not otherwise specified) were

identified between 1998 and 2010, using ICD-9 codes for stroke (International Classification of Diseases). We also utilized the Cause of Death Register with the Population Register to identify all Dutch persons who died from a first-ever stroke outside of the hospital between 1998 and 2010, using ICD-10 codes for stroke (Table 1). The index event was operationalized through selecting the first admission for stroke from 01-01-1998 onwards, since we were unable to identify possible previous strokes before this date. We excluded patients with subarachnoid hemorrhage or cerebral venous sinus thrombosis.

The validity of ICD-codes for identifying patients with ischemic stroke and intracerebral hemorrhage has been demonstrated for stroke patients of all ages,[42,43] but not for young adults specifically. At young age, some stroke mimics like for example migraine and seizures may occur more frequently than in the elderly.[44] Therefore we assessed the validity of the ICD codes for 569 patients with a stroke at young age (301 with an ischemic stroke, 183 patients with intracerebral hemorrhage and 85 with an unspecified stroke), hospitalized between January 1998 and May 2017 in two academic and one large non-academic teaching hospital. We chose to analyze all data that was available to us of patients that had complete files including neuro imaging (n=569), therefore not restricting the validation period to our study period, to sample as many young stroke patients as possible to provide a more reliable validation analysis. We compared all ICD-9 or ICD-10 codes logged as discharge codes in the local hospital administration with the main diagnosis (including findings on neuro-imaging) in the medical files. Ischemic stroke was correctly diagnosed through registered ICD-codes in 90.4% of cases, intracerebral hemorrhage in 86.3%, and unspecified stroke in 87.1% of all cases, comparable to the validity in the general stroke population. Of the 74 unspecified strokes, 67 (90.5%) were ischemic strokes and 7 were intracerebral hemorrhages (9.5%) (Table 2).[42,43]

The HDR contains records of all individual hospital admissions of the participating Dutch hospitals, including information about primary diagnosis (four digit ICD-9 codes) as well as date of birth, sex and numeric part of the postal code. Using these personal identifiers, we linked the HDR admission records containing the selected ICD-9 codes for stroke with the Population Register to link multiple hospital admissions of one person. Approximately 85% of the Dutch population can be identified through a unique combination of their date of birth, sex and postal code.[31] These registers and linkage procedures have been previously described in detail.[31,45,46]

In addition, we identified patients who were not admitted to the hospital because they died outside the hospital either primarily or secondarily from first-ever stroke through the cause of death register using ICD-10 codes (Table 1).

Table 1: Overview of used ICD-9 and ICD-10 codes

ICD-9	
Any stroke	
431	Intracerebral hemorrhage
433	Occlusion and stenosis of pre-cerebral arteries with/without cerebral infarction
434	Occlusion of cerebral arteries with/without cerebral infarction
436	Stroke, unspecified as hemorrhagic or infarction
Intracerebral hemorrhage	
431	Intracerebral hemorrhage
Ischemic stroke	
433	Occlusion and stenosis of pre-cerebral arteries with/without cerebral infarction
434	Occlusion of cerebral arteries with/without cerebral infarction
Unspecified stroke	
436	Stroke, unspecified as hemorrhagic or infarction
ICD-10	
Any stroke	
I61	Intracerebral hemorrhage
I63	Cerebral infarction
I64	Stroke, unspecified as hemorrhagic or infarction
Intracerebral hemorrhage	
I61	Intracerebral hemorrhage
Ischemic stroke	
I63	Cerebral infarction
Unspecified stroke	
I64	Stroke, unspecified as hemorrhagic or infarction

From 2005 onwards fewer hospitals participated in the HDR, leading to an increasing number of missing records. In 2005 1.1% of records were missing, whereas between 2006 and 2010 the percentage of missing records varied between 10.5 and 14.0%. The estimated number of actual strokes by Statistics Netherlands is listed in the Supplementary Material, as well as an overview of contributing centers, and a table concerning the regional coverage of the HDR from 2006 to 2010.

Case definition

Any stroke was defined as a first-ever hospitalization for ischemic stroke, intracerebral hemorrhage or unspecified stroke (either ischemic or hemorrhagic, but not specified as such) or out-of-hospital death due to first-ever stroke. We defined young adults as those aged between 18 to 50 years old at the time of stroke and the reference group as those aged ≥ 50 years.

Table 2: Results of validation procedure

	Ischemic stroke	Intracerebral hemorrhage	Unspecified stroke
Total N	301	183	85
Correct diagnosis, N (%)	272 (90.4%)	158 (86.3%)	74 (87.1%)
Incorrect diagnoses N (%)	29 (9.4%)	25 (13.7%)	11 (12.9%)
	5 (1.7%) – conversion	4 (2.2%) – traumatic ICH	4 (4.7%) – conversion
	4 (1.3%) – vestibulopathy	10 (5.5%) – PMH [f]	3 (3.5%) – neoplasm
	3 (1.0%) – TIA [a]	3 (1.6%) – SAH [c]	2 (2.4%) – TIA
	3 (1.0%) – ICH [b]	8 (4.4%) – ischemic stroke	1 (1.2%) – traumatic ICH
	3 (1.0%) – SAH [c]		1 (1.2%) – CADASIL [g]
	2 (0.7%) – neoplasm		
	2 (0.7%) – encephalitis/meningitis		
	1 (0.3%) – migraine with aura		
	1 (0.3%) – HaNDL syndrome [d]		
	1 (0.3%) – SUSAC syndrome		
	1 (0.3%) – subdural hematoma		
	1 (0.3%) – MS [e]		
	1 (0.3%) – PMH [f]		
	1 (0.3%) – traumatic ICH		

[a] TIA = transient ischemic attack. [b] ICH = intracerebral hemorrhage. [c] SAH = subarachnoid hemorrhage. [d] HaNDL syndrome = 'Headache and Neurological Deficit with cerebrospinal fluid Lymphocytosis'. [e] MS = multiple sclerosis. [f] PMH = perimesencephalic hemorrhage. [g] CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Data analysis

We calculated the crude age-, sex-, and stroke subtype- specific incidence per 100,000 person-years for each consecutive year from 1998 to 2010. For this, we used the age-, sex- and year- specific population estimates from Statistics Netherlands.[47]

We assessed age-specific differences in stroke incidence between men and women by calculating incidence rate ratio's (IRR) including 95% confidence intervals based on Poisson distribution.

We also calculated the relative proportions of stroke subtypes in young adults according to age- and sex-strata and under the age of 50 in the stroke population and compared differences herein by chi-squared test of proportions.

Finally, we calculated the 13-year relative change in incidence for each age- and sex-subgroup by using the following formula: (incidence 2010 – incidence 1998)/ incidence 1998, and tested for significant trends in incidence rates over time by linear regression, by age- and sex-subgroup for individuals 18-50 years and those ≥ 50 years.

We used SPSS Software version 22, R version 3.2.2 (Package rateratio.test), MedCalc statistical software 2018 and Microsoft Office Excel 2007.

Data Availability

All data used for analysis are presented in the tables and supplementary tables. Data will be shared after ethics approval if requested by other investigators for purposes of replicating the results.

Standard protocol approvals

This study was performed according to the guidelines of the local research ethics committees.

Results

We identified 15,257 cases of first-ever stroke in adults aged 18 to 50 years old, between 1998 and 2010. Of these 8,444 (55.3%) were ischemic stroke, 3,077 (20.2%) were intracerebral hemorrhage, and 3,736 (24.5%) were unspecified stroke. 53% of all strokes occurred in women. Mean age at first-ever any stroke was 41.4 (SD 7.0) years for women and 42.3 (SD 6.5) years for men. Less than 1% of cases were out-of-hospital deaths.

Sex-specific variation in age at first-ever stroke

The incidence of first-ever any stroke in young adults increased exponentially with age in both sexes (R2 = 0.98 in men and R2 = 0.99 in women, R2 is a measure of how

close data-points fit a regression line, which in this case indicates an exponential increase). In all age-strata the incidence in women was higher than in men, except in those aged 44-49 years (Table 3). The IRR of women compared to men declined with age from 1.93 (95% CI 1.62-2.31) in 18-24 year olds to 1.06 (95% CI 1.01-1.11) in 45-49 year olds for any stroke. No age-related decline was found for intracerebral hemorrhage (Table 4).

Sex-specific distribution of stroke subtypes in the different age-strata

The proportion of ischemic stroke in the different age groups was significantly different for those aged 18-24 years old, 38.3% in men and 55.9% in women ($p < 0.001$), and those aged 35-39 years old, 51.3% in men and 56.4% in women ($p = 0.018$), but not for the other age-strata. In men, the relative percentage of intracerebral hemorrhage was significantly higher than that in women in the same age-category in younger age-strata, namely 44.0% in men and 26.6% in women aged 18-24 years old ($p < 0.001$) and 34.9% versus 21.1% in those aged 25-29 years old ($p < 0.001$). Similarly results were seen for the age-strata 30-34 years old ($p < 0.001$), 35-39 years old ($p = 0.002$), 40-44 years olds ($p < 0.001$). There was no significant difference in the relative percentage of intracerebral hemorrhage for men and women aged 45-49 years old, 18.5% in men and 18.0% in women ($p = 0.591$). The percentage of unspecified stroke was significantly different in t hose aged 30-34 years old, 17.6% in men and 25.9% in women ($p < 0.001$) (Figure 1).

Sex- and age-specific time trends in the incidence of any stroke

Any stroke incidence among young adults increased from 14.0 per 100,000 person-years in 1998 to 17.2 per 100,000 person-years in 2010, resulting in a relative change of 23% ($p < 0.001$). This increase was present across all age strata over 35 years old, but not in patients aged 18-34 years (Table 3, Figure 2A). The increase of any stroke incidence was observed both in men (23% increase; $p<0.001$) and in women (17% increase; $p<0.001$), and most prominently in those aged 44 to 49 years. In contrast, in patients aged 50 years or older, the incidence of first-ever any stroke declined from 329.1 per 100,000 person-years in 1998 to 292.2 per 100,000 person-years in 2010, a relative decrease of 11% ($p = 0.009$; Table 3). The proportion of stroke in young adults of the total number of stroke across all ages increased significantly over time from 13.3% in 1998 to 15.5% in 2010 ($p < 0.001$).

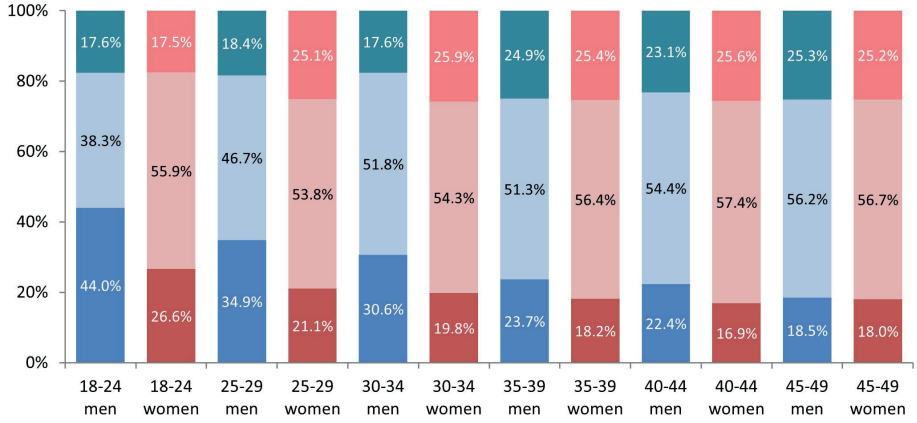


Figure 1: Sex- and age-specific distribution of stroke subtypes

- Stroke undefined (women)
- Ischemic stroke (women)
- Intracerebral hemorrhage (women)
- Stroke undefined (men)
- Ischemic stroke (men)
- Intracerebral hemorrhage (men)

Sex-specific time trends of incidence by stroke subtype

In young adults, the incidence of ischemic stroke increased by 46% from 7.4 in 1998 to 10.8 per 100,000 person-years in 2010 ($p < 0.001$). In women, the incidence of ischemic stroke increased from 8.9 in 1998 to 12.1 per 100,000 person-years in 2010, a relative change of 37% ($p < 0.001$) and in men from 6.0 to 9.5 per 100,000 person-years, a relative change of 60% ($p < 0.001$) (Table 5, Figure 2B).

The incidence of intracerebral hemorrhage and of unspecified stroke remained stable over the course of 13 years (Table 5, Figure 2C and 2D), without any sex differences.

Discussion

This study shows that in young adults the risk of stroke increased exponentially with age, with women more often affected than men in all age strata. The relative distribution of stroke-subtypes was similar in women in all age-strata with ischemic stroke occurring two to three times more frequently than intracerebral hemorrhage. In men the proportion of intracerebral hemorrhages was relatively high in younger age-strata, and declining with increasing age. In young adults, the incidence of ischemic stroke but not of intracerebral hemorrhage and unspecified stroke increased by almost 50% between 1998 and 2010, while the incidence of stroke in older patients decreased by 11%.

We found a relatively high increase of 46% in the incidence of ischemic stroke over a 13-year period among young adults, where previous studies reported percentages varying from 4.7% to 74%.[6,39,48-50] Differences may be explained by variation in the definition of patient groups (due to inclusion of different ICD-codes) and the chosen lower- and upper age-limits that ranged from as low as 15 to as high as 60 years.[6,9,36-41] In our study the increase in stroke incidence was limited to ischemic stroke; incidence was stable for those with an intracerebral hemorrhage and for those younger than 35 years old at their first event. In contrast, others found a clear increase in incidence in those younger than 30 years old.

Table 3: Sex-specific incidence of any stroke from 1998 - 2010

Age in years (y)	Incidence per 100 000 person-years [a]							
	1998	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
18-49 y	13.99	14.00	14.51	14.76	15.26	15.80	16.64	17.60
men	12.13	12.70	13.49	13.01	13.67	15.48	16.06	16.10
women	15.93	15.34	15.56	16.56	16.89	16.12	17.24	19.14
All ages	105.39	105.11	103.12	104.15	110.75	111.84	115.81	117.37
men	104.96	104.21	101.24	102.80	109.80	110.35	116.33	117.62
women	105.81	105.99	104.96	105.48	111.68	113.30	115.31	117.12
18-24 y	2.36	2.31	2.92	2.69	2.31	2.52	2.51	2.43
men	2.18	1.76	1.92	2.80	2.20	2.48	2.19	1.60
women	2.54	2.87	3.94	2.58	2.42	2.56	2.85	3.28
25-29 y	4.40	3.97	3.66	5.09	4.57	3.88	4.76	5.14
men	2.32	2.72	2.19	3.37	3.52	2.31	3.15	3.82
women	6.56	5.26	5.16	6.85	5.64	5.47	6.38	6.47

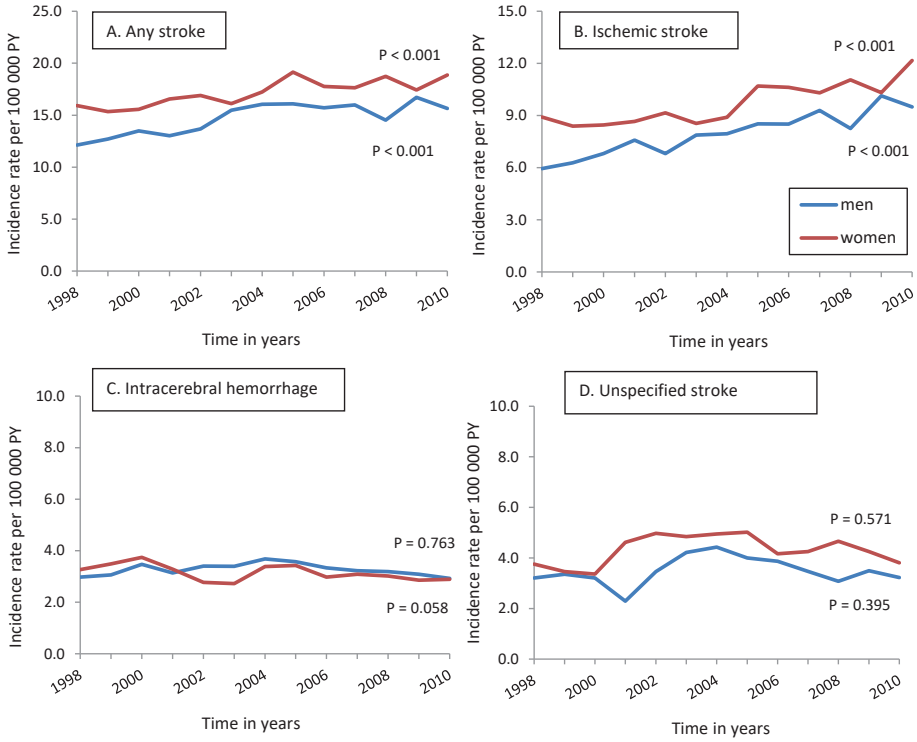


Figure 2. Time trends in incidence of stroke and stroke subtypes in young adults from 1998 to 2010
Incidence per 100,000 person-years calculated with Dutch population estimates.[47]
P-values calculated by linear regression

2006	2007	2008	2009	2010	Change [b]	Time trend [c]
16.73	16.81	16.61	17.07	17.24	0.23	**P < 0.001**
15.71	15.99	14.52	16.72	15.64	0.29	**P = 0.001**
17.77	17.64	18.74	17.43	18.86	0.18	**P < 0.001**
108.50	103.22	102.33	109.64	111.27	0.06	P = 0.450
109.40	102.97	101.12	109.30	111.37	0.06	P = 0.359
107.61	103.46	103.50	109.97	111.17	0.05	P = 0.581
2.36	2.72	2.77	2.28	3.29	0.40	P = 0.232
2.47	2.18	1.87	2.11	2.21	0.01	P = 0.919
2.24	3.29	3.70	2.46	4.41	0.73	P = 0.251
5.04	4.75	4.34	3.53	4.20	-0.05	P = 0.949
4.22	3.43	2.42	2.41	3.98	0.71	P = 0.207
5.86	6.07	6.28	4.66	4.43	-0.32	P = 0.245

Table 3: Continued

Age in years (y)	Incidence per 100 000 person-years [a]							
	1998	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
30-34 y	7.29	5.87	7.61	7.44	8.37	7.10	7.90	8.73
men	6.08	4.92	6.70	4.91	6.73	6.55	6.48	8.69
women	8.56	6.87	8.56	10.06	10.07	7.67	9.34	8.77
35-39 y	10.90	12.73	12.55	10.92	11.96	11.93	14.20	14.31
men	7.56	12.13	10.15	8.86	10.17	11.69	13.88	13.63
women	14.35	13.35	15.03	13.06	13.82	12.17	14.54	15.00
40-44 y	23.79	22.87	23.47	21.61	22.91	23.99	25.44	25.69
men	22.81	19.85	22.46	18.38	19.95	24.62	23.35	23.39
women	24.79	25.96	24.50	24.94	25.95	23.34	27.58	28.06
45-49 y	39.57	40.34	40.11	43.84	43.45	46.74	45.30	48.68
men	35.95	38.75	41.02	42.89	41.51	46.44	47.58	44.75
women	43.33	41.98	39.17	44.83	45.43	47.04	42.97	52.67
≥ 50 y	329.08	322.92	311.66	311.36	328.18	327.11	334.03	333.01
men	355.07	344.92	327.83	329.52	347.61	341.94	355.33	353.71
women	307.02	304.13	297.75	295.67	311.29	314.14	315.31	314.75

Table 4: Sex- and age-specific incidence of stroke subtypes

	Male incidence [a] (N)	**PY [b] at risk**	**Female incidence [a] (N)**
Any stroke			
18-24 y	2.15 (193)	8974907	3.02 (263)
25-29 y	3.03 (212)	6985800	5.78 (398)
30-34 y	6.15 (483)	7859303	8.94 (687)
35-39 y	11.34 (966)	8515778	14.19 (1175)
40-44 y	22.63 (1888)	8342998	25.85 (2102)
45-49 y	43.14 (3385)	7846997	45.62 (3505)
Ischemic stroke			
18-24 y	0.82 (74)	8974907	1.69 (147)
25-29 y	1.42 (99)	6985800	3.11 (214)
30-34 y	3.18 (250)	7859303	4.87 (374)
35-39 y	5.82 (496)	8515778	8.00 (662)
40-44 y	12.32 (1028)	8342998	14.84 (1207)
45-49 y	24.26 (1904)	7846997	25.89 (1989)
Intracerebral hemorrhage			
18-24 y	0.95 (85)	8974907	0.80 (70)
25-29 y	1.06 (74)	6985800	1.22 (84)
30-34 y	1.88 (148)	7859303	1.76 (135)
35-39 y	2.69 (229)	8515778	2.60 (215)

2006	2007	2008	2009	2010	Change [b]	Time trend [c]
9.33	7.77	6.83	6.35	7.20	-0.01	P = 0.808
6.04	6.74	5.85	3.96	5.99	-0.01	P = 0.880
12.64	8.80	7.80	8.73	8.42	-0.02	P = 0.699
12.69	14.20	12.71	13.50	13.21	0.21	**P = 0.029**
11.93	11.77	9.98	14.02	11.84	0.57	P = 0.060
13.47	16.68	15.47	12.99	14.59	0.02	P = 0.403
24.87	25.12	25.33	25.63	23.75	0.00	**P = 0.023**
23.11	26.22	21.66	26.54	21.35	-0.06	P = 0.126
26.68	23.99	29.10	24.69	26.21	0.06	P = 0.314
44.66	43.70	44.37	47.19	47.73	0.21	**P = 0.003**
44.78	42.74	42.15	46.65	44.76	0.24	**P = 0.014**
44.54	44.67	46.63	47.74	50.75	0.17	**P = 0.019**
302.36	281.91	275.17	291.66	292.20	-0.11	**P = 0.009**
322.11	295.46	286.80	303.84	306.66	-0.14	**P = 0.006**
284.87	269.85	264.79	280.73	279.18	-0.09	**P = 0.014**

PY [b] at risk	IRR (95% CI) of women compared to men	P-value
8722640	1.93 (1.62 – 2.31)	**p < 0,001**
6882795	1.91 (1.61 – 2.26)	**p < 0,001**
7680769	1.46 (1.29 – 1.63)	**p < 0,001**
8280089	1.25 (1.15 – 1.36)	**p < 0,001**
8131226	1.14 (1.07 – 1.22)	**p < 0,001**
7683179	1.06 (1.01 – 1.11)	**p = 0.021**
8722640	2.04 (1.54 – 2.74)	**p < 0,001**
6882795	2.19 (1.72 – 2.81)	**p < 0,001**
7680769	1.53 (1.30 – 1.80)	**p < 0,001**
8280089	1.37 (1.22 – 1.31)	**p < 0,001**
8131226	1.20 (1.11 – 1.31)	**p < 0,001**
7683179	1.07 (1.00 – 1.14)	**p = 0.045**
8722640	0.85 (0.61 – 1.18)	p = 0.343
6882795	1.15 (0.83 – 1.60)	p = 0.418
7680769	0.93 (0.73 – 1.19)	p = 0.603
8280089	0.97 (0.80 – 1.17)	p = 0.748

Table 4: Continued

	Male incidence [a] (N)	PY [b] at risk	Female incidence [a] (N)
40-44 y	5.07 (423)	8342998	4.38 (356)
45-49 y	7.98 (626)	7846997	8.23 (632)
Unspecified stroke			
18-24 y	0.38 (34)	8974907	0.53 (46)
25-29 y	0.56 (39)	6985800	1.45 (100)
30-34 y	1.08 (85)	7859303	2.32 (178)
35-39 y	2.83 (241)	8515778	3.60 (298)
40-44 y	5.24 (437)	8342998	6.63 (539)
45-49 y	10.90 (855)	7846997	11.51 (884)

IRR = incidence rate ratio, CI = confidence interval. [a] Incidence per 100,000 person-years calculated with Dutch population estimates.[47] [b] Person years at risk over 13 years (1998-2010).

This might be partially explained by smaller patient numbers, hospital based settings, or a broader definition of stroke also including subarachnoid hemorrhage, TIA, other cerebrovascular disorders and sequelae of stroke (ICD-9 codes 430-438). Incidences and rates of increase may also vary in different parts of the world because of differences in genetic profile and occurrence and control of (cardiovascular) risk-factors.[6,39,49]

We do not see an increase in incidence for intracerebral hemorrhage, that was already detectable with CT in contrast with ischemic stroke that is now more easily diagnosed with help of MRI-DWI. Also intracerebral hemorrhage has a different etiology and is particularly in young patients often due to structural vessel abnormalities, that are less likely to be influenced by the increasing prevalence of modifiable, traditional risk factors like obesity and hypercholesterolemia, that do play an important role in the pathogenesis of ischemic strokes.

We found clear sex-differences in both the overall occurrence and age-related increase in the incidence of stroke in young adults, women being more often affected than men in all age strata. Previous studies have yielded conflicting results, some showing no difference or only in a specific age group, others showing a higher incidence in men, yet again possibly explained by differences in study design, age limits and stroke definition.[36-41,53,57] Differences in prevalence of (women-specific) risk factors between men and women may also contribute to the varying incidences for men and women in the different study populations. [36-41,53,57]

PY [b] at risk	IRR (95% CI) of women compared to men	P-value
8131226	0.86 (0.75 – 1.00)	**p = 0.045**
7683179	1.03 (0.92 – 1.15)	p = 0.061
8722640	1.39 (0.87 – 2.224)	p = 0.174
6882795	2.60 (1.78 – 3.87)	**p < 0,001**
7680769	2.14 (1.65 – 2.81)	**p < 0,001**
8280089	1.27 (1.07 – 1.51)	**p = 0.006**
8131226	1.27 (1.11 – 1.44)	**p < 0,001**
7683179	1.06 (0.96 – 1.16)	p = 0.266

A possible explanation for the excess risk of stroke in young women may be found in risk-factors that are more prevalent in women, such as migraine with aura, auto-immune disorders like the anti-phospholipids syndrome or systemic lupus erythematosus (SLE), or women-specific such as pregnancy or the use of oral anti-conception, especially in combination with smoking.[8,35,58] Because the prevalence of these women-specific risk factors is very low and the exact effect size of their role in incidence unclear, other, yet unknown hormonal factors or genetic differences may also contribute.

Strengths of our study include the large sample size of the cohort, the fact that it was nation-wide, and included patients over a period of more than a decade. The large sample enabled us to perform age-, sex- and stroke subtype specific subgroup analyses. In addition, we were able to investigate the changes of incidence of stroke in young adults over a 13-year period. Finally, we created a cohort of well-defined stroke subtypes, whereas many previous studies were more heterogeneous with the inclusion of transient ischemic attack (TIA), subarachnoid hemorrhage (SAH), unspecified intracranial hemorrhage, several other cerebrovascular diseases and even sequelae of cerebrovascular disorders. We excluded SAH and unspecified intracranial hemorrhage based on their distinct underlying etiologies. Finally, we validated the ICD-codes for young stroke patients specifically.

Our study also has some limitations. First, we could not further specify stroke etiology, e.g. with TOAST classification, or look at underlying causes of intracerebral hemorrhage. Additionally, there was a substantial number of strokes in our cohort classified as unspecified, meaning that the stroke could either be ischemic or

Table 5: Sex-specific incidence of stroke subtypes in young adults (<50 years) from 1998 – 2010

	Incidence per 100,000 person-years[a]						
Stroke subtype	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**
Ischemic stroke	7.40	7.32	7.62	8.11	7.96	8.21	8.42
Men	5.95	6.29	6.81	7.59	6.81	7.87	7.95
Women	8.91	8.39	8.46	8.66	9.15	8.55	8.91
Intracerebral hemorrhage	3.12	3.27	3.60	3.21	3.09	3.06	3.54
Men	2.97	3.06	3.47	3.14	3.40	3.39	3.68
Women	3.27	3.49	3.74	3.28	2.77	2.72	3.39
Unspecified stroke	3.48	3.41	3.28	3.44	4.20	4.53	4.68
Men	3.21	3.35	3.21	2.29	3.46	4.22	4.43
Women	3.75	3.46	3.36	4.61	4.97	4.85	4.94

[a] Incidence per 100,000 person-years calculated with Dutch population estimates.[47b] Change = (Incidence 2010 - Incidence 1998) / Incidence 1998. [c]Time trend tested by linear regression

hemorrhagic.[10] Through our validation of the ICD-codes in young stroke patients in several Dutch medical centers, we found 90.5% of unspecified stroke were in fact ischemic strokes and 9.5% were intracerebral hemorrhages (Table 2). Therefore, it is most likely that the vast majority of these unspecified strokes were in fact ischemic strokes and could be added to this group for trend-analysis. However we chose to analyze the groups separately, thereby safeguarding the purity of the data. Furthermore, the incidence of unspecified stroke did not increase, whereas the incidence of ischemic stroke increased, which may be explained by a more reliable differentiation between ischemic stroke and intracerebral hemorrhage through the implementation of improved imaging techniques, such as the (DWI) MRI, leaving less strokes being classified as unspecified.

Second, we may have overestimated the total number of first-ever strokes because we had no information on strokes prior to 1998 and therefore may have misclassified some recurrent strokes as first-ever strokes. As the risk of recurrent stroke decreases by the number of years of event free survival after the first-ever stroke, the chance of misclassification of a recurrent stroke as first-ever stroke becomes increasingly less likely over time, particularly for the later years of our study.[59,60] Third, because fewer hospitals contributed to the HDR register from 2006 onwards, the data is less reliable for estimating nationwide incidence after 2005. As a consequence, the rate of the increase of the incidence of stroke between 1998 and 2010 may have been underestimated. However, since there is no reason to assume these 'missing records' are not missing at random, this will most likely have led to underestimation of the

2005	2006	2007	2008	2009	2010	Change (%) [b]	Time trend [c]
9.60	9.55	9.80	9.64	10.23	10.82	46.22	**P<0.001**
8.52	8.51	9.29	8.25	10.13	9.49	59.50	**P<0.001**
10.70	10.62	10.31	11.06	10.32	12.16	36.48	**P<0.001**
3.50	3.16	3.16	3.10	2.97	2.91	-6.73	P=0.143
3.57	3.33	3.23	3.19	3.08	2.92	-1.68	P=0.763
3.43	2.98	3.08	3.02	2.85	2.89	-11.62	P=0.058
4.51	4.02	3.86	3.87	3.87	3.52	1.15	P=0.384
4.00	3.87	3.47	3.08	3.50	3.23	0.62	P=0.571
5.02	4.17	4.25	4.66	4.25	3.81	1.60	P=0.395

observed temporal trends of stroke incidence between 2006 and 2010 and does not affect subgroup-analyses for specific age-strata or sex comparisons performed within each year. Stroke care is provided throughout the Netherlands, so it is unlikely that when some centers no longer provide their discharge data this would lead to a specific loss of intracerebral hemorrhage diagnoses or ischemic stroke diagnoses. Finally, we may have missed non-fatal strokes for which patients were not admitted to a hospital. This may have led to underestimation of the incidence estimates but is unlikely to affect subgroup-analyses and time-trends.

If the observed rise in incidence of ischemic stroke in young adults continues, the estimated number of strokes in young adults will have nearly doubled by 2020 in comparison to 2000. This will have large socio-economic consequences. We urgently need to identify the main factors that have led to the increased incidence with a view to counter this worrisome trend. Further investigations of trigger factors, women-specific risk factors and genetic causes may shed further light on the cause of stroke in the young.[61] The continuing increase of stroke in young adults asks for immediate public health strategies, including programs for better awareness of risk factors for vascular disease, already among young adults. This study shows a steep increase in the incidence of ischemic stroke in young adults over time, especially in those aged 35 to 50 years and with a higher incidence in women than in men. The pronounced female predominance in stroke incidence among young adults warrants specific attention to this group.

PART TWO

RISK-FACTORS OF STROKE IN THE YOUNG

Chapter III

Ambient air pollution and the risk of ischaemic and haemorrhagic stroke

Published as: Verhoeven JI, Allach Y, Vaartjes ICH, Klijn CJM, de Leeuw FE. *Ambient air pollution and the risk of ischaemic and haemorrhagic stroke.* Lancet Planet Health. 2021 Aug;5(8):e542-e552.

Summary

Stroke is a leading cause of disability and the second most common cause of death worldwide. Increasing evidence suggests that air pollution is an emerging risk factor for stroke. Over the past decades, air pollution levels have continuously increased and are now estimated to be responsible for 14% of all stroke-associated deaths. Interpretation of previous literature is difficult because stroke was usually not distinguished as ischaemic or haemorrhagic, nor by cause. This Review summarises the evidence on the association between air pollution and the different causes of ischaemic stroke and haemorrhagic stroke, to clarify which people are most at risk. The risk for ischaemic stroke is increased after

short-term or long-term exposure to air pollution. This effect is most pronounced in people with cardiovascular burden and stroke due to large artery disease or small vessel disease. Short-term exposure to air pollution increases the risk of intracerebral haemorrhage, a subtype of haemorrhagic stroke, whereas the effects of long-term exposure are less clear.

Limitations of the current evidence are that studies are prone to misclassification of exposure, often rely on administrative data, and have insufficient clinical detail. In this Review, we provide an outlook on new research opportunities, such as those provided by the decreased levels of air pollution due to the current COVID-19 pandemic.

Introduction

On World Environment Day in 2019, the UN called on governments to more strictly regulate air pollution levels and develop air quality action plans.[62] In the past few decades, it has become clear that short-term and long-term exposure to ambient air pollution is an important risk factor for cardiovascular disease, including stroke.[14,63,64] Worldwide, stroke is the second most common cause of death and an leading cause of disability.[65] Stroke has a yearly global incidence of over 15 million patients and is responsible for over 116 million disability adjusted life years (DALYs), of which an estimated 16.9% can be attributed to air pollution.[53,66] The incidence of air pollution-related stroke is most pronounced in low-income and middle-income countries due to their fast-growing economies, urbanisation and industrialization.[67-69]

During the ongoing COVID-19 pandemic, there was an unprecedented worldwide decrease in outdoor air pollution levels due to the global lockdown. This situation provides a unique opportunity to study if cleaner air results in less air pollution-related disease. Initial research has already shown a remarkable decrease in stroke admissions in centres around the world during the first peak of the COVID-19 pandemic.[70] This decrease might result from patients not seeking the usual medical help, because of fear or because of limited access to emergency rooms. However, reduced air pollution could also translate into a lower stroke incidence. In Europe and China, estimates already suggest ten tens of thousands of all-cause premature deaths have been prevented due to reduced air pollution in 2020 alone.[71,72]

The notion of an association between air pollution and the incidence of stroke is now widely accepted; however methodological limitations prevent demonstration of causality. First, in most studies stroke has been used as an umbrella term combining ischaemic stroke and haemorrhagic stroke. Only a few studies have addressed the differences between these two completely different subtypes of stroke, as well as their different causes and associations with other cardiovascular risk factors. Second, the way that air pollutants are measured and individual exposure is estimated might result in exposure misclassification. Third, most studies use administrative data, which almost always does not include detailed clinical information, which might result in misclassification of stroke occurrence. Finally, the pathophysiological mechanisms of the varying air pollutants leading to stroke remain uncertain.

In this Review, we summarise the current evidence on the association of short-term and long-term exposure to air pollutants with risk of ischaemic stroke and its different causes, stratified by age, sex and presence of cardiovascular risk factors. Additionally, we summarise the risk of haemorrhagic stroke due to short- and long-term exposure to air pollution and underlying pathophysiological mechanisms. We discuss the methods used for air pollution measurement and stroke ascertainment in epidemiological studies. Finally, we conclude by highlighting the societal implications and possible clinical implications, and provide an outlook for future research. Determining which specific patients are at a higher risk will not only provide more insight into the underlying biological mechanisms, but could also be the first step towards targeted intervention strategies to reduce air pollution-related stroke worldwide.

What is air pollution?

Air pollution is generally classified into household pollution and outdoor or ambient air pollution. In this Review, we only discuss the effects of ambient air pollution, because this type of air pollution is reported to be most relevant for stroke incidence.[53] Air pollution consists of small particles (particulate matter; PM) and several toxic gasses. PM is classified by the size of the particles into coarse particles <10 μm in size, PM10), fine particles (<2.5 μm in size, PM2.5) and ultrafine particles (< 1nm in size, PM0.1). The larger particles (PM10) are more common in industrial emissions, whereas the smaller particles (PM2.5 and PM0.1) result mainly from traffic emissions. The most common gaseous pollutants are carbon monoxide (CO), black carbon (BC), nitrogen oxides (NOx), sulphate (SO4-) and ozone (O3). The composition of air pollution depends on the pollution source; for example traffic emission contains high levels of NO2.[73]

The mean concentrations of air pollutants differ substantially between continents (Figure 1). Data published by the WHO showed that mean annual PM2.5 concentrations in 2016 varied: between less than 10 μg/m3 and 25 μg/m3 in Europe, Russia and North-America; between 10-50 μg/m3 in South-America, Africa and the Middle East; and between 15 μg/m3 to more than 50 μg/m3 in Asia.[74]

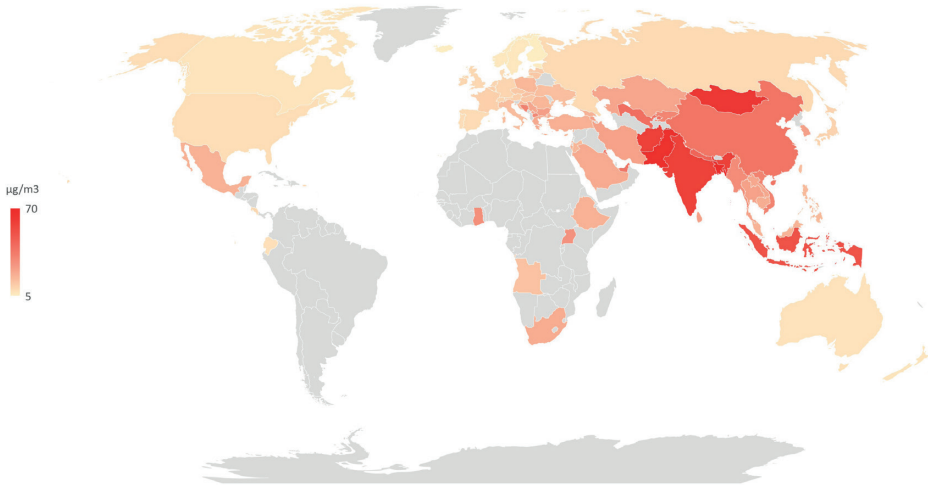


Figure 1: World map of annual mean PM25 (µm/m3) exposure levels per country in 2019
Map was created using data from IQAir.[74] PM = particulate matter

Air pollution and ischaemic stroke

Short-term increased exposure to air pollution and the risk of ischaemic stroke

Short-term exposure relates to the daily variation of air pollution concentration. To assess this association, stroke risk on days with higher pollution levels is compared with days that have lower pollution levels. Many studies have reported an association between short-term increased air pollutant levels and increased risk of ischaemic stroke (Table 1; appendix pp 2-6).[75-96]

A US study showed a small, but statistically significant, increase of 1.03% (95% CI 0.04-2.04) in ischaemic stroke admissions per IQR increase (22.96 µg/m3) in PM10 concentration 1-2 days before stroke onset.[91] A similar risk increase was reported for increases in concentrations of NO2, SO2 and CO.[91] A study that investigated over eight million ischaemic stroke cases in 184 cities in China also supported these findings.[80] The authors reported a 0.29% increase in hospital admissions for ischaemic stroke per 10 µg/m3 increased PM2.5 on the day of stroke.[80] Conversely, other studies, mostly set in Europe or North-America, could not confirm this association.[97-100] There are several reasons for these conflicting results. First, geographic location and, thus, median air pollution levels differ between studies. Furthermore, the variation in hourly or daily pollutant levels are important for the effect of short term exposure. These daily variations are ten times lower in Europe

than those in Asia (Figure 1). This smaller variation in air pollution levels results in an accompanying lower ischaemic stroke risk increase, which makes it harder to detect an association between air pollution levels and ischaemic stroke. The effect of the level of variation in air pollutant concentration is shown by a Swedish study, [88] with a low median PM10 concentration of 16 µg/m3 and 80% of measured daily concentrations ranging between 10 µg/m3 and 29 µg/m3. The authors reported a 13% (95% CI 4-22) increase in ischaemic stroke admissions on the day after high (>30 µg/m3) versus low (<15 µg/m3) pollutant concentrations.[88] Finally, studies done in Asia tend to have larger numbers of patients than European or North-American studies, which provides more power to show small, albeit statistically significant differences.

Table 1: Risk of ischaemic stroke and haemorrhagic stroke after short-term exposure to increased concentrations of air pollution in recent literature [A]

	Location (study period)	Number of subjects	Exposure	Results (95% CI)
Ischaemic stroke and haemorrhagic stroke				
Byrne et al, 2020 [97]	Dublin and Cork, Ireland (2013-17)	15 086	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3	**Ischaemic stroke:** OR of 1.10 (1.06-1.14) per average 8.4 µg/m^3 (IQR) increase of PM_{10} concentration at 0-2 days before stroke, and significant associations for $PM_{2.5}$ and NO_2 concentrations. **Haemorrhagic stroke**: no overall significant associations.
Fisher et al, 2019 [75]	Boston, USA (1999-2010)	731	PM_{10}, $PM_{2.5}$	**Ischaemic stroke**: OR 1.26 (1.03-1.55) per average 14.46 µg/m^3 (IQR) increase of PM_{10} at 0-4 days before stroke, and no significant association for $PM_{2.5}$. **Haemorrhagic stroke**: no overall significant associations.
Gu et al, 2020 [76]	248 cities, China (2013-17)	6 735 204	$PM_{2.5}$	**Ischaemic stroke**: 0.26% increase (0.17-0.35) per 10 µg/m^3 increase $PM_{2.5}$ concentration at same day of stroke. **Haemorrhagic stroke**: no overall significant associations.
Sun et al, 2019 [98]	40 clinical centres, USA (1993-2012)	5417 (all women)	$PM_{2.5}$, SO_2, NOx, NO_2,	**Ischaemic stroke**: no overall significant associations. **Haemorrhagic stroke**: RR of 1.24 (1.01-1.52) per average 8-12 µg/m^3 (IQR) increase of $PM_{2.5}$ at 0-4 days before stroke, as well as significant associations for NO_x but not for $PM_{2.5}$ or SO_2 concentrations.

Table 1: Continued

	Location (study period)	Number of subjects	Exposure	Results (95% CI)
Tian et al, 2019 [67]	184 cities, China (2014-17)	8 834 533	$PM_{2.5}$	**Ischaemic stroke:** 0.29% increase (0.18-0.40) per 10 µg/m^3 increase of $PM_{2.5}$ concentrations at same day as stroke. **Haemorrhagic stroke**: no overall significant associations.
Ischaemic stroke only				
Chen et al, 2020 [78]	5 cities, China (2013-15)	68 122	PM_{10}, $PM_{2.5}$, PM_1	**Ischaemic stroke:** OR 1.005 (1.001-1.009) per average 10 µg/m^3 increase of PM_{10} 0-1 days before stroke, as well as significant associations for PM_1 and $PM_{2.5}$.
Dong et al, 2018 [77]	Changzhou, China (2015-16)	32 840	PM_{10}, $PM_{2.5}$ SO_2, NO_2	**Ischaemic stroke:** 0.208% increase (0.036-0.381) for average 12.0 µg/m^3 (IQR) increase of NO_2 concentration at 0-5 days before stroke, and no significant association for $PM_{2.5}$, PM_{10} or SO_2 concentrations.
Ho et al, 2018 [79]	Shanghai, China (2010-15)	29 384	PSI [B]	**Ischaemic stroke:** IRR 1.10 (1.06-1.13) for days with unhealthy PSI compared with healthy PSI, as well as a significant increase for moderate PSI compared to healthy PSI.
Tian et al, 2018 [80]	172 cities, China (2014-16)	2 032 667	$PM_{2.5}$, SO_2, NO_2, O_3 and CO.	**Ischaemic stroke**: 0.34% increase (0.20-0.48) for 10 µg/m3 increase $PM_{2.5}$ concentration on the day of stroke, and significant associations for NO_2, SO_2, CO concentrations but not for O_3 concentrations.
Tian et al, 2019 [81]	172 cities, China (2014-16)	2 032 667	$PM_{10-2.5}$	**Ischaemic stroke:** 0.91% increase (0.73-1.10) for 10 µg/m3 increase $PM_{10-2.5}$ concentration on the day of stroke.
Qi et al, 2020 [82]	Tianjin, China (2018-19)	520	PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3	**Ischaemic stroke:** OR 1.58 (1.09-2.29) per average 55.5 µg/m^3 (IQR) increase of PM_{10} concentration at 0-3 days before stroke, and no significant associations for $PM_{2.5}$, NO_2, SO_2 or O_3 concentrations.
Vivanco -Hidalgo et al, 2018 [99]	Barcelona, Spain (2005-14)	2742	$PM_{2.5}$, BC	**Ischaemic stroke and transient ischemic attack:** No significant overall associations.

Table 1: Continued

	Location (study period)	Number of subjects	Exposure	Results (95% CI)
Wang et al, 2020 [83]	Shenzen region, China (2008-14)	63 997	PM_{10}, SO_2, NO_2, O_3, CO	**Ischaemic stroke:** RR 1.007 (1.000-1.014) per average 43.21 µg/m^3 (IQR) increase of PM_{10} concentration at 0-12 days before stroke, and significant associations for SO_2, NO_2 and O_3 concentrations but not for CO concentration.
Intracerebral haemorrhage only				
Nzwalo et al, 2018 [101]	Algarve, Portugal (2010-15)	368	$PM_{2.5}$	**Intracerebral haemorrhage:** OR 1.057 (1.020-1.095) per average 10 µg/m3 increase of $PM_{2.5}$ concentration at 0-3 days before stroke.
Wilker et al, 2018 [69]	Boston, USA (2006-11)	577	$PM_{2.5}$, BC, NO_2, O_3	**Intracerebral haemorrhage:** OR 1.62 (1.18-2.22) for lobar intracerebral haemorrhage per average 0.01 ppm increase of O_3 concentration at 0-7 days before stroke, and no significant associations for $PM_{2.5}$, BC or NO_2 concentrations.

BC = black carbon. CO = carbon monoxide. IRR = incidence rate ratio. NO_x = Nitrogen oxides. NO_2 = Nitrogen dioxide. OR = odds ratio, O_3 = Ozone. PM = particulate matter. PSI = Pollutant standards index. SO_2 = Sulphur dioxide.

[A] Recent literature published between 1 January 2018 and 1 July 2020. [B] Pollutant Standards Index is computed from 6 air pollutants ($PM_{2.5}$, PM_{10}, SO_2, CO, O_3 and NO_2) and ranges from 0-50 (good), 51-100 (moderate), 101-200 (unhealthy), 201-300 (very unhealthy) and >300 (hazardous).

Long-term exposure to air pollution and the risk of ischaemic stroke

Attention has increased regarding the association between long -term exposure to air pollution – ranging from weeks to years – and the incidence of ischaemic stroke (Table 2). [64,102-104] A Danish study of 23 423 persons including 1.078 incident cases of stroke reported a hazard ratio (HR) of 1.13 (95% CI 1.01-1.25) for ischaemic stroke per 3.9 µg/m3 (IQR) higher annual mean of PM2.5, with similar HRs for 3- and 23-year averages of PM2.5 concentration.[64] A study in China, spanning 1992 to 2008, reported an HR of 1.20 (95% CI 1.15-1.25) for ischaemic stroke occurrence per average 10 µg/m3 increase in PM2.5 concentrations over a mean follow-up time of 7.5 years.[100]

A 2019 meta-analysis reported a statistically significant association between long-term exposure to increased PM2.5 levels and all-cause stroke within a 1-year to 4-year exposure window, but not for ischaemic or haemorrhagic stroke

separately.[102] The fact that the authors found no association for ischaemic or haemorrhagic stroke specifically could be explained by the small number of studies that separately investigated these stroke subtypes.

Table 2: Risk of ischaemic stroke and haemorrhagic stroke due to long-term exposure to air pollution in recent literature [A]

	Location (study period)	Number of participants; number of cases	Follow-up	Exposure	Results (95% CI)
Ischaemic stroke and haemorrhagic stroke					
Amini et al, 2020 [64]	Denmark (1993, 1999 – 2014)	23 423; 1078	Median 19.45 years	$PM_{2.5}$, PM_{10}, NO_2, NOx	**Ischaemic stroke:** HR of 1.12 (1.01-1.25) per 1-year mean 3.9 µg/m^3 (IQR) increase of $PM_{2.5}$ concentration, and no significant associations for PM_{10}, NOx, NO_2 concentrations. **Haemorrhagic stroke:** no statistically significant associations.
Cai et al, 2018 [102]	Three cohorts: two from the UK (1993 – 2008) and one from Norway (1995 – 2013)	355 732; 1845	Mean 14.1, 10.8, 1.3 years	$PM_{2.5}$	**Ischaemic stroke:** no statistical significant associations per 1-year mean 4.1 µg/m^3 (IQR) increase of $PM_{2.5}$ concentration. **Haemorrhagic stroke**: no statistical significant associations per 1-year mean 4.1 µg/m^3 (IQR) increase of $PM_{2.5}$ concentration.
Huang et al, 2019 [103]	China (1992 – 2008)	119 388; 3540	900 214 person-years	$PM_{2.5}$	**Ischaemic stroke:** HR of 1.20 (1.15-1.25) per average 10 µg/m^3 increased exposure during a mean 7.5 years follow-up. **Haemorrhagic stroke**: HR of 1.12 (1.05-1.20) per average 10 µg/m^3 increased exposure during a mean 7.5 years follow-up.

Table 2: Continued

	Location (study period)	Number of participants; number of cases	Follow-up	Exposure	Results (95% CI)
Yuan et al, 2019 [104]	Meta-analysis of 16 cohort studies: six from North America, six from Europe, three from Asia and one including cases from China, Ghana, India, Mexico, Russa, and South Africa (1980 – 2012)	2.2 million; 49 1149		$PM_{2.5}$	**Ischaemic stroke:** no statistical significant association per 5 µg/m3 increase of $PM_{2.5}$ during a 1-year to 4-year period (four studies) **Haemorrhagic stroke**: no statistical significant association per 5 µg/m3 increase of $PM_{2.5}$ during a 1-year to 4-year window (four studies)
Haemorrhagic stroke only					
Noh et al, 2019 [105]	Korea (2002 – 2013)	62 676; 521	670 431 persons-years	$PM_{2.5}$	**Haemorrhagic stroke:** HR of 1.43 (1.09-1.88) per average 10 µg/m^3 increased exposure of $PM_{2.5}$ concentration during a mean follow-up of 10.7 years.

HR = hazard ratio. PM = particulate matter. NOx = Nitrogen oxides. NO2 = Nitrogen dioxide. A Recent literature published between 1 January 2018 and 1 July 2020.

Table 3: Association between air pollutants and different causes of ischaemic stroke

	Exposure	Results (95% Confidence interval)
Andersen et al, 2010 [84]		
6798 ischaemic stroke cases [A]	PM_{10}, PM_{0-1}, NOx, CO	
4727 without atrial fibrillation		OR 1.05 (1.01-1.09) per 13.5 µg/m3 (IQR) increase of PM_{10} concentration at 3 days before stroke, and significant associations for ischaemic stroke without atrial fibrillation and PM_{0-1}, NO_x and CO.
722 with atrial fibrillation		No statistically significant associations.
Maheswaran et al, 2014 [106]		
833 ischaemic stroke cases [A]	PM_{10}, NO_2	
136 large artery atherosclerosis-associated strokes		No statistical significant associations.
371 cardioembolic strokes		No statistical significant associations.
376 small vessel disease-associated strokes		No statistical significant associations.

Table 3: Continued

	Exposure	Results (95% Confidence interval)
Maheswaran et al, 2016 [94]		
1513 ischaemic stroke cases [A]	PM_{10}, NO_2, O_3, CO, SO_2	
154 large artery atherosclerosis-associated stroke		HR 1.28 (1.07-1.53) per 10.46 µg/m^3 (IQR) increase of PM_{10} concentration on the day of stroke.
420 cardioembolic strokes		HR 1.36 (1.13-1.63) per 12.75 ppb (IQR) increase of O_3 concentration at 5 days before stroke.
382 small vessel disease-associated strokes		HR 1.21 (1.07-1.36) per 10.46 µg/m^3 (IQR) increase of PM_{10} concentration at 6 days before stroke, and significant associations with increased concentrations of SO_2 and NO_2.
557 other strokes		No statistically significant associations.
Vivanco-Hidalgo et al, 2018 [99]		
2742 ischaemic stroke cases [A]	$PM_{2.5}$, BC	
313 large artery atherosclerosis-associated strokes		OR 1.251 (1.001-1.552) per 1.5 µg/m^3 increase of BC concentration at 2 days before stroke.
923 cardioembolic strokes		No statistically significant associations.
581 small vessel disease-associated strokes		No statistically significant associations.
1595 other strokes		No statistically significant associations.

BC = black carbon. CO = carbon monoxide. HR = hazard ratio. NOx = nitrogen oxides.NO_2 = Nitrogen dioxide. OR = odds ratio. O_3 = Ozone. PM = Particulate Matter. SO_2 = sulphur dioxide. [A] number of participants in subgroup analysis for causal attributions of stroke.

Association of air pollution and the different causes of ischaemic stroke

Ischaemic stroke can be due to several causes, commonly classified into five categories according to the Trial of Org 10172 in Acute Stroke Treatment (commonly known as TOAST) criteria: large artery atherosclerosis, small vessel disease, cardioembolic stroke, rare causes and cryptogenic stroke.[107] These causes may be differently affected by air pollution. Because most epidemiological studies have used administrative datasets, the studies were not able to distinguish between causes of ischaemic stroke. However, a few hospital based studies have been able to distinguish between causes (Table 3).[84,94,99,106]

One study reported an increased risk of stroke caused by large artery atherosclerosis per day-to-day increase of 10.46 µg/m3 (IQR) of PM10 concentration (HR 1.28; 95% CI 1.07-1.53; p<0.001). As well as an increased risk with similar HRs for stroke caused

by small vessel disease for increased levels of PM10 and SO2 at 6 days pre-stroke and per mean IQR increase of NO2 concentration 0-6 days pre-stroke.[94] The risk of cardioembolic stroke was only associated with increased O3 concentration at 5 days pre-stroke. [94] There was no association between air pollutants and stroke due to rare causes or cryptogenic stroke.[94] A study among 2500 patients with ischaemic stroke in Spain reported an increased risk of stroke caused by large artery atherosclerosis per 1.5 µg/m3 increase of BC concentration at 2 days pre-stroke (odds ratio [OR] 1.251; 95% CI 1.001-1.552).[99] The authors reported no association between BC or PM2.5 and stroke caused by small vessel disease, cardioembolic stroke, stroke to rare causes or cryptogenic stroke.[99]

Stroke caused by large artery atherosclerosis and small vessel disease is related to classical vascular risk factors and atherosclerotic disease. Air pollution could have an additive effect on the association between the classical cardiovascular risk profile and ischaemic stroke.[108]

Effect modifiers

Studies have shown inconsistent results for the modifying effect of age on air pollution-related ischaemic stroke.[13,75,77,79,80,82,87,109] A recent study classified daily air pollution levels into unhealthy and good days according to the Pollutant Standards Index.[79] This scale is devised by the Environmental Protection Agency and takes six pollutants into account. The scale range includes 0-50 (good), 51-100 (moderate), 101-200 (unhealthy), 201-300 (very unhealthy) and more than 300 (hazardous). When comparing unhealthy days with good days, there was only an increased risk of ischaemic stroke for patients older than 65 years (incidence rate ratio 1.18; 95% CI 1.06-1.18), but not for younger patients (incidence rate ratio 1.05; 95% CI 1.00-1.11).[79] A study that included over 2 million hospital admissions across 172 cities in China reported an increase in ischaemic stroke admissions per 10 µg/m3 increase of PM2.5 concentration on the same day in patients aged 75 years or older (0.45%) and for patients aged 18-64 (0.11%, p=0.004).[80] Although the risk of ischaemic stroke admission was significantly higher for patients aged 75 years or older compared with those aged 18–64 years, the risk in patients older than 75 years was not significantly increased compared with those aged 65–75 years.[80]

Conversely, a study from Israel among 4000 patients with ischaemic stroke (mean age of 70) reported an increased risk of ischaemic stroke only in adults younger than 55 years.[13] Due to poorer respiratory function and ventilation, older individuals (>65 years) might be more susceptible to air pollutants because of a higher

deposition rate of PM in the airways.[108,110] Additionally, older people more often have other cardiovascular risk factors that might increase the risk of air pollution-related stroke. By contrast, it has also been suggested that the vessel wall in adults younger than 55 years might be more susceptible to air pollutants. Their vessel wall is still more reactive, whereas increased arterial stiffness is more prominent in people older than 55 years.[13] The effect of age might also be explained by potential exposure misclassification. Generally, people older than 60 years spend more time inside the house, which might result in overestimation of the effect of ambient air pollution. Whereas adults younger than 60 years spend more time outside or away from their home address.[87] Hence, the effect of age on the association between air pollution and ischaemic stroke remains unclear and should be investigated further.

Most studies report similar effect sizes for men and women in terms of ischaemic stroke related to air pollution, with only few exceptions.[63,64,77,79,80,83,87,109,111] One Swedish study showed a significantly increased risk of ischaemic stroke for women (HR 2.16; 95% CI 1.15-4.06) but not for men (HR 1.07; 95% CI 0.61–1.86) per 10 µg/m3 higher mean PM10 concentration the year before stroke.[63] The higher risk in women could be explained by the smaller diameter of the conducting airways, which leads to more particle deposition in the lungs.[112] However, a Chinese study of 1000 patients with a first-ever ischaemic stroke reported a significant increased risk of stroke exclusively in men (increase of 6.5%; 95% CI 0.5-12.9) per 10 µg/m3 increased O3 concentration at 2-3 day lags.[111] Similar to the age-associated effect, the effect of sex might be modified by exposure misclassification. Some survey-based studies have reported that women tend to spend more time indoors compared to men and, therefore, exposure to outdoor air pollution might be slightly overestimated in women.[113]

The risk increase of ischaemic stroke due to air pollution is higher in those who have one or more cardiovascular risk factors, especially patients with diabetes.[79,82,90,96] A Canadian study of over 9000 patients reported an 11% (95% CI 1-22%) increased ischaemic stroke risk per 10 µg/m3 increase of PM2.5 exclusively in patients with diabetes.[96] Another study reported a significantly higher risk increase for people who had had a previous stroke compared to those who did not. The ORs were 2.31 (95% CI 1.39-3.83) versus 1.25 (95% CI 0.87-1.80 per 5.8 µg/m3 (IQR) average increase of NO2 in the 3 days before stroke.[90] The authors also showed a non-significant trend towards increased ischaemic stroke risk for those patients taking anti-diabetic medications and those with a history of heart disease.[90] Smoking and socioeconomic status did not seem to significantly modify the effect of air pollutants on ischaemic stroke.[64,75,79,80,82,98,102,114] One Chinese study reported that a

diet containing low fruit and vegetable had a significant effect (OR 1.03, 95% CI 1.00-1.08) on the association between short-term increased PM2.5 and a higher risk of ischaemic stroke.[114]

Other environmental factors, such as traffic noise, could also modify the effect of air pollutants on stroke. Traffic emissions are considered to be responsible for over 90% of air pollution in urbanised areas.[115] Traffic noise might activate the hypothalamus-pituitary axis, which promotes the release of stress hormones, leading to cardiovascular disease.[96] A 2020 study showed that the significant risk increase of ischaemic stroke and haemorrhagic stroke after long-term increased PM2.5 exposure remained unchanged after correcting for traffic noise.[64]

Air pollution and haemorrhagic stroke

Short-term exposure to air pollution and risk of haemorrhagic stroke

Haemorrhagic stroke includes intracerebral haemorrhage and subarachnoid haemorrhage. Only a small number of studies have investigated haemorrhagic stroke, separate from all-cause stroke.[75,76,80,84-86,90,91,97,98,101,116] Even fewer studies focused specifically on intracerebral haemorrhage.[69,101,105,117,118] One Taiwanese study reported a 12% risk increase in intracerebral haemorrhage admissions per 17.46 µg/m3 (IQR) increased PM2.5 levels on the day of stroke compared to other days.[117] A 2019 study of just under 400 patients showed a 5.7% (95% CI 1.02-1.10; p=0.002) increased risk of spontaneous intracerebral haemorrhage per 10 µg/m3 increase of PM2.5 concentration. The same study reported a higher risk of non-lobar intracerebral haemorrhage versus lobar intracerebral haemorrhage.[101] Non-lobar intracerebral haemorrhage usually results from chronic damage to the basal ganglia, thalamus, internal or external capsule, brainstem, and cerebellum due to several vascular risk factors, including hypertension (small vessel disease). Lobar intracerebral haemorrhage is often caused by cerebral amyloid angiopathy, but hypertension is also an important risk-factor.[119] Recent studies reported no statistically significant association between air pollution and haemorrhagic stroke overall.[75,76,97] This finding might suggest that air pollutants exclusively increase intracerebral haemorrhage risk and not subarachnoid haemorrhage.[75,101,117]

The long-term exposure to air pollution and risk of haemorrhagic stroke

All long-term exposure studies have used haemorrhagic stroke, and not intracerebral haemorrhage, as an outcome.[64,102-105] Two recent European studies

did not find any association between PM2.5 exposure and incident haemorrhagic stroke during a mean follow-up of over 15 years.[64,102] By contrast, two recently published Asian studies did find an increased risk of haemorrhagic stroke after long-term increased PM2.5 exposure.[103,105] One study estimated long-term exposure as a time-varying cumulative average of PM2.5 during follow-up, using annual mean exposure levels over a mean follow-up of 10.7 years.[105] The authors reported an increased risk of haemorrhagic stroke per 10 µg/m3 increased PM2.5 (HR 1.43; 95% CI 1.09-1.88).[105] The other study calculated long-term exposure as time-varying average exposure weighted for time spent at each residential address over a mean follow-up of 7.5 years. The authors also reported an increased risk of haemorrhagic stroke per 10 µg/m3 increased PM2.5 concentration (HR 1.12; 95% CI 1.05-1.20).[103]

This regional haemorrhagic stroke difference might, again, be caused by the lower and less varied air pollutant concentrations in European countries compared with Asian countries.

Pathophysiological mechanisms

There are several proposed mechanisms by which air pollutants may acutely trigger cardiovascular events. After inhalation pollutants are deposited in the lungs, in which the smaller particles (PM2.5 and PM0.1) and gaseous pollutants are directly diffused or translocated into the systemic circulation, larger particles are taken up by macrophages, which triggers local inflammation in the lungs and, consequently, release of pro-oxidative and pro-inflammatory mediators. In the systemic circulation, gaseous pollutants and small particles react with nitric oxide, thereby resulting in reactive oxygen species, which rapidly leads to endothelial dysfunction.[120] Short-term PM2.5 exposure has been shown to increase markers of plaque vulnerability, namely matrix metalloproteinases and to increase systemic inflammation and thrombogenicity.[121] All of these processes have a central role in the occurrence of acute cerebrovascular disease. Therefore, these mechanisms might be most important in patients with pre-existing cardiovascular conditions and could result mainly in ischaemic stroke due to atherosclerosis. Another important trigger mechanism involves the autonomic respiratory reflex arcs, in which the pollutants trigger an autonomic reflex via pulmonary receptors, barorecepters, and chemical receptors. This occurrence leads to increased vascular resistance, arrythmias, and hypertension.[115] This mechanism might result in cardioembolic ischaemic stroke due to cardiac ischaemia or cardiac arrythmia, or in intracerebral haemorrhage.

Long-term exposure to environmental PM is associated with accelerated progression of atherosclerosis through reactive oxygen species formation and systemic inflammation.[120,122] These mechanisms also cause or worsen conditions such as obesity or diabetes after prolonged exposure, which in turn increases the risk of ischaemic stroke in the long term.[123] Additionally, chronic exposure to PM and gaseous pollutants might directly and indirectly damage the brain; indirectly through the previously mentioned autonomic respiratory reflex arcs, or directly through the diffusion or uptake of nanoparticles and gaseous pollutants through the blood-brain barrier, which locally induces neuro-inflammation and neuronal damage.[115]

One study reported that O3 is specifically associated to lobar intracerebral haemorrhage, but not with haemorrhagic stroke overall.[69] The authors hypothesised that O3 might trigger the deposition of amyloid in cerebral amyloid angiopathy.[69] However, to our knowledge, no studies have directly explored the effect of air pollution on the pathology of cerebral amyloid angiopathy.

Two most methods to estimate individual air pollution exposure are most commonly used. The first involves air pollution monitoring systems. These systems can be ground monitoring systems that measure the concentration of the air pollutants. They can be found in most populated areas and provide hourly or daily mean concentrations of most known pollutants. Satellites that measures air pollution concentration in the air are also used as a monitoring system.[13,87] Mean concentrations are used to estimate individual exposure. This estimation is done by taking the mean concentrations of the combined monitoring systems in one geographical area, or through extrapolating the daily mean concentration of the pollutant from the monitoring system that is closest to the home address of the patient.[68,80,89,91] The second method estimates the individual exposure using advanced modelling of known sources of air pollution, such as the proximity of busy roads, powerplants and industrial grounds to a person's home address.[63,106]

In all of the aforementioned approaches, there is the risk of exposure misclassification. This misclassification is caused by extrapolating mean pollutant concentrations of a city or geographical area to individual exposure. This extrapolation is flawed for at least two reasons. First, this approach does not consider that people spend time at places that are not their home address or the city they live in; for example, for work or vacation. This misclassification might be most pronounced in (younger) people who work. This approach might, depending on differences in air pollution between their residential and working area, result in either underestimation or

overestimation of exposure. Finally, the methods do not differentiate between time spent inside and outside the home, which might also differ for age groups and men and women. This potential non-differential misclassification of individual exposure might lead to non-random error in the overall results. Another methodological issue that needs to be discussed to adequately interpret the results are possible confounders and proper adjustments. All recent studies have corrected for environmental confounders, such as temperature, relative humidity, day of the week, and seasonality.[69,80,82,83,97,99] Most studies chose a case-crossover design, in which participants are their own controls.[99,106] It also remains hard to prove the true effect of each individual pollutant. Air pollutants are never singularly present and can show high levels of collinearity. Therefore, single pollutant models should be interpreted with caution.[80,83] For example, Tian and colleagues excluded PM10 from their multi-pollutant model because of very high collinearity with PM2.5 (Spearman coefficient > 0.9).[80] The authors still reported an independent significant effect for short-term increased SO2, NO2 and PM2.5 concentrations and ischaemic stroke incidence.[80]

Stroke assessment as an outcome

Most of the epidemiological studies have used administrative databases for the assessment of stroke as an outcome. These databases can be regional or national stroke registries or insurance data. In these registries, in-hospital diagnoses are converted into codes, often based on the International Classification of Disease (ICD). This approach is useful because these datasets provide large patient samples, resulting in more power. However, this approach also comes with downsides. First, there is considerable misclassification when using administrative codes. As shown by validation studies reporting moderate-to-good, but not excellent, agreement for using ICD-9 or ICD-10 codes for stroke.[43] A second downside is the scarcity of clinical detail. Many studies have used all-cause stroke as an outcome, by combining the administrative codes for ischaemic stroke and haemorrhagic stroke, despite the fact that these are different diseases with different causes and outcomes. Furthermore, all-cause stroke also includes "stroke, not further specified as ischaemic or haemorrhagic".[124] Although, widening the inclusion criteria provides larger patients samples, this action will hamper finding the true effect of air pollutants for different subtypes of stroke. The scarcity of clinical detail also means that it is often not possible to study subtypes of causal attributions and cardiovascular risk factors of ischaemic stroke and haemorrhagic stroke in relation to air pollution. From a clinical perspective, information on cause and risk factors of

stroke is important because this information gives insight into which patients are most at risk of air pollutant-related stroke.

Future perspectives

Currently, knowledge on air pollution-related stroke is based on observational big-data studies, mostly limited to distinct geographical areas and containing insufficient clinical detail with, at best, inconclusive results. Future research should focus on limiting this potential exposure misclassification. In the past years, wearable sensors have become available. These sensors measure individual exposure and can also correct for differences in metabolic activity through, for example, registering breathing rate and step counting. These personal sensors are promising for identifying patient groups most at risk.[125] This knowledge is the first step towards personalised preventive strategies; for example, advising high risk patients at high risk of air pollution-related stroke to avoid highly polluted areas, or not to go exercising outside during rush hour or near large powerplants.[126] Another intriguing development is agent-based modelling. Agent-based modelling is a technique that can simulate individual human behaviour. The agents are software objects that represent humans and are programmed to show individual behaviour based on a set of behavioural rules. This type of modelling could more accurately estimate individual risk of air pollution-related stroke compared with studies simply using a home address as estimator of individual exposure. This approach is possibly more suited for larger patient sample studies and for studies into long-term exposure.[127]

Currently, the risk of ischaemic stroke and intracerebral haemorrhage related to air pollution is most pronounced in low-income and middle-income countries. These regional differences in air pollution levels are important to put the results reported in different studies into perspective. Several meta-analyses have included studies from different continents and presented a HR standardized per 10 µg/m3 increase in air pollutant concentration. This standardisation is useful to prove an overall effect of air pollutants on stroke incidence. However, especially in European and North American studies, the low end of the IQR is often lower than 10 µg/m3. Therefore, a statistically significant overall effect might not always have the same clinical relevance.[14,128] Also, the question remains if the difference in risk increase found in low-income to middle-income countries compared with most high-income countries is solely the result of higher air pollution levels, or if this difference is modified by ethnicity or behavioural differences. Almost all low-income to middle-

income countries investigated are in Asia, whereas most high-income countries are in Europe or North-America. Therefore, less studied continents, such as Africa, the Middle East and other high-income countries should also be investigated.

Estimations suggest that 91% of people worldwide live in places with mean air pollution levels exceeding the standards set by the WHO. Most of these patients live in low-income and middle-income countries.[126] The Global Burden of Disease Study calculated that ambient air pollution contributed to 18% of the stroke burden in low-income to middle-income countries compared with 10% of the burden in high-income countries. However, the combined contribution of other modifiable (vascular) risk factors was similar.[53] Steps should be taken to decrease air pollutant levels, particularly in low-income and middle-income countries; for example through promoting the use of clean energy sources. Another possibility could be separating living areas more from industrial areas, or by making public transport more accessible to reduce polluting road traffic. Furthermore, several studies have shown that even air pollutant exposure below the levels set by the WHO are still associated with an increased risk of ischaemic and haemorrhagic stroke.[67-70] Therefore, even in Europe and North America, it is important to further improve the air quality and even perhaps to revisit the guidelines set by the WHO.[129]

During the global COVID-19 lockdown there has been an acute drop in air pollution levels, as well as a drop in the number of hospital admissions for stroke.[130] On one hand, this decrease in stroke admissions could be explained by behavioural changes, such as not seeking medical help because of fear of contracting the virus or unnecessarily burdening medical services. On the other hand, there could also be fewer strokes because of fewer acute triggers. Presumably, during the lockdown there is less physically strenuous activity and less work-related stress. Conversely, people have adopted a more sedentary lifestyle, an unhealthier diet, and more mental health issues.[131] One clearly less prevalent acute trigger is ambient air pollution. Future studies should investigate whether stroke occurrence will increase again while the quality of air is still improved and the fear in society and the strain on hospital care has decreased. These studies should also aim to correct for the prevalence of other acute triggers and indoor air pollution. Particularly, indoor air pollution might have become more relevant during the lockdown, given that much more time is spend inside. It will be interesting to see if after COVID-19 there is still reduced work-related traffic or if people continue to wear face masks, and if these factors will affect the association between air pollutants and stroke incidence.

Search strategy and selection criteria

We searched PubMed for all articles published before 1st of July 2020, using the terms: "stroke", "isch(a)emic stroke", "h(a)emorrhagic stroke" and "intracerebral h(a)emorrhage individually in combination with one of the following terms: "air pollution", "air pollutants", "particulate matter", "PM10", "PM2.5", "ultrafine particles", "UFP", "nitrogen (di)oxide", "carbon monoxide", "ozone", "sulphate" and "black carbon". We used English search terms and only included articles with full-text available in English. We screened all title and abstracts for relevance to the aim of our study. Epidemiological studies, cohort studies and reviews were considered if ischaemic stroke and haemorrhagic stroke were separate outcomes and the studies reported specifically on stroke incidence. Studies on pathophysiological mechanisms on the risk of air pollution were also considered. We screened citation lists of studies considered relevant to identify other potentially relevant articles. To ensure novelty, we focused on studies published after 2017 in the main text and tables. Finally, we searched PubMed for articles on "COVID-19" and "air pollution" and/or "ischaemic stroke incidence" published between 1st of march 2020 and 1st of October 2020 to add up to date perspective on the issue.

Chapter IV

Risk Factors and Causes of Ischemic Stroke in 1322 Young Adults

Published as: Ekker MS, Verhoeven JI, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers PJAM, Arntz RM, van Dijk GW, Gons RAR, van Uden IWM, den Heijer T, de Kort PLM, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Zonneveld TP, Kerkhoff H, Rooyer FA, van Rooij FG, van den Wijngaard IR, Klijn CJM, Tuladhar AM, de Leeuw FE. *Risk Factors and Causes of Ischemic Stroke in 1322 Young Adults.* Stroke. 2023 Feb;54(2):439-447. Epub 2022 Dec 13.

Abstract

Background: Identification of risk factors and causes of stroke is key to optimize treatment and prevent recurrence. Up to one-third of young patients with stroke have a cryptogenic stroke according to current classification systems (Trial of ORG 10172 in Acute Stroke Treatment [TOAST] and atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection [ASCOD]). The aim was to identify risk factors and leads for (new) causes of cryptogenic ischemic stroke in young adults, using the pediatric classification system from the IPSS study (International Pediatric Stroke Study).

Methods: This is a multicenter prospective cohort study conducted in 17 hospitals in the Netherlands, consisting of 1322 patients aged 18 to 49 years with first-ever, imaging confirmed, ischemic stroke between 2013 and 2021. The main outcome was distribution of risk factors according to IPSS classification in patients with cryptogenic and non-cryptogenic stroke according to the TOAST and ASCOD classification.

Results: The median age was 44.2 years, and 697 (52.7%) were men. Of these 1322 patients, 333 (25.2%) had a cryptogenic stroke according to the TOAST classification. Additional classification using the ASCOD criteria reduced the number patients with cryptogenic stroke from 333 to 260 (19.7%). When risk factors according to the IPSS were taken into account, the number of patients with no potential cause or risk factor for stroke reduced to 10 (0.8%).

Conclusions: Among young adults aged 18 to 49 years with a cryptogenic ischemic stroke according to the TOAST classification, risk factors for stroke are highly prevalent. Using a pediatric classification system provides new leads for the possible causes in cryptogenic stroke, and could potentially lead to more tailored treatment for young individuals with stroke.

Introduction

An estimated 10% to 15% of all strokes occur in young adults (18–49 years), resulting in about 2 million young adults who are affected by stroke worldwide every year, with incidence increasing over the past decade.[53,132,133] Stroke at young age comes with high socioeconomic costs and patients encounter lifelong consequences.[53,134] Rapid identification of causes and risk factors of ischemic stroke in young adults is key to optimize treatment and prevent recurrence. Still, in up to one-third of all cases with ischemic stroke at young age, no clear cause is identified after thorough clinical work-up and the use of stroke classification schemes such as the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification and the ASCOD (atherosclerosis, small vessel disease, cardiac pathology, other causes, dissection) classification.[9,107,135,136]

However, these classifications have been developed for ischemic stroke patients often older than 65 years. They have gradually been implemented in clinical practice of patients with stroke at younger ages, without any formal evaluation and validation in this specific domain. This may result in unjustified classification of patients with a cryptogenic stroke, while in fact causes or risk factors for stroke are present that are *not* recognized as such within the conventional developed classification schemes. In addition, the currently used classifications lump patients with diverse and rare causes and underlying pathophysiological mechanisms into 1 other determined category, thereby ignoring the possible different long-term prognosis of stroke depending by the different causes.

In contrast to the classification schemes used in adults, the classification developed for childhood- and adolescent stroke by the IPSS study (International Pediatric Stroke Study) designates not 1 single cause of stroke. The IPSS allows multiple risk factor categories that are not mutually exclusive and recognizes age-specific presumed risk factors and etiologies that are not included in the TOAST and ASCOD.[12] Although a risk factor is not necessarily synonymous with a cause, rapid identification of risk factors is an important step to initiate treatment and counseling of patients.

We therefore investigated the causes and risk factors of stroke in young adults in a prospective cohort study of young patients with imaging proven ischemic stroke according to the TOAST, ASCOD, and IPSS criteria to search for clues that help find potential causes in cryptogenic stroke.

Methods

Data Availability

The raw and anonymized data used in this study can be shared upon and after permission of our institutional review board. Written proposals can be addressed to the corresponding author and will be assessed by ODYSSEY (Observational Dutch Young Symptomatic StrokE studY) investigators for appropriateness of use, and a data sharing agreement in accordance with Dutch regulations will be put in place before data are shared.

Study Description

This study is part of the ODYSSEY, a Dutch multicenter prospective cohort study in 17 centers on the risk factors and prognosis of patients with a first-ever, ischemic stroke or intracerebral hemorrhage aged 18–49 years. Details of the study have been described previously. For this study, we included patients with ischemic stroke. Patients were included consecutively between May 2013 until end of inclusion in February 2021.

In short, our study comprises consecutive patients aged 18–49 years with first-ever symptomatic ischemic stroke with radiological evidence of cerebral ischemia. Patients with transient symptoms (<24 hours) all had diffusion weighted imaging positive lesions (DWI+) on magnetic resonance imaging and as such were included as (minor) stroke according to the tissue based definition.[2]

Baseline Data Collection

Information on (vascular) risk factors, stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) on admission and modified Rankin Scale (mRS) at discharge, treatment in the acute phase and at discharge were systematically collected as were results of neuroimaging, laboratory and cardiac diagnostic tests. Case-fatality was defined as death within the first 30 days after stroke. Case fatality was ascertained by checking all medical files, in combination with an interview by phone as part of the regular follow-up. When patients were lost to follow-up case fatality was ascertained by contacting their general practitioners. In addition, patients completed a standardized structured questionnaire on level of education, marital status, employment and additional potential risk factors such as illicit drug use. We provide a complete case analysis.

Risk Factors and Causes of Stroke

To limit missing data, patient's medical files, including diagnostic tests, risk factors, and the cause of ischemic stroke, were systematically assessed for all patients by 1 of 4 raters (ME, JV, MS, or EB) according to the modified TOAST criteria (including a subdivision into high-risk and medium-risk sources of cardio-embolism and in large artery atherosclerosis and likely atherothrombotic disease) (further referred to as TOAST),[137-139] ASCOD criteria,[136] and modified IPSS criteria (referred to as IPSS Table S1).[12]

In case of doubt or disagreement of a risk factor of cause, a consensus meeting was held with a vascular neurologist (FEdL). The adjudicated causes and risk factors for stroke according to the TOAST, ASCOD, and IPSS classification were reviewed by 2 separate raters in the first 100 patients with an interrater agreement of 98%.

Statistical Analyses

We reported categorical variables as numbers and frequencies unless otherwise stated. Continuous variables were reported as median and interquartile range (IQR). Age- and sex-specific analyses for causes and risk factors were performed by predefined age-groups: 18–25, 26–30, 31–35, 36–40, 41–45, and 46–49 years.

Categorical variables were compared through Pearson χ^2 or Fisher Exact tests, whichever was appropriate. Continuous variables were compared by Student *t* test or Mann Whitney *U* test and the Kruskal-Wallis test was used for comparing median age, NIHSS, and mRS between men and women and between stroke subtypes.

For all analyses, 2-sided *P* values of <0.05 were considered statistically significant. Data were analyzed using SPSS Software version 22 (IBM), R version 3.6.2 (R Project for Statistical Computing) and Microsoft Office Excel 2007.

Ethical Approval

The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study (NL41531.091.12). Informed consent was obtained for all patients. Additional approval was obtained for Inclusion of patients that died within the first 30 days after stroke without informed consent for those who had been unable to provide informed consent.

Results

Demographics

In total, 1223 (92.5%) patients had an ischemic stroke with symptoms lasting longer than 24 hours, and 99 (7.5%) with symptoms <24 hours. Median age was 44.2 years (IQR [38.4–47.5]), 697 were men (52.7%), and 38 (2.9%) patients died within the first 30 days (case fatality; Table 1). Work-up was according to clinical practice and local protocols for young patients with stroke, including neuroimaging for all patients: 1114 (84.3%) patients underwent computed tomography, 1160 (87.7%) underwent magnetic resonance imaging, 953 (72.1%) both computed tomography and magnetic resonance imaging, 96.0% had imaging of the carotid arteries (658 [49.8%] computed tomography angiography, 627 [47.4%] magnetic resonance angiography, 517 [39.1%] an ultrasound of the carotids). An electrocardiogram was made in 1279 patients (96.7%), 1131 patients had a least 24 hours of cardiac rhythm monitoring (85.5%), 1071 patients (81.0%) had a transthoracic echocardiography, and 249 patients (18.8%) underwent a transesophageal echocardiography. Of the 213 patients (16.1%) that did not receive any cardiac ultrasound, 31 patients (2.3%) had no clear cause for their stroke. The other 182 patients (13.8%) without cardiac ultrasound had a clear other cause of stroke, deeming cardiac ultrasound unnecessary for the etiologic diagnosis. Laboratory diagnostics for antiphospholipid syndrome[140] was performed in >70% of all patients.

Causes According to Modified TOAST Criteria, Stratified by Age and Sex

Large artery atherosclerosis was identified as the cause of stroke in 59 (4.5%) patients, likely atherothrombotic stroke in 172 (13.0%), small vessel disease in 166 (12.5%), and cardio-embolic stroke in 226 (17.1%) patients (Table 1; Table S3 for cardio-embolic causes). Other determined cause of stroke was present in 287 (21.7%) patients (Table 2) and multiple causes in 79 (6.0%) patients (Table S4). In 333 (25.2%) patients, the stroke had an undetermined cause and was classified as cryptogenic. Patients with a cryptogenic stroke were younger (median age of 43.3 years; IQR [36.2–46.7]), than those with non-cryptogenic stroke (median age 44.6; IQR [39.1–47.6]; P=0.001).

The cause of stroke according to the TOAST classification differed between age-groups (Figure 1; Table S5).

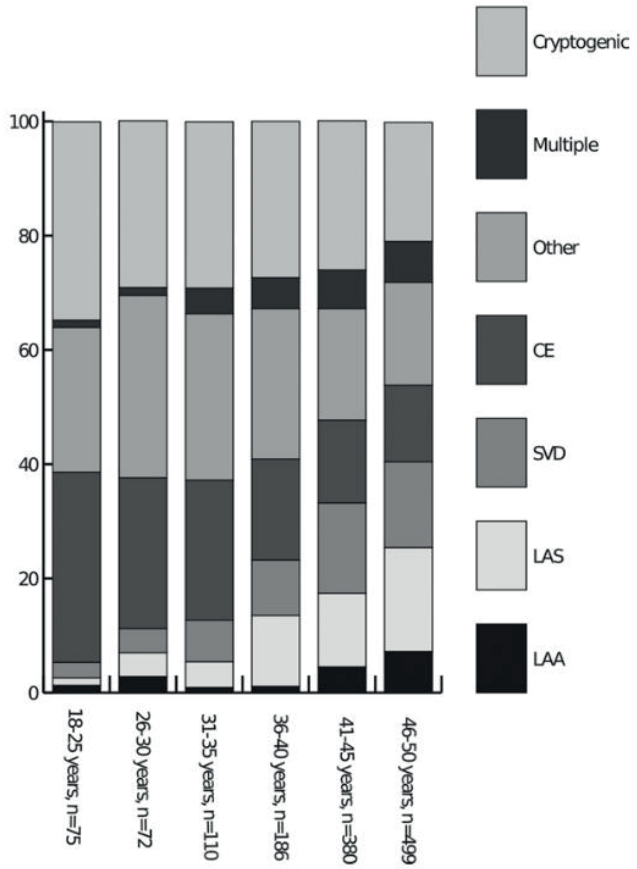


Figure 1: TOAST etiology distribution among different age-groups

Significant differences between age groups and the percentages of the smallest groups that are not shown in the Figure are shown in Table S5.

CE indicates cardioembolic stroke; LAA, large artery atherosclerosis; LAS, likely atherothrombotic stroke; Other, other determined cause of stroke; and SVD, small vessel disease.

ASCOD Classification

Of the 333 patients with a cryptogenic stroke according to the TOAST classification, 73 could be assigned to 1 of the ASCOD categories (Table S6). The 260 patients in whom the stroke remained cryptogenic were younger (median age 43.1 years; IQR [36.4–46.5]) than the 1062 patients classified otherwise according to TOAST and ASCOD (median age 44.6; IQR [39.0–47.6]; $P<0.001$).

Table 1: Baseline Characteristics

Demographics	**n (%)** [A]
18-49 years	1322 (100)
Median age, years (IQR)	44.2 (7.5)
Age groups	
18-25 years	75 (5.7)
26-30 years	72 (5.4)
31-35 years	110 (8.3)
36-40 years	186 (14.1)
41-45 years	380 (28.7)
46-50 years	499 (37.7)
Men	697 (52.7)
Stroke characteristics	
Median NIHSS at admission, median (range)	3.0 (0-42)
Median NIHSS at discharge (range)	1.0 (0-42)
Median mRS at discharge (IQR)	2.0 (1.5)
Case fatality	38 (2.9)
Territorial stroke	1035 (78.3)
Lacunar stroke	287 (21.7)
Localization	
Left hemisphere	588 (44.5)
Right hemisphere	589 (44.5)
Bilateral	145 (11.0)
Acute interventions	
Intravenous thrombolysis	241 (18.2)
Intra-arterial thrombectomy	34 (2.6)
Both	88 (6.7)
Cardiovascular risk factors [B]	
Hypertension	499 (37.7)
Smoking	657 (49.6)
Excessive alcohol consumption	92 (7.0)
Dyslipidemia	864 (65.4)
Diabetes mellitus	138 (10.4)
Positive family history cardiovascular disease <60yrs	386 (29.2)
BMI 25 to 30	369 (27.9)
BMI 30 to 35	187 (14.1)

Table 1: Continued

Demographics	**n (%) [A]**
BMI > 35	81 (6.1)
TOAST classification	
Large artery atherosclerosis	59 (4.5)
Likely atherothrombotic	172 (13.0)
Small vessel disease	166 (12.6)
Cardio-embolic	226 (17.1)
Other determined cause	287 (21.7)
Multiple causes	79 (6.0)
Cryptogenic	333 (25.2)

Abbreviations: IQR, interquartile range; NIHSS, The National Institutes of Health Stroke Scale; mRS, modified Ranking Scale; BMI, Body mass index

[A] number with percentage between brackets, unless otherwise specified in the left column.

[B] Definitions of vascular risk factors: arterial hypertension: treated or known blood pressure before stroke >140/90 mm Hg or hypertensive retinopathy; current smoking or smoking stopped within the last 6 months; excessive alcohol use: use of more than 200 grams of alcohol/week; dyslipidemia: treated or known low-density lipoprotein before the stroke >160 mg/dl or 4.1 mmol/l and/or high-density lipoprotein 7 mmol/l or HbA1c > 48 mmol/L.

IPSS Classification

Distribution of risk factors according to the IPSS is shown in Table 3 for the whole cohort and for patients with a cryptogenic stroke according to the TOAST criteria. Of the 333 patients, 18 (5.4%) reported illicit drug use in the year before stroke. Coagulation abnormalities were found in 85 of 333 patients (25.5%). Given that the risk factors migraine, oral contraceptive use and smoking in the IPSS are known for their increased risk of stroke in interaction, (16,17) these were investigated: Migraine was present in 92 of the 333 patients (27.6%), of whom 34 women (18.9%) also used oral contraceptives. An estimated 122 of the 333 patients with a cryptogenic stroke according to the TOAST criteria (36.6%) were smokers, of whom 31 women (17.3%) used oral contraceptives. Thirteen women (7.3%) used both oral contraceptives, had migraine and were smokers.

Differences Between the IPSS Classification in Cryptogenic and Non-cryptogenic Strokes According to TOAST Classification

In comparison with patients with a non-cryptogenic stroke according to TOAST, patients with a cryptogenic stroke less often had arteriopathies (4.5% versus 35.6%) and cardiac conditions (6.6% versus 32.4%), more often had a prothrombotic state (44.7% versus 38.3%) and a chronic systemic condition (9.0% versus 4.3%; Table 3). Risk factors for early atherosclerosis were highly prevalent in both groups (90.1% versus 91.8%).

Discussion

We found that 25.2% of young patients with an ischemic stroke had a cryptogenic stroke according to the modified TOAST and 19.7% when further classified according to ASCOD criteria. Only 0.8% of 1322 patients had a cryptogenic stroke without any potential risk factors when applying the IPSS classification.

Using the TOAST classification, we found a lower percentage of patients with a cryptogenic stroke than most European cohort studies.[135,141] This might be due to both our systematic approach and to differences in time period between studies, since radiological, cardiac and laboratory testing have become more extensive over the last decade resulting in more identifiable causes. Both the TOAST and ASCOD classification, though often applied in young patients with stroke, were not designed to classify stroke in the young. This might explain why 46.9% of all strokes are classified as other determined- and cryptogenic strokes. Although the ASCOD classification separates patients with an arterial dissection from the other determined causes, other categories are similar to the TOAST classification. As such ASCOD has limited added value in clinical practice to identify additional causes of stroke. Current classification systems developed for stroke patients in general (often >65 years) seem therefore inadequate to classify stroke causes and risk factors in young adults.

Evaluating patients with the IPSS classification can broaden the view of clinicians on potential risk factors, or factors that in interaction can play a role, such as oral contraceptive use, migraine, and smoking.[142,143] The IPSS may shed light on (new) mechanisms that potentially lead to stroke in young adults, by subdividing risk factors in many different categories, based on a presumed pathophysiological mechanism. These different categories may help by forming a foundation for constructing a classification more specific for young adults with stroke. In contrast, the TOAST and ASCOD only have separate categories for large and small vessel disease, cardio-embolism, and dissection (ASCOD). Although we found a potential risk factor in many patients according to the IPSS classification, this is not synonymous with causality. Classical concepts about the cause of a disease include an event, condition, or characteristic that plays an essential role in producing an occurrence of the disease, and multiple component causes can act in combinations to produce different sufficient causes for a disease.[144] In addition, strength of association, consistency, specificity, temporality, biological plausibility of a risk factor, and the occurrence of stroke support causality.[144] For many of the risk factors included in the IPSS, causality remains to be demonstrated. However, this also holds true for some of the causes in the TOAST and ASCOD systems (eg,

mild hyperhomocysteinemia). Searching for risk factors in the large group of young adults with cryptogenic stroke using a risk factor system designed for children and adolescents can provide leads for new causes and potential treatable targets, but also help in developing a more structured, cost-effective diagnostic work-up linked to an etiological classification. Evaluating causality of certain common yet presumed risk factors in young adults with stroke would be an important area of future research,[145] and to further prove causality, evaluation of the long-term prognosis for patients with different presumed risk factors is key, as is comparison of the prevalence of some presumed risk factors in the general population. Examples we found in this study are the high number of young adults with coagulation abnormalities with or without a patent foramen ovale in both the cryptogenic and non-cryptogenic category.[146] Also, cannabis is frequently used among young adults, often with concomitant use of alcohol and other substances, but it is rarely considered the cause of stroke. Meanwhile, a study in the United States showed a rising trend in hospital admissions for cardiovascular events in young adults due to cannabis use without concomitant use of other substances.[147]

Table 2: Other determined causes of stroke (within TOAST other determined and multiple causes category)

Cause of stroke	n	Comments
Carotid artery dissection	92	
Vertebral artery dissection	64	Including basilar top dissection (1)
Antiphospholipid syndrome	50	APS in combination with increased factor VIII activity (1)
Illicit drug use	16	Cocaine (9), cocaine + XTC + cannabis (2), cocaine + methadone (1), cocaine + cannabis (1), amphetamine(1), amphetamine + ketamine (1), cocaine induced vasculitis (1)
Hyperhomocysteinemia	12	
Pregnancy/puerperium	9	
Active malignancy	7	Cervical cancer (1), metastatic paraganglioma (1), metastatic anal carcinoma (1), metastatic pancreatic carcinoma (1), thyroid carcinoma (1), colon carcinoma (1), metastatic non-small-cell lung carcinoma (1)
Moyamoya	6	
Radiotherapy induced vasculopathy	6	
Migrainous stroke	6	
Hematological (thrombocytosis)	7	Positive JAK2 mutation (1), thrombocytosis, anemia and leukocytosis (1), essential thrombocytosis (1), TTP (2), Polycythemia Vera (2)
SLE and SLE-like disease	4	SLE-like disease (1)

Table 2: Continued

Cause of stroke	n	Comments
Iatrogenic	4	During placement of device in carotid (study) (1), cardio-thoracic surgery for aorta rupture (1), for type A dissection (1), during endovascular treatment of ACOM aneurysm (1)
PACNS	3	
Reversible vasoconstriction syndrome	2	
Sneddon syndrome	3	
HIV-associated	3	
Acute systemic infection preceding stroke	3	Bacterial empyema with reactive vasculitis of middle cerebral artery (1), herpes zoster (1), varicella zoster (1)
Neurological infection	3	Neurosarcoidosis (1), neuroborreliosis (1), neurolues (1)
Other rare causes	3	Exophytic thrombus in brachiocephalic trunc (1), thrombus brachiocephalic artery (1), aneurysm carotid artery with mural plaque(1)
MELAS	2	
Takayasu arteritis	2	
Intracranial dissection	2	
Hypotension	2	Suicide attempt with blood pressure lowering medication (1), blood pressure lowering in hypertensive crisis (1)
Inadequate oral coagulation therapy	2	Low INR (1.9) in Wegener disease on oral coagulation therapy (1), forgotten doses of rivaroxaban in patient with history of pulmonary embolism and small PFO (1)

Single cases were found for homozygous factor V Leiden, sickle cell disease, fibromuscular dysplasia, toxic induced stroke due to cisplatinum-induced thrombosis, hemolytic anemia as paraneoplastic phenomenon, migraine with aura in combination with oral contraceptive use, patent foramen ovale (PFO), and pulmonary embolism, a fat embolus after femur fracture, and a congenital predisposition disorder. ACOM indicates anterior communicating artery; APS, antiphospholipid syndrome; HIV human immunodeficiency viruses; INR, international normalized ratio; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; TTP, thrombotic thrombocytopenic purpura; and XTC, ecstasy. In 10 of the 333 patients with cryptogenic stroke, according to the TOAST criteria (3.0%), not a single IPSS risk factor could be identified (Table 3). The group of 10 patients without any IPSS risk factor consisted of 5 men and 5 women (median age 42.3 years; 36.6–45.8). Eight of these patients had an ischemic stroke with symptoms lasting >24 hours, and 2 had symptoms lasting <24 hours.

Table 3: IPSS risk factor categories for all patients, cryptogenic patients according to TOAST and all non-cryptogenic patients according to TOAST criteria.

IPSS risk factor categories	Total cohort, N = 1322 (%)	TOAST cryptogenic, N = 333 (%)	TOAST non-cryptogenic, N = 989 (%)
Arteriopathy	367 (27.8)	16 (4.8)	351 (35.5)
Arterial dissection	163 (12.3)	0 (0.0)	163 (16.5)
Carotid artery stenosis (<50%)	77 (5.8)	4 (1.2)	73 (7.4)
Arteriopathy, otherwise*	65 (4.9)	8† (2.4)	57 (5.8)
Carotid artery stenosis (>50%)	35 (2.6)	0 (0.0)	35 (3.5)
Focal arterial stenosis	24 (1.8)	4 (1.2)	20 (2.0
Moyamoya	6 (0.5)	0 (0.0)	6 (0.6)
Radiotherapy-induced vasculopathy	6 (0.5)	0 (0.0)	6 (0.6)
RCVS	4 (0.3)	1 (0.3)	3 (0.3)
PACNS	3 (0.2)	0 (0.0)	3 (0.3)
Takayasu	2 (0.2)	0 (0.0)	2 (0.2)
Sickle cell arteriopathy	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac condition	342 (25.9)	22 (6.6)	320‡ (32.4)
Patent foramen ovale	196 (14.8)	6§ (1.8)	190 (19.2)
Cardiac condition otherwise‖	68 (5.1)	14 (4.2)	54 (5.5)
Atrial fibrillation	33 (2.5)	0 (0.0)	33 (3.3)
Atrial septal aneurysm	26 (2.0)	2 (0.6)	24 (2.4)
Hypokinetic segment of left ventricle	17 (1.3)	1 (0.3)	16 (1.6)
Mitral valve insufficiency	14 (1.1)	1 (0.3)	13 (1.3)
Dilated cardiomyopathy	14 (1.1)	0 (0.0)	14 (1.4)
Congestive heart failure	12 (0.9)	0 (0.0)	12 (1.2)
Akinetic segment of left ventricle	10 (0.8)	0 (0.0)	10 (1.0)
Myocardial infarction < 4 wk	10 (0.8)	0 (0.0)	10 (1.0)
Mechanical valve prothesis	8 (0.6)	0 (0.0)	8 (0.8)
Left ventricle thrombus	10 (0.8)	0 (0.0)	10 (1.0)
Infectious endocarditis	7 (0.5)	0 (0.0)	7 (0.7)
Atrial myxoma	6 (0.5)	0 (0.0)	6 (0.6)
Atrial flutter	5 (0.4)	0 (0.0)	5 (0.5)
Aortic valve insufficiency	4 (0.3)	0 (0.0)	4 (0.4)
Cardiac intervention <72 h	4 (0.3)	0 (0.0)	4 (0.4)
Left atrial thrombus	3 (0.2)	0 (0.0)	3 (0.3)
Aortic valve stenosis	3 (0.2)	1 (0.3)	2 (0.2)
Mitral valve stenosis	2 (0.2)	0 (0.0)	2 (0.2)
Myocardial infarction (1-6 mo)	2 (0.2)	0 (0.0)	2 (0.2)
Noninfectious endocarditis	2 (0.2)	0 (0.0)	2 (0.2)

Table 3: Continued

IPSS risk factor categories	Total cohort, N = 1322 (%)	TOAST cryptogenic, N = 333 (%)	TOAST non-cryptogenic, N = 989 (%)
Chronic systemic conditions	206 (15.6)	48 (14.4)	158 (16.0)
Other chronic systemic condition	72 (5.4)	30 (9.0)	42 (4.3)
Illicit drug use¶	68 (5.1)	18 (5.4)	50 (5.1)
Auto-immune disorders	44 (3.3)	11 (3.3)	33 (3.3)
Solid extracranial tumor	12 (0.9)	0 (0.0)	12 (1.2)
Hematological malignancy	6 (0.5)	1 (0.3)	5 (0.5)
Fibromuscular dysplasia	3 (0.2)	1 (0.3)	2 (0.2)
Ehlers Danlos syndrome	3 (0.2)	0 (0.0)	3 (0.3)
MELAS	2 (0.2)	0 (0.0)	2 (0.2)
Prothrombotic state#	528 (39.9)	149 (44.7)	379 (38.3)
Oral contraceptive use	298 (22.5)	99 (29.7)	199 (20.1)
Hyperhomocysteinemia	121 (9.2)	25 (7.5)	96 (9.7)
Mild hyperhomocysteinemia <40 µmol/l	102 (7.7)	24 (7.2)	78 (7.9)
Antiphospholipid antibodies	63 (4.8)	2 (0.6)	61 (6.2)
Increased factor VIII activity	49 (3.7)	14 (4.2)	35 (3.5)
Antithrombin deficiency	43 (3.3)	16 (4.8)	27 (2.7)
Other acquired	36 (2.7)	11 (3.3)	25 (2.5)
Factor V Leiden mutation**	33 (2.5)	14 (4.2)	19 (1.9)
Prothrombin mutation	18 (1.4)	8 (2.4)	10 (1.0)
Other genetic	8 (0.6)	3 (0.9)	5 (0.5)
Protein C deficiency	14 (1.1)	3 (0.9)	11 (1.1)
Protein S deficiency	7 (0.5)	3 (0.9)	4 (0.4)
Diffuse intravasal coagulation		0 (0.0)	2 (0.2)
Acute systemic conditions	21 (1.6)	4 (1.2)	17 (1.7)
Other acute systemic condition	16 (1.2)	3 (0.9)	13 (1.3)
<72 h after surgery	4 (0.3)	0 (0.0)	4 (0.4)
Hypotension	1 (0.1)	0 (0.0)	1 (0.1)
Need of vasopression	1 (0.1)	0 (0.0)	1 (0.1)
Chronic head/neck condition	374 (28.3)	95 (28.5)	279 (28.2)
Migraine	348 (26.3)	92 (27.6)	256 (25.9)
Head/neck tumor otherwise	12 (0.9)	0 (0.0)	12 (1.2)
VP drain	8 (0.6)	1 (0.3)	7 (0.7)
Brain tumor or metastasis	7 (0.5)	0 (0.0)	7 (0.7)
Intracranial AVM	4 (0.3)	3 (0.9)	1 (0.1)
Cerebral aneurysm	4 (0.3)	0 (0.0)	4 (0.4)
Acute head/neck condition	25 (1.9)	2 (0.6)	23 (2.3)
Trauma <3 mo	13 (0.1)	2 (0.6)	11 (1.1)
Other acute head/neck injury	10 (0.8)	0 (0.0)	10 (1.0)
Meningitis <4 wk	1 (0.1)	0 (0.0)	1 (0.1)
Head/neck surgery <72 h	1 (0.1)	0 (0.0)	1 (0.1)
Pregnancy related	15 (1.1)	4 (1.2)	11 (1.1)
Pregnant	7 (0.5)	3 (0.9)	4 (0.4)
Postpartum <6 wk	7 (0.5)	0 (0.0)	7 (0.7)

Table 3: Continued

IPSS risk factor categories	Total cohort, N = 1322 (%)	TOAST cryptogenic, N = 333 (%)	TOAST non-cryptogenic, N = 989 (%)
Risk factor for early atherosclerosis	1208 (91.4)	300 (90.1)	908 (91.8)
Dyslipidemia	864 (65.4)	186 (55.9)	678 (68.6)
Cigarette smoking in last year	657 (49.7)	122 (36.6)	535 (54.1)
Hypertension	499 (37.7)	70 (21.0)	429 (43.3)
Family History positive <60 y	386 (29.2)	94 (28.2)	292 (29.5)
BMI 25-30	369 (27.9)	101 (30.3)	268 (27.1)
BMI 30-35	187 (14.1)	37 (11.1)	150 (15.2)
Diabetes mellitus	138 (10.4)	10 (3.0)	128 (12.9)
Excessive alcohol consumption	92 (7.0)	19 (5.7)	73 (7.4)
BMI > 35	81 (6.1)	12 (3.6)	69 (7.0)
No IPSS risk factors	10 (0.8)	10 (3.0)	0 (0.0)

AVM indicates arteriovenous malformation; IPSS, International Pediatric Stroke Society; RCVS, reversible cerebral vasoconstriction syndrome; and VP, ventriculoperitoneal.

* Among arteriopathy condition otherwise conditions like stenosis of vertebral artery, vessel wall irregularities, drug-induced vasculopathy, iatrogenic induced stenosis carotid artery, cerebral media artery occlusion, dural AV-fistula, varicella zoster angiopathy, vasculitis-like appearance of the vessels, fibromuscular dysplasia, thrombosis in giant aneurysm, late vasospasms and thrombi due to type A dissection were listed.

† Not considered as causal by the treating physician and rater.

‡ Patients with both TOAST cardio-embolic stroke and multiple causes.

§ Very small patent foramen ovale or atrial septum aneurysm without patent foramen ovale, not considered the cause of stroke.

|| Conditions listed as cardiac condition otherwise were atrial septum defect type 2, myocardial infarction (>1 year before stroke), closed ventricular septal defect (VSD) in childhood, floppy or hypokinetic intra-atrial septum, pericarditis, pacemaker, congenital AV-block, fibroelastoma of the valves, focal arterial stenosis, Marfan syndrome, bicuspid aortic valve, cor triventriculare, rhythm abnormalities otherwise and hypertrophic cardiomyopathy.

¶ Use of soft- and/or hard drugs on regular basis.

When use of oral contraceptives is counted as a chronic systemic condition instead of a prothrombotic state, numbers are as follows (chronic systemic condition vs prothrombotic state): Total cohort: 467 (35.3%) vs 315 (23.8%), TOAST cryptogenic 137 (41.1%) vs 80 (24.0%).

** Only 2 patients had a homozygous Factor V Leiden mutation.

†† All prothrombin mutations were heterozygous.

However, studies on differences in the prevalence of these coagulation abnormalities between patients and the healthy population, as well as studies on the long-term effects and causality of cannabis on cardiovascular outcomes are scarce.[148]

Our study has several strengths. First, this study is a large, prospective cohort study investigating stroke in young adults in the last decade. Patients were therefore analyzed and treated according to the latest guidelines including magnetic resonance imaging an extensive cardiac work-up. The large number of patients allowed for detailed subgroup analysis between men and women, different age-groups, stroke subtype and different etiologies. Second, stroke misclassification was not present as all strokes were confirmed on neuroimaging, and checked independent from the treating physicians. Third, information was gathered in both a detailed and structured manner and verified by 2 from a pool of 4 investigators. Risk factor and cause designation was done systematically by 4 raters, checked by one another afterwards in 100 cases and overall discussed to reduce the interrater variability. Fourth, the study has a nation-wide character, with consecutive patients from both academic and nonacademic hospitals in different regions of the Netherlands. By also including patients who visited outpatient clinics (minor strokes) and patients who died within the first 30-days of stroke (very severe) selection bias was limited. In addition, this provides a good reflection of the stroke population of young adults and increases the generalizability of our results to other European countries.

Limitations

Our study also has limitations. First, there were no demands on diagnostic work-up for hospitals that participated in the ODYSSEY study, and therefore, the 333 patients classified as cryptogenic according to TOAST included some incomplete work-up cases. For example, 8.1% of our patients without a cause of stroke did not receive a cardiac ultrasound, or had a transthoracic echocardiography without bubble study, potentially leading to overestimation of the number of cryptogenic strokes and an underestimation of the number of patent foramen ovale. Similarly, intracranial vascular imaging by computed tomography angiography or magnetic resonance angiography was not performed in 24% of our patients and not all cryptogenic patients received complete laboratory testing for antiphospholipid syndrome. However, we think that, for example, a missed diagnosis of vasculitis seems highly unlikely in patients with unavailable intracranial vascular imaging without anamnesis of headache, without other inflammatory laboratory parameters and with neuro-imaging without strokes in multiple territories. Regarding patients

without complete laboratory testing for antiphospholipid syndrome, stroke was the first thrombo-embolic event for all patients, and the women (44%) had no history of pregnancy complications. Second, all 17 participating centers included consecutive patients, although this was not always possible, for example, during the COVID period (March 2020 – February 2021). However, these were most likely missing at-random. Third, besides the standardized questionnaires, all patient's files were checked for all the risk factors in the IPSS; however, on some risk factors such as illicit drug use, amount of alcohol consumption, and cigarette smoking, patient's answers could possibly have not been honest in the questionnaire and in medical history taking with their treating physician, leading to an underestimation of some of these risk factors. In contrast, attribution bias might have played a role, since all patients with stroke have been seen by a neurologist, and the professional tendency to attribute stroke to a cause. Therefore, over reporting of risk factors by patients might have occurred.

Conclusions

Current stroke classification systems developed for stroke in general (often in patients over 65 years) cannot identify the cause of stroke in many patients, leaving a large group of cryptogenic strokes in young adults <50 years of age. Many additional potential risk factors for stroke can be found using a risk factor classification system designed for children and adolescents, providing leads for (new) causes, although further research should elaborate on the actual causality of some of these factors and the prevalence in the general population. Whether a more extensive modified pediatric risk factor classification can serve as a stepping stone for a new classification scheme that may aid in the development of tailored diagnostic work-up and treatment for young patients with stroke needs to be further evaluated. However, detailed, correct etiological classification is essential for future studies, both on therapy, secondary prevention and prognosis, for comparison of patients with similar diagnostic work-up and cause.

PART THREE

STROKE IN THE YOUNG: CANCER IN DISGUISE?

Chapter V

Association of stroke at young age with new cancer in the years after stroke among patients from the Netherlands

Published as: Verhoeven JI, Fan B, Broeders MJM, Driessen CML, Vaartjes ICH, Klijn CJM, de Leeuw FE. *Association of stroke at young age with new cancer in the years after stroke among patients in the Netherlands.* JAMA Network Open. 2023;6(3)e235002.

Abstract

Importance: Stroke may be a first manifestation of an occult cancer or may be an indicator of an increased cancer risk in later life. However data, especially in younger adults, are limited.

Objectives: To assess the association of stroke with new cancer diagnoses after first-ever stroke, stratified by stroke subtype, age, and sex, and to compare this association with that in the general population.

Design, setting and participants: This registry- and population-based study included 390 398 patients in the Netherlands aged 15 years or older without a history of cancer and with a first-ever ischemic stroke or intracerebral hemorrhage (ICH) between January 1, 1998, and January 1, 2019. Patients and outcomes were identified through linkage of the Dutch Population Register, Dutch National Hospital Discharge Register, and National Cause of Death Register. Reference data were gathered from the Dutch Cancer Registry. Statistical analysis was performed from January 6, 2021, to January 2, 2022.

Exposure: First-ever ischemic stroke or ICH. Patients were identified by administrative codes from the *International Classification of Disease (ICD), Ninth Revision, and the International Classification of Disease and Related Health Problems, Tenth Revision*.

Main outcomes and measures: The primary outcome was the cumulative incidence of first-ever cancer after index stroke, stratified by stroke subtype, age, and sex, compared with age-, sex- and calendar year- matched peers from the general population.

Results: The study included 27 616 patients aged 15 to 49 years (median age 44.5 years, IQR 39.1-47.6 years); 13 916 women [50.4%]; 22 622 with ischemic stroke [89.1%]) and 362 782 patients 50 years or older (median age 75.8 years, IQR 66.9-82.9 years; 181 847 women [50.1%]; 307 739 with ischemic stroke [84.8%]). The cumulative incidence of new cancer at 10 years was 3.7% (95% CI 3.4-4.0) among patients aged 15 to 49 years and 8.5% (95% CI 8.4-8.6%) among those aged 50 years or older, the cumulative incidence of new cancer after any stroke was higher among men (Gray test statistic, 943.1, P <.001). In the first year after stroke, compared with peers from the general population, patients aged 15 to 49 years were more likely to receive a diagnosis of a new cancer after ischemic stroke (standardized incidence

ratio [SIR], 2.6 [95% CI 2.2-3.1]) and ICH (SIR 5.4 [95% CI 3.8-7.3]). For patients aged 50 years or older, the SIR was 1.2 (95% CI 1.2-1.2) after ischemic stroke and 1.2 (95% CI 1.1-1.2) after ICH.

Conclusions and relevance: This study suggests that patients, aged 15 to 49 years, may have a 3- to 5- fold increased risk of cancer in the first year after stroke, whereas this risk is only slightly elevated for patients aged 50 years or older. Whether this has implications for screening remains to be investigated.

Introduction

Stroke and cancer are two of the most common causes of morbidity and mortality worldwide.[149] In some cases, the 2 are related, as stroke may be a first manifestation of an underlying occult cancer. Patients with cancer are at increased risk of stroke because of direct tumor effects, prothrombotic effects, and treatment effects.[17,18,150] Also, many cancers and stroke have joint risk factors, such as smoking and obesity. [17,20,151,152]

A previously unidentified cancer can be identified in 2% to 5% of all patients with ischemic stroke within the first year after stroke, and possibly in even higher percentages of patients after stroke without a clear cause (cryptogenic stroke). This cancer can be considered in hindsight as occult, although already active, at time of stroke.[18,19] Cryptogenic stroke is rare among older populations, but it represents up to one-third of all patients aged 18 to 49 years at the time of stroke.[9] Thus, we hypothesize that the association between stroke and poststroke cancer is most pronounced among younger adults. However, to our knowledge, literature on the incidence of cancer among young ischemic stroke survivors is scarce.[150,153,154] Moreover, literature on the incidence of cancer after intracerebral hemorrhage (ICH) is very limited in both younger and older patients.

We therefore assessed age- and sex- specific cumulative incidence rates of first-ever cancer, stratified for organ-specific cancer, in the years after a first-ever ischemic stroke or ICH, compared with the general population.

Methods

This study was performed according to the guidelines of the medical ethical review board Arnhem/Nijmegen. No ethical review or individual patient consent was required based on the ethical review requirements of the local research ethics committee and due to the use of deidentified data. All analyses were performed in a secured environment of Statistics Netherlands in accordance with Dutch privacy legislation. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Participants and study design

We created a cohort of patients with first-ever stroke, through linking the Dutch Hospital Discharge Register, the Population Register and the National Cause of Death Register, all property of Statistics Netherlands and available from 1995 to 2018. The exact linkage procedures have been described previously.[31,45,46] We included patients admitted between January 1, 1998 and January 1, 2019 (date of last available data), to ensure at least 3 years of available medical history for all patients, to be able to select first-ever and not recurrent events. First-ever stroke was defined as the first known hospitalization with either a primary (main) or secondary discharge diagnosis of ischemic stroke, ICH or stroke not otherwise specified based on *the International Classification of Diseases, Ninth Revision (ICD-9)* and *International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes. (eTable1 in Supplement 1). The *ICD-9* and *ICD-10* codes have been proven reliable for the identification of stroke.[42,43] The accuracy of *ICD-10* codes has been shown to be 85% accurate for all stroke subtypes,[132] with 80% of all patients with a stroke not otherwise specified having ischemic strokes (eTable 2 in Supplement 1).[132] Therefore, ischemic stroke was defined by using the *ICD-9* and *ICD-10* codes for both ischemic stroke and stroke not otherwise specified. To ascertain the expected incidence of age-, sex- and calendar year- matched peers from the general population, we used the Dutch Cancer Registry. This registry contains all cancer diagnoses from all Dutch citizens between 1989 and 2020 and is 97% complete.[155]

We included only patients aged 15 years or older at first-ever stroke because pediatric stroke differs from stroke in adults in terms of causes and risk factors. We used 15 years as the lower age limit instead of 18 years, which is more common in literature on stroke among young adults, because reference data from the Dutch Cancer Registry was only available in 5-year intervals.

Outcomes

Cancer during follow-up was defined as a first-ever hospital diagnosis of any invasive malignant neoplasm after index stroke, excluding primary central nervous system (CNS) cancers, cancers with known CNS metastases at diagnosis, and nonmelanoma skin cancers. Primary CNS cancers and metastases were excluded because of the risk of misclassification of the index stroke. Nonmelanoma skin cancers were excluded because the *ICD-9* and *ICD-10* codes did not enable us to differentiate between squamous cell carcinomas and basal cell carcinomas; basal cell carcinomas are generally excluded from studies investigating cancer incidence.[156] The cancers were classified as hematologic, lung, breast, gastrointestinal (subdivided into upper gastrointestinal, colorectal and pancreas/gall bladder), urogenital tract (subdivided into urological and cancer of male and female genitalia) and "other". (eTable 1 in Supplement 1) When a patient received diagnoses of multiple cancers, only the first diagnosis after stroke was considered.

Patients were followed up from date of the index stroke to date of first cancer diagnosis, date of death, date of censoring, or January 1, 2019, whichever came first. Patients were censored if they emigrated during follow-up (1441 of 390 398 [0.4%]), if their personal linkage key became no longer unique and could not be reliably followed over time (7073 of 390 398 [1.8%]) (Figure 1), or if they received a diagnosis of a primary CNS cancer, CNS metastases at time of diagnosis or nonmelanoma skin cancer.

Statistical analyses

Statistical analysis was performed from January 6, 2021, to January 2, 2022. We calculated cumulative incidence with 95% CIs of any cancer, treating death as a competing risk for all patients.[157,158] We stratified for ischemic stroke and ICH. We also stratified for the following age groups: 15 to 49 years (younger adults) and 50 years or older (older adults), as 49 years of age is a commonly accepted upper age limit in literature. Subsequently, we divided the younger adults into 2 groups, split close to the median, to differentiate between the rare very young adults with stroke (15-39 years) and the more common 40- to 49-year-old adults with stroke. Finally, we stratified for sex. We tested for differences in cumulative incidences with the Gray test for equality.[159,160] Person-Years of follow-up were calculated for each patient. We also calculated the expected numbers and rates of new cancer per 1000 person-years of any cancer and by cancer subtype based on 5-year age groups, sex and calendar year-specific cancer incidence rates from the Dutch Cancer Registry, multiplied by the corresponding number of person-years at risk. We calculated standardized incidence ratios (SIRs) and the absolute excess risk of

new cancer after stroke by dividing the observed number by the expected number, expressed per 1000 person-years. For calculation of the 95% CIs, we assumed a Poisson distribution.

A 2-sided P <.05 was considered statistically significant. For the SIR analyses, we set the threshold for significance to a P =.006 after Bonferroni adjustment for 8 subgroup analyses. Data analysis was performed using R version 3.6.2 (Packages: rateratio.test, survival, survminer, cmprsk; R Group for Statistical Computing) and Prism version 5.03 (GraphPad Software).

Results

Our cohort consisted of 390 398 patients with a first-ever stroke: 27 616 (7.1%) patients aged 15 to 49 years and 362 782 (92.9%) aged 50 years or older (Figure 1). Of the 27 616 younger adults (13 916 women [50.4%], median age 44.5 years [IQR 39.1-47.6]) 22 622 (81.9%) had an ischemic stroke and 4 994 (18.1%) an ICH (Table 1). At the end of the follow-up period (median follow-up 5.7 years [IQR 2.1-11.7]) 3 902 of 27 616 patients (14.1%) had died. Of the 362 782 older adults (181 847 women [50.1%], median age 75.8 years [IQR 66.9-82.9] 307,739 (84.8%) had an ischemic stroke and 55 043 (15.2%) an ICH, and 195 790 patients (54.0%) had died at end of follow-up (median of 2.4 years [IQR 0.3-5.9]).

During follow-up there were 961 (3.5%) newly diagnosed cancers among the younger group and 23 371 (6.4%) among the older adults (Table 1). Among the younger adults, the 3 most common categories were breast cancer (213 [22.2%]), gastrointestinal cancer (192 [20.0%]), and lung cancer (190 [19.8%]). Among the older patients the 3 most common categories were gastrointestinal (6 660 [28.5%]), urogenital (5 685 [24.3%]), and lung cancer (4 393 [18.7%]).

Cumulative incidence of any newly diagnosed cancer after stroke

The cumulative incidence of new cancer after any stroke among younger patients was higher among women than men (Gray test statistic, 22.2; P<.001). The cumulative incidence of new cancer at 10 years after ischemic stroke was 3.7% (95% CI, 3.4-4.0%) among younger adults and 8.5% (95% CI, 8.4-8.6%) among older adults (Figure 2).

Among younger patients, women were also more likely than men to receive a diagnosis of a new cancer after ischemic stroke (Gray test statistic, 17.0; P<.001).

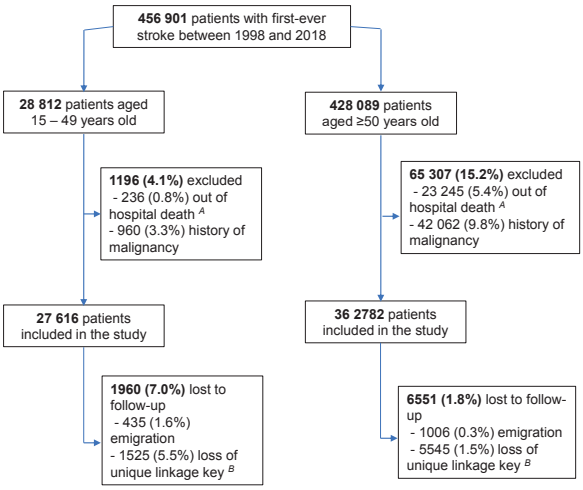


Figure 1: Flowchart of Inclusion and Follow-up

A Out of hospital deaths; Persons who died from a first-ever stroke without ever reaching the hospital.

B Loss of unique linkage key: Patients who lost their unique combination of date of birth, sex and postal code between 1998 and 2013, and could therefore not be reliably followed over time. After 2013 everyone remained unique due to linkage based on the Dutch Personal Identifier Number.

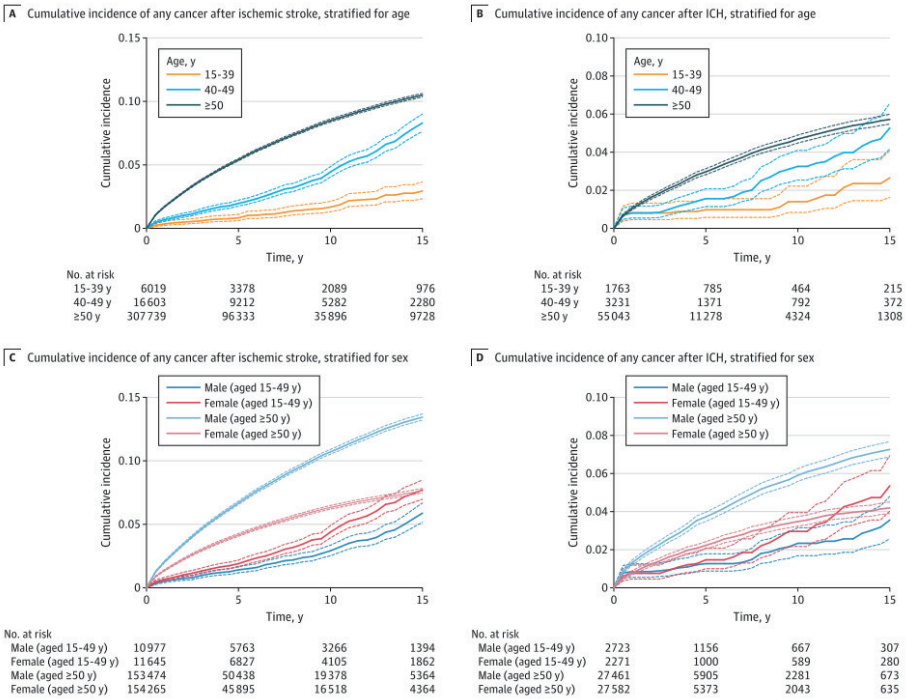


Figure 2: Cumulative Incidence of Any Cancer After Stroke, Stratified by Stroke Subtype, Age, and Sex

Dotted lines indicate 95% Cis. ICH indicates intracerebral hemorrhage.

Table 1: Demographics of younger and older stroke population, stratified by stroke-subtype

	Younger adults (15-49 y), No. (%)		
Characteristic	**Any stroke**	**Ischemic stroke**	**ICH**
Sex	**(n=27 616)**	**(n= 22 622)**[A]	**(n=4994)**
Women	13916 (50.4)	11645 (51.5)	2271 (45.5)
Men	13700 (49.6)	10977 (48.5)	2723 (54.5)
Median age (IQR), y	44.5 (39.1-47.6)	44.7 (39.5-47.7)	43.5 (36.3-47.2)
Follow-up			
follow-up, years median (IQR), y	5.7 (2.0-11.7)	6.0 (2.4-12.0)	3.8 (0.2-10.1)
At ≥ 5 y	14746 (53.4)	12590 (55.7)	2156 (43.2)
At ≥ 10 y	8627 (31.2)	7371 (32.6)	1256 (25.2)
Total No. of person-years	198215	168942	29273
Cancer during follow-up			
Any cancer	961 (3.0)	837 (3.7)	124 (2.5)
Breast [B]	213 (1.5)	188 (1.6)	25 (1.1)
Gastrointestinal tract	192 (0.7)	173 (0.6)	19 (0.4)
Upper gastrointestinal	45 (0.2)	ND[E]	ND[E]
Colorectal	112 (0.4)	ND[E]	ND[E]
Pancreas & gall bladder	35 (0.1)	ND[E]	ND[E]
Lung cancer	190 (0.7)	169 (0.6)	21 (0.4)
Urogenital tract	139 (0.5)	128 (0.5)	11 (0.2)
Urological tract [C]	68 (0.2)	ND[E]	ND[E]
Female genital organs [B]	38 (0.3)	ND[E]	ND[E]
Male genital organs [B]	33 (0.2)	ND[E]	ND[E]
Hematological cancers	92 (0.3)	71 (0.3)	21 (0.4)
Other sites [D]	135 (0.5)	108 (0.4)	27 (0.5)

Abbreviations: ICH = intracerebral hemorrhage, ND = Not Disclosed. [A] Ischemic stroke was defined by International Classification of Diseases, Ninth Revision codes 434, 436 and International Classification of Diseases and Related Health Problems, Tenth Revision codes I63, I64 for ischemic stroke and stroke not otherwise determined. [B] Percentages of breast cancer and cancer of female genital organs are calculated on the total number of women in this group; percentage of cancer in male genital organs are calculated on the total number of men in this group. [C] Of the 68 urological cancers in young adults 34 were located in the kidney and 34 in the bladder or ureter. In older adults of the 2673 urological cancers, 718 were located in the kidney and 1955 in the bladder and ureter. [D] Cancer of other sites include: Melanoma, bone, soft tissue, endocrine organs, head- and neck cancers, cancers of miscellaneous sites, cancer with unknown primary location, metastases with an unregistered primary cancer, and multiple primary cancers at the same time. [E] Not disclosed because subgroups were too small in patient numbers to adequately protect privacy according to legislation regarding the use of this register-based dataset of Statistics Netherlands

	Older adults (≥ 50 y), No. (%		
	Any stroke	**Ischemic stroke**	**ICH**
	(n=362 782)	**(n=307 739)**[A]	**(n=55 043)**
	181847 (50.1)	154265 (50.1)	27582 (50.1)
	180935 (49.9)	153474 (49.9)	27461 (49.9)
	75.8 (66.9-82.9)	75.8 (66.9-82.9)	76.0 (67.0-82.8)
	2.4 (0.3-5.9)	2.7 (0.6-6.2)	0.4 (0.0-4.0)
	107611 (29.7)	96333 (31.3)	11278 (20.5)
	40220 (11.1)	35896 (11.7)	4324 (7.9)
	1413676	148425	1265251
	23371 (6.4)	21168 (6.9)	2203 (4.0)
	1964 (1.1)	1748 (1.1)	216 (0.8)
	6660 (1.8)	6123 (2.0)	537 (1.0)
	1498 (0.4)	1374 (0.4)	124 (0.2)
	4109 (1.1)	3782 (1.2)	327 (0.6)
	256 (0.1)	196 (0.1)	86 (0.2)
	4393 (1.2)	4012 (1.3)	381 (0.7)
	5685 (1.6)	5125 (1.7)	560 (1.0)
	2673 (0.7)	2423 (0.8)	250 (0.5)
	442 (0.2)	399 (1.4)	43 (0.2)
	2570 (1.4)	2303 (1.5)	267 (1.0)
	1851 (0.5)	1668 (0.5)	183 (0.3)
	2818 (0.8)	2492 (0.8)	326 (0.1)

The cumulative incidence of new cancer at 10 years after ICH was 2.6% (95% CI, 2.1-3.3%) among younger adults and 4.7% (95% CI, 4.5-4.9%) among older adults. After ICH, there was no difference in the cumulative incidence of new cancer between men and women among the younger group (Gray test statistic, 3.3; *P*=.07). Among the older group, the cumulative incidence of new cancer after any stroke was higher among men than women (Gray test statistic, 1683; *P* <.001). Among the older group, men were more likely to receive a diagnosis of a new cancer of both ischemic stroke and ICH (Ischemic stroke: Gray test statistic, 1683.6; *P*<.001, ICH: Gray test statistic, 164.8; *P*<.001) (Figure 2).

Risk of any newly diagnosed cancer after stroke compared with the general population

Younger adults were 2.6 (95% CI, 2.2-3.1) times more likely to receive a diagnosis of a new cancer within the first year after ischemic stroke compared with peers from the general population. The cumulative SIR of any cancer decreased over the years but remained significantly increased for eight years after stroke. After ICH at younger age, the SIR in the first year was 5.4 (95% CI, 3.8-7.3) and remained significantly increased for 6 years after ICH (Table 2). The SIR of new cancer decreased similarly with age after both ischemic stroke and ICH and was only significantly increased for older adults in the first year after stroke. For patients aged 50 years or older, in the first year after stroke, the SIR was 1.2 (95% CI, 1.2-1.2) after ischemic stroke and 1.2 (95% CI, 1.1-1.2) after ICH. The SIRs of new cancer over the years stratified by age and sex are shown in Figure 3.

Types of newly diagnosed cancer diagnosed after stroke compared with the general population

For younger adults after ischemic stroke, the risk of newly diagnosed lung cancer (1-year SIR, 6.9 [95% CI, 4.7-10.0]) was highest compared with the general population, followed by hematologic cancer (1-year SIR, 5.2 [95% CI, 3.4-7.7]) (Table 2). The SIRs of lung cancer and of hematologic cancer remained significant for at least 15 and 6 years, respectively, after stroke. Among older adults after ischemic stroke, the SIR of lung cancer (1-year SIR, 1.7 [95% CI, 1.6-1.8]), but not any of the other cancers, was significantly increased compared with the general population. This increased risk remained significant until 15 years after stroke. After ICH, the SIR for younger patients was highest for hematologic cancers (1-year SIR, 14.2 [95% CI, 7.1-25.4]) for at least 15 years after ICH. Among older patients after ICH, the SIR for lung cancer (1-year SIR, 1.6 [95% CI, 1.3-1.9]) was increased for 2 years compared with the general population.

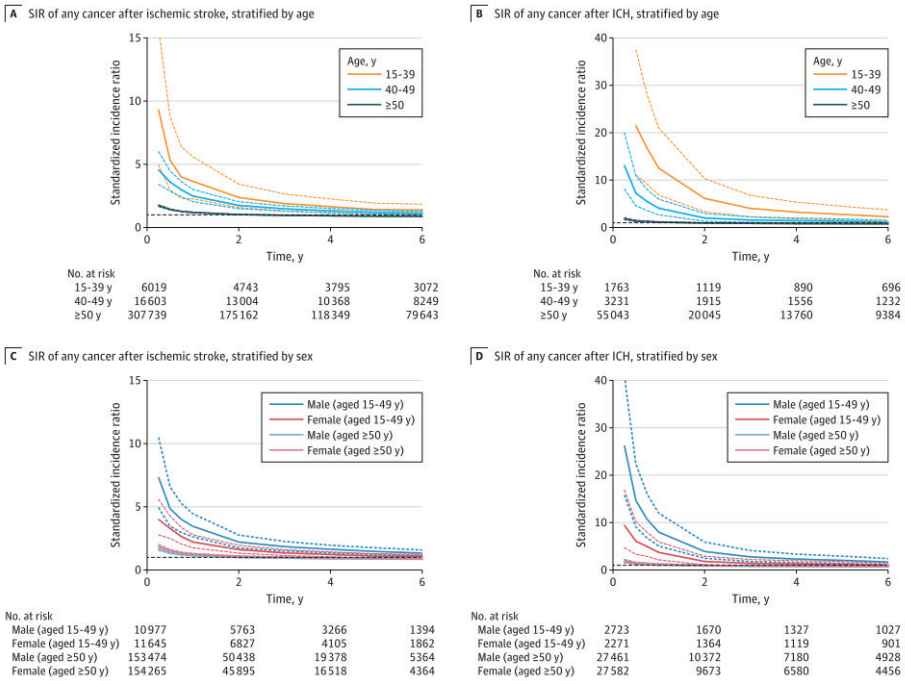


Figure 3: Standardized Incidence Rates (SIRs) of Cancer After Stroke, Stratified by Stroke Subtype, Age, and Sex

Dotted lines indicate 95% Cis. ICH indicates intracerebral hemorrhage.

Table 2. SIRs for Developing a New Cancer After Stroke Among Younger Adults (15-49 Years), Stratified by Stroke Subtype, age and Sex [A]

	Person-years at risk, No.	Observed events, No.	Observed events per 1000 person-years, No.	Expected events [B], No.	Expected events per 1000 person-years, No.
Ischemic stroke [G]					
New cancer (n = 22 622)					
1-year	20794	134	6.4	51	2.5
5-year	87465	320	3.7	260	3.0
Male patients (n = 10 977)					
1-year	10046	58	5.8	16.8	1.7
5-year	41596	130	3.1	88.2	2.1
Female patients (n = 11 645)					
1-year	10747	76	3.2	34.2	2.2
5-year	45869	190	4.1	171.7	3.8
Aged 15-39 y (n = 6019)					
1-year	5546	21	3.8	5.7	1.0
5-year	23740	43	1.8	30.2	1.3
Aged 40-49 y (n = 16 603)					
1-year	15248	113	7.4	45.3	3.0
5-year	63725	277	4.4	229.7	3.6
Lung cancer (n = 22 622)					
1-year	20794	29	1.4	4.2	0.2
5-year	87465	68	0.8	24.2	0.3
Hematologic cancers (n = 22 622)					
1-year	20794	25	1.2	4.8	0.2
5-year	87465	40	0.5	23.9	0.3
Gastro intestinal tract (n = 22 622)					
1-year	20794	23	1.1	7.3	0.4
5-year	87465	52	0.6	39.9	0.3
Breast (n = 22 622)					
1-year	10747	17	1.6	19.0	1.8
5-year	45869	60	1.3	95.9	2.1
Urological tract (n = 22 622)					
1-year	20794	ND [F]	ND [F]	ND [F]	ND [F]
5-year	87465	23	0.3	16.4	0.3

	Excess event rate per 1000 person-years [C]	SIR (95 % CI) [D]	P-value [E]
	3.9	2.6 (2.2-3.1)	<.001
	0.7	1.2 (1.1-1.4)	<.001
	4.1	3.5 (2.6-4.5)	<.001
	1	1.5 (1.2-1.8)	<.001
	3.9	2.2 (1.8-2.8)	<.001
	0.4	1.1 (1.0-1.3)	.15
	2.8	3.7 (2.3-5.6)	<.001
	0.5	1.4 (1.0-1.9)	.02
	4.4	2.5 (2.1-3.0)	<.001
	0.7	1.2 (1.1-1.4)	.002
	1.2	6.9 (4.7-10.0)	<.001
	0.5	2.8 (2.2-3.6)	<.001
	1.0	5.2 (3.4-7.7)	<.001
	0.2	1.7 (1.2-2.3)	.002
	0.7	3.2 (2.0-4.7)	<.001
	0.3	1.3 (1.0-1.7)	.05
	-0.2	0.9 (0.5-1.4)	.76
	-0.8	0.6 (0.5-0.8)	<.001
	ND [F]	ND [F]	ND [F]
	0	1.4 (0.9-2.1)	.09

Table 2. Continued

	Person-years at risk, No.	Observed events, No.	Observed events per 1000 person-years, No.	Expected events [B], No.	Expected events per 1000 person-years, No.
Female genital tract (n = 22 622)					
1-year	10747	ND [F]	ND [F]	ND [F]	ND [F]
5-year	45869	18	0.4	16.3	0.4
Intracerebral hemorrhage					
New cancer (n = 4994)					
1-year	3604	40	11.1	7.5	2.1
5-year	15158	60	4.0	38.4	2.5
Male patients (n = 2723)					
1-year	2008	23	11.5	2.9	1.4
5-year	8347	31	3.7	15.0	1.8
Female patients (n = 2271)					
1-year	1596	17	10.7	4.6	2.9
5-year	6810	29	4.3	23	3.4
Aged 15-39 y (n = 1763)					
1-year	1330	14	10.5	1.1	0.8
5-year	5616	16	2.9	5.8	1.0
Aged 40-49 y (n = 3231)					
1-year	2273	26	11.4	6.4	2.8
5-year	9542	44	4.6	32.6	3.4
Lung cancer (n = 4994)					
1-year	3604	ND [F]	ND [F]	ND [F]	ND [F]
5-year	15158	10	0.7	3.6	0.2
Hematologic cancers (n = 4994)					
1-year	3604	11	3.1	0.8	0.2
5-year	15158	13	0.9	3.8	0.3
Gastro intestinal tract (n = 4994)					
1-year	3604	ND [F]	ND [F]	ND [F]	ND [F]
5-year	15158	ND [F]	ND [F]	ND [F]	ND [F]
Breast (n = 4994)					
1-year	1596	ND [F]	ND [F]	ND [F]	ND [F]
5-year	6810	ND [F]	ND [F]	ND [F]	ND [F]
Urological tract (n = 4994)					
1-year	3604	ND [F]	ND [F]	ND [F]	ND [F]
5-year	15158	ND [F]	ND [F]	ND [F]	ND [F]

	Excess event rate per 1000 person-years [C]	SIR (95 % CI) [D]	P-value [E]
	ND [F]	ND [F]	ND [F]
	0	1.1 (0.7-1.7)	.57
	9	5.4 (3.8-7.3)	<.001
	1.5	1.6 (1.2-2.0)	<.001
	10.1	8.0 (5.1-12.0)	<.001
	1.9	2.1 (1.4-2.9)	<.001
	7.8	3.7 (2.2-5.9)	<.001
	0.9	1.2 (0.8-1.8)	.21
	9.7	12.5 (6.8-21.0)	<.001
	1.9	2.8 (1.6-4.5)	<.001
	8.6	4.1 (2.7-6.0)	<.001
	1.2	1.4 (1.0-1.8)	.05
	ND [F]	ND [F]	ND [F]
	0.5	2.8 (1.4-5.2)	.002
	2.9	14.2 (7.1 -25.4)	<.001
	0.6	3.4 (1.8-5.8)	<.001
	ND [F]	ND [F]	ND [F]
	ND [F]	ND [F]	ND [F]
	ND [F]	ND [F]	ND [F]
	ND [F]	ND [F]	ND [F]
	ND [F]	ND [F]	ND [F]
	ND [F]	ND [F]	ND [F]

Table 2. Continued

	Person-years at risk, No.	Observed events, No.	Observed events per 1000 person-years, No.	Expected events [B], No.	Expected events per 1000 person-years, No.
Female genital tract (n = 4994)					
1-year	1596	ND [F]	ND [F]	ND [F]	ND [F]
5-year	6810	ND [F]	ND [F]	ND [F]	ND [F]

Abbreviations: ICH = Intracerebral hemorrhage, ND = not disclosed.
[A] Absolute numbers and rates reported in this table are cumulative. [B] Expected events retrieved from data of the National Cancer Registry matched for age in 5-year groups, sex and calendar year. [C] The excess event rate was calculated as (observed events-expected events) / person-years at risk expressed per 1000 person-years.
[D] Standardized incidence rate is the ratio of the observed event rate divided by the expected event rate, assuming the observed events follow a Poisson distribution. [E] Two-sided p-values calculated according to a Poisson distribution. For subgroups of any stroke and subtypes of stroke, the significance threshold was set to a Bonferroni-adjusted P<.006. [G] Ischemic stroke was defined by ICD-9 codes 434, 436 and ICD-10 codes I63, I64 for ischemic stroke and stroke not otherwise determined. [F] Not disclosed because subgroups were too small in patient numbers to adequately protect privacy according to legislation regarding the use of this register-based dataset of Statistics Netherlands.

Discussion

This study, with a large sample size and representative cohort, showed that younger patients with ischemic stroke or ICH were approximately 3 to 5 times more likely to receive a diagnosis of a new cancer in the first year after stroke compared with peers from the general population. This risk remained increased for 8 years after ischemic stroke and 6 years after ICH. The elevated cancer risk was mainly due to lung cancer, cancer of the gastrointestinal tract, and hematologic cancer. The SIR for newly diagnosed cancer among older patients with stroke was only slightly increased in the first year after stroke.

Previous studies have reported a variable cancer incidence after stroke at all ages: from 1% to 5% at 1 year and between 11% and 30% after 10 years.[156,160-165] To our knowledge, there have been only 2 studies describing the incidence of poststroke cancer among younger patients. One study described a risk of 0.5% in those aged 18 to 50 years in the first year after stroke,[163] and another study with a longer follow-up described a cumulative risk of 17.3% in the 10 years after stroke in patients aged 18 to 55 years.[156]

	Excess event rate per 1000 person-years [C]	SIR (95 % CI) [D]	P-value [E]
	ND [F]	ND [F]	ND [F]
	ND [F]	ND [F]	ND [F]

Our findings are at the lower end of this spectrum, which may have several explanations. First, although most of these studies also used a registry-based design,[156,161,163,164] some used a broader range of *ICD-9* and *ICD-10* codes defining cancer and also included in situ neoplasms.[163,164] Second, we corrected for death as a competing risk. The short- and long-term risk of death among the younger patients with stroke,[166] but even more among the older patients with stroke, is high and may associated with an overestimation of the cancer risk when not treating death as a competing risk.[160] Third, we excluded patients with a history of cancer, which eliminated the risk of stroke being the result of previous cancer treatments.[20]

We found that, for younger adults, the SIR remained elevated for more than 5 years after stroke. We found the highest SIR for lung cancer, gastrointestinal cancer and haematologic cancer. Although the cumulative incidence of breast cancer among young women was the highest, the SIR for breast cancer was not increased, and was even significantly decreased at 5 years after stroke. This finding might be explained by the relatively high background risk of breast cancer in the young Dutch population.[167] The significantly lower risk of breast cancer 5 years after stroke for the younger group may be due to the selection of patients. As breast cancer is

relatively common among young women, relatively more women with a history of breast cancer may have been excluded, thereby leaving the women with a possibly lower lifetime risk of breast cancer. It may also indicate that the association between stroke and cancer varies for different types of cancer. This finding highlights the importance of using matched peers as a control group for this type of research.

Although some cancers of the gastrointestinal tract do not equally share smoking as a causative risk factor, most gastrointestinal and lung cancers and are strongly associated with smoking, which is a widely accepted risk factor for stroke.[168,169] This may mean that the association stroke with cancer might be confounded by shared risk factors such as smoking.[151] However, this finding cannot explain the increased risk of haematologic cancers because most are not associated with smoking or other cardiovascular risk-factors,[152] nor does it explain why the SIR was much higher for younger compared to older patients with stroke. The difference in SIR between younger and older patients is likely also associated with the higher background incidence of cancer at older ages and heightened medical surveillance among older people compared with younger people.

Our study shows that the SIR is highest the first year after stroke, with a gradual decrease thereafter, which supports the hypothesis of a causal mechanism between cancer and the stroke.[156,162] It has previously been stated that if cancer is diagnosed within 1 year after stroke, one can assume it was already present at time of stroke and may have played a role in causing it.[156] An important possible causal mechanism is the hypercoagulable state; cancer induces a proinflammatory state that activates the coagulation cascade and increases the risk of stroke.[17,150] Increased D-dimer and C-reactive protein levels, reflective of a hypercoagulable state, are independently associated with occult cancer among patients with stroke.[170,171] More specifically, adenocarcinomas produce and release mucin into the bloodstream; mucin is a "sticky" molecule, which triggers the coagulation cascade.[17,150] Also, there may be direct tumour thrombi due to local invasion of blood vessels or nonbacterial thrombotic endocarditis. Haematologic cancers may cause stroke through, for example, hyperleukocytosis in leukaemia and hyperviscosity due to elevated blood protein levels in multiple myeloma.[17] Finally, a patent foramen ovale may play an important role in enabling a venous to arterial embolism formation because venous embolisms have extensively been associated with active cancer.[150]

We observed a trend toward a higher SIR of cancer after ICH than after ischaemic stroke, which was mainly associated with an increased risk of haematologic cancers. To our knowledge, this finding has not been described before, although it has been

hypothesized that haematologic cancers may be associated with an increased risk of ICH by affecting coagulation (eg, through causing thrombocytopenia or through haemorrhagic infarcts due to direct tumour thrombi).[17,150] On the other hand, in some cases bleeding in a cerebral tumor localization may have been misclassified as a primary ICH.

Because the SIR in the younger group was higher compared with the older group, these mechanisms might be more pronounced in younger adults. However, our study design does not allow us to draw conclusions on causal mechanisms. Another explanation for the time association between ischaemic stroke or ICH and newly diagnosed cancer may be that patients remain under intensified medical surveillance in the first few year after stroke. However, if this were the only explanation for the increased SIR, we would expect the risk increase to be similar for younger and older patients.

Currently, the diagnostic workup of stroke in young adults includes searching for several rare (clotting) disorders, although screening for cancer is not regularly performed. This study can be considered a stepping stone for future studies investigating the usefulness of screening for cancer after stroke.

Limitations

Our study has some limitations. First, misclassification may occur when using administrative data. However, previous studies showed good validity of *ICD-9* and *ICD-10* codes for ischemic stroke and ICH.[43,132] Second, because the Dutch Hospital Discharge Register was available from 1995 onward, prestroke cancer may have been missed for some patients who had cancer before 1995 and perhaps received therapy that increased stroke risk. Third, we used hospital admissions data to identify a cancer diagnosis during follow-up. Because we had no information on prior outpatient clinic visits, the exact date of diagnosis may vary somewhat from the admission date. Therefore, some of the cancers classified as new after stroke may have already been diagnosed before stroke, leading to some overestimation of early new cancer diagnoses. However, we expect that most (especially younger) patients would have been hospitalized for treatment quickly after receiving their diagnosis. Some cancer diagnoses might have been missed if the patients were treated without hospital admission, which might have led to an underestimation of cancers diagnosed during follow-up. This applies probably mainly to prostate and bladder cancers and, therefore, the elderly male population.[172] Also, due to loss to follow-up and patients who were included in the final years of the study with only a short follow-up, we could have slightly underestimated the number of new

cancer diagnoses after stroke. Fourth, the lack of clinical data on patient risk factors as well as stroke and cancer characteristics means that we could not further study assumed pathophysiological mechanisms and possible confounding of shared risk factors between (occult) cancer and stroke.

Conclusions

This cohort study suggests that, especially for younger adults there is an increased risk of cancer in the first several years, most prominent in the first year, after ischemic stroke and ICH compared with peers from the general population. Large cohorts with sufficient follow-up of extensively phenotyped patients are needed to further clarify the mechanistic link between cancer and stroke, especially among younger adults.

Chapter VI

Patient- and stroke characteristics in young adults with ischemic stroke or transient ischemic attack associated with underlying cancer

Submitted as: Verhoeven JI, Veen I, Hilkens NA, Ekker MS, Schellekens MMI, Boot EM, van Alebeek ME, Brouwers PJAM, Arntz RM, van Dijk G, Gons RAR, van Uden IWM, den Heijer T, van Tuijl J, de Laat KF, van Norden AGW, Vermeer SE, van Zagten MSG, van Oostenbrugge RJ, Wermer MJH, Nederkoorn PJ, Kerkhoff H, Rooyer FA, van Rooij FG, van den Wijngaard IR, Tuladhar AM, Driessen CML, Broeders MJM, Klijn CJM, de Leeuw FE. *Patient- and stroke characteristics in young adults with ischemic stroke or transient ischemic attack associated with underlying cancer*. *Submitted.*

Abstract

Background: In more than one third of young patients (18-49 years) with stroke, no cause of stroke is identified. Especially in (young) patients with a cryptogenic etiology, stroke may be a manifestation of underlying cancer. In addition, characteristics associated with an underlying cancer in stroke patients remains controversial and has not been studied in the young.

Aims: We aimed to investigate the prevalence of underlying cancer in young stroke patients and the association between patient- and stroke characteristics of an underlying cancer with ischemic stroke or transient ischemic attack (TIA) in the young.

Methods: We conducted a prospective observational cohort study including patients aged 18-49 years old at first-ever ischemic stroke or TIA from two existing Dutch cohorts. One single-center study (FUTURE) with inclusion between 1989-2010, and one multi-center study (ODYSSEY) with inclusion between 2013-2021. Outcomes were assessed through linkage to the Netherlands Cancer Registry. Main outcomes were the prevalence of underlying cancer (cancer diagnosis within one-year pre- or post-stroke) and characteristics associated with underlying cancer, assessed with multivariable logistic regression. In additional exploratory analysis, we constructed a prediction score to potentially identify young patients at highest risk of underlying cancer.

Results: In 17 (1.0%) of 1729 patients (median age 44.0 years; interquartile range 37.5 – 47.3, 49.4% women) we found an underlying cancer. Cryptogenic stroke (odds ratio [OR] 4.1, 95% confidence Interval [CI] 1.7 – 10.7), anemia (OR 3.6, 95% CI 1.4 – 8.7) and three arterial territories involved on neuro-imaging (OR 12.1, 95% CI 2.2 – 49.1) were independently associated with underlying cancer. The exploratory prediction score including these factors had fairly good discrimination (c-statistic 0.7 [95% CI 0.6 – 0.8]) and accurate calibration, with a mean predicted probability of an underlying cancer of 14.7% (95% CI 1.4 – 52.9) in patients with three arterial territories involved on neuro-imaging combined with anemia or a cryptogenic stroke.

Conclusions: Although in young patients with ischemic stroke an underlying cancer is rare, it should be suspected in patients with three arterial territories involved on neuro-imaging combined with anemia or cryptogenic stroke. Future studies would need to validate the provided exploratory prediction score and investigate whether screening for early diagnosis of cancer might be beneficial in a selected group of patients.

Introduction

Ischemic stroke and cancer are intimately related as an ischemic stroke occurs in approximately 15% of patients with active cancer,[173] and is even the first manifestation of cancer in up to 5% of cases.[19,171] We recently reported that young adults (18-49 years) are three times more likely to receive a new cancer diagnosis within one year after their ischemic stroke compared to peers from the general population.[174] Given this short ischemic stroke to cancer diagnosis interval, these cancers are presumably already present at the time of stroke (underlying) and may even be the cause of ischemic stroke.[17,175]

As cancer treatment has dramatically improved over the past decades, diagnosing cancer at an early stage has become more important to ensure good outcome. Therefore, identifying stroke patients with an underlying cancer may contribute to timely diagnosis and treatment. Several hospital-based studies have investigated clinical characteristics of cancer-associated stroke in the overall stroke population.[19,21,153,156,170,171,176-182] These studies found prothrombotic markers like d-dimer,[19,161,171,177,178,181] and elevated C-reactive protein (CRP),[177] also lower hemoglobin,[19,171,180] smoking,[19,153,156,161] cerebral acute ischemia in multiple arterial territories,[21,177,178] and cryptogenic stroke,[19,182] to be possible predictors of occult cancer, but these findings were not consistent over the studies. The majority of earlier studies were retrospective and all included very few young patients.

With this study, we aimed to investigate the prevalence of underlying cancer in young patients aged 18-49 years old with a first-ever ischemic stroke or TIA, and patient- and stroke-characteristics of young patients with ischemic stroke or TIA associated with an underlying cancer, in order to identify a subgroup of patients with the highest risk.

Methods

Study population

We included patients from two observational cohort studies, the FUTURE and ODYSSEY Study, both prospectively included young patients with ischemic stroke or TIA in the Netherlands. The first study was the FUTURE (Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation), which included patients aged 18-49 years old with ischemic stroke or TIA from the Radboud University Medical Centre between 1 January 1980 and 1 November 2010.[11,29]

The second study was the ODYSSEY (Observational Dutch Young Symptomatic StrokE studY), which included patients aged 18-49 years old with ischemic stroke or TIA from 17 hospitals in the Netherlands between 1 May 2013 and 1 February 2021.[28,183] Exclusion criteria for both studies were similar: history of TIA or stroke, cerebral venous thrombosis and retinal infarction. In the ODYSSEY also patients with transient monocular blindness were excluded.[28,29] TIA and ischemic stroke in the FUTURE study were defined according to the World Health Organization (WHO) criteria, and distinguished from haemorrhagic stroke through neuro-imaging.[1] In the ODYSSEY neuro-imaging confirmation of both TIA and ischemic stroke was required. For this study, we defined TIA according to the time-based definition of symptoms persisting less than 24 hours.

Baseline data collection

In both studies baseline information on (vascular) risk factors and stroke severity according to the National Institutes of Health Stroke Scale (NIHSS) at admission was systemically collected.[28,29] Definition of vascular risk factors was similar (eTable 1).[28,29] Results of neuroimaging and laboratory studies were also collected systematically in both studies. We dichotomized haemoglobin-levels at admission into anaemia *yes* or *no* according to the WHO criteria (<7.5 mmol/L [<12.0 g/dL] in women and <8 mmol/L [<13.0 g/dL] in men). Based on CT- and MRI-imaging (DWI), patterns of acute ischemia were divided into: one arterial territory involved (unilateral single or multiple acute ischemic lesions involving one arterial supply of either the anterior *or* posterior circulation), two territories involved (unilateral single or multiple lesions in one anterior circulation *and* the posterior circulation *or* bilateral involvement of the anterior circulation), or three territories involved (single or multiple acute ischemic lesions in *both* anterior circulations *and* the posterior circulation).[21] Evidence of non-recent cerebral ischemia on CT or MRI was not used for defining the number of vascular territories affected. Aetiology of stroke was assessed according to the modified TOAST criteria.[11,183] Patients with an underlying cancer, who did not receive systemic (thrombogenic) treatment and did not fulfil the criteria for (likely) large-artery disease, small vessel disease or cardioembolic cause, were classified as cryptogenic.

Outcome assessment

To increase the power of this study, underlying cancer was defined as a first-ever cancer diagnosis within one year pre- or post-ischemic stroke or TIA, which has been done previously.[19] We hypothesized that in both groups (known [within one year pre-stroke] and occult [within one year post-stroke]) the pathophysiological mechanisms and therefore the patient- and stroke-characteristics associated with

the cancer are the same. With this reasoning, we excluded patients who received systemic treatment for a known cancer at the time of ischemic stroke or TIA because these treatments may interfere with the assumed prothrombotic state caused by the underlying cancer. We also excluded patients who had a history of cancer (>1 year pre-stroke), and patients with a primary intracerebral malignancy (Figure 1: Flowchart of inclusion). Information on cancer diagnoses was retrieved through available medical records, as well as linkage to the Netherlands Cancer Registry (NCR). The NCR is owned by the Netherlands Comprehensive Cancer Organization and contains detailed data on all newly diagnosed cancers diagnosed from 1989 onwards in the Netherlands. Validation studies reported it to be 98% reliable for electronic linkage to prospective cohort studies.[32,155] Linkage was performed on 23 July 2021. For all cancer diagnoses, we ascertained date of diagnosis, location and pathology. Because the NCR does not contain data before January 1st 1989, patients from the FUTURE study included before this date, were excluded from this study. We also excluded patients who died within 30 days of the index event (Figure 1).

Statistical analysis

We divided the study population into a group with or without an underlying cancer. We tested for differences in baseline characteristics between the two groups with the chi-squared test or Fisher-exact test for categorical variables and the independent t-test or Kruskal-Wallis test for continuous variables. Potential risk factors were based on existing literature and presumed overlapping pathophysiological mechanisms between cancer and ischemic stroke or TIA, and included: sex, age (per year increase), diabetes at baseline, hypertension at baseline, dyslipidaemia at baseline, deep venous thrombosis or pulmonary embolism in medical history, active smoking, excessive alcohol consumption, NIHSS at admission (per point increase), anaemia, leukocyte levels (per 1x10^9/L increase), thrombocyte levels (per 1x10^9/L increase), CRP levels (per 1.6 g/dL [1mmol/L] increase), multiple arterial territories involved at neuro-imaging (per territory increase), cryptogenic aetiology (reference: non-cryptogenic stroke) and recurrent vascular event within 30 days of index event (eTable 1). Missing observations in predefined risk factors (2.9% in total) were imputed with single imputation, using the MICE package for R software. Risk factors for testing associations with underlying cancer through univariable and multivariable logistic regression were chosen based on the descriptive statistics of the predefined variables. In multivariable analysis we corrected for *all* before mentioned predefined risk factors. For sensitivity analysis, we performed a complete case analysis (N = 1252). Previous studies including acute ischemia in multiple arterial territories as a characteristic were singularly

based on DWI+ lesions on MRI, therefore we performed additional univariable and multivariable logistic regression in the subgroup of patients that underwent MRI (N = 1365) (eTable 2-4).

In additional exploratory analysis we constructed a prediction score by choosing independent predictors through multivariable logistic regression with backwards regression based on Aikake's information criterion. We performed bootstrapping for internal validation and corrected for optimism through multiplying the regression coefficients with a shrinkage factor estimated by bootstrap procedure (B=200). We allocated points to the selected predictors in the final model through dividing the shrunken coefficients by the smallest coefficient and rounded them to the nearest integer. Model performance was assessed through discrimination and calibration. Discrimination refers to the ability of the model to discriminate between patients with and without underlying cancer and was quantified by the optimism-adjusted c-statistic. Calibration refers to the concurrence of the predicted and observed probabilities and was evaluated through a calibration plot. Based on the regression coefficients of the predictors in the final model we developed a prediction score and generated the mean predicted probabilities per point increase in the score.

A 2-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R, version 4.1.3 (R Group for Statistical Computing).

Ethical approval

All patients included in this study signed informed consent for participation in the ODYSSEY or FUTURE study. The Medical Review Ethics Committee region Arnhem-Nijmegen gave their approval and granted a waiver of consent for this study, including linkage to the NCR. Linkage to the NCR was also assessed and approved by the NCR's Supervisory Committee for compliance with Netherlands Comprehensive Cancer Organization objectives and Dutch national privacy legislation.

Results

We included 1729 patients with ischemic stroke or TIA. The median age was 44.0 years (Interquartile range [IQR]: 37.5-47.3) and 49.4% were women (N = 854); 1469 patients had an ischemic stroke (85.0%) and 260 patients had a TIA (15.0%). The most common cause of stroke was cryptogenic in 28.2% of patients (N = 487) (Table 1).

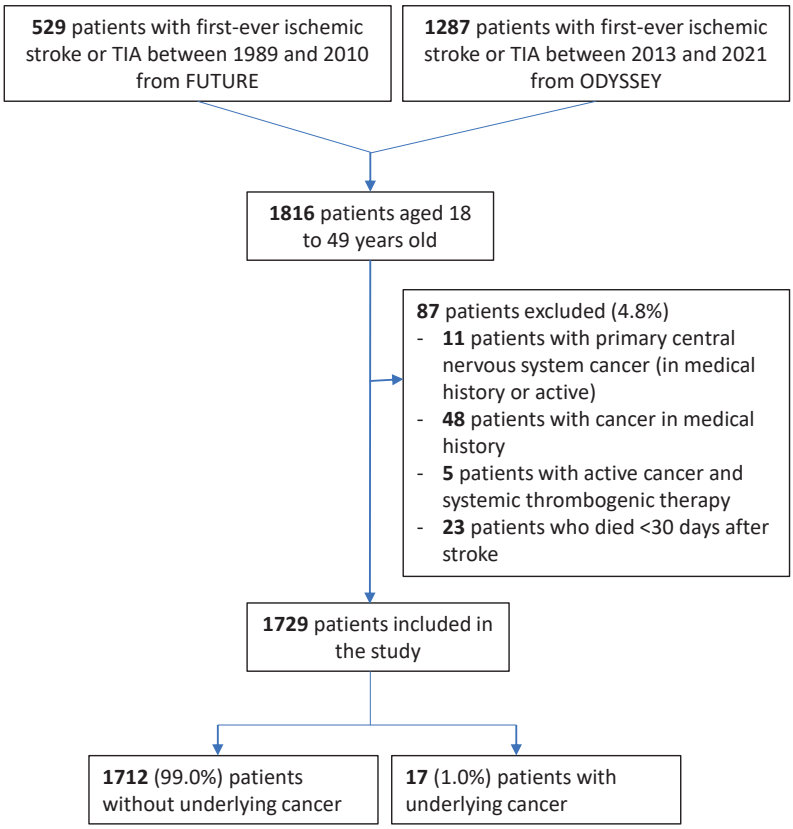


Figure 1: Flowchart of inclusion

Underlying cancer types

There were 17 cases (1.0%) with underlying cancer. Three were diagnosed in the year before the presenting stroke but did not (yet) receive systemic therapy. The other 14 patients were diagnosed within one year post-stroke with a median time between index event and cancer diagnosis of 146 days (IQR 22 – 208). Localizations of the underlying cancers included the digestive tract (N = 3), hematologic (N = 3), lung (N = 2), thyroid (N = 2), female genital tract (N = 2) and other localizations (N = 5). Adenocarcinoma was the most common cancer pathology (N = 8, 47.0%).

Associated patient- and stroke characteristics with underlying cancer

In the underlying cancer group significantly more patients had a cryptogenic stroke compared to those without cancer (N = 10 [58.8%] vs. N = 477 [28.2%]; p=0.01) and they were more likely to have anaemia at baseline (N = 6 [37.5%] vs. N = 192 [11.7%]; p<0.01). They were also more likely to have multiple arterial

territories involved on neuro-imaging (two territories N = 2 [12.5%] vs. N = 80 [4.7%]; three territories, N = 2 [12.5%] vs. N = 13 [0.8%]; p<0.01), and they had a higher risk of death within one year after stroke (N = 2

[11.8%] vs. N = 15 [0.9%]; p=0.02). Patients with underlying cancer tended to less often have hypertension at baseline (N = 2 [11.8%] vs. N = 648 [37.9%]; p=0.05). Cryptogenic stroke, anaemia and three arterial territories involved on neuro-imaging were significantly associated with underlying cancer in univariable analysis and remained independently associated with cancer in multivariable analysis with an OR for cryptogenic stroke of 4.1 (95% CI 1.7 – 10.7; p=0.01), 3.5 (95% CI 1.4 – 8.7; p=0.02) for anaemia, and 12.1 (95% CI 2.2 – 49.1; p<0.01) for three arterial territories involved on neuro-imaging (Table 2). Two arterial territories involved on neuro-imaging was not significantly associated with an underlying cancer in both univariable and multivariable logistic regression.

The univariable and multivariable logistic regression models in the complete case analysis (total N = 1252, underlying cancer in N = 10) demonstrated cryptogenic aetiology, anaemia and both two arterial territories and three arterial territories involved on neuro-imaging to be independently predictive of an underlying cancer (eTable 2). In univariable analyses of the subset of patients who underwent MRI (total N = 1365, underlying cancer in N = 13) only anaemia and three territories involved on neuro-imaging were significantly associated with underlying cancer. However in multivariable analysis, also involvement of two arterial territories on neuro-imaging became independently associated (eTable 3-4).

Exploratory prediction score

After backwards elimination with bootstrap procedure and shrinkage; cryptogenic stroke (adjusted β-coefficient 1.2), three arterial territories involved on neuro-imaging (adjusted β-coefficient 2.3) and anaemia (adjusted β-coefficient 1.2) were selected as predictors of underlying cancer in the final model. Three arterial territories involved on neuro-imaging yielded 2 points, anaemia at baseline 1 point and cryptogenic aetiology also 1 point. The model yielded a decent optimism-adjusted c-statistic of 0.7 (95% CI 0.6 – 0.8) (ROC curve is depicted in Figure 2A), and accurate calibration, as shown by the calibration plot in Figure 2B. The adjusted and unadjusted regression coefficients are listed in eTable 5. The mean predicted probability ranged from 0.4% (95% CI 0.15 – 1.1%) for 0 points to 14.7% (95% CI 1.4 – 52.9%) for 3 points (Figure 3). There were no patients with 4 points in our cohort.

Table 1: Baseline characteristics of patients with ischemic stroke or TIA with underlying and without cancer

	All patients	Patients without cancer	Patients with underlying cancer	p-value [D]
Total, N (%)	1729	1712 (99.0)	17 (1.0)	
Women	854 (49.4)	843 (49.2)	11 (64.7)	0.31
Median age, years (IQR)	44.0 (37.5 – 47.3)	44.0 (37.4 – 47.2)	42.3 (38.7 – 47.8)	0.97
Study cohort: ODYSSEY	1248 (72.2)	1237 (72.3)	11 (64.7)	0.68
Study cohort: FUTURE	481 (27.8)	475 (27.2)	6 (35.3)	
Event type, N (%)				
Ischemic stroke	1469 (85.0)	1475 (85.1)	12 (70.6)	0.18
TIA	260 (15.0)	255 (14.9)	5 (29.4)	
Aetiology (TOAST), N (%)				
Definite large artery disease	83 (4.8)	83 (4.8)	0	
Likely large artery disease	254 (14.7)	253 (14.8)	1 (5.8)	
Cardioembolic aetiology	265 (15.3)	265 (15.5)	0	
Small vessel disease	224 (13.0)	222 (13.0)	2 (11.8)	
Rare causes	344 (19.9)	341 (19.9)	3 (17.7)	
Cryptogenic aetiology	487 (28.2)	477 (27.9)	10 (58.8)	**0.01** [E]
Multiple causes	72 (4.2)	71 (4.1)	1 (5.9)	
Cardiovascular risk profile, N (%)				
Smoking [A, C]	844 (49.2)	837 (43.9)	7 (41.2)	0.67
Excessive alcohol use	117 (6.8)	116 (6.8)	1 (5.9)	1
Hypertension at baseline	650 (37.6)	648 (37.9)	2 (11.8)	0.05
Diabetes mellitus at baseline	169 (9.8)	167 (9.8)	2 (11.8)	1
Dyslipidaemia [C]	1165 (69.9)	1154 (69.9)	11 (78.6)	0.68
Deep venous thrombosis in medical history [D]	44 (2.5)	44 (2.6)	0	
Ancillary investigations, N (%)				
Anaemia [C]	192 (11.7)	186 (11.4)	6 (37.5)	**<0.01**
Leukocytes (number) [C], median (IQR)	8.7 (6.7 – 10.9)	8.7 (6.7 – 10.9)	8.0 (6.0 – 10.9)	0.69
Thrombocyte (number) [C], median (IQR)	260 (218 – 309)	260 (218 – 309)	258 (222 – 331)	0.71
C-reactive protein levels [C], median (IQR)	4.0 (1.0 – 9.0)	4.0 (1.0 – 9.0)	8.0 (2.0 – 9.5)	0.24

Table 1: Continued

	All patients	Patients without cancer	Patients with underlying cancer	p-value [D]
Two territories involved on neuro-imaging [C]	82 (4.8)	80 (4.7)	2 (12.5)	**<0.01**
Three territories involved on neuro-imaging [C]	15 (0.9)	13 (0.8)	2 (12.5)	
Follow-up, N (%)				
Recurrent vascular event <30 days [C]	64 (3.8)	62 (3.8)	2 (11.8)	0.28
Death <1 year	17 (1.0)	15 (0.9)	2 (11.8)	**<0.01**

[A] Definitions of risk-factors are listed in eTable 1. [B] Anaemia was classified according to the definition of the World Health Organization (<12.0 g/dl in women and <13.0 g/dl in men). [C] Missing data: Lacunar or territorial stroke missing in 30 patients, smoking status missing in 15 patients, dyslipidaemia at baseline missing in 63 patients, thrombosis in medical history missing in 1 patient, anaemia missing in 85 patients, leukocyte levels missing in 89 patients, thrombocyte levels missing in 109 patients, C-reactive protein levels missing in 337 patients, number of territories involved on neuro-imaging was missing in 26 patients, recurrent vascular event <30 days of index event missing in 65 patients. [D] p-values calculated for categorical variables with chi-squared analyses or fisher-exact test, for continuous variables with independent t-testing of Kruskal-Wallis, whenever appropriate. [E] Cryptogenic stroke was separate compared to non-cryptogenic stroke (all other TOAST categories combined) through chi-squared analysis.

Table 2: Univariable and multivariable logistic regression of patient- and stroke characteristics with underlying cancer

	Univariable		Multivariable [A]	
	odds ratio (95% Confidence interval)	P value	odds ratio (95% Confidence interval)	P value
Hypertension	0.2 (0.0 – 0.6)	**0.04**	0.2 (0.0 – 0.7)	0.06
Cryptogenic stroke	3.6 (1.6 – 8.5)	**<0.01**	4.1 (1.7 – 10.7)	**0.01**
Anaemia	4.1 (1.7 – 9.3)	**<0.01**	3.6 (1.4 – 8.7)	**0.02**
Two arterial territories involved on neuro-imaging	3.1 (0.7 – 9.5)	0.14	4.0 (0.8 – 13.0)	0.08
Three arterial territories involved on neuro-imaging	19.2 (4.1 – 64.1)	**<0.01**	12.1 (2.2 – 49.1)	**<0.01**

[A] Risk factors corrected for in multivariable logistic regression: sex, age (per year increase), cryptogenic stroke (reference: non-cryptogenic stroke), diabetes mellitus at baseline, hypertension at baseline, dyslipidaemia at baseline, CRP levels (continuous per mmol/L increase), smoking (dichotomous), excessive alcohol consumption (dichotomous), NIHSS at admission (per point increase), leukocyte levels (continuous per 1x10^9/L increase), thrombocyte levels (continuous per 1x10^9/L increase), multiple arterial territories (one arterial territory as reference category) at baseline neuroimaging (ordinal) and second arterial event within 30 days of index event. [B] Deep venous thrombosis in medical history was not included in the logistic regression model because there were no cases in the underlying cancer-group.

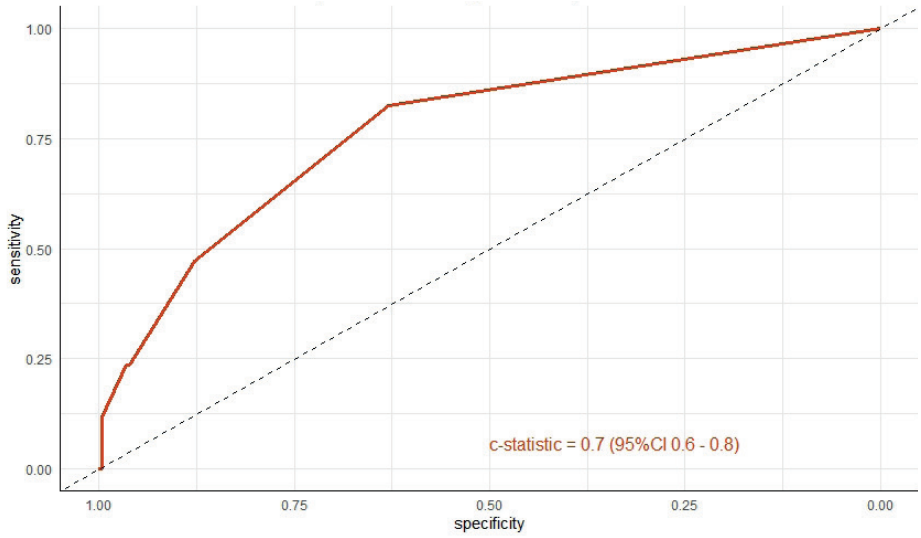
Discussion

In this study of young adults with ischemic stroke or TIA, we demonstrated that an underlying cancer can be identified in 1% of patients. We showed that a cryptogenic aetiology, anaemia, and having three arterial territories affected on neuro-imaging were independently associated with an underlying cancer in this patient group. In addition, we developed a candidate prediction score based on these predictors, in which a score of 3 points yields a mean predicted probability of underlying cancer of 15%. This score needs to be validated in another cohort before usage in clinical practice.

The 1.0% prevalence of underlying cancer in our cohort is at the lower end of the spectrum of what previous hospital-based studies found, this is most likely due to the lower background risk of cancer for young individuals compared to older individuals.[18,180] In our cohort, 14 out of 17 patients with underlying cancer, were diagnosed within one year after stroke, which could in hindsight be considered as occult at the time of stroke. Previous studies demonstrated incidences of occult cancer varying between 0.4% to 7.6% in patients with ischemic stroke, however the median age in these studies was higher and ranged between 52 and 70 years.[178,181,182] Two registry based studies in patients <50 years demonstrated a comparable incidence of 0.4% to 0.8% new cancer diagnoses in the first year after ischemic stroke.[156,174]

We showed that patients with underlying cancer at the time of their ischemic stroke or TIA were more likely to have a cryptogenic stroke compared to patients without underlying cancer. Especially in these patients with cryptogenic stroke, the underlying cancer might be considered the cause of stroke.[17,20] We also showed that anaemia at baseline was independently associated with an underlying cancer. This association might be age dependent, and therefore more relevant in young patients, as the overall prevalence of anaemia is higher at older age.[19,171,180,184] One previous retrospective study showed that having three arterial territories affected with acute ischemic lesions (DWI+) on MRI, called the three territory sign, was a strong predictor of occult malignancy and could also differentiate from a cardioembolic cause.[21] We used the same definitions for the multiple arterial territories, but to increase external validity, CT was also used for identification of acute ischemia in multiple arterial territories. With this approach we were also able to demonstrate a strong association with three arterial territories involved on neuro-imaging with underlying cancer.[175,177,178] In line with others, we were not able to prove a significant association between underlying cancer and two arterial territories

Panel A: ROC curve



Panel B: Calibration plot

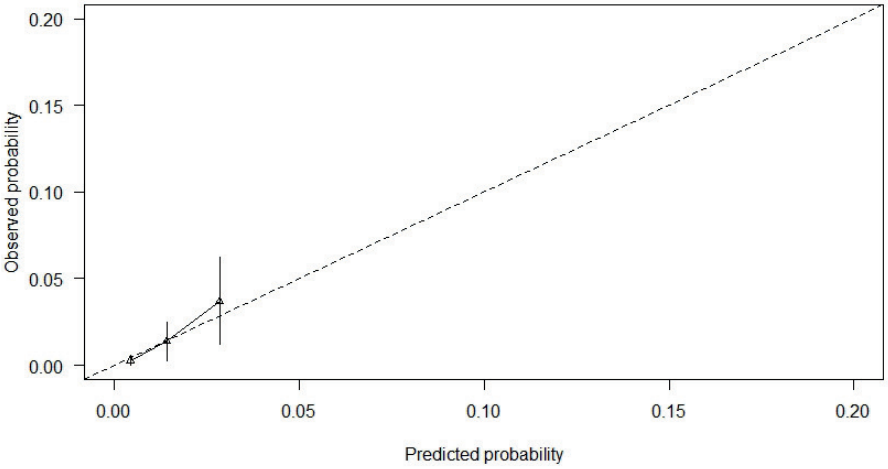


Figure 2: ROC and calibration curve of the exploratory prediction model

The triangles in figure 2B represent the observed probabilities in the study cohort by quartiles (first two quartiles overlap) with corresponding 95% CIs.

affected.[21] However, there was a trend towards a positive association between the two and this association was statistically significant when selecting only patients who underwent MRI (eTable 4). The association between multiple affected arterial territories and cancer is likely to be explained by a systemic hypercoagulable state that is considered to be the dominant pathophysiological pathway in cancer-associated stroke, and/or a non-bacterial thrombotic endocarditis.[17,20]

Unfortunately, we did not have information on D-dimer levels in our patients, which in existing literature seems to be one of the more promising predictors of occult cancer.[19,170,171,176-178] Elevated D-dimer levels, and to a lesser degree elevated CRP, are indicative of a prothrombotic state. However, both measures are non-specific and can be elevated in a wide range of inflammatory and infectious diseases. We did not find an association between elevated CRP levels and underlying cancer in our study population. In literature, there are currently two suggested predictive scores for predicting an occult cancer in stroke patients.[19,185] Both models were similarly not externally validated in another cohort and therefore remain exploratory. In addition they mainly included older patients. Unfortunately, we could not validate these models in our cohort because of the missing d-dimer levels. However, as the background risk of varying cancers and stroke etiology in young patients is different, it stands to reason that a separate score might be of added value.

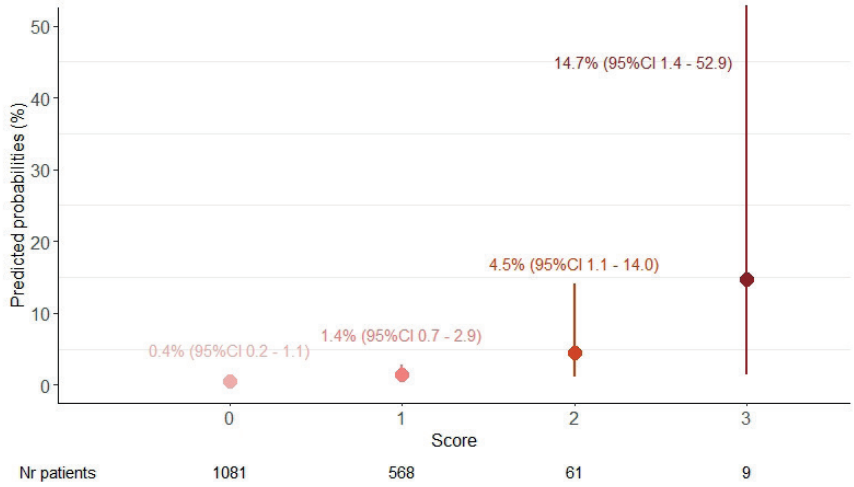


Figure 3: Prediction score with mean predicted probabilities of underlying cancer for each score

The score on the x-axis is based on the presence of anaemia at baseline (1 point), cryptogenic aetiology of stroke (1 point) and three territories involved on neuro-imaging (2 points). On the y-axis the predicted probabilities are the mean predicted probabilities within each score group with corresponding 95% CI. There were no patients with a score of 4, therefore the figure does not include 4.

As of yet, there is no consensus on whether to look for an underlying cancer in patients with ischemic stroke or TIA. Some studies that performed variations of a cancer screening in patients with ischemic stroke demonstrated a relatively high prevalence (2.2% to 20.4%) of occult cancer in stroke patients, implying a possible benefit.[177,181] A prediction score might therefore be useful in clinical practice to assess which young patients with ischemic stroke or TIA should receive additional screening for early diagnosis of cancer. Future research is needed to evaluate which screening modalities for underlying cancer in high-risk young stroke patients would be optimal, also taking into account the large variation of cancer localizations we found in our study cohort. In addition, future research needs to assess the benefit-harm, and cost-effectiveness ratio, of adding screening modalities to the diagnostic work-up of a selection of young patients with stroke.

The main strengths of this study are the use of two large and highly phenotyped existing cohorts of young patients with first-ever stroke or TIA, creating a detailed and representative patient group. As well as, the innovative linkage to the NCR allowed for thorough investigation of the association between an underlying cancer and relevant patient- and stroke characteristics and underlying cancer.

There are also some limitations to our study that should be taken into account when considering the results. First, the number of cases with underlying cancer in our cohort was limited. Therefore, we were not able to identify specific cancer characteristics associated with stroke at young age, for example pathology, cancer-stage or localization. Second, the prediction score we devised should be considered as not more than exploratory, since it was based on a small sample of patients and is therefore highly likely to be overfitted. We tried to limit this overfitting through bootstrapping and shrinkage of the model. Still, this score should be interpreted with caution and first be externally validated before it might be used in clinical practice. However, at this moment published, sizeable cohorts of young patients with stroke that contain all variables of interest to externally validate this predictive score model are not (yet) available.

Conclusions

We demonstrated that an underlying cancer in young patients with ischemic stroke or TIA is rare, but it should be suspected in patients with a cryptogenic stroke, anaemia, and acute ischemia in three arterial territories on neuro-imaging. As these factors were independently associated with an underlying cancer in young patients with ischemic stroke or TIA. We provided an exploratory prediction score based on these three easily available parameters that yielded a mean predicted

probability of an underlying cancer in <1% for 0 points to 15% for 3 points. Before this prediction score might be employed in clinical practice, it should be externally validated in another cohort. Future studies should investigate the possible benefit, and potential harm, of adding cancer screening to the diagnostic work-up of a selected group of young adults with stroke.

PART FOUR

LONG-TERM CONSEQUENCES IN YOUNG ADULTS WITH FIRST-EVER STROKE

Chapter VII

Association of Stroke Among Adults Aged 18 to 49 Years With Long-term Mortality

Published as: Ekker MS*, Verhoeven JI*, Vaartjes I, Jolink WMT, Klijn CJM, de Leeuw FE. *Association of Stroke Among Adults Aged 18 to 49 Years With Long-term Mortality.* JAMA. 2019 Jun 4;321(21):2113-2123. doi: 10.1001/jama.2019.6560. PMID: 31121602; PMCID: PMC6547225.
**Shared first authorship*

Abstract

Importance: Stroke remains the second leading cause of death worldwide. Approximately 10-15% of all strokes occur in young adults. Information on prognosis and mortality specifically in young adults is limited.

Objective: To determine short- and long term mortality risk after stroke in young adults, according to age, sex, and stroke subtype, time trends in mortality, and causes of death.

Design, setting and participants: Registry- and population-based study in the Netherlands of 15 527 patients aged 18-49 years with first stroke between 1998 to 2010, and follow-up until January 1st, 2017. Patients and outcomes were identified through linkage of the national hospital discharge register, national cause of death register and the Dutch population register.

Exposure: First stroke occurring at age 18-49 years, documented using ICD-9 and ICD-10 codes for ischemic stroke, intracerebral hemorrhage and for stroke not otherwise specified.

Main outcomes: Primary outcome was all cause cumulative mortality in 30-day survivors at end of follow up, stratified by age, sex and stroke subtype and compared to all cause cumulative mortality in the general population.

Results: The study population included 15 527 patients with stroke (median age 44 (IQR 38-47) years; 53.3% women). At end of follow-up, a total of 3 540 cumulative deaths had occurred, including 1 776 deaths within 30 days after stroke and 1 764 (23.2%) deaths during a median duration of follow-up of 9.3 years (IQR 5.9-13.1 years). 15-year mortality in 30-day survivors was 17.0% (95%CI 16.2-17.9). The standardized mortality rate (SMR) compared to the general population was 5.1 (95%CI 4.7-5.4) for ischemic stroke (observed mortality rate 12.0/1 000 py with 95% CI: 11.2-12.9/100 py, expected rate 2.4/1 000 py, excess 9.6/1 000 py), the SMR of intracerebral hemorrhage was 8.4 (95%CI 7.4-9.3; observed 18.7/ 1 000 py with 95% CI: 16.7-21.0/1000 py, expected 2.2/1 000 py, excess 16.4/1 000 py).

Conclusions and relevance: Among young adults aged 18-49 years in the Netherlands who were 30-day survivors of first stroke, mortality risk compared to the general population remained elevated up to 15 years later.

Introduction

Stroke is the second leading cause of death worldwide. In 2013, over 10 million people experienced a stroke, and over 6 million died.[65,186,187] Approximately 10-15% of all strokes occur in young adults aged 18-49 years.[39,132] Information on the risk of death in this subgroup is limited.[35]

Previous studies of mortality after stroke in young adults were often small, hospital based, had limited periods of follow-up, or included patients who had their stroke between 1980 and 2000.[52,188,189] Over the past decades, both acute treatment and secondary prevention have improved. Because of the small number of patients younger than age 50 with stroke included in previous studies, it has not been possible to estimate mortality according to age-, sex-, and stroke subtypes.[22,23,45,188,190-192]

This study aimed to investigate case fatality-, cumulative 1-year-, 5-year-, 10-year and 15-year mortality and trends over time of first stroke in young adults aged 18-49 years, stratified by age, sex and stroke-subtype, excess mortality after stroke compared to the general population and causes of death.

Methods

The Medical Ethics Review Committee Arnhem/Nijmegen assessed the protocol and waived the requirement for ethical review. We performed all analyses in a secured environment of Statistics Netherlands according to the Dutch privacy legislation.

Exposure

We constructed a nationwide cohort of patients aged 18-49 years with first stroke (ischemic stroke, intracerebral hemorrhage, or stroke not otherwise specified) through linkage of the Dutch nationwide hospital registry (HDR) and Dutch population registry from January 1st 1998 to January 1st 2011 and the National Cause of Death registry (CDR) from January 1st 1998 to January 1st 2017, by using ICD-9 and -10 codes for stroke (ischemic stroke, intracerebral hemorrhage and stroke not otherwise specified; WHO International Classification of Diseases) (Supplementary Table 1). We did not include transient ischemic attacks (TIA) and subarachnoid hemorrhage (SAH). Details of these registries and linkage procedures have been described previously.[31,45,46]

ICD-9 and ICD-10 codes for the identification of stroke has been proven to be reliable in studies of patients with stroke of all ages.[42,43] For this study, we specifically assessed the accuracy of ICD-10 codes for young adults (aged 18-49 years old). We checked final diagnoses in medical records against the attached ICD-10 code at discharge of 569 patients admitted in two university medical centers and one large general hospital between 1995 and 2017. For ischemic stroke the ICD-code was correct in 90.4% of cases (n=301), for intracerebral hemorrhage in 86.3% (n=183), and for stroke not otherwise specified in 87.1% of cases (n=85) (Supplementary Table 2).

For all individuals the Charlson-Comorbidity-Index (CCI) at the time of the index event was estimated based on previously documented hospital admissions. The CCI is a score from one to six based on 19 primary medical conditions such as congestive heart failure, diabetes, malignancies and other organ dysfunction and has previously been shown a valid tool to predict outcome.[193]

Outcomes

Primary outcome was all-cause cumulative mortality at the end of follow-up, stratified for age, sex and stroke subtype in 30-day survivors. Secondary outcomes were case fatality and cumulative 1-year, 5-year, 10-year and 15-year mortality in the 30-day survivors. Other secondary outcomes were the annual risk of death, excess mortality after stroke compared to the general population, time-trends of case fatality, 1-year and 5-year mortality in 30-day survivors after first stroke in young adults and causes of death, all stratified by age, sex and stroke-subtype. Out of hospital deaths were identified if an ICD-10 code for stroke was registered in the CDR without previous hospitalizations in the HDR for this individual. Individuals that have emigrated have been censored. The number of hospitals participating in the HDR declined from 2005 to 2010, resulting in an increasing number of missing records, varying from 1.1% to 14%, resulting in some missing index strokes. Date and cause of death were retrieved from the CDR. In the Netherlands all deaths are recorded in the CDR by Statistics Netherlands. Cause of death was missing for 1 patient (0.05%); this patient was excluded from the analysis. Data regarding other variables, age, sex, CCI and length of stay, were complete for all patients. Follow-up after first stroke between 1998 and 2010 was defined as the time until death or the end of follow up (January 1st, 2017), whichever occurred first. Case fatality was defined as death occurring within 30 days after stroke. For survival analysis only survivors beyond these 30 days were included. Causes of death were analyzed by ICD-10 codes.

Statistical Analysis

We used Kaplan-Meier analysis to estimate the risk of death for all-cause stroke, ischemic stroke, intracerebral hemorrhage and stroke not otherwise specified for men and women separately. We calculated the number of person-years (py) at risk for each individual patient from date of stroke to the date of death or until January 1st 2017, whichever occurred first. We censored the Kaplan-Meier curves at 16 years after the index event because thereafter the number of py at risk became too small to provide reliable estimates of mortality. We calculated 1-year-, 5-year-, 10-year and 15-year cumulative mortality by sex and stroke-subtype. Survival curves were compared between men and women using log-rank analysis.

For comparison of mortality in young adults with stroke to mortality in the general population, we used mortality data of the general Dutch population matched by sex, age and calendar year.[46] The annual risk of the observed mortality after stroke as well as the expected mortality in the general population was calculated using the formula: 1-[(1-Ic)(1/n)], where n is the number of years after the index event and Ic is the cumulative mortality at n years, obtained by Kaplan-Meier analysis.

We calculated standardized mortality ratio's (SMRs) by dividing the observed deaths in our cohort by the expected deaths of their peers from the general population for each stroke subtype, for both sexes and for different age-categories (18-29, 30-39 and 40-49). The expected matched mortality rates were retrieved from the Worldwide Human Mortality Database (www.mortality.org).[194] The 95% CIs were calculated by assuming a Poisson distribution. Additionally, for each subgroup, we calculated an absolute excess number of deaths by taking the difference between the observed and expected deaths, divided by the person-years at risk. Differences of the SMRs by sex and stroke subtype were evaluated by tests of interactions through univariate and multivariable linear regression modeling.

We assessed the association of age at index event, sex, CCI, and length of stay with the risk of long-term mortality, stratified for stroke subtypes, through Cox proportional hazard models, and expressed the associations as hazard ratios (HR) with 95% CIs. After univariate analysis, all four variables were entered simultaneously to obtain a multivariable model. Assumption of proportionality in the Cox regression model was evaluated graphically assessing the log(-log(Survival)) plots for all covariates. We found no indication of violating the assumption. In addition, we plotted the scaled Schoenfeld residuals against time, which confirmed proportionality. We calculated time trends in case fatality, 1-year and 5-year mortality rates in yearly average percentage change (APC) and tested

change over time with linear regression analysis. We used R-squared (R2) to assess the goodness of fit of the linear regression analyses. Time trends regarding 10-year and 15-year mortality were not calculated because we did not have a complete 10- and 15- year follow up period for all inclusion years. Also time trends were calculated for mean length of stay and tested through linear regression.

In the Netherlands, cause of death is established among all patients that die (both inside or outside the hospital) by a coroner or physician who is required by law to complete the death certificate. This death certificate is then sent to coders employed by Statistics Netherlands who assign a ICD-10 code for the primary (underlying disease) and secondary causes of death (possible complications, such as pneumonia) accordingly. Studies on the reliability of these ICD-10 codes found an intercoder-agreement of 78% and intracoder-agreement of 89%. The highest reliability was found for major causes of death (malignancy and acute myocardial infarction).[195] We categorized causes of death based on the ICD 10 codes for primary cause in 30-day survivors. (Supplementary Table 3). Proportion of causes of death were compared through chi-squared analyses. We tested for interactions between stroke subtype and different causes of death separately through using a Poisson regression model, with adjustment for sex through adding this as a covariate to a multivariable Poisson model.

Two sided p-values of .05 were considered statistically significant. For the SMR analyses, we set the threshold for significance to a p-value of.005 after Bonferroni adjustment for ten subgroup analyses.

Data was analyzed with SPSS Software 22, R version 3.22 (Packages rateratio.test, survival, survminer), STATA version 12 and Microsoft Office Excel 2007."

Results

We identified 15 257 young adults with a stroke (53.3% women, median age 44 years, IQR 38-47). 8 444 (55.3%) had ischemic stroke, 3 077 (20.2%) had intracerebral hemorrhage and 3 736 (24.5%) had a stroke not otherwise specified. Less than 1% of strokes were out of hospital deaths, and the majority had no comorbidity (n=12 803, 83.9%) (Table 1). The median duration of follow-up was 9.3 years (IQR=5.9-13.1 y; Table 1).

Following any stroke, 1 776 patients (11.6%) died in the first 30 days. Case fatality after ischemic stroke was 7.4% (n=629), 7.6% (n=291) in men, 7.4% (n=338) in women), after intracerebral hemorrhage 32.3% (29.8% (n=991) in men, 34.8% (n=519) in women), and after stroke not otherwise specified 4.2% (3.8% (n=65) in men, 4.4% (n=91) in women). This resulted in a cohort of 13 481 30-day survivors of patients with any stroke (7 815 ischemic stroke, 2 086 intracerebral hemorrhage and 3 580 stroke not otherwise specified; Supplementary Table 4).

Cumulative mortality

At end of follow-up a total of 3 540 (23.2%) patients had died. In 30-day survivors, the cumulative mortality after any stroke increased from 3.1% (95%CI, 2.8%-3.4%) after 1 year to 7.0% (95% CI 6.6-7.4) at 5 years, 11.5% (95% CI 11.0-12.1) at 10 years and 17.0% (95% CI 16.2-17.9) after 15 years (Figure 1a-d; Supplementary Table 5).

Sex-specific annual risk of death by stroke subtype

The annual risk of death of 30-day survivors was highest in the first years after stroke and then stabilized (Figure 1e-h). After ischemic stroke the risk of death after 1 year was 2.0% (95% CI 1.8-2.3) for men and 1.6% (95% CI 1.4-1.8) for women, and after 10 years decreased to an annual risk of 1.4% (95% CI 1.2-1.6) for men and 0.9% (95% CI 0.7-1.1) for women.

For intracerebral hemorrhage the annual risk of death was 4.8% (95%CI 4.4-5.1) for men and 3.9% (95%CI 3.6-4.3) for women after 1 year and after 10 years decreased to an annual risk of 1.9% (95%CI 1.7-2.1) for men and 1.4% (95%CI 1.2-1.6) for women (Figure 1e-h).

Long-term mortality in 30-day survivors of stroke compared to the general population

The standardized mortality ratio for young adults with any stroke compared to peers from the general population matched by sex, age and calendar year, was 5.6 (95%CI 5.3-5.9). The observed mortality rate was 13.3 per 1 000 py (95% CI: 12.6-14.0 per 1 000 py) versus an expected rate of 2.4 per 1 000 py with an excess of 10.9 deaths per 1 000 py. The SMR for ischemic stroke was 5.1 (95% CI 4.7-5.4) with an observed mortality rate of 12.0 per 1 000 py (95% CI: 11.2-12.9 per 1 000 py), and expected mortality rate of 2.4 per 1000 py and an excess of 9.6 per 1 000 py. For intracerebral hemorrhage the SMR was 8.4 (95%CI 7.4-9.3; observed mortality rate 18.7 per 1000 py; 95% CI: 16.7-21.0 per 1 000 py, expected rate 2.2 per 1 000 py, excess of 16.5 per 1 000 py). The SMR for stroke not otherwise specified was 5.2 (95% CI 4.7-5.8; observed rate 12.9; 95% CI: 11.7-14.3, expected rate 2.5,

excess 10.5 per 1 000 py). There were no significant differences in SMR between men and women (univariate linear regression model; p=0.738, multivariable model including stroke subtype and age-groups; p=0.068). Results stratified for age-groups and sex are summarized in Table 2.

The association of age, sex, comorbidity and length of stay with the risk of death after index stroke

In univariate Cox regression analysis for any stroke age was associated with mortality during follow-up of 30-day survivors (35-39 y: HR 2.3, 95% CI 1.5-3.8, p<.001; 40-44 y: HR 2.6, 95% CI 1.7-4.2, p<.001; 45-49 y: HR 3.8, 95% CI 2.4-5.9, p<.001; all compared to the reference group aged 18-24years). Age-groups 25-29 and 30-34 were not significantly associated with a higher risk of mortality. Male sex was associated with a higher risk of mortality with a HR of 1.5 (95%CI 1.4-1.6; p<.001), as well as a CCI above 0 (CCI of 1: HR 2.1, 95% CI 1.9-2.4, p<.001; CCI of 2 HR 6.5, 95% CI 5.6-7.5, p<.001; CCI of 3 or higher: HR 9.4 95%CI 7.5-11.7, p<.001). In addition, length of hospital stay longer than 14 days was associated with mortality (HR 2.2, 95% CI 1.9-2.5, p<.001). In the multivariable Cox regression model all of the above associations remained significant. Table 3 shows HRs of the uni- and multivariable Cox regressions models specified per stroke subtype.

Time trends in case fatality, 1-year, 5-year mortality and length of stay for any stroke and for stroke subtypes

Case fatality after any stroke decreased from 15.2% (n=160) in 1998 to 6.9% (n=86) in 2010 (yearly APC -5.5%, 95%CI -13.1-2.0%; p<.001, R2=0.9), for ischemic stroke from 8.4% (n=47) in 1998 to 4.9% (n=38) in 2010 (yearly APC -1.3%, 95%CI -17.1-14.6%; p<.001, R2=0.6), for intracerebral hemorrhage from 37.9% (n=89) in 1998 to 21.1% (n=44) in 2010 (yearly APC -3.8%, 95%CI -11.9-4.4%; p<.001, R2=0.8) and for stroke not otherwise specified from 4.6% (n=12) in 1998 to 1.2% (n=3) in 2010 (yearly APC -0.4%, 95%CI -36.3-35.5%; p=.006, R2=0.5).

One-year mortality in 30-day survivors after any stroke decreased from 3.7% (n=39) in 1998 to 2.3% (n=29) in 2010 (yearly APC -2.2%, 95%CI -13.0-8.6%; p=.002, R2=0.6). In ischemic stroke, 1-year mortality decreased from 3.3% (n=18) in 1998 to 1.2% (n=9) in 2010 (yearly APC -2.8%, 95%CI -20.2-14.7%; p=.005, R2=0.5) whereas in intracerebral hemorrhage 7.8% (n=18) in 1998 and 6.1% (n=13) in 2010; yearly APC 5.4%, 95%CI -18.6-29.4%; p=.07, R2=0.3) and in stroke not otherwise specified 1-year mortality remained stable (3.6% (n=9) in 1998 and 2.8% (n=7) in 2010; yearly APC 24.1%, 95%CI -18.8-67.0%; p=.97, R2=0.0).

Table 1: Demographics including age, sex, comorbidity and follow-up of patients with stroke aged 18-50 years

		Any stroke			Ischemic stroke			Intracerebral hemorrhage			Stroke not otherwise specified		
		Total	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**	**Total**	**Men**	**Women**
	N (%)	15257 (100%)	7127 (46.7%)	8130 (53.3%)	8444 (100%)	3851 (45.6%)	4593 (54.4%)	3077 (100%)	1585 (51.5%)	1492 (48.5%)	3736 (100%)	1691 (45.3%)	2045 (54.7%)
	Mean age, y (SD[a])	41.8 (6.8)	42.3 (6.5)	41.4 (7.0)	42.0 (6.6)	42.6 (6.1)	41.4 (7.0)	40.7 (7.5)	40.7 (7.5)	40.8 (7.5)	42.2 (6.4)	42.9 (6.0)	41.6 (6.7)
Charlson comorbidity index[b]	**N score 0 (%)**	12803 (83.9%)	5951 (83.5%)	6852 (84.3%)	7178 (85.0%)	3262 (84.7%)	3916 (85.2%)	2539 (82.5%)	1307 (82.4%)	1232 (82.6%)	3086 (82.6%)	1382 (81.7%)	1704 (83.3%)
	N score 1 (%)	1694 (11.1%)	810 (11.4%)	884 (10.8%)	879 (10.4%)	397 (10.3%)	482 (10.5%)	353 (11.5%)	189 (11.9%)	164 (10.9%)	462 (12.4%)	223 (13.2%)	238 (11.6%)
	N score 2 (%)	574 (3.8%)	275 (3.9%)	299 (3.7%)	299 (3.5%)	152 (3.9%)	147 (3.2%)	137 (4.5%)	63 (4.0%)	74 (5.0%)	138 (3.7%)	69 (4.1%)	78 (3.8%)
	N score >=3 (%)	186 (1.2%)	91 (1.3%)	95 (1.2%)	88 (1.0%)	40 (1.0%)	48 (1.0%)	48 (1.6%)	26 (1.6%)	22 (1.4%)	50 (1.3%)	25 (1.5%)	25 (1.2%)
Duration of Follow up[c]	**Median Follow up, y (IQR[d])**	9.3 (5.9-13.1)	9.2 (5.8-12.9)	9.5 (6.0-13.3)	9.5 (6.3-13.2)	9.3 (6.2-12.9)	9.7 (6.4-13.4)	6.9 (0.0-11.9)	7.1 (0.0-11.9)	6.7 (0.0-11.8)	10.3 (7.0-13.5)	10.2 (6.9-13.3)	13.7 (7.2-13.7)
	Follow up > 5y, N (%)	12541 (82.2%)	5789 (81.2%)	6752 (83.0%)	7355 (87.1%)	3314 (86.1%)	4041 (88.0%)	1842 (59.9%)	969 (61.1%)	873 (58.5%)	3344 (89.5%)	1509 (89.2%)	1838 (89.9%)
	Follow up > 10y, N (%)	6928 (45.4%)	3138 (44.0%)	3790 (46.6%)	3903 (46.2%)	1716 (44.6%)	2187 (47.6%)	1059 (34.4%)	549 (34.6%)	510 (34.2%)	1966 (52.6%)	873 (51.6%)	1093 (53.4%)

[a] SD = standard deviation.

[b] Charlson Comorbidity Index score ranges from 0 to 6, with higher scores indicating more comorbidity.

[c] Duration of Follow up is defined as the time, in years, between event and death or end of study, whichever occurred first in years

[d] IQR = interquartile range

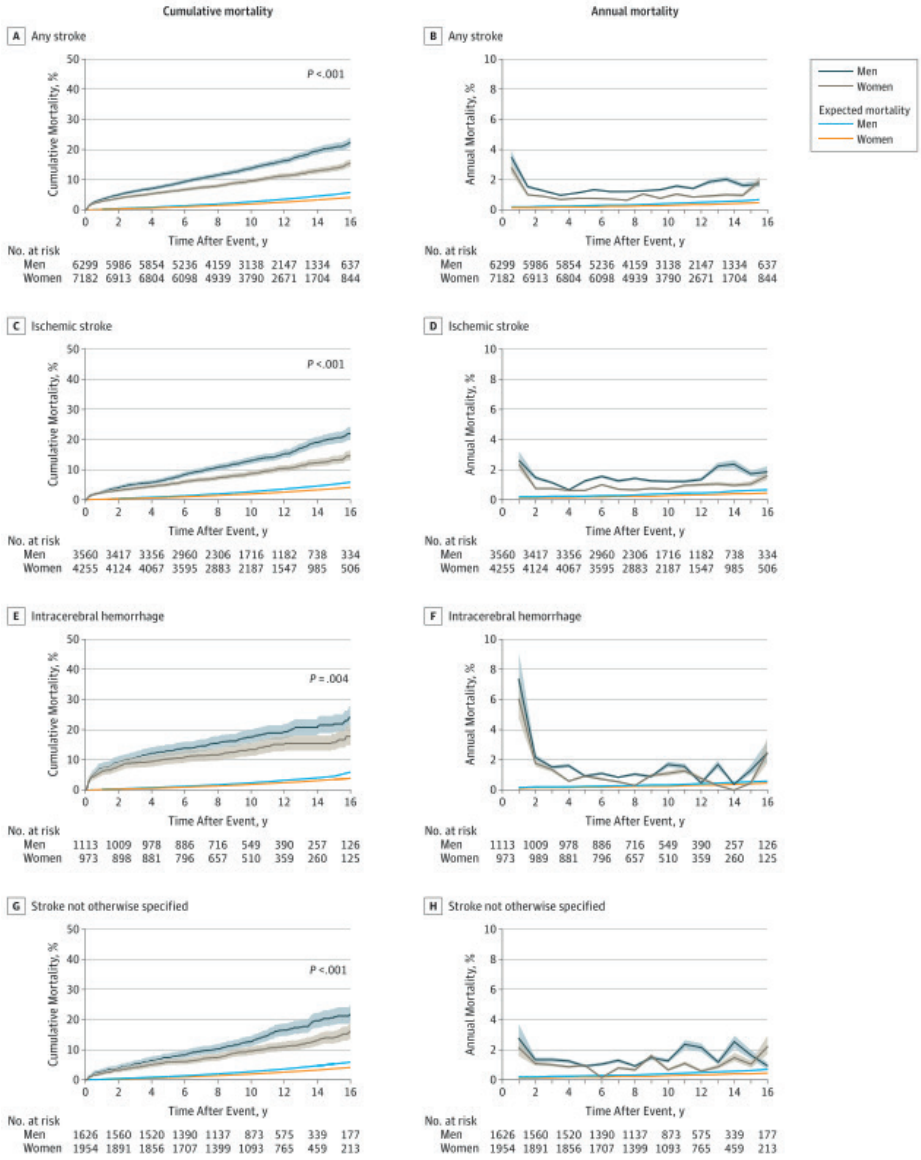


Figure 1: Cumulative Mortality and Annual Mortality Over Time in 30-Day Stroke Survivors

For men and women, the median (IQR) observation time was 10.0 years (6.7-13.4) and 10.3 years (7.3-13.8), respectively, for stroke (A); 9.8 years (7.8-13.3) and 10.2 years (7.2-13.7) for ischemic stroke (C); 9.9 years (6.6-13.6) and 10.4years (6.9-14.3) for intracerebral hemorrhage (E); and 10.5 years (7.3-13.7) and 10.7 years (7.6-13.8) for stroke not otherwise specified (G). The log-rank test was used for differences between men and women. Shaded regions indicate 95%CIs.

Cumulative 5-year mortality in 30-day stroke survivors decreased significantly over time in any stroke from 8.4% (n=89) in 1998 to 5.2% (n=64) in 2010 yearly APC -3.1%, 95%CI -10.2-4.0%; p<.001, R2=0.8), in ischemic stroke from 8.0% (n=45) to 3.0% (n=23) (yearly APC -6.2%, 95%CI -17.2-4.8%; p<.001, R2=0.8), and in stroke not otherwise specified from 8.4% (n=22) to 7.2% (n=18) (yearly APC 2.8%, 95%CI -11.7-23.4%; p=.046, R2=0.3). Cumulative 5-year mortality remained stable in intracerebral hemorrhage (9.6% (n=23) in 1998 and 12.1% (n=25) in 2010; yearly APC 5.9%, 95%CI -13.7-19.3%; p=.98, R2=0.0) (Supplementary Table 6).

From 1998 to 2010 length of stay after any stroke decreased significantly from a mean of 18.2days to a mean of 8.6days, resulting in a yearly decrease of -0.8 days (95%CI -0.2--1.32; p<.001, R2=0.4). This was also true for ischemic stroke, intracerebral hemorrhage and stroke not otherwise specified.

Causes of death

Of the 30-day survivors, a total of 1 764 patients died during follow-up (13.1%), of which 267 (15.1%) were due to recurrent stroke or were stroke-related and 302 (17.1%) due to other cardiovascular diseases. The main cause of death was malignancy (n = 577), 32.7%). The remaining patients (n=617) (34.9%) died as a result of infection, trauma and miscellaneous causes. The proportion of deaths attributable to malignancies was higher in the intracerebral hemorrhage group than the group with an ischemic stroke as index event (41.5% (n=145) versus 28.8% (n=273); $\chi 2=18.9$, p<.001). The proportion of cardiovascular related deaths was higher in the ischemic stroke group than the intracerebral hemorrhage group (19.4% (n=184) versus 7.2% (n=25); $\chi 2=28.4$, p<.001). Also, the Poisson regression model showed significant interaction between stroke subtype and malignancies, as well as cardiovascular related deaths (p<0.001), even after correcting for sex in this model (p<0.001). The different categories of causes of death stratified by stroke subtype are listed in Table 4.

Discussion

Among young adults aged 18-49 years in the Netherlands with first stroke, mortality risk compared to the general population remained elevated up to 15 years later.

Major strengths of this study include the population-based setting with a large number of young patients with stroke (15 257 patients <50 years), whereas in other large studies patients were included up to 55 years (with substantially less patients

<50 years). In addition, this population based setting increased the likelihood of complete ascertainment of (cause of) death, whereas referral bias has occurred in previous other studies with a hospital based setting, because the more severely affected patients are more likely to die already at home and will not be included in hospital based populations.

This study reports, to our knowledge, for the first time the risk and causes of death, cumulative mortality and annual mortality after intracerebral hemorrhage at young age in large numbers that allow for sufficient power to perform age- and sex stratified analysis. Another strength of this study is that ICD-codes for all stroke subtypes were validated in young age groups specifically.

Furthermore, due to the availability of longitudinal data in combination with the very large numbers this study was able to report on differential time trends of mortality including case-fatality after ischemic stroke and intracerebral hemorrhage.

Additionally, this study reports on outcomes of patients who were treated with stroke-unit care, intravenous thrombolysis and hemicraniectomy and secondary preventive treatment, whereas earlier studies included patients that had their stroke years before the implementation of these therapies.[196-198]

In addition, within this large cohort it was possible to analyze cause specific causes of death in more detail than previous studies, with information available on subtypes of malignancies. Previous studies have presented this only for patients with ischemic stroke and not for patients with intracerebral hemorrhage, and causes of death were limited to recurrent stroke, other cardiovascular disease, malignancies and other causes.

A limited number of earlier studies with a comparable duration of follow-up have shown comparable mortality rates of 4.6% (3-year) and 16% (16-year).[23,188,189,192] Most previous studies on long-term mortality after stroke in young adults were hospital-based, had varying inclusion criteria or also included SAH or TIA. These disorders may have a different prognosis than ischemic stroke and intracerebral hemorrhage and may therefore bias the mortality rates after stroke. In young patients with TIA, the 1-year cumulative mortality was shown to be only 0.7% and in the years thereafter 0.2% per year.[23,188,189] In contrast, patients with a SAH had a 17% excess mortality compared to the general population after 20 years of follow-up.[199]

The excess long-term mortality in young adults following stroke compared to age- and sex-matched individuals in the general population may suggest that even after treatment for stroke and treatment of associated risk factors according to current standards, the risk of death of young patients with stroke remained increased compared to their population peers. From 1998 to 2017, the already low risk of death in young adults in the general population has continued to decrease, possibly because of improved treatment of other life-threatening diseases like malignancies and because of fewer traffic accidents.[200]

The observed decreasing trend observed in mortality after ischemic stroke in young adults could be partially due to improved diagnosis of ischemic stroke with better and more imaging techniques available. In this way minor and resolved syndromes can be increasingly diagnosed as stroke (by MRI), which would partially explain decreasing rates of post-stroke mortality only for ischemic stroke. This hypothesis is supported by the fact that the 1- and 5-year mortality rates of intracerebral hemorrhage do not decrease significantly over the study period, which can be readily diagnosed purely by use of a CT-scan, which was already available in the earlier years of the study period.

A previous study also found male sex as risk factor for long-term mortality.[189] The increased risk of death in men may be due to differences in risk factors and etiology between men and women (e.g. higher prevalence of traditional vascular risk factors and more large artery disease in men,[9,34,36] since incidence of stroke in the study period was higher in young women.[132] When compared to the general population, no significant differences between men and women in their risk of death were found.

In Sweden, a decline in case fatality of ischemic stroke was seen in men aged 30 to 84 years, but not in women. A similar difference with significant decrease of case fatality only in men was seen in the Framingham study.[201,202] The decrease in case-fatality of ischemic stroke this study found for both young men and women might be attributable to both the change in the organization of stroke care with better education, introduction of stroke units in the early nineties and the introduction of hemicraniectomy for space occupying infarctions,[196,203] and the higher detection of more minor and resolved syndromes as mentioned above. The reason that case-fatality of intracerebral hemorrhage has remained stable over time, may be the limited treatment options for this type of stroke compared to ischemic stroke.[203-206]

Table 2: Long-term mortality in 30 day stroke survivors compared to mortality of the general population

	Total	Patient Years (PY) at risk	Observed deaths	Observed deaths per 1000 PY	95% Confidence interval	
Any stroke	13481	102184	1356	13.27	12.60	14.00
Men	6299	46937	756	16.11	15.01	17.29
Women	7182	55247	600	10.86	10.03	11.76
18-29	928	7477	52	6.95	5.30	9.12
Men	340	2635	28	10.63	7.35	15.36
Women	588	4842	24	4.96	3.33	7.39
30-39	2951	23423	228	9.73	8.55	11.08
Men	1285	9958	128	12.85	10.82	15.27
Women	1666	13465	100	7.43	6.11	9.03
40-49	9602	71284	1076	15.09	14.23	16.02
Men	4674	34344	600	17.47	16.14	18.91
Women	4928	36939	476	12.89	11.79	14.09
Ischemic stroke	7815	58668	704	12.00	11.15	12.91
Men	3560	26228	382	14.56	13.18	16.09
Women	4255	32440	322	9.93	8.9	11.07
18-29	487	3903	26	6.66	4.54	9.77
Men	162	1247	10	8.02	4.33	14.87
Women	325	2656	16	6.02	3.70	9.82
30-39	1667	13414	100	7.45	6.13	9.06
Men	696	5510	52	9.44	7.20	12.37
Women	971	7904	48	6.07	4.58	8.05
40-49	5661	41351	578	13.98	12.89	15.16
Men	2702	19471	320	16.43	14.74	18.32
Women	2959	21880	258	11.79	10.44	13.31
Intracerebral hemorrhage	2086	15560	291	18.70	16.69	20.96
Men	1113	8158	174	21.33	18.41	24.71
Women	973	7402	117	15.81	13.21	18.92
18-29	228	1835	17	9.26	5.77	14.87
Men	109	866	11	12.70	7.06	22.85
Women	119	969	6	6.19	2.79	13.75
30-39	515	3864	72	18.63	14.82	23.42
Men	279	2042	46	22.53	16.93	29.98
Women	236	1822	26	14.27	9.74	20.9
40-49	1343	9861	202	20.49	17.87	23.48
Men	725	5250	117	22.29	18.63	26.66
Women	618	4611	85	18.44	14.93	22.76

Expected deaths[b]	Expected deaths per 1000 PY	Excess[b] per 1000 PY	Standardized Mortality Rate[c] (95% CI[d])		
242.82	2.38	10.89	**5.58**	5.29	5.89
131.07	2.79	13.31	**5.77**	5.36	6.18
111.75	2.02	8.84	**5.37**	4.94	5.80
3.29	0.44	6.52	**15.83**	11.57	20.40
1.55	0.59	10.04	**18.12**	11.65	25.24
1.74	0.36	4.60	**13.79**	8.62	19.54
25.15	1.07	8.66	**9.06**	7.91	10.26
12.28	1.23	11.62	**10.42**	8.63	12.29
12.87	0.96	6.47	**7.77**	6.29	9.32
214.38	3.01	12.09	**5.02**	4.72	5.32
117.24	3.41	14.06	**5.12**	4.71	5.53
97.14	2.63	10.26	**4.90**	4.47	5.34
139.12	2.37	9.63	**5.06**	4.69	5.43
73.52	2.80	11.76	**5.20**	4.68	5.73
65.61	2.02	7.90	**4.91**	4.37	5.46
1.66	0.43	6.23	**15.62**	10.21	21.62
0.73	0.59	7.43	**13.66**	5.46	23.22
0.93	0.35	5.67	**17.15**	9.65	25.72
14.48	1.08	6.38	**6.91**	5.59	8.29
6.83	1.24	8.20	**7.61**	5.56	9.81
7.65	0.97	5.11	**6.28**	4.58	8.11
122.98	2.97	11.00	**4.70**	4.32	5.09
65.95	3.39	13.05	**4.85**	4.32	5.40
57.03	2.61	9.19	**4.52**	3.98	5.09
34.82	2.24	16.46	**8.36**	7.41	9.34
20.45	2.51	18.82	**8.51**	7.29	9.78
14.36	1.94	13.87	**8.15**	6.67	9.68
0.84	0.46	8.81	**20.35**	10.78	31.13
0.50	0.58	12.12	**21.96**	9.98	35.94
0.33	0.35	5.85	**17.94**	5.98	32.90
4.07	1.05	17.58	**17.71**	13.77	21.89
2.40	1.18	21.35	**19.14**	13.73	24.97
1.66	0.91	13.35	**15.63**	10.22	21.65
29.91	3.03	17.45	**6.75**	5.85	7.69
17.55	3.34	18.94	**6.67**	5.47	7.92
12.37	2.68	15.75	**6.87**	5.42	8.41

Table 2: Continued

	Total	Patient Years (PY) at risk	Observed deaths	Observed deaths per 1000 PY	95% Confidence interval	
Stroke not otherwise specified	3580	27956	361	12.91	11.66	14.31
Men	1626	12551	200	15.93	13.89	18.28
Women	1954	15405	161	10.45	8.96	12.19
18-29	213	x[e]	x	x	x	x
Men	69	x	x	x	x	x
Women	144	x	x	x	x	x
30-39	769	6145	56	9.11	7.02	11.83
Men	310	2406	30	12.47	8.74	17.79
Women	459	3739	26	6.95	4.74	10.2
40-49	2598	20072	296	14.75	13.17	16.51
Men	1247	9624	163	16.94	14.55	19.72
Women	1351	10449	133	12.73	10.75	15.07

[a] Expected deaths retrieved from mortality data of the Dutch population matched for age-, sex- and calendar year- characteristics (Human mortality database)

[b] Excess was calculated as (observed deaths - expected deaths) / PY at risk expressed per 1000 PY

[c] SMR is the ratio of the observed mortality rate divided by expected mortality rate, assuming the observed deaths follow a Poisson distribution

[d] 95% Confidence intervals. For subgroup analyses within any stroke and the different stroke subtypes the significance threshold was set to a Bonferroni adjusted p-value of.005. P-values <.001 for all rows that have data

[e] x relates to missing data (subgroup was too small in number of patients to adequately protect privacy according to legislation regarding the use of this register-based dataset of Statistics Netherlands)

	Expected deaths[b]	Expected deaths per 1000 PY	Excess[b] per 1000 PY	Standardized Mortality Rate[c] (95% CI[d])		
	68.88	2.46	10.45	**5.24**	4.70	5.79
	37.10	2.96	12.98	**5.39**	4.66	6.15
	31.78	2.06	8.39	**5.07**	4.31	5.85
	x	x	x	**x**	x	x
	x	x	x	**x**	x	x
	x	x	x	**x**	x	x
	6.61	1.08	8.04	**8.47**	6.35	10.74
	3.05	1.27	11.20	**9.84**	6.56	13.45
	3.56	0.95	6.00	**7.30**	4.77	10.11
	61.49	3.06	11.68	**4.81**	4.28	5.37
	33.74	3.51	13.43	**4.83**	4.09	5.57
	27.75	2.66	10.07	**4.79**	4.00	5.62

Table 3: Associated factors with mortality among 30 day stroke survivors according to stroke subtype

	Univariate analysis[a]			Multivariable analysis[b]		
	HR	**95%CI**		**HR**	**95%CI**	
Any stroke						
Age at index event, y[c]						
25-29	1.48	0.86	2.57	1.53	0.88	2.65
30-34	1.49	0.90	2.46	1.43	0.87	2.37
35-39	2.35	1.47	3.75	2.26	1.41	3.62
40-44	2.65	1.67	4.19	2.54	1.60	4.01
45-49	3.76	2.39	5.92	3.36	2.13	5.28
Sex, men[d]	1.50	1.37	1.65	1.41	1.29	1.55
Charlson Comorbidity Index[e]						
1	2.10	1.85	2.38	2.07	1.83	2.35
2	6.48	5.59	7.51	5.91	5.10	6.86
>= 3	9.36	7.49	11.69	7.72	6.17	9.65
Length of stay[f]						
3-7 days	1.09	0.92	1.30	1.19	1.00	1.41
8-14 days	1.18	0.99	1.40	1.28	1.08	1.53
>= 15 days	2.17	1.85	2.55	2.24	1.91	2.63
Ischemic stroke						
Age at index event, y[c]						
25-29	1.48	0.70	3.14	1.37	0.64	2.90
30-34	0.89	0.43	1.83	0.83	0.40	1.72
35-39	1.92	1.00	3.67	1.90	0.99	3.65
40-44	2.36	1.26	4.45	2.24	1.19	4.23
45-49	3.50	1.87	6.54	3.13	1.67	5.84
Sex, men[d]	1.54	1.35	1.75	1.42	1.25	1.62
Charlson Comorbidity Index[e]						
1	2.05	1.72	2.45	2.02	1.69	2.41
2	6.29	5.12	7.72	5.54	4.51	6.81
>= 3	9.74	7.10	13.37	7.56	5.50	10.40
Length of stay[f]						
3-7 days	1.19	0.93	1.53	1.29	1.00	1.65
8-14 days	1.23	0.96	1.57	1.34	1.04	1.72
>=15 days	2.30	1.82	2.90	2.35	1.86	2.96

[a] Charlson Comorbidity Index score ranges from 0 to 6, with higher scores indicating more comorbidity. [a] Hazard ratios (95%CI) were computed separately for age at index event, sex, Charlson Comorbidity Index and length of stay. [b] Age at index event, sex, Charlson Comorbidity Index and length of stay were entered simultaneously in a Cox proportional hazards model. [c] Reference category for age at index event was "18-24 years", [d] Reference category for sex was "women". [e] Reference category for Charlson Comorbidity Index was "a score of 0", [f] Reference category for length of stay was "0-2 days.

	Univariate analysis[a]			Multivariable analysis[b]		
	HR	95%CI		HR	95%CI	
Intracerebral hemorrhage						
Age at index event, y[c]						
25-29	2.65	0.93	7.52	3.20	1.13	9.10
30-34	3.04	1.17	7.92	2.77	1.06	7.24
35-39	4.46	1.78	11.15	3.60	1.44	9.03
40-44	4.36	1.77	10.74	4.02	1.63	9.90
45-49	5.09	2.09	12.40	4.63	1.90	11.29
Sex, men[d]	1.35	1.09	1.68	1.35	1.09	1.68
Charlson Comorbidity Index[e]						
1	1.66	1.25	2.21	1.73	1.30	2.30
2	8.24	6.09	11.15	8.26	6.08	11.22
>= 3	9.53	6.06	14.98	9.34	5.91	14.78
Length of stay[f]						
3-7 days	1.19	0.77	1.84	1.28	0.83	1.99
8-14 days	1.23	0.82	1.86	1.27	0.84	1.92
>= 15 days	1.99	1.38	2.86	2.08	1.44	3.00
Stroke not otherwise specified						
Age at index event, y[c]						
25-29	0.67	0.18	2.48	0.72	0.19	2.69
30-34	1.73	0.60	4.99	1.67	0.58	4.84
35-39	1.98	0.72	5.48	1.73	0.62	4.77
40-44	2.20	0.81	5.98	1.95	0.72	5.30
45-49	3.36	1.25	9.02	2.64	0.98	7.11
Sex, men[d]	1.47	1.22	1.76	1.40	1.16	1.68
Charlson Comorbidity Index[e]						
1	2.50	1.98	3.14	2.41	1.91	3.03
2	5.47	4.05	7.38	5.03	3.72	6.79
>= 3	7.72	5.00	11.91	6.32	4.08	9.80
Length of stay[f]						
3-7 days	0.95	0.70	1.28	1.05	0.78	1.43
8-14 days	1.08	0.79	1.47	1.19	0.87	1.43
>= 15 days	2.05	1.55	2.70	2.10	1.59	2.78

Table 4: Causes of death in 30 day survivors, stratified by stroke subtype and sex

	Index event:											
	Any stroke						Ischemic stroke					
Causes of death	total		men		women		total		men		women	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	1763	100	987	100	776	100	947	100	524	100	423	100
Stroke related	267	15.1	147	14.9	120	15.5	129	13.6	72	13.7	57	13.5
Ischemic stroke	35	2.0	20	2.0	15	1.9	28	3.0	x	X	x	X
Intracerebral hemmorhage	49	2.8	26	2.6	23	3.0	12	1.3	x	X	x	X
Other stroke related deaths	183	10.4	101	10.2	82	10.6	89	9.4	50	9.5	39	9.2
Cardiac and other vascular events	302	17.1	194	19.7	108	13.9	184	19.4	113	21.6	71	16.8
Malignancies	577	32.7	273	27.7	304	39.2	273	28.8	127	24.2	146	34.5
Lung cancer	145	25.1	53	19.4	92	30.3	83	30.4	31	24.4	52	35.6
Brain tumor	86	14.9	56	20.5	30	9.9	29	10.6	16	12.6	13	8.9
Hematological malignancies	47	8.1	22	8.1	25	8.2	x	X	x	X	x	X
Breast cancer	40	6.9	X	X	x	X	22	8.1	x	X	x	X
Melanoma	28	4.9	X	x	x	X	x	X	x	X	x	X
Other forms of malignancies	232	40.2	128	46.9	103	33.9	115	42.1	71	55.9	44	30.1
Infections	87	4.9	50	5.1	37	4.8	52	5.5	32	6.1	20	4.7
Trauma	78	4.4	53	5.4	25	3.2	42	4.4	29	5.5	13	3.1
Miscellaneous	452	25.6	270	27.4	182	23.5	267	28.2	151	28.8	116	27.4

ICD codes used to define the categories of causes of death are listed in Supplementary Table 3

[a] Blank values relate to missing data (subgroup was too small in number of patients to adequately protect privacy according to legislation regarding the use of this register-based dataset of Statistics Netherlands.

This study explored the causes of death in young adults after stroke, which may provide evidence for possible underlying disease mechanisms. For example, a higher percentage of patients that died of malignancies and cardiovascular disease was found compared to the general population. Malignancies were responsible for 32.7% of deaths in this cohort, where in corresponding age groups in published records of Statistics Netherlands 25.6% died from malignancy in the period 1998-2010.[207] 17.1% Of patients died from cardiovascular diseases, whereas in corresponding age groups from the general population this percentage was 10.6% according to Statistics Netherlands.[207] This may suggest that the underlying risk

Intracerebral hemorrhage						Stroke not otherwise specified					
total		men		women		total		men		women	
N	%	N	%	N	%	N	%	N	%	N	%
349	100	210	100	139	100	467	100	253	100	214	100
79	22.6	42	20.0	37	26.6	59	12.6	33	13.0	26	12.1
x	X	x	X	x	X	x	X	x	X	x	X
x	X	x	X	x	X	x	X	x	X	x	X
50	14.3	26	12.4	24	17.3	44	9.4	25	9.9	19	8.9
25	7.2	x	X	x	X	93	19.9	63	24.9	30	14.0
145	41.5	80	38.1	65	46.8	159	34.0	92	26.1	126	43.5
14	9.7	x	X	x	X	48	30.2	x	X	x	X
44	30.3	32	40.0	12	18.5	13	8.2	34	51.5	38	40.9
x	X	x	X	x	X	x	X	x	X	x	X
x	X	x	X	x	X	12	7.5	x	X	x	X
21	14.5	10	12.5	11	16.9	x	X	x	X	x	X
46	31.7	24	30.0	22	33.8	70	44.0	33	50.0	37	39.8
19	5.4	x	X	x	X	16	3.4	x	X	x	X
12	3.4	x	X	x	X	24	5.1	x	X	x	X
69	19.8	50	23.8	19	13.7	116	24.8	69	27.3	47	22.0

factors and causes of stroke continue to expose patients to new events throughout the rest of their lives. However, results of causes of death that are based on small patient numbers should be interpreted with caution.

Limitations

This study has several limitations. First, due to the registry based study design, there was an inability to control for possible confounders (e.g. stroke severity, family history, medication) and comorbidity could only be assessed with the CCI, which provides a reliable measure of someone's comorbidity, but without information

about actual risk factors and underlying etiology.[193] Specifically for young patients with stroke, with a wide variety of risk factors and causes, more detailed information would have been desirable. Because the CCI is composed of comorbidities defined by a previous hospital admission before the time of index event this may underestimate the effect of comorbidity on long-term mortality when comorbidity increases between index stroke and death. Conversely, the adjustment for baseline CCI may result in overestimation when comorbidity decreases after the index stroke until death. This possible bias is expected to be very low since young adults are less likely to have major comorbidity than elderly patients.

Second, because fewer hospitals contributed to the HDR register from 2006 onwards, the incidence of stroke could have been underestimated. If these records were not missing completely at random, some bias may have been introduced into the analysis. Third, strokes between 1998 and 2010 were defined as first if no earlier admission for stroke was registered between 1995 and 2010. A limitation of this method is that a very small proportion of incident strokes may have been misclassified as "first", if these patients would have had a stroke before 1995.[208] However, given the 2% yearly risk of recurrent stroke 3 years after index stroke, this risk of misclassification is considered very low.[208]

Fourth, using the general population as a control group includes young adults with stroke, which could possibly bias the study toward the null. However, since only a very small proportion of the controls will have had a stroke (in the order of a few cases per thousands of controls) this is unlikely to have had a major effect on the findings. Fifth, given that recent advances in management of ischemic stroke with mechanical thrombectomy occurred largely after the end date of the data included in this study, the risk of mortality after ischemic stroke may not entirely be generalizable to reflect contemporary management.

Conclusions

In adults aged 18-49 years who survived 30-days after stroke, long-term mortality after stroke remained increased compared to the general population up to 15 years after stroke.

Chapter VIII

Long-term mortality in young patients with spontaneous intracerebral haemorrhage: Predictors and causes of death

Published as: Verhoeven JI, Pasi M, Casolla B, Hénon H, de Leeuw FE, Leys D, Klijn CJ, Cordonnier C. *Long-term mortality in young patients with spontaneous intracerebral haemorrhage: Predictors and causes of death.* Eur Stroke J. 2021 Jun;6(2):185-193. Epub 2021 Jun 18.

Abstract

Introduction: Intracerebral haemorrhage (ICH) in young adults is rare but has devastating consequences. We investigated long-term mortality rates, causes of death and predictors of long-term mortality in young spontaneous ICH survivors.

Patients and methods: We included consecutive patients aged 18-55 years from the Prognosis of Intracerebral Haemorrhage cohort (PITCH), a prospective observational cohort of patients admitted to Lille University Hospital (2004-2009), who survived at least 30 days after spontaneous ICH. We studied long-term mortality with Kaplan-Meier analyses, collected causes of death, performed uni-/multivariable Cox-regression analyses for the association of baseline characteristics with long-term mortality.

Results: Of 560 patients enrolled in the PITCH, 75 patients (75% men) met our inclusion criteria (median age 50 years, interquartile range [IQR] 44-53 years). During a median follow-up of 8.2 years (IQR 5.0-10.1), 26 patients died (35%), with a standardized mortality ratio of 13.0 (95% confidence interval [95% CI] 8.5-18.0) compared to peers from the general population. Causes of death were vascular in 7 (27%) patients, non-vascular in 13 (50%) and unknown in 6 (23%). Global cerebral atrophy (hazard ratio [HR] 3.0, 95% CI 1.1-8.6), modified Rankin Score >2 before ICH (HR 3.4, 95% CI 1.0-11.0), and excessive alcohol consumption (HR 3.3, 95% CI 1.1-10.2) were independently associated with long-term mortality.

Discussion: We found a 13-fold higher mortality risk for young ICH survivors compared to the general French population. Predictors of long-term mortality were pre-existing conditions, not ICH-characteristics.

Conclusion: Young ICH survivors remain at increased mortality risk of vascular and non-vascular death for years after ICH.

Introduction

Spontaneous (non-traumatic) intracerebral haemorrhages (ICH) are rare in young adults, but are associated with poor functional outcomes and high mortality rates.[209] The incidence ranges from 1.9 per 100.000 person-years in those 44 years and younger, to 19.0 per 100.000 persons-years between 45 and 55 years.[210] ICH in young adults has devastating consequences, including a higher number of disability-adjusted life years and consequent increase of the socioeconomic burden.[134] The main predictors of early mortality are similar to those found in older people, and are mainly related to ICH characteristics.[211,212] However, causes and predictors of long-term mortality might differ from those of older people.[23,213] Spontaneous ICH at a young age may indicate pre-existing brain fragility, possibly in combination with general poor health. This supposed brain fragility may be reflected by the presence of small vessel disease (SVD) markers on neuro-imaging. Currently, the predictive value for mortality of SVD markers, such as white matter hyperintensities, lacunes or cerebral microbleeds (CMBs), is unknown in young survivors of spontaneous ICH.

The aim of this study was to investigate the long-term mortality rate, causes of death and predictors of long-term mortality in young 30-day survivors of ICH.

Methods

Study design and patient selection

We included patients from the Prognosis of Intracerebral Haemorrhage Cohort (PITCH),[30] a prospective observational cohort of consecutive patients with ICH (first-ever and recurrent), confirmed on imaging, admitted to Lille University Hospital between November 2004 and April 2009.[30] Exclusion criteria were: pure intraventricular haemorrhage, ICH resulting from vascular malformation, cerebral venous thrombosis, head trauma, intracranial tumour, haemorrhagic transformation of an ischaemic stroke and patients referred from other hospitals.[30,214] For this study we included adults aged from 18 to 55 years at onset, who were still alive at 30 days following index event. The design of the PITCH cohort was in line with the PROGRESS (Prognosis Research Strategy) recommendations.[30,215]

Baseline clinical data

We collected age, sex and level of education (dichotomized in less or more than eight years of education). We recorded history of previous ischaemic stroke, ICH,

transient ischaemic attack (TIA), ischaemic heart disease, arterial hypertension, diabetes mellitus and atrial fibrillation, as previously reported.[30] We defined current smoking as everyday smoking or cessation less than 1 year before, excessive alcohol consumption as a weekly consumption of more than 300 grams of alcohol (30 units),[30,216] and hypercholesterolemia as a total cholesterol level of 2.3 g/l or more, or any treatment by statin or fibrate (except when given for coronary reasons).[30] We also collected the use of antihypertensive and antidiabetic drugs, statins, antiplatelet and anticoagulation drugs at admission, as previously stated. [30,216] The pre-existing level of dependency was assessed with the modified Rankin Scale (mRS), with a pre-ICH score of 0-2 indicating independency and mRS pre-ICH >2 indicating dependency.[217] We evaluated the severity of the neurological deficit at admission with the National Institutes of Health Stroke Scale (NIHSS).[218]

Baseline radiological assessment

At admission all patients underwent a brain CT-scan. The location of the ICH was classified into deep (lenticular or caudate nuclei, internal or external capsule or posterior fossa if the haemorrhage originated from the brainstem or cerebellum) or lobar (frontal, temporal, parietal or occipital origin of the haemorrhage), according to the origin of bleeding.[216] There were six patients with multiple localizations of ICH, all locations were scored separately in the different location categories. We recorded intraventricular breakthrough and the presence of blood in the fourth ventricle. The volume of the haemorrhage was measured according to the AxBxC/2 method.[214]

During hospitalization all patients underwent at least one CT-angiogram or MR-angiogram of the brain to rule out structural underlying causes of the ICH.[30] All patients without contra-indications underwent a 1.5 Tesla Brain MRI scan, including at least T1-weighted fluid-attenuated inversion recovery (FLAIR), and T2*gradient-echo (GRE) weighted sequences (echo time: 22·8 ms, repetition time: 700 ms; flip angle: 25°; field of view: 250 mm; matrix: 352 × 224; slice thickness: 5 mm; and interslice gap: 1·5 mm).[219]

For every MRI, we evaluated the presence of white matter hyperintensities using the Fazekas 4-point score. The presence of lacunes was evaluated following the definition of a lacune being deep, subcortical or pontine ovoid lesions (3-15mm) with cerebrospinal fluid-like signal with or without hyperintense fluid-attenuated inversion recovery border. [220] Cerebral microbleeds were defined as round foci of hypointense signal (≤10mm) in the brain parenchyma of T2* Gradient-Echo-Weighted images and rated using the Brain Observer Microbleed Scale (BOMB).[220]

We assessed global cortical atrophy according to the 4-point scale (Global Cortical Atrophy Scale).[221] Finally, we calculated a composite score of small vessel disease burden according to the simple SVD score.[222]

Follow-up

All patients were followed up at 6 months, 12 months and annually thereafter.[223] For this study, we retrospectively obtained the causes of death through medical records, contact with general practitioners (GP) or other physicians listed in the medical records. We classified the primary causes of death into four categories, according to a previously reported classification: vascular deaths (recurrent ICH, ischaemic stroke, other), non-vascular deaths and death from an unknown cause due to lack of information.[224] Non-vascular deaths were divided into infection-related (death presumed as a direct result of the infection or due to systemic complications or organ failure reasonably linked to the infection), cancer or malignant hemopathies (death presumed as a direct result of an identified malignancy or metastases, or death due to secondary complications reasonably linked to the underlying malignancy) and metabolic causes (death presumed as a direct result of or complications of a metabolic disorder, such as death resulting from liver cirrhosis due to hepatic encephalopathy or portal hypertension).

Statistical analysis

We expressed quantitative variables as mean with standard deviation (SD), or as a median values with interquartile range (IQR), as appropriate. We expressed categorical variables as a number with percentages. We assessed the risk of all-cause long-term mortality through Kaplan-Meier analyses. We calculated the number of person-years of each individual patient from the date of ICH to the date of death or the date of final follow-up. We calculated cumulative mortality at 1, 5 and 10 years with 95% confidence intervals following the index ICH. Additionally, we calculated the annual risk of mortality with the following formula: $1-([1-Ic]^{[1/n]})$, where Ic is the cumulative mortality at n (number) of years after index event.

We calculated standardized mortality ratios (SMRs) by dividing the observed deaths in our cohort with the number of expected deaths or peers from the general French population, matched by age, sex and calendar year. The expected mortality rates were retrieved from the global Human Mortality Database (http://www.mortality.org).[194]

We used dichotomized variables for the MRI markers. Global cerebral atrophy was scored as absent (0-1) and present (2-3), white matter hyperintensities as absent (0-1) or present (2-3), and lacunes and cerebral microbleeds as absent or present.

We assessed the association of baseline characteristics with long-term mortality through Cox Proportional Hazard models, expressed through hazard ratios with 95% confidence intervals and corresponding p-values. First, we tested the association of all baseline characteristics with long-term mortality through univariate cox-regression analyses. We subsequently added all characteristics with a univariate p-value of <0.10 simultaneously into a multivariable cox proportional hazards model. The area under the curve of the multivariable prediction model was calculated through Harrell's C-statistic. Assumption of proportionality in the cox-regression model was evaluated and confirmed through calculating Schoenfeld residuals. Finally, we performed descriptive analyses for the different causes of death and calculated mean time to death for each category.

Statistical significance was set at 0.05 with two-sided p-values for all analyses. We performed statistical analyses with Excel (Microsoft Office version 16.28), SPSS (IBM version 26) and R Project for Statistical Computing.

Ethics Protocol Approval and Patients Consent

The study protocol was regarded as observational by the Internal Review Board of the Lille University Hospital, which granted ethics approval for this study. Patients, or their relatives or primary caregiver, gave informed consent for follow-up.

Data availability

The raw and anonymized data used in this study can be shared upon request from a qualified investigator and authorization of our IRB.

Results

Patient inclusion

Of the 560 patients with spontaneous ICH included in the PITCH Cohort, 116 (20.7%) were between 18 and 55 years at the time of ICH. Forty-one patients (35.3%) were excluded because they died within 30 days of their index event. This resulted in a cohort of 75 patients (Figure 1).

Baseline clinical and radiological characteristics

Of the 75 patients included in this study, 56 (74.7%) were men. The median age was 50 (IQR 44-53) years. Table 1 summarizes clinical and radiological baseline characteristics. MRI-scans were performed in 64 patients (85.3%), with a median ICH-MRI interval of 6 (IQR 3-9.8) days.

All-cause long-term mortality

During a median follow-up period of 8.2 (IQR 5.0-10.1) years, 26 patients died (34.7%). In the first year following the index ICH 5 patients (6.7%, 95% CI 2.8-15.3) had died and after 5 years 16 patients (21.7%, 95% CI 13.9-33.0) had died. After 10 years, the cumulative mortality was 37.2% (95% CI 27.0-49.8). (Figure 2, panel A) The mean annual mortality risks remained stable over time.

The standardized mortality ratio (SMR) was 13.0 (95% CI 8.5-18.0, p<0.001) for the young ICH patients compared to matched peers from the general population. The SMR was 15.7 (95% CI 9.4-22.7, p<0.001) for men and 8.3 (95% CI 2.8-15.2, p<0.001) for women.

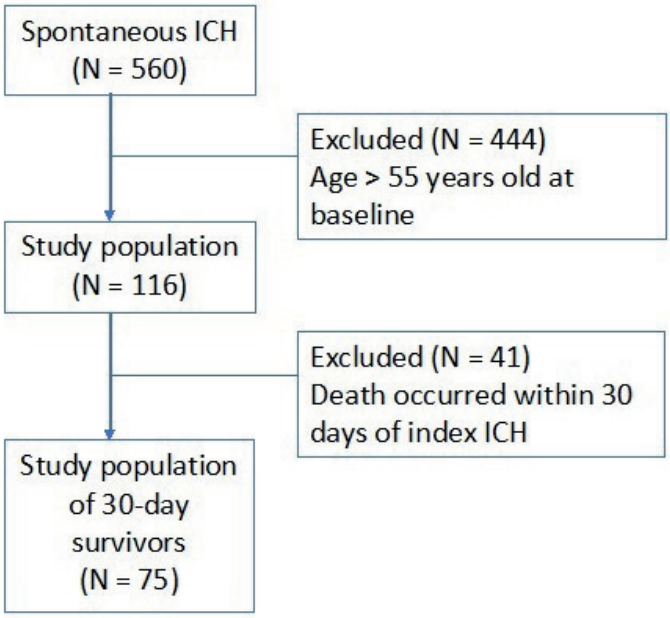


Figure 1: Flowchart of patient inclusion:
ICH = intracerebral hemorrhage, N = number.

Causes of long-term mortality

The cause of death was identified in 20 out of 26 patients (76.9%). Seven patients died from a vascular cause (35%) after a median period of 1.1 (inter quartile range [IQR] 0.3-4.8) years. Three patients died of long-term complications of the index ICH. Four patients died from a new stroke, a recurrent ICH in two and acute neurological worsening attributed to a new stroke of undetermined type in two. Thirteen patients died from a non-vascular cause (65%) after a median period of 5.0 (IQR 2.1-7.2) years (Table 2). Three were due to sepsis, three to metabolic disorders, in all cases the result of liver failure due to excessive alcohol consumption and seven were due to malignancy. Five patients died from lung cancer and two from hepatic carcinomas. All were smokers and six out of seven had a history of excessive alcohol consumption. The cancer had been diagnosed before ICH in one patient, diagnosed in the acute stage of the ICH in one patient, and diagnosed during follow-up in the other five.

Baseline clinical and radiological characteristics associated with long-term mortality

In univariable analysis global atrophy on MRI was the only significant predictor of long-term mortality with a hazard ratio of 4.7 (95% CI 1.8-12.5) (Table 3). In multivariable analysis, including pre-ICH dependency (HR 3.4, 95% CI 1.0-11.0), excessive alcohol consumption (HR 3.3, 95% CI 1.1-10.2), and global cerebral atrophy (HR 3.0, 95% CI 1.1-8.6) in the model, all three were independently associated with long-term mortality (Table 4 & Figure 2 panels B-D). The fit of this model was good, with an area under the curve of 0.7 (Harrell's C). The separate SVD markers or SVD score were not associated with long-term mortality.

Table 1: Baseline clinical and radiological characteristics of 30-day survivors of ICH in patients 18-55 years

Demographics		**Neurological status at baseline**	
Total	75 (100)	Mean NIHSS (SD)	11.5 (9.2)
Mean age, years (SD)	47.8 (7.2)	**CT Characteristics**	
Male sex	56 (74.7)	Location ‡	
≥8 Years of education †	39 (54.9)	Brainstem	13 (17.3)
mRS pre-ICH > 2	9 (12.0)	Cerebellar	2 (2.7)
Medical history		Deep	42 (56.0)
Arterial hypertension	37 (49.3)	Lobar	23 (30.7)
Diabetes mellitus	9 (12.0)	Undetermined	1 (1.3)
Hypercholesterolemia	13 (17.3)	Intraventricular haemorrhage	22 (29.3)
Smoking	34 (45.3)	ICH-volume (mL); mean (SD) §	18.3 (21.7)
Excessive alcohol consumption	31 (41.3)	**MRI features**	
Previous ICH	7 (9.3)	MRI Performed during admission	64 (85.3)
Previous ischaemic stroke	5 (6.7)	White matter hyperintensities	19 (29.7)
Previous TIA	2 (2.7)	≥1 Lacunes	22 (34.4)
Previous myocardial infarction	4 (5.3)	≥1 Microbleeds	27 (42.2)
Treatment used at baseline		Global cortical atrophy	11 (17.2)
Antihypertensive therapy	29 (38.7)	Simple SVD score ‖	
Statins	10 (13.3)	Simple SVD score 0	32 (50.0)
Antiplatelet therapy	13 (17.3)	Simple SVD score 1	16 (25.0)
Oral anticoagulation therapy	3 (4.0)	Simple SVD score 2	9 (14.1)
		Simple SVD score 3	7 (10.9)

Data listed are numbers (%) or median (IQR), unless otherwise specified. † Level of education known in 71 patients, % out of known number of patients. ‡ six cases with multiple ICH locations, therefore this adds up to 81 ICH-locations. § ICH volume calculated with the AxBxC/2 method. ‖ simple SVD score calculated according to Staals, et al (2010).[225]

Abbreviations: ICH = intracerebral haemorrhage, mRS = modified Rankin Score, TIA = transient ischaemic attack

Table 2: Causes of death in 30-day survivors of ICH aged 18 to 55 years old

	N (%)	Median time to death, years (IQR)
Total	26 (100)	4.5 (1.4-6.6)
Vascular death	7 (26.9)	1.1 (0.3-4.8)
Neurovascular	7 (26.9)	
Death due to complications of index stroke	3 (11.5)	
Death due to a new stroke	4 (15.4)	
Other vascular	0 (0.0)	
Coronary death	0 (0.0)	
Other vascular event (e.g. pulmonary embolism)	0 (0.0)	
Non-vascular death	13 (50.0)	5.0 (2.1-7.2)
Infection-related death	3 (11.5)	
Cancer or malignant hemopathies	7 (26.9)	
Metabolic disorder	3 (11.5)	
Unknown	6 (23.1)	4.9 (2.0-6.5)

Abbreviations used: IQR = interquartile range

Table 3: Univariable analyses of possible predictors of long-term mortality in young 30-day survivors of ICH

Demographics	**Patients who died at end of follow up**	**Survivors at end of follow up**	**p-value**	**Hazard ratio (95% CI)**
Total	N = 26	N = 49		
Mean age, years (SD)	49.9 (4.5)	46.7 (8.03)	0.105	1.1 (1.0-1.2)
Male sex	20 (76.9)	36 (73.5)	0.812	1.2 (0.5-2.8)
≥ 8 Years of education †	10 (38.5)	29 (59.2)	0.126	0.5 (0.2-1.2)
mRS pre-ICH >2	5 (19.2)	4 (8.16)	*0.087*	*2.4 (0.9-6.3)*
Medical history				
Arterial hypertension	15 (57.7)	22 (44.9)	0.361	1.4 (0.7-3.1)
Diabetes mellitus	4 (15.4)	5 (10.2)	0.496	1.5 (0.5-4.2)
Hypercholesterolemia	4 (15.4)	9 (18.4)	0.839	0.9 (0.3-2.6)
Smoking	15 (57.7)	19 (38.8)	0.119	1.9 (0.9-4.1)
Excessive alcohol consumption	1	16 (32.7)	*0.061*	*2.1 (1.0-4.6)*
Previous ICH	4 (15.4)	3 (6.1)	0.180	2.1 (0.7-6.0)
Previous ischaemic stroke	2 (7.7)	3 (6.1)	0.851	1.2 (0.3-4.9)
Previous myocardial infarction	2 (7.7)	2 (4.1)	0.351	2.0 (0.5-8.4)

Table 3: Continued

Demographics	Patients who died at end of follow up	Survivors at end of follow up	p-value	Hazard ratio (95% CI)
Treatment used at baseline				
Antihypertensive therapy	12 (46.2)	17 (34.7)	0.323	1.5 (0.7-3.2)
Statins	2 (7.7)	8 (16.3)	0.370	0.5 (0.1-2.2)
Antithrombotic therapy	7 (26.9)	9 (18.4)	0.403	1.5 (0.6-3.5)
Neurological status at presentation				
Mean NIHSS (SD)	10.0 (9.7)	12.2 (8.9)	0.253	1.0 (0.9-1.0)
ICH characteristics at CT				
Deep location	15 (57.7)	37 (75.5)	0.136	0.6 (0.3-1.2)
Intraventricular haemorrhage	8 (30.8)	14 (28.6)	0,776	1.1 (0.5-2.6)
Mean ICH-volume ‡ (SD)	16.9 (24.7)	19.0 (20.2)	0,594	1.0 (1.0-1.0)
MRI Features				
White matter hyperintensities	7 (38.9)	12 (26.1)	0.280	1.7 (0.7-4.4)
≥1 Lacunes	8 (44.4)	14 (30.4)	0.177	1.9 (0.8-4.9)
≥1 Microbleeds	7 (38.9)	20 (43.5)	0.172	1.8 (0.8-4.4)
Global cortical atrophy	7 (38.9)	4 (8.7)	***0.002***	***4.7 (1.8-12.5)***
Simple SVD score || ≥ 1	9 (34.6)	23 (46.9)	0.96	1.0 (0.4-2.6)
Simple SVD score || ≥ 2	7 (34.6)	9 (22.4)	0.168	2.0 (0.8-6.0)
Simple SVD score || ≥ 3	3 (11.5)	4 (8.2)	0.538	1.5 (0.4-5.1)

Data listed are numbers (%), unless otherwise specified. † Level of education known in 71 patients, % out of known number of patients. ‡ ICH volume calculated with the AxBxC/2 method. || simple SVD score calculated according to Staals, et al (2010) and hazard ratio's compared to Simple SVD score of 0.[225]

Table 4: Multivariable analysis of predictors associated with long-term mortality in 30-day survivors of ICH

	Hazard ratio (95% CI)	p-value according to multivariable cox-regression
Clinical and radiological predictors †		
mRS pre-ICH >2	3.4 (1.0-11.0)	**0.044**
Excessive alcohol consumption	3.3 (1.1-10.2)	**0.039**
Presence of global cortical atrophy	3.0 (1.1-8.6)	**0.039**

† Predictors were chosen for the multivariable model if p<0.1 in the univariate cox-regression analyses (table 2).

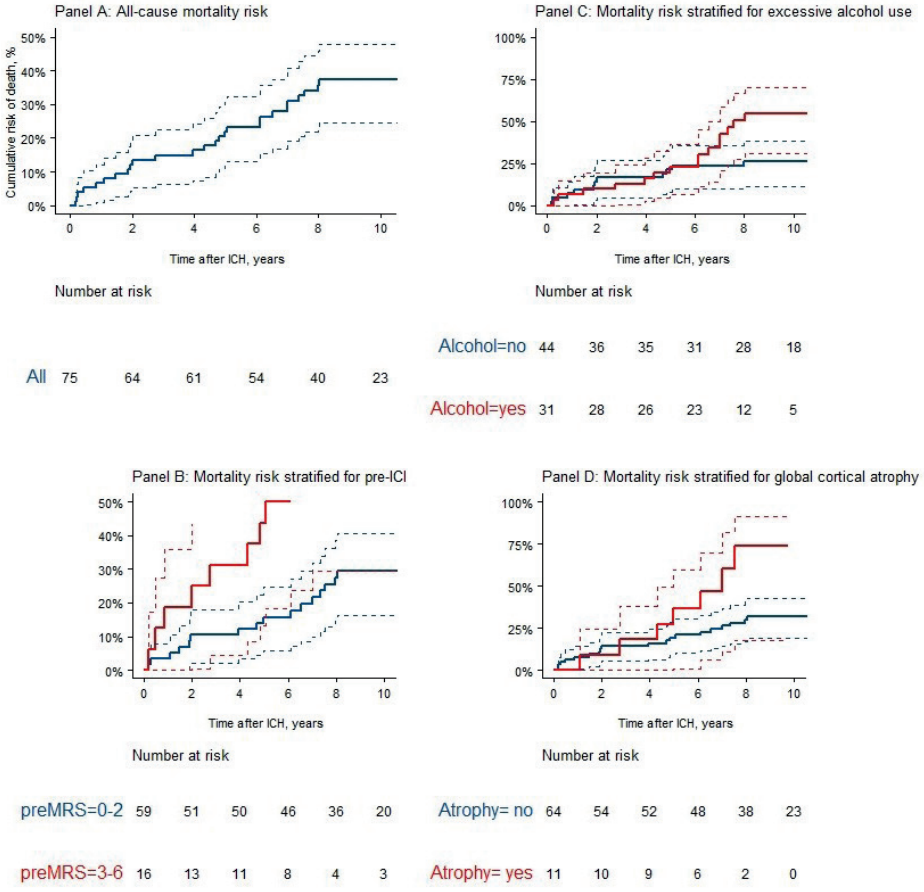


Figure 2: All-cause mortality risk:

(a) All-cause mortality risk. (b) All-cause mortality risk stratified for mRS pre-ICH. (c) All-cause mortality risk stratified for excessive alcohol consumption at baseline. (d) All-cause mortality risk stratified for global cortical atrophy at baseline. Dotted lines represent 95% confidence intervals. P-values according to log-rank analysis.

Discussion

In a prospective cohort of 75 consecutive young 30-day survivors of ICH, we found a substantial risk of long-term mortality of around 37%, which is 13 times higher compared to peers from the general population. Causes of death were vascular disease in one out of four patients and non-vascular causes, including infections, malignancies, and metabolic disorders in half of patients. Independent predictors

of death were excessive alcohol consumption at baseline, pre-stroke dependency and global cortical atrophy on MRI.

The long-term risk of mortality in young 30-day survivors of ICH in our study was higher than in two previously published hospital-based prospective cohort studies. One Finnish study found a cumulative mortality of 9.5% in a median follow-up of 9.7 years and a Dutch study found a cumulative mortality of 12.8% during a mean follow-up of 11.3 years.[23,213] It is also higher than in one Dutch population-based study, that demonstrated a 10-year cumulative mortality of 15.7% in young ICH survivors and a SMR of 8.4 (95% CI 7.4-9.3).[166] This could be explained in several ways. First, our inclusion-criteria differed from the previous studies in upper age-limit and causes of ICH. We used an upper age limit of 55 years instead of 49 in the three previously mentioned studies. Higher age was positively associated with a higher risk of mortality in the Dutch population-based and hospital-based study.[166,213] However, age was not a significant predictor of the risk of long-term mortality in the Finnish study, nor in our own study.[23] Second, in our study all patients with secondary causes of ICH, such as vascular malformations, were excluded. Whereas in the previous three studies, ICH due to secondary causes were included. Third, the patients in our study may have had a higher background mortality-risk, independent of the ICH. This study was carried out in the north of France, where the proportion of smokers and excessive alcohol consumption is high compared to other European places. [216] The proportion of excessive alcohol users in our cohort was higher than the Dutch hospital-based cohort. [213] The Finnish study and Dutch population-based study did not report smoking or alcohol use.[23,166]

This study is the first to include functional status before ICH and MRI-characteristics of SVD as predictors of long-term mortality in young ICH survivors. These factors might be relevant for predicting long-term mortality because they reflect early brain damage due to vascular risk factor burden and underlying health conditions. Both pre-stroke dependency and cerebral global atrophy were found to be predictors of long-term mortality in the PITCH cohort when including 30-day survivors of all ages, as well as higher age, male sex, higher NIHSS at baseline and any recurrent stroke or dementia during follow-up.[223]

In these young 30-day ICH survivors, cerebral atrophy was the only radiological predictor of long-term mortality. An explanation could be that cerebral atrophy can be considered as an expression of severe brain damage secondary to both cerebral small vessel disease and neurodegeneration (e.g. Alzheimer disease type) or associated to excessive alcohol consumption.

We have also shown that pre-stroke dependency and excessive alcohol consumption at baseline are independently associated with a higher long-term mortality risk. Excessive alcohol consumption was not found to be predictive of long-term mortality in the PITCH cohort of all ages and therefore may be specific to this young subgroup of this cohort.[223] Previously, excessive alcohol consumption has been shown to be associated with a higher mortality risk in ICH patients of all ages.[216,226]

The Finnish hospital-based study found male sex and diabetes at baseline to be predictors of long-term mortality, however they did not take alcohol use, mRS pre-ICH or MRI-markers into account.[23] The Dutch population-based study found age, male sex, a higher number of comorbidities (Charlson Comorbidity index) and longer hospital stay to be associated with an increased risk of long-term mortality.[23,166,193] The Charlson Comorbidity index includes various diseases such as liver disease, dementia and cardiovascular disorders. These may reflect liver failure due to excessive alcohol consumption and cerebral damage or atrophy due to cardiovascular burden or neurodegenerative conditions. Therefore, the predictive value of higher comorbidity found in the Dutch population-based study may mirror the predictive value of excessive alcohol consumption, mRS pre-ICH >2 and global cerebral atrophy found in our study.

Our finding that non-vascular causes were the main cause of death in our population of young ICH patients, supports the hypothesis that the increased long-term mortality rate is driven by underlying risk-factors and/or health conditions and not factors directly related to the ICH itself. The high number of malignancies and alcohol-related deaths may be explained by the high percentage of shared risk-factors such as smoking for ICH as well as cancer, and excessive alcohol consumption for ICH as well as metabolic deaths. Additionally, cancer influences the coagulation system and therefore may play a role in causing the ICH, and therefore ICH may even be a first symptom of an underlying malignancy.[17,156] In the Dutch hospital-based cohort, the percentage of vascular deaths was higher reaching 70%, whereas in the population-based cohort the percentage of vascular deaths was similar to our cohort with 29.8%.[166,213] Cause of death was not reported in the Finnish study.[23]

Strengths of our study are it is prospective design with systematic and detailed data collection, the long follow-up period, and the fact we were able to study small vessel disease on MRI in most patients. However, this study also has some limitations. First, although the total number of patients was large for this specific subgroup, the absolute number was still limited. A second limitation is that we did not have any information on illicit drug use in our study population, which is a relevant risk-

factor for ICH at a young age.[227] Third, MRI was not performed in all patients and therefore there is a risk of underestimating the association between MRI-markers and mortality risk. Fourth, we acknowledge a partial overlap between this cohort and the one of a recent published study.[223] However, the target population and research question are different.

Conclusions

The high long-term mortality we found in these young ICH survivors is worrisome and needs to be clarified further in prospective studies with larger patient numbers that combine extensive clinical and MRI phenotyping with a long follow-up period. Our results demonstrate that vascular risk factors such as excessive alcohol use are a serious issue in this population and need to be addressed. Additionally, our results show that these young ICH survivors remain at increased mortality risk of vascular and non-vascular death years after their ICH and therefore long-term multidisciplinary follow-up is needed.

Chapter IX

Long-term Risk of Bleeding and Ischemic Events After Ischemic Stroke or Transient Ischemic Attack in Young Adults

Published as: Verhoeven JI, van Lith TJ, Ekker MS, Hilkens NA, Maaijwee NAM, Rutten-Jacobs LCA, Klijn CJM, de Leeuw FE. *Long-term Risk of Bleeding and Ischemic Events After Ischemic Stroke or Transient Ischemic Attack in Young Adults.* Neurology. 2022 Aug 9;99(6):e549-e559. Epub 2022 Jun 2.

Abstract

Background and objectives: Guidelines recommend antithrombotic medication as secondary prevention for patients with ischemic stroke or transient ischemic attack (TIA) at young age based on results from trials in older patients. We investigated the long-term risk of bleeding and ischemic events in young patients after ischemic stroke or TIA.

Methods: We included 30-day survivors of first-ever ischemic stroke or TIA aged 18-50 years from the Follow-Up of TIA and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study, a prospective cohort study of stroke at young age. We obtained information on recurrent ischemia based on structured data collection from 1995 until 2014 as part of the FUTURE study follow-up, complemented with information on any bleeding and ischemic events by retrospective chart review from baseline until last medical consultation or June 2020. Primary outcome was any bleeding, secondary outcome any ischemic event during follow-up. Both were stratified for sex, age, etiology, and use of antithrombotic medication at discharge. Bleeding and ischemic events were classified according to location and bleeding events also by severity.

Results: We included 544 patients (56.1% women, median age of 42.2; interquartile range [IQR] 36.5-46.7 years) with a median follow-up of 9.6 (IQR 2.5-14.3) years. Ten-year cumulative risk of any bleeding event was 21.8% (95% confidence interval [CI] 17.4-26.0) and 33.9% (95% CI 28.3-37.5) of any ischemic event. Risk of bleeding was higher in women with a cumulative risk of 28.2% (95% CI 21.6-34.3) versus 13.7% (95% CI 8.2-18.9) in men ($p<0.01$), mainly due to gynecological bleeds. Female sex ($p<0.001$) and age between 40 and 49 years old ($p=0.04$) were independent predictors of bleeding.

Discussion: Young patients after ischemic stroke or TIA have a substantial long-term risk of both bleeding (especially women) and ischemic events. Future studies should investigate the effects of long-term antithrombotics in young patients, taking into account the risk of bleeding complications.

Introduction

Two million people, aged between 18 and 50 years, are yearly affected by stroke worldwide.[228] The incidence of stroke in young adults has been rising over the past two decades, whereas the incidence of stroke in older patients has remained stable or decreased.[132] For these young patients, long-term prognosis is particularly relevant because they still have decades to live. They remain at risk of recurrent ischemic events, for which they are prescribed antithrombotic medication for the rest of their lives, based on information from randomized clinical trials in which young patients were underrepresented.[25,26,229-232]

At the same time, the long-term use of anti-thrombotic secondary preventive medication also carries a risk of bleeding complications. However, specifically in young patients, the long-term risk of recurrent ischemia has a high interindividual variability depending on the cause of the ischemic stroke or TIA.[132,166,208,233] Despite these differences, young patients often receive antithrombotic medication according to a "one-size-fits-all" approach.[8] In older patients with an ischemic stroke, the benefits of antithrombotic medication have been shown to outweigh the side effects.[234] Whether this also holds true for young adults with ischemic stroke or TIA, and whether they should continue the antithrombotic treatment life-long, is unknown. A better understanding of the balance between these risks may lead to more individualized secondary preventive treatment options after stroke in the future.

The aim of this study was to investigate the long-term risk of bleeding events and risk of ischemic events in young adults after a first-ever ischemic stroke or TIA, stratified for age, sex, cause of stroke and use of antiplatelet therapy at discharge.

Methods

Patients

This work is an extension of the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study, a prospective cohort study of patients with an ischemic stroke, TIA or intracerebral hemorrhage (ICH) at young age.[29] Details of the study have been described previously.[208] In short, the FUTURE study comprises 1,005 consecutive patients aged 18-50 years with a first-ever TIA, ischemic stroke, or ICH, admitted to the Radboud University Medical Centre Nijmegen between 1980 and 2010.[208] For this study, we included

patients with first-ever ischemic stroke or TIA between 1995 and 2010, who survived at least 30 days after their index event. TIA was defined as a rapidly evolving focal neurological deficit without positive phenomena, with vascular cause only, persisting less than 24 hours. Stroke was defined as a focal neurological deficit lasting more than 24 hours. Stroke was further classified into ischemic stroke and ICH based on radiological findings.[29,208] This time window was chosen because for patients included before 1995, the original patient medical files were no longer available. Therefore, information regarding bleeding events could not be reliably ascertained.

Baseline data collection

Information on demographics, the index event, presence of vascular risk-factors and antithrombotic medication at discharge was systematically collected at baseline.[29] Presence of vascular risk-factors was defined as the risk-factor either being present in the medical history of the patient or if the risk-factor was identified during admission for the index event. Definitions used to define the presence of vascular risk-factors have been described previously.[208] Antithrombotic medication at discharge was categorized into 3 groups: "no antithrombotic medication", use of "only antiplatelet therapy" and the use of "other antithrombotic medication" (e.g., vitamin K antagonist, direct oral anticoagulant monotherapy, or one of the before mentioned combined with antiplatelet therapy).

Cause of the index event was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria,[107] and severity was assessed with the NIH Stroke Scale (NIHSS).[235] Functional status at discharge was determined according to the modified Rankin Scale (mRS) and dichotomized with an mRS-score of 0-2 indicating functional independence at discharge and an mRS-score of 3-5 meaning functional dependence.

Outcomes

The primary outcome of this study was the occurrence of a first bleeding event that required a visit to the hospital (a visit to the outpatient clinic, a visit to the emergency room or a hospital admission) during follow-up. We included spontaneous and trauma-related bleeding events as well as bleeding events secondary to surgery (defined as an unexpected and unnecessary bleeding complication for this type of surgical procedure). Bleeding events were classified in 3 ways. First, by severity according to the Bleeding Academic Research Consortium (BARC) criteria for bleeding events (eTable 1, links. lww.com/WNL/C100), distinguishing 6 levels of clinical severity ranging from BARC type 0 (no bleeding) to BARC type 5 (fatal

bleeding).[236] In our study, BARC type 0 and 1 were not taken into account because they do not require a hospital visit. Minor bleeding was defined as bleeding with BARC types 2 to 3a, and major bleeding was defined as bleeding with BARC types 3b to 5. Second, we classified bleeding events by type (spontaneous, surgery-related or trauma-related) and third, by location (intracranial, intraocular, pulmonary, pericardial, gastrointestinal, retroperitoneal, urogenital, soft-tissue and anemia due to bleeding of an unknown location).

Secondary outcome was the occurrence of any non-fatal or fatal ischemic event during follow-up, which was defined as a composite vascular event of recurrent stroke, TIA, myocardial infarction or peripheral artery disease, whichever occurred first. Definitions of ischemic events can be found in eTable 1 (links. lww.com/WNL/C100). All ischemic events reported by the patients were verified by a neurologist or cardiologist.(18) There were no cases of stroke not further specified as hemorrhagic or ischemic or unexplained sudden (assumed vascular) deaths during follow-up.

Follow-up

For follow-up we used a 2-staged approach. First, we obtained information on recurrent ischemia from the available follow-up data from the FUTURE study that were systematically collected in 2010 through a structured interview at the outpatient clinic and in 2014 through a structured interview by telephone. At these two time-points, only ischemic events were collected.[208,237] Second, we complemented these data with information on any bleeding and ischemic events by retrospective chart review between date of index event and June 1, 2020. Bleeding and ischemic events were only recorded when diagnosed by a medical specialist. Duration of follow-up was defined as the time between the index event and either the date of death or the date of last medical consultation registered in the patient medical files

Statistical analysis

We calculated cumulative risks with 95% CI for primary and secondary outcomes using Kaplan-Meier analyses. We stratified all analyses for sex, age at index event, stroke etiology and antithrombotic medication used at discharge. We tested for group differences with single log-rank analysis for dichotomous variables and multiple comparison log-rank analysis correcting for multiple testing through the Bonferroni-Holm method for variables with more than two groups, such as stroke etiology. In the survival analyses, patients were subdivided into 3 age categories: 18-29, 30-39 and 40-49 years.

As sensitivity analyses, we performed the long-rank analyses for stroke etiology according to TOAST groups excluding patients using other antithrombotic medication at baseline. Similarly, we performed the log-rank analyses for the use of antithrombotic medication at discharge excluding patients with stroke or TIA due to cardio-embolism. This was performed because patients with stroke or TIA due to cardio-embolism more often use other antithrombotic medication, and therefore, these groups overlap considerably. Of the 61 patients using other antithrombotic medication in our study population, 4 strokes or TIAs were due to large artery disease, 30 due to cardio-embolism, 3 due to small vessel disease, 11 due to rare causes, 11 due to cryptogenic stroke and 2 due to multiple causes. Of 69 patients with stroke or TIA due to cardio-embolism, 36 used other antithrombotic medication, 3 used no antithrombotics and 30 used only antiplatelet therapy.

The survival plots were curtailed at 15 years because of the limited patient numbers thereafter, whereas all events were retained in the analyses. We calculated annual risks of bleeding and ischemic events using the following formula: 1-([1 – Ci]^[1/n]). Ci was the cumulative incidence of the event at n years and n was the number of years after the index event, obtained by Kaplan-Meier analysis.

We assessed possible predictors of any bleeding event and any ischemic event by Cox proportional hazards univariable analyses, expressed as hazard ratios (HR) with 95% CI. We confirmed proportionality of all assessed predictors through plotting Schoenfeld residuals against time. All predictors with a p-value of <0.2 in univariable analysis were included into a multivariable model. We assessed the predictors in the full study population as well as in the subgroup of patients using only antiplatelet therapy at baseline, because we hypothesized that the bleeding risk would be different in patients with only antiplatelet therapy compared to other antithrombotic medication. Differences in the median follow-up duration for patients without any event, with any bleeding event, and with any ischemic event were tested with the Mann-Whitney U test to evaluate whether risk differences between the groups could be explained by differences in duration of follow-up.

Two-sided P values less than 0.05 were considered statistically significant. Data were analyzed with SPSS Software version 22 (IBM), R version 3.6.2 (packages survival, survminer; R Project for Statistical Computing) and GraphPad Prism version 5.03.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients who participated in the follow-up assessments of 2010 and 2014 of the FUTURE study signed an informed consent form.[22,208] For this study, the Medical

Review Ethics Committee region Arnhem-Nijmegen gave their approval and granted a waiver of consent to collect information in the patient files for follow-up up to 2020.

Data availability

The raw and anonymized data used in this study can be shared upon request, for analysis with individual patient data. Written proposals can be sent to the corresponding author and will be assessed by the research group and the medical ethics committee Arnhem-Nijmegen. A data sharing agreement will be put in place before any data is shared.

Results

Baseline characteristics

Of the 709 patients enrolled in the FUTURE study after 1995, 544 met our inclusion criteria (eFigure 1). The median age at the time of the index event was 42.2 (Interquartile range [IQR] 36.5-46.7) years, and 305 (56.1%) were women. Of the 544 patients, 359 (66.0%) had an ischemic stroke and 185 (34.0%) a TIA. Patient characteristics are listed in Table 1. The median duration of follow-up was 9.6 (IQR 2.5-13.4) years.

Cumulative risk of bleeding events

During follow-up, 152 bleeding events occurred in 98 patients (18.0%). Thirty-one patients (5.7%) had more than 1 bleeding event. Of the 152 bleeding events, 115 were minor (75.6%) and 37 (24.3%) were major bleeds (Table 2). Gynecological bleeds were the most common (N = 57; 37.5%) of which 38 (25.0%) required a hospital visit. After 10 years, 82 patients had at least 1 bleeding event (cumulative risk of 21.8%; 95% CI 17.4-26.0) (Figure 1, panel A). In the first year after ischemic stroke or TIA the risk of bleeding was highest (3.6%; 95% CI 1.9-5.2). After the first year, the annual risk declined to 2.4% at 10 years (95% CI 1.9-3.0) (Figure 1, panel B).

The cumulative risks of any minor or major bleeding are shown in Figure 2, panel A. The cumulative risk of any bleeding event (minor or major) increased, but not significant with age. (Figure 2, panel B). After 10 years, 59 out of 305 women (28.2%; 95% CI 21.6%- 34.3%) and 23 out of 239 men (13.7%; 95% CI 8.2-18.9; $p<0.01$) had developed any bleeding event (Figure 2, panel C). Risk was higher for women than men, both for major ($p=0.03$) and minor bleeds ($p<0.01$). The cumulative risk of any bleeding event did not differ between ischemic stroke

vs TIA as index event (p=0.13). Patients with stroke or TIA due to cardio-embolism had a significantly higher risk of bleeding during follow-up compared with patients with stroke due to large artery disease (p<0.01), small vessel disease (p=0.03), rare causes (p<0.01), and cryptogenic stroke (p<0.01). Patients using other antithrombotic medication had a higher cumulative risk of bleeding compared to patients using only antiplatelet therapy at discharge (p<0.001) (Figure 2, panel D). When excluding patients using other antithrombotic medication at baseline (N=61), the difference in risk of bleeding between stroke or TIA due to cardio-embolism compared to all other groups disappeared. When excluding patients with stroke or TIA due to cardio-embolism (N=69), patients using other antithrombotic medication retained a higher risk of bleeding compared with patients using only antiplatelet therapy at discharge (p=0.03).

Univariable and multivariable predictors of bleeding eventsPredictors (univariable) of any bleeding are listed in eTable 2 and eTable 3. In the multivariable analyses, female sex (HR 2.6; 95% CI 1.6-4.0) and an age of 40-49 years old (HR 2.3; 95% CI 1.0-4.9) were independent predictors of any bleeding during follow-up (eTable 2). When we restricted the analysis to only antiplatelet users (N=430), female sex (HR 2.8; 95% CI 1.6-5.1) remained an independent predictor, in this subgroup also stroke or TIA due to cardio-embolism was an independent risk-factor for any bleeding during follow-up compared to cryptogenic stroke (HR 2.7; 95% CI 1.2-5.7) in multivariable analysis (eTable 3). Median duration of follow-up in those without an event was 7.1 (IQR 1.4-12.3) years and was significantly shorter compared with those with a bleeding event (11.6; IQR 8.9-14.1 years; p<0.001) and compared with patients with an ischemic event (11.2; IQR 6.3-14.8 years; p<0.001).

Cumulative risk of ischemic events

During follow-up, we observed 292 ischemic events in 161 (29.6%) patients. Of the 161 first ischemic events during follow-up, 62 were ischemic stroke (38.5%), 58 were TIA (36.0%), 31 were myocardial infarction (19.2%) and 10 were peripheral artery disease (6.2%) (Table 2). After 10 years 128 patients had had 1 ischemic event (cumulative risk 33.1%; 95% CI 28.3-37.6%) (Figure 1, panel A). In the first year, 57 patients already had 1 ischemic event (8.5%, 95% CI 6.7-10.2%); this annual risk stabilized in subsequent years at around 4% (Figure 1, panel B).

The risk of any ischemic event did not differ between age groups, sex or ischemic stroke or TIA as index event (Figure 3, panel B). The cumulative risk of any ischemic event was significantly higher for stroke or TIA due to large artery disease (p<0.01) and cardio-embolism (p<0.01) compared with cryptogenic stroke (Figure 3; panel C).

According to log-rank analysis, the type of antithrombotic therapy used at discharge did not modify the risk of recurrent vascular events.

Table 1. Baseline characteristics of all patients aged 18-49 years old at first-ever ischemic stroke or TIA

	Total	Men	Women	P-value[§]
Total	**544 (100)**	**239 (43.9)**	**305 (56.1)**	
Patient characteristics				
TIA	185 (34.0)	83 (34.7)	102 (33.4)	0.75
Ischemic Stroke	359 (66.0)	156 (65.3)	203 (66.6)	
Age at index event, mean (SD)	40.7 (7.4)	42.0 (7.0)	39.7 (7.7)	**<0.01**
Hypertension	179 (32.9)	85 (35.6)	94 (30.8)	0.24
Dyslipidaemia[*]	391 (71.9)	173 (72.4)	218 (71.5)	0.82
Diabetes mellitus	41 (7.5)	25 (10.5)	16 (5.2)	**0.02**
Smoking status[†]	253 (46.5)	106 (44.4)	147 (48.2)	0.38
Atrial fibrillation	6 (1.1)	4 (1.7)	2 (0.7)	0.28
Stroke etiology: TOAST classification				
(Likely) large artery disease	108 (19.9)	52 (21.8)	56 (18.4)	0.32
Cardioembolic cause	69 (12.7)	31 (13.0)	38 (12.5)	0.86
Small vessel disease	70 (12.9)	32 (13.4)	38 (12.5)	0.76
Rare causes	102 (18.8)	36 (15.1)	66 (21.6)	0.05
Cryptogenic	178 (32.7)	82 (34.3)	96 (31.5)	0.49
Multiple causes	17 (3.1)	6 (2.5)	11 (3.6)	0.46
Stroke severity				
NIHSS at admission	2 (0 – 5)	2 (0 – 6)	2 (0 – 5)	0.28
mRS 0-2 at discharge	455 (83.6)	199 (83.3)	256 (83.9)	0.85
mRS 3-5 at discharge	89 (16.4)	40 (16.7)	49 (16.1)	
Medication at discharge				
Antiplatelet therapy	430 (79.0)	184 (77.0)	246 (80.7)	0.29
Other antithrombotic therapy[‡]	61 (11.2)	39 (16.3)	22 (7.2)	**<0.01**
No antithrombotic medication	49 (9.0)	15 (6.3)	34 (11.1)	0.05
Unknown	4 (0.7)	1 (0.4)	3 (1.0)	0.42
Follow-up				
Follow-up time	9.6 (2.5 – 13.4)	9.6 (2.3 – 13.8)	9.5 (2.7 – 13.0)	0.58
Follow-up duration of ≥5 years	368 (67.6)	163 (68.2)	205 (67.2)	0.80
Follow-up duration of ≥10 years	253 (46.5)	115 (48.1)	138 (45.2)	0.19

Abbreviations: IQR = Interquartile range, mRS = modified Rankin Scale, NIHSS = NIH Stroke Scale, TIA = transient ischemic attack, TOAST = Trial of Org 10172 in Acute Stroke Treatment. Data are n (%) or median (IQR). Statistically significant values are given in bold. § Categorical data was tested with chi-squared analyses and continuous data with independent t-tests. * Dyslipidemia was missing in 58 cases (23 in men, 35 in women). † Smoking was missing in 12 cases (7 in men, 5 in women). ‡ Anticoagulant or other therapy entails vitamin K antagonists, low-molecular heparin, direct anticoagulants or a combination thereof.

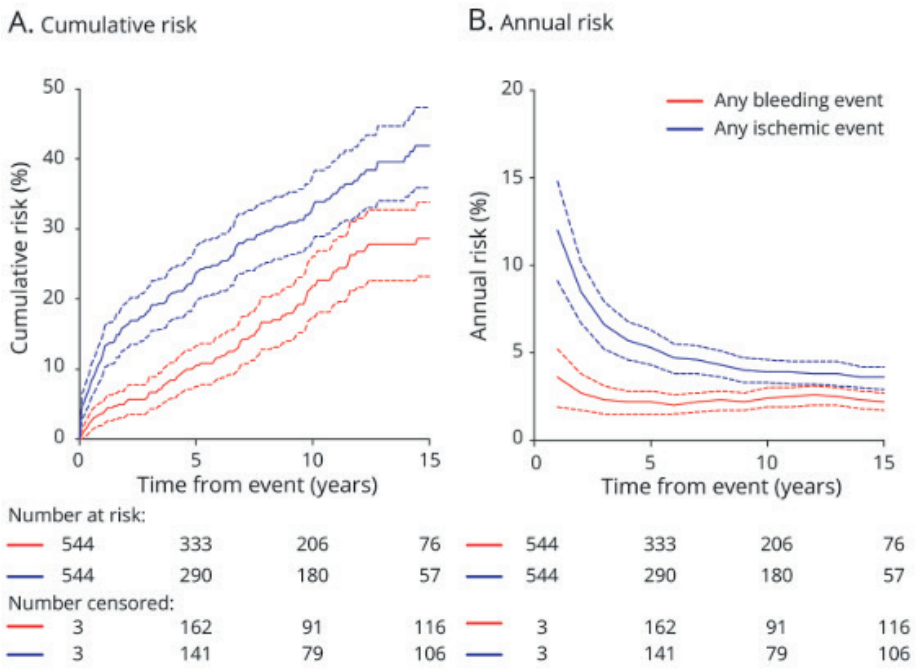


Figure 1: Risk of Any Bleeding Event and Ischemic Event During Follow-up
Dotted lines indicate 95% CIs.

Univariable and multivariable predictors of ischemic events

Based on the univariable Cox proportional hazards model, hypertension, diabetes mellitus, TOAST and types of antithrombotic medication were included in the multivariable model. Diabetes mellitus (HR 1.8; 95% CI 1.1-3.0; p=0.03), stroke or TIA due to large artery disease (HR 2.0; 95% CI 1.2-3.2; p<0.01) and cardioembolism (HR 2.8; 95% CI 1.6-5.0; p<0.01) compared with cryptogenic stroke remained significant independent predictors of any ischemic event during follow-up. Use of other antithrombotic medication was related to a lower risk of ischemic events compared with no antithrombotic medication (HR 0.4; 95% CI 0.2-0.8, p=0.01) (eTable 2, links.lww.com/WNL/C100). When restricting the analyses to patients using only antiplatelet therapy at discharge (N=430) in the multivariable model, stroke due to cardio-embolism (HR 2.5; 95% CI 1.3-4.8; p=0.01) remained an independent predictor of any ischemic event. In this subgroup, female sex was associated with a lower risk of recurrent ischemia (HR 0.7; 95% CI 0.5-1.0; p=0.03) (eTable 3).

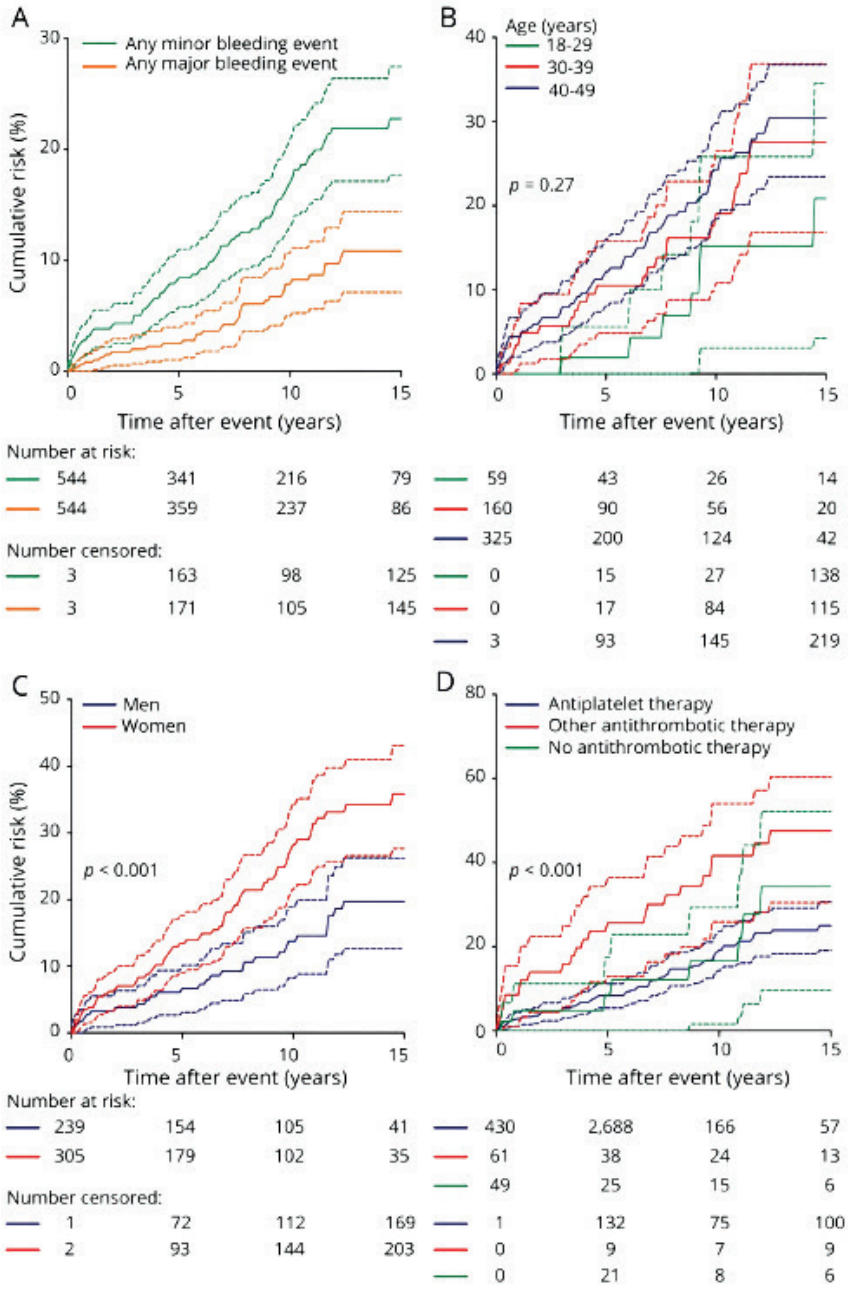


Figure 2: Cumulative Risk of Any Bleeding Stratified for Minor and Major Bleeding, Age, And Sex

p values reported in the figures are according to log-rank testing. *With pairwise comparison using log-rank analyses, antiplatelet therapy was statistically significant from other antithrombotic medication (p<.001); other pairwise comparisons between groups were not statistically significant. Dotted lines indicate 95% CIs.

Table 2: Bleeding and ischemic events during follow-up

	All events	Women	Men	**First-ever events**	Women	Men
Bleeding events						
Total of bleeding events	152	108 (71.1)	44 (28.9)	98	69 (70.4)	29 (29.6)
Severity*						
Minor	115 (75.7)	80 (74.0)	35 (79.5)	70 (71.4)	49 (71.0)	21 (30.4)
Type 2	101 (66.4)	72 (66.7)	29 (65.9)	64 (65.3)	45 (65.2)	19 (27.5)
Type 3A	14 (9.2)	8 (7.4)	6 (13.6)	6 (6.1)	4 (5.8)	2 (2.9)
Major	37 (24.3)	28 (25.9)	9 (20.5)	28 (28.6)	20 (29.0)	8 (11.6)
Type 3B+C	35 (23.0)	27 (25.0)	8 (18.2)	26 (26.5)	19 (27.5)	7 (10.1)
Type 5	2 (1.3)	1 (0.9)	1 (2.3)	2 (2.0)	1 (1.4)	1 (1.4)
Occurrence						
Surgery-related	20 (13.2)	12 (11.1)	8 (18.2)	12 (12.2)	6 (8.7)	6 (8.7)
Trauma-related	11 (7.2)	6 (5.6)	5 (11.4)	7 (7.1)	3 (4.3)	4 (5.8)
Spontaneous	121 (79.6)	90 (83.3)	31 (70.4)	79 (80.6)	60 (8.7)	19 (27.5)
Location						
Intracranial	9 (5.9)‡	6 (5.6)	3 (6.8)	7 (7.1)	4 (5.8)	3 (4.3)
Intraocular	5 (3.3)	4 (3.7)	1 (2.3)	4 (4.1)	3 (4.3)	1 (1.4)
Gastro-intestinal	21 (13.8)	12 (11.1)	9 (20.5)	11 (11.2)	6 (8.7)	5 (7.2)
Retroperitoneal	5 (3.3)	3 (2.8)	2 (4.5)	4 (4.1)	2 (2.9)	2 (2.9)
Pulmonary	12 (7.9)	6 (5.6)	6 (13.6)	7 (7.1)	4 (5.8)	3 (4.3)
Urogenital	71 (46.7)	68 (63.0)	3 (6.8)	47 (48.0)	46 (66.7)	1 (1.4)
Gynecological †	57 (37.5)	57 (52.8)	0	42 (42.9)	42 (61.0)	0
Soft tissue	23 (15.1)	8 (7.4)	15 (34.1)	15 (15.3)	4 (5.8)	11 (15.9)
Anemia due to bleeding of unknown location	3 (2.0)	1 (0.9)	2 (4.5)	1 (1.0)	0	1 (2.3)
Other location	3 (2.0)	0	3 (6.8)	2 (2.0)	0	2 (4.5)
Ischemic events						
Total of Ischemic events	292	144	148	161	86	75
Location						
Cerebral ischemia	205 (70.2)	109 (75.7)	96 (64.9)	120 (74.5)	66 (76.7)	54 (62.8)
(Recurrent) stroke	116 (39.7)	63 (43.8)	53 (35.8)	62 (38.5)	36 (41.9)	26 (30.2)
(Recurrent) TIA	89 (30.5)	46 (31.9)	43 (29.1)	58 (36.0)	30 (34.9)	28 (32.6)
Myocardial infarction	49 (16.8)	18 (12.5)	31 (20.9)	31 (19.2)	15 (17.4)	16 (18.6)
Peripheral artery disease	38 (13.0)	17 (11.8)	21 (14.2)	10 (6.2)	5 (5.8)	5 (5.8)

Abbreviations: BARC = Bleeding Academic Research Consortium, TIA = transient ischemic attack. Data are n (%). * Severity according to the BARC classification (eTable 1, links.lww.com/WNL/C100).(17) ‡ Of the 9 intracranial bleeding events, 7 were spontaneous, 1 was trauma related and 1 was surgery related. † Gynecological bleeds represent a subgroup of urogenital bleeding events.

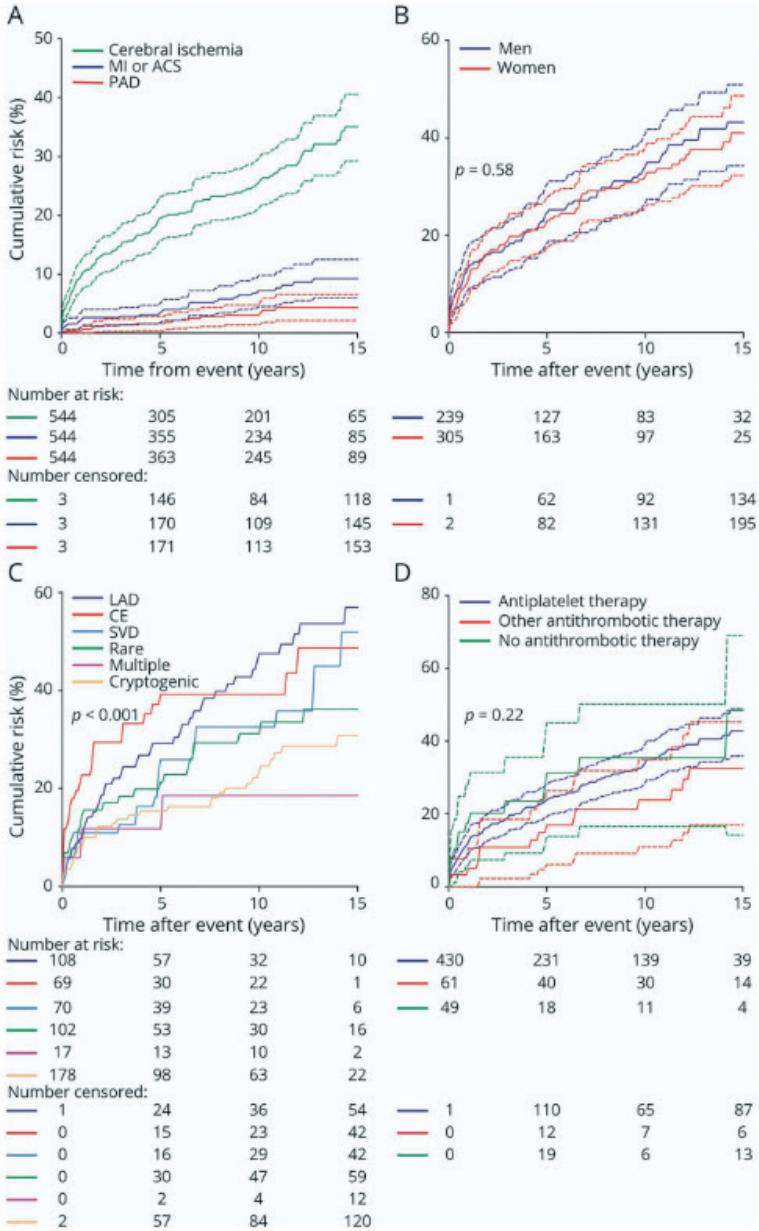


Figure 3: Cumulative Risk of Any Ischemic Event, Stratified for Type of Ischemia, Sex, And Etiology of Index Event

p values reported in the figures are according to log-rank testing. *For clarity, the CIs were left out of panel C; LAA was significantly different from CE ($p < 0.01$) and CE was significantly different from SVD ($p = 0.03$); other pairwise comparisons between groups were not statistically significant. Dotted lines indicate 95% CIs. CE = cardioembolic cause; LAA = (likely) large artery disease; SVD = small vessel disease.

Discussion

This study shows that in patients who experienced an ischemic stroke or TIA at young age, the cumulative risk of any bleeding event is almost as high as the cumulative risk of any new ischemic event after a median follow-up of almost 10 years. The risk of minor and major bleeding events was significantly higher in women than in men, which was largely driven by a high incidence of gynecological bleeds. Most bleeding events were minor. Older age (40-49 years) at the time of ischemic stroke or TIA was also an independent predictor of any bleeding event.

In our study population, 2 out of 10 patients with ischemic stroke or TIA at young age had at least 1 bleeding event and around 1 in 20 young stroke survivors had a major bleeding event in the first 10 years after their ischemic stroke or TIA. There are no previous studies focusing specifically on young patients after ischemic stroke or TIA. There have been two previous observational studies; both investigated a stroke population of all ages older than 18 years old.[27,238] In 1 registry-based study (mean age 74.5 years, mean duration of follow-up 2 years), the risk of any bleeding was 2.6 (95% CI 2.4-2.7) per 100 person-years (PY) after ischemic stroke and 2.4 (95% CI 2.3-2.5) per 100 PY in single antiplatelet users.[238] This is slightly higher than we found (2.0 [95% CI 1.6-2.4] per 100 PY in the overall group and 1.7 [95% CI 1.3-2.2] per 100 PY in only antiplatelet users), although the definition of bleeding was the same. The difference could be due to the higher mean age in the previous study and the shorter duration of follow-up because we have shown that the risk of bleeding is highest in the first year after stroke or TIA and declines thereafter.[239] Another observational study of patients (mean age of around 70 years old; median duration of follow-up 4.3 years) after ischemic stroke, TIA or acute myocardial infarction, showed an annual rate of any bleeding requiring medical attention of just under 2%.[27] Bleeding due to trauma or surgical procedures were excluded in this study, which may explain why the annual risk was slightly lower than the annual risk of any bleeding we found in our study population.

The increased risk of minor as well as major bleeding among women is a new finding and might be specific to young women receiving antithrombotic therapy because it was mostly due to excessive menstrual bleeding, which only occur in premenopausal women. Because almost all trials into antithrombotic medication as secondary prevention after stroke have excluded patients younger than 40 years, this probably explains why this risk of gynecological bleeding events has not been described before.[230,232] However, we could not compare this risk of gynecological bleeds in our population with the general population because we did not have

a control group and thus could not calculate the excess risk of gynecological bleeding events in young women after stroke or TIA. A previous Dutch study found an annual incidence of heavy menstrual bleeding of 9.3 (95% CI 8.5-10.2) per 1,000 person-years in pre-menopausal women at the general practitioner compared with 15.6 (95% CI 10.9-20.3) per 1,000 person-years we found.[240] Our finding of this sex-dependent high bleeding risk underscores the need to study adverse events specifically in patients who experience a stroke at young age, instead of extrapolating findings from studies performed in older patients. The increasing risk of any bleeding event with age has been described previously.[27,241] However, it is important to note that the oldest patients in our population represented the youngest patients in previous observational studies and randomized controlled trials.[26,27,238]

Strengths of our study were the large number of young patients with ischemic stroke or TIA considering the relative rarity of stroke at young age, the long period of follow-up and the standard way of classifying bleeding events according to the BARC criteria. All patients in the FUTURE study were seen in the Radboudumc in Nijmegen, the Netherlands. Our academic hospital serves as a tertiary referral center for a large area in the eastern part of the Netherlands. Because most patients with a stroke at young age usually are referred to a university medical center somewhere along the course of the disease, we most likely included the majority of patients in our catchment area. We therefore believe our results can be generalized to other Dutch patients with a stroke at young age, as well as to patients with a stroke at young age in other Western societies. In addition, this cohort was well-phenotyped, which allowed for relevant subgroup analyses.

This study also has some limitations. First, data-collection of outcomes was partly retrospective and single-center oriented. Which means that we may have missed events that took place in another hospital. We reduced this bias by limiting individual follow-up to the last moment the patient was seen in the hospital where they were followed-up after their TIA or stroke. This approach may have led to an underestimation of the number of bleeding and ischemic events.[208,237] This underestimation may be more pronounced for bleeding events than for ischemic events because between 1995 and 2014 ischemic events were also collected prospectively through patient interviews. On the other hand, limiting the follow-up to last medical evaluation may also have led to overestimation of bleeding and ischemic events because patients without events may have visited the hospital less and therefore had a shorter follow-up. Second, during the follow-up period patients could have switched or stopped treatment following new events or as a result

of changed guidelines. Therefore, we could only compare the effect of different groups of antithrombotic medication stratified at baseline and this does not allow for causal inference on antithrombotic use and the risk of bleeding events. In addition, given that mRS scores were also only collected at discharge, this may have led to an overestimation of the severity of the index event), since outcome of some patients could still have improved further as part of the natural disease course or with therapy and rehabilitation. Third, the inclusion period was relatively long (1995-2010). Recommendations on antithrombotic therapy after TIA/ischemic stroke have changed, both during the inclusion period and during the follow-up. Therefore, extrapolation of our findings toward the current young patients with stroke should be performed with care.

Over the past years, there has been a growing discussion on whether routine lifelong secondary prevention in the form of antithrombotic medication is necessary in all young stroke survivors.[8] Especially in the subgroup of patients with a relatively low risk of new ischemic events, the potential benefits of lifelong continuation of antiplatelet therapy may not outweigh the harms. It is important to identify groups who are on the one hand most at risk of bleeding and on the other hand most at risk of ischemia in the long run. For example, women with a cryptogenic stroke may be at a disproportionally high risk of severe bleeding compared with the low risk of recurrent ischemia. Future studies should investigate in these young patients, if and to what extent the bleeding risk is related to which kind of antithrombotic therapy. Future work should also consider the relative severity of possible bleeding events and possible recurrent ischemic events and weigh them against each other. We found most bleeding events in this study to be minor, although we did not have information on the severity of recurrent stroke. However, about one-third of all 292 ischemic events during follow-up were TIAs (N = 89; 30.5%), which could also be considered as "minor" events." In addition, 38 participants suffered from peripheral arterial disease (N = 28; 13.0%) and 49 individuals had a myocardial infarction (N = 49, 16.8%) that can usually be managed well with either intervention or antithrombotic/thrombolytic therapy. A future trial specifically designed for young patients with ischemic stroke or TIA with a low risk of recurrent ischemia should investigate the effect of usual antiplatelet treatment vs discontinuing antiplatelet therapy, to determine whether antiplatelet treatment can be safely ceased in these patients.

IX

PART FIVE

SUMMARY AND GENERAL DISCUSSION

Chapter X

Summary

This thesis is dedicated to unravelling risk-factors, causes and long-term prognosis of stroke at a young age. Although stroke in the young is relatively rare, it has devastating and often life-long consequences. Despite an extensive diagnostic work-up, no cause of stroke is found in almost one third of young patients. Not knowing the cause of stroke can lead to uncertainty for patients, but may also result in uncertainty regarding adequate treatment. To be able to provide optimal care it is crucial to identify novel risk-factors, causes of stroke and prognosis as many of these young patients still have a life-expectancy of thirty to sixty years, compared to a life expectancy of on average less than 10 years in the older stroke population. This provides a whole different meaning to the term: "long-term prognosis". In comparison to older stroke survivors, the prevalence of classical vascular risk-factors, comorbidities and causes of stroke is much lower in this patient group. Hence, the "very" long-term prognosis of these young stroke patients cannot simply be extrapolated from studies performed in the older stroke population.

In this thesis I combined epidemiological research in large nationwide datasets and clinical research in different observational cohort studies. The cohort studies used are the ODYSSEY, FUTURE and PITCH. The ODYSSEY is a multi-center observational prospective cohort study that included 1492 patients aged 18-49 years with ischemic stroke (n=1322) or ICH (n=170) between 2013 and 2021 from 17 centers across the Netherlands. This study was set up and coordinated by our group at the Radboud university medical center and succeeded the FUTURE study. FUTURE comprises 1005 consecutively included patients aged 18-49 with ischemic stroke (n=630), TIA (n=227) or ICH (n=98) who were treated in the Radboud university medical center between 1980 and 2010. PITCH is a prospective cohort study of 560 patients of all ages with a spontaneous ICH who primarily presented at Lille University Hospital between 2004 and 2009, from which we included patients aged 18-55 years (n=75). For the registry based studies we made use of the nationwide Dutch Hospital Discharge Registry between 1998 and 2018, which was linked to the Dutch Population Registry and Cause of Death Registry. In addition, data from the Dutch Cancer Registry was used through linkage to the ODYSSEY and FUTURE cohorts.

In the next paragraphs I will summarize the main results of the seven original studies and one narrative review from this thesis (The Dutch summary can be found in **chapter XII**). In **chapter XI**, I will discuss the main findings, as well as methodological strengths and challenges of the studies included. I will finish that chapter by providing an outlook on future research and possible clinical implications.

Epidemiology and risk-factors of stroke in the young

Chapter II describes the incidence of ischemic stroke and ICH in the Netherlands between 1998 and 2010. In these two decades the incidence of ischemic stroke increased by almost 50% in patients aged 18-49 years, whereas it decreased by approximately 10% in patients ≥50 years old at first-ever stroke. The increasing incidence of ischemic stroke was primarily driven by the rise in those aged 35-49 years old, whereas the incidence did not significantly increase in the very young (aged 18-34 years old). The incidence of ICH did not increase in either patients aged 18-49 or patients aged ≥50 years old in this time period, and was similar for men and women. Young women were more likely to be hospitalized with an ischemic stroke compared to men; this difference was most pronounced in the very young women (18-44 years), and the disparity disappeared with increasing age.

In recent years, more and more attention has been paid to environmental risk-factors for many diseases, including cerebrovascular disease, on a global scale. **Chapter III** summarizes the current knowledge on the association between air pollutants and the incidence of ischemic stroke and ICH. Despite serious methodological limitations in the studies performed, which restrict inferences about causality, there is a clear association between both short-term increases in air pollution levels and acute stroke, as well as between long-term exposure to high levels of air pollution and the life-time risk of stroke. The risk-increase of stroke incidence both after short- and long-term exposure is dependent on the degree of exposure to air pollution and therefore most pressing in low to middle income countries, as mean pollution levels and peak exposures are much higher compared to those in most high-income countries. Based on pathophysiological studies it seems that pollutants affect the cardiovascular system in a variety of ways and act synergistically to classic cardiovascular risk-factors. As of yet, there are no evidence based interventions to reduce the individual risk of pollution related stroke, which highlights the dire need to address this issue in research and society.

In **chapter IV** the baseline characteristics, risk-factors and etiologies of young patients with ischemic stroke from the ODYSSEY study are described according to the TOAST, ASCOD and the less-often used IPSS classification. TOAST is the most commonly used classification system in clinical practice, but it is based on, and validated in, the older stroke population and therefore relies heavily on classic cardiovascular mechanisms. ASCOD is aimed more at the younger population as it separately recognizes "arterial dissection" as a cause, although the other categories are still very similar to TOAST. The IPSS is a risk-factor based classification and used in children and young adults. It identifies a variety of (supposed) risk-factors not

taken into account in TOAST or ASCOD. In the ODYSSEY cohort of 1322 young patients with ischemic stroke, 25% of strokes were still classified as cryptogenic (without cause) according to the modified TOAST classification. Using the ASCOD criteria in the same population led to a modest improvement; with 20% of strokes remaining cryptogenic. When applying the IPSS classification, no risk-factors could be identified in only 10 patients (3%). Interestingly, around 90% of patients classified as cryptogenic according to the TOAST criteria, did have at least one classic cardiovascular risk factor.

Stroke in the young: Cancer in disguise?

In **Chapter V** we studied the risk of receiving a new cancer diagnosis in the first 10 years following ischemic stroke or ICH, comparing younger and older adults. The absolute risk of receiving a cancer diagnosis in the first 10 years after an ischemic stroke was around 4% for young adults and 9% for adults ≥50 years old. When we compared these risks to the background risk of matched peers from the general population, the risk of new cancer at a young age was 2.6 times higher in the first year after ischemic stroke and 5.4 times higher after ICH. In patients ≥50 years the cancer risk was increased only 1.2 times within one year after both ischemic stroke and ICH. The risk-increase was highest for lung cancer, hematologic malignancies and gastro-intestinal cancers. Conversely the risk in young stroke patients was lower for breast cancer compared to matched peers, which suggests a selective association with certain cancer types. There was a clear time dependent effect, with the highest risk-increase compared to the matched peers in the first one to two years after stroke, which is suggestive of a causal association. However, with this study design we could not prove causality.

In **Chapter VI** we further studied the prevalence of underlying cancer, and associated risk-factors in young patients with ischemic stroke and TIA in a combined clinical cohort of ODYSSEY and FUTURE patients without a history of cancer. Through linkage to the Dutch Cancer Registry, we found an underlying cancer in 17 (1.0%) of the 1729 patients. Underlying cancer was defined as a first-ever cancer diagnosed within one year pre-stroke, excluding patients who underwent systemic treatment at the time of stroke, or a first-ever cancer diagnosed within one year post-stroke. Patients with an underlying cancer were significantly more likely to have anemia at baseline, a cryptogenic etiology of ischemic stroke or TIA and three arterial territories affected on neuro-imaging, compared to patients without an underlying cancer. These three characteristics were also independently predictive of an underlying cancer and were combined in a prediction model that showed

moderate discrimination and accurate calibration. A maximum of three points led to a mean predicted probability of an underlying cancer of 15% in our cohort.

Long-term prognosis of stroke in young adults

This thesis contains two studies on long-term mortality of stroke at young age. The first is reported in **chapter VII** and demonstrates the long-term risk of mortality in 15 257 30-day survivors of first-ever ischemic stroke or ICH aged between 18 and 49 years old. These results are based on administrative data from Statistics Netherlands between 1998 and 2018. We found a high cumulative mortality of 17% in the 15 years post-stroke for ischemic stroke and ICH patients combined. Compared to matched peers from the general population the risk of death during on average 8.2 years follow-up was five times higher for young adults after ischemic stroke and eight times higher after ICH. For 30-day survivors of both ischemic stroke and ICH, male sex, higher age, a higher Charlson Comorbidity Index score (CCI) and a longer hospital stay (after the index event) were independently associated with a higher long-term mortality. In the 1763 patients who died during follow-up, the main causes of death were all-vascular causes combined in one third of patients, and cancer, also in one third of patients.

The second study on long-term mortality is reported in **chapter VIII** and describes a high long-term cumulative mortality in young survivors of spontaneous ICH. Patients in this study were included from the PITCH cohort and aged between 18 and 55 years old. Patients with an underlying structural abnormality causative of the ICH were excluded. We demonstrated a 35% long-term cumulative mortality after a median follow-up of 8 years, which was 13 times higher compared to matched peers from the general population. Excessive alcohol consumption, global atrophy on MRI and a pre-ICH mRS >2 were independent predictors of a higher risk of long-term mortality. These predictors were more a reflection of underlying health issues rather than directly ICH-related, which is different from the predictors of short-term mortality after ICH in young patients.

In **chapter IX** we studied the long-term risk of both recurrent ischemic events and bleeding events after ischemic stroke or TIA in 544 patients from the FUTURE study aged 18-49 years. As young patients have a long life-expectancy, in addition to their long-term risk of recurrent ischemia, they are also at prolonged risk of bleeding complications related to the often life-long prescribed antithrombotic therapy. During follow-up, 2 out of 10 patients experienced at least one minor bleeding event (severity classified according to the BARC criteria) and additionally one in 20 patients suffered a major bleeding event. This accumulated to a cumulative

risk of any bleeding event of 22% over 10 years, which was lower compared to the 34% cumulative risk of any recurrent ischemic event, however still considerable. Risk of bleeding was highest in women with an HR of 2.6 compared to men, and mostly due to gynecological bleeding events.

Conclusion

The studies in this thesis show an increasing incidence of ischemic stroke at young age in the Netherlands between 1998-2010, as well as a remarkably high long-term mortality after both ischemic stroke and ICH at young age. We found that in one out of four young patients with an ischemic stroke, no clear cause can be found, despite an extensive work-up. Although not recognized in the TOAST criteria, over 90% of these patients have at least one known risk factor according to the IPSS, often one of the classical vascular risk-factors. One possible risk factor that is currently undervalued and may contribute to the increasing stroke incidence at young age is air pollution; both as a trigger and long-term risk factor. The risk of receiving a first-ever cancer diagnosis is significantly increased in the first years after ischemic stroke and ICH at young age and thus some of these cryptogenic strokes may in fact be caused by an underlying, yet unidentified cancer.

Apart from the high long-term mortality risk, the risk of a recurrent ischemic event after an ischemic stroke or TIA is also high, though variable per etiological subtype. In addition, a substantial number of young patients, mainly women, suffer from bleeding events in the long-term, possibly due to life-long prescribed anti-thrombotic medication.

Future work should focus on identifying novel risk-factors and causes of ischemic stroke in young adults, and developing an etiological classification more suited to these young patients. In addition, the association between stroke at young age and cancer should be investigated further to examine whether adding cancer screening to the diagnostic work-up of a selected group of patients may be beneficial. Finally, future randomized clinical trials should evaluate the balance between recurrent ischemia and bleeding complications in young patients with ischemic stroke and TIA to better tailor treatment and improve prognosis.

X

Chapter XI

General discussion and future perspectives

Around 10-15% of patients with a first-ever stroke is between 18 and 50 years old, which amounts to around 2 million young adults affected worldwide every year. A stroke at young age has devastating consequences, that impact the rest of these patients' lives. The young stroke population is much more heterogenous than the older stroke population in both etiology and risk-factors, but also with regards to their long-term prognosis. Therefore, data generated from the older stroke population cannot simply be extrapolated to this young patient group. Tailored information on both causes and consequences is key for these young patients for counseling, but also for providing optimal treatment.

In this thesis, I investigated the incidence of stroke at a young age in the Netherlands and aimed to elucidate risk-factors and causes, with specific emphasis on underlying cancer. In addition, I investigated the long-term prognosis regarding mortality in both young ischemic stroke and ICH patients and the recurrent ischemia risk versus the bleeding risk after ischemic stroke or TIA at young age.

This thesis includes seven chapters with original data, based on three prospectively included observational cohort studies (ODYSSEY study, FUTURE study and the PITCH study), and data from administrative registries from Statistics Netherlands and the Netherlands Comprehensive Cancer Organization.

In this chapter, I will first discuss the methodological considerations of the studies included in this thesis. Then I will discuss the main findings and their implications for clinical practice and future perspectives.

Methodological considerations

The methodology of a study is important to consider when interpreting the results. In the next few paragraphs I will discuss the strengths and limitations of the study designs, as well as the internal validity, precision, and external validity of the studies with original data.

Study design

The studies in **chapter II**, **V** and **VII** use data from the nationwide Dutch Hospital Discharge registry linked to the Dutch Population Register and Cause of death registry, which are owned by Statistics Netherlands. This linkage made it possible to construct a cohort of patients who were hospitalized with a first-ever ischemic stroke, ICH or stroke not otherwise determined based on the corresponding ICD-9/-10 codes

between 1998 and 2010 in the Netherlands, with follow-up for mortality until 2018. The advantage of this nationwide approach is the large sample size combined with a long follow-up period without some of the limitations that lead to selection bias in cohort studies. The disadvantage of this approach is the lack of clinical detail, for example on the cause of stroke or presence of (cardiovascular) risk-factors. This means we were not able to study in more detail the associations between clinical characteristics and the rising stroke incidence, risk of post-stroke cancer or high long-term mortality.

The ODYSSEY study described in **chapter IV** and **chapter VI** is a multicenter prospective cohort study, in which young patients aged 18 to 49 years were consecutively included between 2013 and 2021 with a first-ever neuro-imaging proven ischemic stroke and TIA (= minor stroke) or ICH. 17 Centers participated in this study, both general and academic hospitals, in 7 out of the 12 provinces in the Netherlands. The resulting cohort is unique in its size with a high level of clinical detail. Data was uniformly gathered by four researchers, but the diagnostic work-up varied somewhat between the participating hospitals and was not complete for all cases. Therefore, in some cases, risk-factors or causes could have been missed, which might have resulted in a slight overestimation of the number of cryptogenic strokes and slight underestimation of the number of risk-factors present according to the IPSS.

In **chapter VI** a combined subset of patients from the ODYSSEY and FUTURE cohort was linked to the Dutch Cancer Registry to identify an underlying cancer diagnosis in the 12 months pre- or post-index stroke. This linkage was necessary because both in the baseline data and follow-up of both studies, cancer diagnoses were not explicitly noted or asked for. Because the Dutch Cancer Registry was only available from 1989 onwards, patients from the FUTURE study who were included between 1980 and 1989 had to be excluded, which limited the sample size.

The clinical study described in **chapter VIII** uses data from the PITCH cohort, which is also an observational prospective cohort study with consecutive inclusion of patients of all ages with a spontaneous ICH between 2004 and 2009 from Lille University Hospital. For this substudy, we included only patients between 18 and 55 years. The major advantage of this study is the routinely performed MRI and long-term follow-up, which provided new insights in the association between MRI markers and long-term mortality in this patient group. A concern was the relatively high number of missing causes of death, which led to uncertainty on the distribution of causes of death in this patient group, as the missing data might not have been missing at random.

For the study in **chapter IX** we extended the follow-up of the FUTURE study with retrospective chart review identifying additional ischemic and all bleeding events. Patients aged 18 to 49 years old were prospectively included in the FUTURE study with a first-ever ischemic stroke or TIA between 1980 and 2010 in the Radboud University Medical Center. There have previously been two follow-up waves with structured questionnaires in 2010 and 2014. Unfortunately bleeding events were not systemically identified in the follow-up questionnaires and were now singularly identified with retrospective chart review from inclusion date up to 2021, whereas data on recurrent ischemic events was systemically collected and verified between the inclusion date and 2014, and complemented with additional events up to 2021 based on chart review. As we only had access to the medical files from the Radboud University Medical Center, if a patient was admitted with a bleeding event to another hospital during the follow-up period, this would have been missed. This might have resulted in an underestimation of the number of bleeding events during the follow-up period.

Internal validity

The internal validity is the extent to which a study can demonstrate a causal relationship between the two variables studied. The internal validity can be compromised by random or systematic errors, which can be classified as: selection bias (sampling), information bias (validity of measurements) and confounding (interference of confounding variables).

Selection bias occurs when participation of subjects in the study depends on either the determinant (independent variable) or the outcome (dependent variable).

In the ODYSSEY study the median NIHSS was 3, which is quite low and may reflect a bias towards patients with less severe strokes. This is probably because patients who died very soon after their stroke were not included in all centers. In some of the centers, in an attempt to correct for this bias, these patients were included post-mortem based on chart review without needing informed consent. In addition, patients who were severely affected might have been less likely to be included, as the patients themselves or their legal representatives may have been more reluctant to join the study. A bias towards less severe strokes may have influenced the distribution of causes and risk-factors of stroke, as strokes due to large artery disease or cardiac embolism tend to be more severe. The same bias may have influenced the results of the FUTURE (median NIHSS: 2) and PITCH study (median NIHSS 10). In PITCH the inclusion of patients with less severe ICH may have

influenced the distribution of causes of death, as in more severe ICH death might be more likely due to the ICH itself or complications thereof.

Over 95% of patients included in the ODYSSEY study was of Caucasian descent and the cohort therefore does not accurately represent the cultural diversity of the Dutch population. Information on ethnicity of patients was not collected in the FUTURE or PITCH study. The underrepresentation of non-Caucasian patients might have been due to language restrictions, as patients who did not speak sufficient Dutch could not be included in the study as they could not give reliable informed consent or take part in adequate follow-up through structured questionnaires. In addition, there may be cultural differences in the willingness to participate in these studies. The overrepresentation of patients of Caucasian descent may have influenced the observed prevalence of (cardiovascular) risk-factors and rare causes. For example, hypertension and diabetes are more common at this age in Black and Asian populations compared to the Caucasian population. [133]

The FUTURE study and PITCH cohort are single center studies performed in academic hospitals, and therefore prone to selection bias of more academic cases, which are not always representative of the general population. Academic referrals are generally more complex cases with more often rare risk-factors, (e.g. rare coagulopathies) and more severe comorbidities (e.g. patients requiring third line treatments for advanced cancers or auto-immune diseases). This possible selection bias may therefore influence the etiological distribution of risk-factors and causes of stroke in our study population, as well as the long-term prognosis, as in patients with more rare risk-factors/causes or severe comorbidities current secondary preventive care might be less successful. However, as the Radboud University Medical Center is an expertise center for stroke in the young, it is likely that cases in the region would frequently have been referred to the Radboudumc for evaluation. Therefore, the population included is likely to reflect most of the region. In the PITCH study this selection bias was limited because it included patients who had been directly referred to the hospital through the emergency room, and not academic (third opinion) referrals.

These possible selection biases encountered in the observational cohort studies, are less important in the studies using administrative data as no informed consent is required. However, there are two other possible sources of selection bias that may play a role in studies of administrative data. First, the Dutch Hospital Discharge registry only includes patients that were hospitalized, meaning that patients who were only seen at the outpatient clinic or emergency room without hospitalization

were not included. This could result in a bias towards more severe strokes being included and less severe strokes being missed. This might have led to a slight underestimation of the true number of ischemic strokes in the Netherlands, and perhaps an overestimation of the mortality risk. However, we expect the large majority of young patients with a first-ever ischemic stroke to be hospitalized, as this was standard clinical practice during the study period. In recent years there has been a trend towards not routinely admitting all (young) patients with a minor ischemic stroke. Because patients with a TIA are most often not hospitalized, and because the ICD-codes were shown to be unreliable, we did not include these in the administrative studies. For ICH, we expect that all patients with this diagnosis were hospitalized as is common clinical practice. Second, between 1998 and 2013 persons could be followed over time based on a unique combination of personal identifiers (postal code, date of birth and sex), which was estimated to be unique in around 85% of Dutch citizens. When the linkage key was not unique, the patients were excluded from follow-up. Therefore, twins and persons in highly populated areas (where postal codes are more likely to overlap) may have been underrepresented in the studies. After 2013, this was resolved, as persons could be followed based on their personal identification number (BSN). This may have led to a minor underestimation of the stroke incidence before 2013.

Information bias (misclassification)

Information bias occurs when the determinant (independent variable) and/or outcome (dependent variable) are inaccurately measured, or when definitions used are multi-interpretable or vary between contributing centers.

When using administrative data there is an inherent risk of misclassification of the qualifying event, in this case the stroke diagnosis. In the Netherlands, all admissions to a hospital are coded with a primary and possible secondary diagnosis-code based on the international classification of disease upon discharge. These codes are provided in the Dutch hospital discharge registry and were used in this thesis to identify patients with a first-ever stroke. Usage of these administrative codes had been previously validated in the general stroke population and is considered reliable.[31,43] We additionally validated the codes specifically for the young population with ischemic stroke and ICH in two academic and one general hospital, proving them correct in >90% of cases. However, this means that in around 10% of cases a stroke mimic was coded as a stroke, and the registered diagnosis was in fact wrong, which may have led to an overestimation of the stroke incidence at young age. Conversely, we could have missed patients who unjustly did not receive an ICD-code for stroke, which could have led to an underestimation of the incidence.

In **chapter V** the admission codes from the Dutch Hospital Discharge registry are also used for the outcome event, which in this study was a new cancer diagnosis, with the possibility of misclassification. Also, patients with cancer who were never hospitalized may have been missed, leading to an underestimation of the cancer risk post-stroke. In addition, there is a risk of temporal misclassification as we used the date of admission as a proxy for the date of diagnosis, whereas in many cases the date of diagnosis may have been prior to the first admission to hospital. This could have led to an overestimation of the true number of post-stroke cancer diagnoses in the first few weeks after the index stroke, as the cancer could have already been known at the time of stroke. However, especially in the young patient group, we expect that most patients who receive a cancer diagnosis are hospitalized within a few days to two weeks for further diagnostic testing and/or treatment. When considering mortality as an outcome when using these administrative datasets, the risk of misclassification is low. The cause of death registry is mandatory in the Netherlands, and for all persons who die, the treating physician is required to fill out a form noting the primary and secondary causes of death.

In contrast to the ODYSSEY study, in the FUTURE study no neuro-imaging confirmation of ischemic stroke was required, as imaging, especially MRI, was not routinely performed during the study period (1980-2010). Therefore, some of the index ischemic strokes and TIAs in the FUTURE study may have been stroke mimics, which is a form of misclassification. This may have led to some degree of underestimation of the long-term risk of recurrent ischemic events as stroke mimics have better long-term prognosis. Also, as stroke mimics most likely are not associated with an underlying cancer, the post-stroke prevalence of cancer may have been slightly underestimated.

Confounding

Confounding occurs when a factor is associated with the determinant (independent variable) and outcome (dependent variable), but not part of the causal chain, and therefore influences the association found between the determinant and the outcome.

In the studies based on the clinical cohorts that included associative modeling, we corrected for known confounders as best we could. We mainly adjusted for age, sex and presence of different vascular risk-factors. The possibility to correct for possible confounders in the studies including administrative data was limited, as there was little clinical data; we did adjust for age and sex. For the study of long-term mortality we also assessed the CCI, which is a validated proxy for the level of comorbidity when using admissions-data with ICD-codes.

Precision

Precision refers to the degree of random error in a study, reflected by wider confidence intervals and possible false-positive or false-negative associations. The imprecision of a study can be minimized by using large sample sizes and validated outcome measurements.

The cohorts and linked datasets used in this thesis had large to very large sample sizes, and we therefore were able to obtain relatively precise results. Especially the studies with administrative data in **chapters II**, **V** and **VII** describe very large cohorts, which is reflected by the mostly narrow confidence intervals around the estimates in these studies. In **chapter V**, some of the subgroups were of limited size, reflecting the rarity of the combination of both a stroke at young age and subsequent cancer diagnosis. For **chapter VI**, in order to produce precise results, we chose to combine the ODYSSEY and FUTURE studies to reliably investigate patient- and stroke characteristics of young patients with an underlying cancer, though the number of cases was still relatively low. To improve the precision of future studies on this topic (international) individual data meta-analysis would be optimal. Finally, in the ODYSSEY study we included only patients with an imaging proven stroke which resulted in a uniform study population, leading to a lesser degree of random error.

External validity

The external validity is the extent to which a study can be generalized towards the general population.

As studies in **chapter II**, **V** and **VII** were nationwide and informed consent was not required, we expect these study populations to be well representative of the general Dutch population. Also, the ODYSSEY study is expected to be well representative of the Dutch population as it included patients from 17 centers across the country in both academic and general hospitals. Because of the system of care in the Netherlands and the high proportion of persons of Caucasian descent, the results can probably be generalized to most other European countries.

In the ODYSSEY study we only included patients with neuro-imaging proof of cerebral ischemia. This provided a homogenous study population but perhaps limits somewhat the extrapolation of results to the "real" world. In the Netherlands it is rather common practice to perform MRI to confirm cerebral ischemia in this young patient group, but resources may be more limited elsewhere. Additionally we employed the tissue based definition, meaning we excluded patients with transient

symptoms without DWI+ lesions on MRI, and classified patients with transient symptoms but with DWI+ lesions as a minor stroke and not a TIA. In clinical practice, the time based definition is often still used and therefore our results especially for patients with transient symptoms might not simply be extrapolated to all TIA patients in clinical practice.

In **chapter VI** the ODYSSEY and FUTURE cohorts were combined to identify patients with an underlying cancer. Because of the small absolute number of patients with an underlying cancer, the external validity is limited. Especially the prediction model needs to be validated in another cohort of young patients with ischemic stroke or TIA before it can be used in clinical practice.

The PITCH study described in **chapter VIII** included a patient sample that is highly selective because of both the inclusion criteria and the region in which this study was performed. This is demonstrated by the very high long-term mortality we found, and the high number of comorbidities and risk-factors already at baseline. For example, over 40% of patients at baseline had excessive alcohol consumption and one in ten patients was already functionally dependent before the ICH. The population in the North of France is known to have high numbers of smokers and people with excessive alcohol consumption and this has to be kept in mind when extrapolating these results to other populations.[216]

Discussion of the main findings

Epidemiology of stroke in the young

In this thesis, I demonstrate that the incidence of ischemic stroke at young age has increased almost 50% between 1998 and 2010 in the Netherlands (7.4 to 10.8 per 100.000 person-years). In contrast, the incidence of ICH in young adults did not increase over the same time period. This could be partially explained by the routine implementation of the MRI that may have led to ischemic stroke being more often diagnosed because of improved detection. The implementation of the MRI would not have influenced the ICH incidence as it can be reliably detected on CT. However, the increasing incidence in ischemic stroke was not present among all age-strata, but only in those aged 35-49 years old. The benefit of better imaging would be expected to increase detection in all age strata, suggesting that this cannot fully explain the increase. Because we found a decreasing trend in the incidence of ischemic stroke in people ≥50 years old, it seems more likely that there is a *cohort effect*, with patients being younger when affected by an ischemic stroke

for the first time. This may be due to the escalating burden of classical vascular risk-factors, which is reflected by the huge number of adolescents currently struggling with obesity and diabetes type 2.[37,242] In addition, there may be novel risk-factors that became more apparent during this period and may have a separate or additive effect on the development of cardiovascular disease. One of these emerging risk-factors is illicit drug use, of which especially amphetamines are clearly associated with ischemic stroke. Also air pollution, and potentially other environmental risk-factors, could be important contributors, as it has been shown that air pollutants worsen the progression of atherosclerosis and therefore may result in cardiovascular disease manifesting earlier.[121,122]

The observation of a high burden of cardiovascular risk-factors at young age is confirmed by the results of the ODYSSEY study. We found that over 90% of patients with a cryptogenic stroke had at least one classic cardiovascular risk factor. However, a large proportion of these patients are classified as cryptogenic according to the TOAST classification, which means that the mechanism leading to an ischemic stroke in these patients is not fully understood. Possibly, yet unknown risk-factors interplay with or aggravate these known risk-factors leading to a stroke at young age. Apart from unelucidated risk-factors, also trigger factors like cola consumption, vigorous physical exercise, sexual activity, illicit drug use, fever, and flu-like disease, may play a role in stroke manifesting at young age.[243] In addition, some of these patients may be more susceptible to classic cardiovascular risk-factors because of a yet unknown genetic predisposition.[244,245]

Although the proportion of patients with a cryptogenic stroke in the ODYSSEY study was lower compared to older studies, it was still 25%. Which means that in one out of four patients no cause was identified and the strategy for optimal secondary prevention remains unsure. As the TOAST criteria were set up in the nineties, and applicable to older stroke patients, they do not capture many age-specific or more novel risk-factors.[107] A risk factor based classification (like the IPSS) that does include a wide variety of risk-factors could provide insight into the possible mechanisms underlying these cryptogenic strokes through investigating common clusters of risk-factors. For example, a young woman with an ischemic stroke with the risk-factors oral contraceptives, migraine and active smoking is considered cryptogenic according to the TOAST classification, whereas this cluster of risk-factors can be considered causative.[246] Application of the IPSS might identify additional risk factor clusters that may lead to a stroke at young age. However, caution is advised as many of the factors included in the IPSS are presumed risk-factors and causal relationships or even unequivocal associations have not always

been proven. For example the causal association between auto-immune diseases and incident ischemic stroke is still mostly hypothetical.

Stroke in the young: Cancer in disguise?

In current clinical practice, the association between idiopathic deep venous thrombosis and cancer is widely recognized and patients are often screened to some degree to find an occult cancer.[247] In this thesis, I investigated the association between arterial thrombosis (stroke) and occult cancer, as the supposed causative mechanisms broadly overlap with idiopathic deep venous thrombosis. In **chapter V** I showed an increased risk of a first-ever cancer diagnosis in young patients with stroke, especially in the first year after stroke, compared to peers from the general population. This effect was much less clear in the elderly stroke population. As many risk-factors for stroke and cancer overlap, e.g. smoking, an increased risk of cancer in stroke patients is not surprising. However the temporal association is striking, and is suggestive of a causal relation. If the association was purely based on shared risk-factors, one would expect the risk of cancer to remain increased in the long-term. In addition, we did not exclusively find an increased risk for cancers related to cardiovascular risk-factors, such as lung cancer, but also with for example hematologic malignancies. Especially the association between ICH and an increased risk of hematologic malignancies was very strong, in which case the association is likely due to altered coagulation. Another explanation for the heightened risk of a cancer diagnosis in the year directly post-stroke would be the intensified medical monitoring, leading to symptoms being recognized earlier. However, if that was the only explanation, one would expect this effect to be consistent for all ages and that is not what we found.

The absolute number of patients with a stroke at young age, potentially caused by an underlying/occult cancer is very low, as reflected by the ±1% incidence of a new cancer diagnosis in the year post-stroke. Therefore screening all young patients with an ischemic stroke will probably not be beneficial nor cost-effective. In **chapter VI** we showed strong and independent associations of anemia at baseline, a cryptogenic etiology and three arterial territories affected at neuro-imaging with an active cancer. These factors were also included in the exploratory prediction model which was shown to be accurate in our study population. However due to the small number of cases in our study, this model cannot be used in clinical practice before it is externally validated in another cohort of young patients with ischemic stroke. However, our results are in line with previous studies in older patients, which adds to the credibility of the findings.[18] Thus, in young patients with ischemic stroke and at least one of these risk-factors the clinician should be suspicious

of an underlying cancer. The next question is how to best screen patients for an underlying malignancy, as there are currently no recommendations on this topic in stroke guidelines. Awareness of the association with underlying malignancy may trigger thorough history taking and physical examination in young stroke patients with at least one of the previously mentioned predictive factors. In addition, ancillary investigations may be considered.

Long-term prognosis of stroke in young adults

The long-term risk of mortality in young adults with ischemic stroke or ICH is generally considered to be low, in particular in comparison to the risk of mortality in older stroke patients. However, when compared to peers from the general population in the same age group, the cumulative mortality risk is five times higher. The high number of deaths due to recurrent vascular events reflects that most of these young patients who suffer a first ischemic stroke or ICH at young age remain at increased risk of vascular disease throughout their lives. This prolonged risk could be due to continuous exposure to underlying risk-factors, such as obesity and smoking. It could be argued that current secondary prevention strategies aimed at reducing these known modifiable risk-factors are unsuccessful, however it should be kept in mind that secondary prevention studies have hardly been performed in young patients. It also highlights that the "one size fits all" approach of treatment with life-long antiplatelet therapy after ischemic stroke at young age might not always be effective, because underlying causes that require different treatment (and not necessarily with antiplatelet therapy) might still be missed with the current diagnostic work-up. An equal percentage of young ICH and ischemic stroke patients in the long-term died of recurrent vascular disease and various forms of cancer.

In the Dutch young population the long-term risk of mortality after ICH was 8 times higher compared to age and sex matched peers, and 13 times higher in the Northern French population. It is well known that the short-term mortality of ICH is much higher compared to ischemic stroke,[209,213] but based on these two studies this also seems to be the case in the long-term. Whereas the short-term mortality of ICH at both young and older ages is mostly related to ICH-characteristics; such as mass effects leading to intracranial herniation, the long-term mortality is associated with factors related to underlying health issues and comorbidities. Therefore, it stands to reason that an ICH in younger patients is not only a very serious event, but also a clear expression of a poor health status and it would seem that these patients deserve rigorous long-term control of vascular risk-factors. However, high level evidence on secondary prevention, e.g. blood pressure lowering treatment,

antiplatelet therapy and lipid-lowering treatment, in both young and older ICH patients is limited. ICH as an index event was usually underrepresented or even excluded in most large randomized controlled clinical trials on secondary prevention after stroke.[248-250] Because of the high long-term mortality of these young ICH survivors specifically, ongoing and future randomized controlled trials into secondary preventive measures should pay attention to young ICH survivors as a relevant subgroup.

In **chapter IX** we showed that young patients with an ischemic stroke or TIA had a cumulative risk of 34% of recurrent vascular events in the first 10 years after the index event. The majority of these vascular events were recurrent stroke or TIA and a minority myocardial infarctions or peripheral artery disease. In addition, there was a substantial risk of bleeding events in young ischemic stroke or TIA survivors, which may be related to the secondary preventive treatment with antithrombotic therapy. The cumulative risk of any bleeding event was almost 22%, with one in twenty patients suffering a major bleeding event, meaning bleeding events requiring surgical intervention, bleedings requiring vasoactive medication or a hemoglobin drop of more than 3 mmol.[236] The bleeding risk was highest in young women and most often concerned gynecological bleeding events, such as hypermenorrhea, that in some cases led to a hysterectomy. This high risk of bleeding events in the long-term and especially this high risk in women has not been described previously. Studies concerning bleeding complications of antiplatelet therapy generally include older patients and have a follow-up limited to one or two years.[26,27,238]. This highlights the importance of separately investigating young adults with stroke from older stroke patients, as they inherently differ.

In recent years the need of routinely prescribed life-long antiplatelet therapy in young patients after ischemic stroke or TIA has increasingly been questioned. Clearly, there is a patient group with a high risk of recurrent vascular events that should be treated long-term, as we have shown that the recurrence risk of vascular events in the young patient group as a whole is high. However, there may also be an identifiable patient group with a low recurrence risk that does not need this long-term treatment. In this discussion on the duration of routinely prescribed antiplatelet therapy, it is not only important to consider who will have the most and least potential benefits of antiplatelet therapy, but also to consider who will have the most and least potential *harms* of this therapy, like bleeding events. Potentially, young women with cryptogenic stroke may have the lowest vascular recurrence risk and the highest bleeding risk in the long term. This balance of harms and benefits of antiplatelet therapy in young patients should be investigated in future studies.

Clinical relevance

The increasing incidence of ischemic stroke at young age means that more and more clinicians will encounter young adults with ischemic stroke or TIA in their emergency room or clinical practice. It is important for clinicians to be aware of this, and not to simply rule out ischemic stroke or TIA as a cause of neurological focal symptoms because of a relatively young age of a patient. In addition, this increasing incidence leads to an increasing burden on our healthcare system because these patients have a much longer life expectancy than older stroke patients. In addition, this increasing incidence leads to a worrisome socio-economic impact because of working life years lost.[65] As more and more young adults will have to live with the long lasting consequences of a stroke at young age, being able to inform these patients on their future risks and treating them properly is becoming increasingly vital.

Clinicians should be aware that young patients with stroke are much more heterogenous in their risk-factors and etiology compared to older patients with stroke. The diagnostic approach of young patients should include extensive history taking as well as appropriate ancillary investigations.

Apart from individually modifiable risk-factors like diabetes mellitus type 2 or smoking, there is increasing attention for population wide modifiable risk-factors like the influence of air pollution on cerebrovascular disease.[7] It is estimated that 16% of the 116 million disability adjusted life years worldwide due to stroke can be attributed to air pollution.[66] As there are currently no evidence based individual ways to limit exposure to air pollutants, there may be a role for us as clinicians and stroke researchers to join the debate about the importance of governmental action regarding air pollution. The increasing levels of air pollution are not only bad for our planet, but also harmful to our health.

Stroke at young age may in rare cases be a first manifestation of an occult cancer. Clinicians should consider this possibility especially in young patients with a stroke of cryptogenic etiology, anemia at the time of stroke and mostly in patients with evidence of acute ischemia in three arterial territories on neuro-imaging. It is important to note that routinely screening young stroke patients for an underlying cancer is not advised, as the absolute risk remains very low. Also, it is unknown which screening modalities are optimal and the benefit-harm and cost-effectiveness ratio is of yet unclear. Though extensive history taking and physical examination may be advised in young stroke patients at risk of having an underlying cancer.

Chapters VII to **IX** in this thesis describe a worrisome long-term prognosis for young adults with ischemic stroke or ICH concerning a high long-term risk of mortality compared to age- and sex- matched peers from the general population, as well as a high long-term risk of recurrent vascular events. These findings warrant rigorous medical management for years after their initial stroke, but also an open mind to personalized secondary prevention as risks (both for cardiovascular events and mortality) differ tremendously by cause. In addition, there is an important role for clinicians to counsel young patients with ischemic stroke or TIA on antiplatelet therapy with regard to the potential bleeding complications. During medical surveillance physicians should actively ask patients about these complications, especially in young women, as these bleeding events may seriously impact their quality of life.

Future perspectives

Future epidemiological research should continue to monitor trends in age-specific stroke incidence and it should investigate geographical differences in stroke incidence, to provide insight in possible new risk-factors and pathophysiological mechanisms, and to raise awareness and provide more targeted primary prevention. Apart from epidemiological research in the wake of the ODYSSEY study, there remains an important role for highly clinically detailed observational studies with a large sample size of patients to further identify novel risk-factors. In addition to identifying novel risk-factors, the supposed contribution of trigger factors of stroke at young age should be further studied.[243] To provide more insight into possible pathophysiological mechanisms and trigger factors of ischemic stroke at young age, the ODYSSEY NEXT study has been initiated; *(protocol paper in preparation)*. This study has extensive laboratory and neuro-imaging work-up to delve deeper into the etiology of stroke at young age.

We should also aim to investigate epidemiological trends, (novel) risk-factors and trigger-factors on a larger, global scale. The GOAL initiative,[133] is such an international collaboration, studying global differences in risk-factors, etiology and outcome of ischemic stroke at young age. International collaboration provides opportunities to study relatively rare diseases either through combining existing cohorts or setting up international patient registries. In addition, international collaboration is key for studying regional and ethnic differences in stroke incidence, etiology and prognosis. Knowledge of these differences and dedicated analysis of etiology and prognosis in ethnoracial subgroups is crucial to improve clinical

care. Currently the differences in long-term prognosis, but e.g. also in air pollution related stroke, between low-to-middle income countries and high income countries are decidedly troublesome and we should strive to minimize these disparities.[7,133]

Our work on the association between underlying cancer and stroke at young age deserves further investigation. Firstly, it is important that the exploratory predictive model described in **chapter VI** will be externally validated. If validated, the score could be of added value in clinical practice because the score is easy to use and is based on data that is routinely collected. Secondly, we should further evaluate which possible screening modalities for occult cancer have befitting positive and negative predictive values in this select high risk group of young stroke patients. In addition, cost-effectiveness should be evaluated. This work would then be a stepping stone to investigate whether adding cancer screening to the diagnostic work up of (young) stroke patients would be beneficial.

Regarding the long-term prognosis of young stroke patients, the high risk of long-term mortality of both young ischemic stroke and ICH patients warrants further attention. Future studies should investigate why this risk remains high even years after the index event and should study possible relevant interventions, like more extensive multidisciplinary medical management. In addition, future research should pay attention to important long-term outcomes that are highly relevant in these young patients, such as being able to return to work, cognitive functioning, and mental health.[251,252] With the ongoing follow-up from the ODYSSEY study these outcomes will be investigated. In the follow-up of the ODYSSEY study and the extended ODYSSEY NEXT, attention should be paid to the sex differences in etiologies, risk-factors, but also recurrent stroke, risk of bleeding events and risk of long-term mortality.

We have shown an overall high, but greatly variable long-term risk of recurrent stroke as well as bleeding events. Because of the high variability in recurrent stroke risk, it would be beneficial for both counseling and selection for future secondary preventive trials to be able to better predict the individual risk in young patients with ICH or ischemic stroke.[253] Future work should focus on more individualized prediction models designed for young patients. The high long-term risk of bleeding events clearly demonstrates that long-term antithrombotic therapy is not without risk. The ongoing follow-up of the ODYSSEY study will provide prospectively gathered data on bleeding events related to antithrombotic medication in these young patients. There is likely to be a group of young stroke patients in which the possible harms of long term antiplatelet therapy may outweigh the supposed

benefits. This will be further studied in the "Long-term risk of major cardiovascular events after stopping versus continuing antiplatelet therapy in persons under 50 years of age with cryptogenic stroke: a randomized multicenter non-inferiority trial" (STOP trial) for which funding was obtained this year at the Radboudumc. This study will investigate discontinuing versus continuing antiplatelet therapy and the effect on recurrent vascular events and bleeding complications in the years post-stroke in young patients. The study will include 1316 patients who had a cryptogenic stroke three to ten years ago and they will be randomized to continuing antiplatelet therapy or stopping antiplatelet therapy. Patients will be followed for five years and main outcomes will be the number of cardiovascular events, bleeding events and also quality of life. This trial will be a huge step towards tailored secondary prevention in young stroke patients.

Chapter XII

Nederlandse samenvatting

In dit proefschrift heb ik me gericht op het onderzoeken van risicofactoren, oorzaken en lange termijn prognose van beroertes op jonge leeftijd. Hoewel beroertes bij jongvolwassenen relatief zeldzaam zijn, hebben ze vaak verwoestende en levenslange gevolgen. Ondanks het momenteel uitgebreide diagnostische traject wordt bij bijna een derde van de jonge patiënten geen oorzaak voor de beroerte gevonden. Het niet weten van de oorzaak kan niet alleen leiden tot onzekerheid bij patiënten maar kan ook invloed hebben op het geven van de juiste behandeling. Om optimale zorg te kunnen bieden, is het daarom cruciaal om nieuwe risicofactoren en daarmee samenhangende oorzaken te identificeren. Ook het onderzoeken van de lange termijn prognose bij deze jonge patiënten is essentieel omdat veel van deze jonge patiënten nog een levensverwachting van dertig tot zestig jaar hebben vergeleken met een gemiddelde levensverwachting van minder dan 10 jaar bij oudere patiënten die een beroerte krijgen. In vergelijking met deze oudere patiënten, komen klassieke vasculaire risicofactoren, andere bijkomende aandoeningen en gangbare oorzaken van een beroerte veel minder voor bij de jongere groep patiënten. De “zeer” lange termijn prognose van deze jonge patiënten met een beroerte kan daarom niet eenvoudig worden overgenomen van studies uitgevoerd bij oudere patiënten.

Voor dit proefschrift heb ik epidemiologisch onderzoek in grote landelijke datasets gecombineerd met klinisch onderzoek op basis van verschillende observationele cohortstudies. De cohortstudies die ik heb gebruikt, zijn de ODYSSEY, FUTURE en PITCH. De ODYSSEY-studie is een observationele prospectieve cohortstudie met 1492 patiënten tussen de 18 en 49 jaar met herseninfarct (1322 patiënten) of intracerebrale bloeding (170 patiënten) tussen 2013 en 2021, geïncludeerd in 17 centra verspreid door Nederland. Deze studie is opgezet en gecoördineerd door onze onderzoeksgroep vanuit het Radboudumc en volgde de FUTURE-studie op. De FUTURE bestaat uit 1005 patiënten tussen 18 en 49 jaar met een herseninfarct (630 patiënten), TIA (227 patiënten) of intracerebrale bloeding (98 patiënten) die tussen 1980 en 2010 in het Radboudumc werden behandeld. De PITCH-studie is een prospectieve cohortstudie met 560 patiënten van alle leeftijden met een primaire intracerebrale bloeding, die zich primair hebben gepresenteerd bij het Universiteitsziekenhuis in Lille tussen 2004 en 2009, waarvan we patiënten tussen de 18 en 55 jaar (75 patiënten) hebben opgenomen. Voor de epidemiologische studies hebben we gebruikgemaakt van landelijke medische registraties (afkomstig van het CBS) tussen 1998 en 2018, welke werden gekoppeld aan het Nederlandse Bevolkingsregister en Overlijdensregister. Daarnaast zijn gegevens vanuit het Nederlandse Kankerregister gebruikt middels koppeling aan de ODYSSEY en FUTURE cohorten.

In de volgende paragrafen in deze samenvatting worden de belangrijkste resultaten van de zeven verschillende studies (**hoofdstukken II, IV-IX**) en een verhalende review (**hoofdstuk III**) uit dit proefschrift samengevat. In **hoofdstuk X** van dit proefschrift staat de Engelstalige samenvatting en **hoofdstuk XI** bespreek ik de belangrijkste bevindingen, evenals de methodologische sterke punten en beperkingen van de opgenomen studies. Ik sluit dat hoofdstuk af met een blik op toekomstig onderzoek en de klinische implicaties.

Epidemiologie en risicofactoren van beroerte bij jongeren

Hoofdstuk II beschrijft de incidentie van herseninfarcten en intracerebrale bloedingen in Nederland tussen 1998 en 2010. In deze twee decennia is de incidentie van een herseninfarct op jonge leeftijd (18-49 jaar) met bijna 50% toegenomen, terwijl deze met ongeveer 10% is afgenomen bij oudere patiënten (>50 jaar). De toenemende incidentie van herseninfarcten werd grotendeels verklaard door de stijging in de middelste leeftijdsgroep (35-49 jaar), terwijl de incidentie bij allerjongsten (18-34 jaar) niet significant toenam. De incidentie van intracerebrale bloedingen steeg zowel niet voor jongere (18-49 jaar) als oudere patiënten (>50 jaar), en was gelijk voor mannen en vrouwen. Jonge vrouwen werden echter wel vaker opgenomen met een herseninfarct vergeleken met mannen. Dit verschil was het meest uitgesproken in de jongste vrouwen (18-44 jaar) en vervaagde bij de hogere leeftijdsgroepen.

De afgelopen jaren is er steeds meer aandacht gekomen voor de wereldwijde bijdrage van verschillende omgevingsfactoren aan verschillende aandoeningen, waaronder ook beroertes. **Hoofdstuk III** vat de huidige kennis samen over de associatie tussen luchtvervuiling en de incidentie van herseninfarcten en hersenbloedingen. Ondanks serieuze methodologische beperkingen in de verschillende studies, die aannames ten aanzien van oorzakelijk verband beperken, is het evident dat er een associatie tussen zowel een kortdurende toename van luchtvervuiling en het optreden van beroertes, als tussen langdurige blootstelling aan hoge niveaus van luchtvervuiling en het levenslange risico op beroerte. Het risico op een beroerte na zowel korte- als lange-termijnblootstelling is afhankelijk van de mate van blootstelling aan luchtvervuiling. Daarmee is dit het meest urgent in lage- tot middeninkomenslanden, aangezien de gemiddelde vervuilingsniveaus en piekblootstellingen daar veel hoger zijn dan in de meeste hoge inkomenslanden. Op basis van pathofysiologische studies lijkt het erop dat de verontreinigende

stoffen in luchtvervuiling het cardiovasculaire systeem op verschillende manieren beïnvloeden en een synergetisch effect hebben met de klassieke cardiovasculaire risicofactoren. Tot nu toe zijn er geen op wetenschappelijk bewijs gebaseerde interventies om het individuele risico op een luchtvervuiling-gerelateerde beroerte te verminderen, wat de noodzaak onderstreept om dit probleem zowel met wetenschappelijk onderzoek als maatschappelijk aan te pakken.

In **Hoofdstuk IV** worden de patiëntkenmerken van de jonge patiënten met herseninfarct uit de ODYSSEY-studie beschreven, en de risicofactoren en oorzaken ingedeeld volgens de TOAST, ASCOD en de minder vaak gebruikte IPSS-classificatie. De TOAST-classificatie wordt het meest gebruikt in de klinische praktijk, maar is ontworpen voor-, en gevalideerd bij de oudere beroertepopulatie en is met name gericht op klassieke cardiovasculaire mechanismen. De ASCOD is meer gericht op de jongere populatie door “arteriële dissectie” als afzonderlijke categorie te erkennen, hoewel de andere categorieën nog steeds veel lijken op de TOAST. De IPSS is niet een oorzaak, maar een risicofactoren-gebaseerde classificatie die wordt gebruikt bij kinderen en jongeren. Deze classificatie identificeert een groot aantal (vermeende) risicofactoren die niet in TOAST of ASCOD worden meegenomen. In het ODYSSEY-cohort van 1322 jonge patiënten met een herseninfarct werd nog steeds 25% van de beroertes als cryptogeen (zonder oorzaak) geclassificeerd volgens de criteria van de TOAST. Het gebruik van de ASCOD-criteria in dezelfde populatie leidde tot een bescheiden verbetering; met 20% cryptogene beroertes. Bij toepassing van de IPSS-classificatie kon bij slechts 10 patiënten (3%) geen enkele risicofactor worden geïdentificeerd. Interessant is dat in ongeveer 90% van de patiënten die volgens de TOAST-criteria een cryptogene beroerte hadden, toch minstens een klassieke cardiovasculaire risicofactor hadden.

Beroerte bij jongvolwassenen: Uiting van een onderliggende kanker?

In **Hoofdstuk V** hebben we het risico op een nieuwe kankerdiagnose onderzocht in de eerste 10 jaar na een herseninfarct of intracerebrale bloeding. Hierbij hebben we jongvolwassenen (18-49 jaar) en oudere volwassenen (>50 jaar) met elkaar vergeleken. Het absolute risico op het krijgen van een nieuwe kankerdiagnose in de eerste 10 jaar na een herseninfarct was ongeveer 4% voor jongvolwassenen en 9% voor volwassenen van 50 jaar en ouder. Wanneer we deze risico's vergeleken met het achtergrondrisico van leeftijdsgenoten uit de algemene bevolking in Nederland, was het risico op een nieuwe kanker op jonge leeftijd 2,6 keer zo hoog

in het eerste jaar na een herseninfarct en 5,4 keer zo hoog na een intracerebrale bloeding. Bij patiënten van 50 jaar en ouder was het kanker risico slechts 1,2 keer zo hoog in het eerste jaar na zowel een herseninfarct of intracerebrale bloeding. De risicotoename was het grootst voor longkanker, hematologische kankers en gastro-intestinale kankers. Daarentegen was het risico op borstkanker lager in jonge patiënten met een beroerte vergeleken met leeftijdsgenoten, wat wijst op een selectieve associatie met bepaalde types kanker. Er was ook een duidelijk tijdsafhankelijk effect, met het grootste toegenomen risico tussen patiënten en gezonde leeftijdsgenoten in de eerste twee jaar na de beroerte. Dit suggereert een mogelijk oorzakelijk verband. Echter was het met de opzet van deze huidige studie niet mogelijk om een oorzakelijk verband aan te tonen.

In **Hoofdstuk VI** onderzochten we de prevalentie van een onderliggende kanker en bijbehorende risicofactoren in jonge patiënten met een herseninfarct of TIA zonder kanker in de voorgeschiedenis, in een gecombineerd klinisch cohort van ODYSSEY en FUTURE-patiënten. Via koppeling met het Nederlandse Kankerregister vonden we een onderliggende kanker bij 17 (1,0%) van de 1729 patiënten. In deze studie was een onderliggende kanker gedefinieerd als een eerste kanker die binnen één jaar voor de beroerte of TIA werd gediagnosticeerd, met uitzondering van patiënten die tijdens de beroerte een systemische behandeling ondergingen, óf een eerste kanker die binnen één jaar na de beroerte werd gediagnosticeerd. Patiënten met een onderliggende kanker hadden significant vaker bloedarmoede ten tijde van de beroerte, een cryptogene oorzaak van het herseninfarct of de TIA, en betrokkenheid van alle drie de arteriële stroomgebieden op cerebrale beeldvorming, in vergelijking met patiënten zonder onderliggende kanker. Deze drie kenmerken waren onafhankelijk voorspellend voor een onderliggende kanker en zijn gecombineerd in een exploratief predictiemodel met een gemiddelde discriminatie en nauwkeurige kalibratie. Een maximaal aantal van 3 punten in dit model, leverde een gemiddelde voorspelde kans op een onderliggende kanker van 15%, ten opzichte van een gemiddelde voorspelde kans van <1% bij 0 punten.

Lange termijn prognose van beroerte bij jonge volwassenen

Dit proefschrift bevat twee studies over het risico op overlijden op de lange termijn na een beroerte op jonge leeftijd. De eerste studie wordt besproken in hoofdstuk VII en beschrijft het lange termijn risico op overlijden bij 15 257 patiënten tussen de 18 en 49 jaar oud bij een eerste herseninfarct of intracerebrale bloeding. In deze

studie werden patiënten die binnen 30 dagen na de beroerte zijn overleden niet meegenomen, om specifiek de lange termijn sterfte te onderzoeken. In deze studie hebben we gebruik gemaakt van administratieve data van ziekenhuisopnames uit heel Nederland, verzameld door het Centraal Bureau voor Statistiek tussen 1998 en 2018. We vonden een hoog overlijdensrisico van 17% in de eerste 15 jaar na de beroerte (herseninfarct of intracerebrale bloeding). Vergeleken met gezonde leeftijdsgenoten uit de algemene bevolking was het risico op overlijden tijdens een gemiddelde follow-up van 8,2 jaar vijf keer zo hoog na een herseninfarct en acht keer zo hoog na een intracerebrale bloeding. In deze patiënten met een herseninfarct of een intracerebrale bloeding, waren het mannelijk geslacht, een hogere leeftijd, een hogere Charlson Comorbidity Index score (een maat voor de ernst en hoeveelheid comorbiditeiten gebaseerd op administratieve ziekenhuisgegevens), en een langer ziekenhuisverblijf onafhankelijk geassocieerd met een hoger risico op overlijden in de jaren na de beroerte. Bij de 1763 patiënten die tijdens de follow-up zijn overleden, overleed een derde aan hart- en vaatziekten, een derde aan kanker en een derde aan verscheidene andere oorzaken.

De tweede studie over het lange termijn risico op overlijden in **hoofdstuk VIII** toont een hoog overlijdensrisico bij jonge patiënten na een primaire intracerebrale bloeding. De patiënten in deze studie komen uit het PITCH-cohort en waren tussen de 18 en 55 jaar oud ten tijde van de bloeding. Patiënten met een (secundaire) intracerebrale bloeding ten gevolge van een onderliggende structurele afwijking, zoals een afwijkend bloedvat of tumor, werden niet meegenomen in deze studie. We lieten zien dat het risico op overlijden na een mediane follow-up van 8 jaar ongeveer 35% was. Dit risico was 13 keer zo hoog als het sterfterisico bij leeftijdsgenoten uit de algemene (gezonde) bevolking. Overmatig alcoholgebruik, globale atrofie (afname van de hersenmassa) zichtbaar op MRI en een modified Rankin Score >2 (maat voor functionele onafhankelijkheid tussen de 1-6; waarbij patiënten met een score boven de 2 niet zelfstandig kunnen lopen) waren onafhankelijke voorspellers van een hoger overlijdensrisico op de lange termijn. Deze voorspellers zijn niet direct gerelateerd aan de bloeding zelf (zoals bijvoorbeeld volume of locatie), maar meer een weerspiegeling van onderliggende gezondheidsproblemen. Dit verschilt van de voorspellers van het overlijdensrisico in de acute fase van een intracerebrale bloeding bij jongvolwassenen en ook ouderen. In de acute fase zijn de voorspellers wel vooral gerelateerd aan de kenmerken van de bloeding zelf.

Ondanks de relatief hoge lange termijnsterfte bij jonge patiënten met een beroerte, hebben deze patiënten een evident langere levensverwachting dan oudere patiënten. Dat betekent dat deze jonge patiënten nog tientallen jaren

een risico blijven lopen op een nieuwe beroerte, andere hart- en vaatziekten of bijwerkingen van de bloedverdunners die ze meestal levenslang voorgeschreven krijgen. In **Hoofdstuk IX** hebben we daarom onderzoek gedaan naar het zeer lange termijnrisico op bloedingen, en ook op nieuwe hart- en vaatziekten (zoals een nieuw herseninfarct of een hartinfarct) na een eerste herseninfarct of TIA op jonge leeftijd. Hiervoor hebben we 544 patiënten uit de FUTURE-studie van 18 tot 49 jaar onderzocht. Tijdens de follow-up periode hadden 2 op de 10 patiënten ten minste een kleinere bloeding (ernst geclassificeerd volgens de BARC-criteria) en had één op de 20 patiënten een ernstige bloeding. Gecombineerd resulteerde dit in een bloedingsrisico van gemiddeld 22% in de eerste 10 jaar na een herseninfarct of TIA op jonge leeftijd. Het risico op nieuwe hart- en vaatziekten was wel hoger, namelijk rond de 34%. Het risico op bloedingen was het hoogst bij jonge vrouwen (2,6 keer zo hoog als bij jonge mannen) waarbij dit voornamelijk kwam door een grote hoeveelheid aan gynaecologische bloedingen.

Conclusie

De studies in dit proefschrift tonen een toenemende incidentie van herseninfarcten op jonge leeftijd in Nederland tussen 1998 en 2010 aan, evenals een opmerkelijk hoge lange termijn sterfte zowel na een herseninfarct, als na een intracerebrale bloeding op jonge leeftijd. We vonden dat bij één op de vier jonge patiënten met een herseninfarct geen duidelijke oorzaak kan worden gevonden, ondanks uitgebreide diagnostiek. Meer dan 90% van deze patiënten bleek wel ten minste één bekende risicofactor te hebben volgens de IPSS, voornamelijk een of meerdere klassieke cardiovasculaire risicofactoren.

Een momenteel ondergewaardeerde risicofactor, welke zou kunnen hebben bijgedragen aan de stijgende incidentie van herseninfarcten op jonge leeftijd, is luchtvervuiling; zowel als acute trigger en als risicofactor op de langere termijn. Het risico op het krijgen van een eerste kankerdiagnose is aanzienlijk verhoogd in de eerste paar jaar na een herseninfarct of intracerebrale bloeding op jonge leeftijd. Sommige van de huidig als cryptogeen geclassificeerde beroertes zouden potentieel door deze, ten tijde van de beroerte nog onbekende, kanker kunnen zijn veroorzaakt.

Naast het hoge risico op overlijden op de lange termijn na een beroerte op jonge leeftijd, is ook het risico op een nieuwe hart- en vaatziekten (zoals een nieuwe beroerte) hoog, hoewel variabel per oorzaak van de eerste beroerte. Daarnaast

krijgt een aanzienlijk aantal jonge patiënten, voornamelijk vrouwen, last van bloedingen op lange termijn, mogelijk gerelateerd aan de meestal levenslang voorgeschreven bloedverdunners.

Toekomstig onderzoek zou zich moeten richten op het identificeren van aanvullende nieuwe risicofactoren en oorzaken van een herseninfarct bij jongvolwassenen, en het ontwikkelen van een etiologische classificatie die beter past bij deze jonge patiëntengroep. Verder is het belangrijk om de relatie tussen kanker en een beroerte op jonge leeftijd verder te onderzoeken om te beoordelen of het mogelijk toevoegen van diagnostiek naar een onderliggende kanker na een beroerte bij een geselecteerde groep jonge patiënten zinvol kan zijn.

Tot slot is het essentieel dat er verder onderzoek wordt gedaan naar de balans tussen het risico op nieuwe hart- en vaatziekten versus bloedingen bij jonge patiënten met een herseninfarct of TIA om de behandeling met bloedverdunners beter op de individu te kunnen afstemmen de prognose voor deze jonge patiënten te kunnen verbeteren.

PART SIX

APPENDICES

A I: List of Abbreviations

ACOM	Anterior communicating artery
APC	Annual Percentage Change
ASCOD	Atherosclerosis, Small vessel disease, Cardiac pathology, Other causes, Dissection
BARC	Bleeding Academic Research Consortium
BC	Black Carbon
BMI	Body Mass index
BOMB	Brain Observer Microbleed Scale
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CBS	Statistics Netherlands / Centraal bureau voor Statistiek
CDR	Cause of Death Register
CE	Cardioembolic stroke
CI	Confidence Interval
CMB	Cerebral Microbleed
CNS	Central Nervous System
CRP	C-Reactive Protein
CT	Computed Tomography
COVID-19	Coronavirus disease / Sars-CoV-2
DALYs	Disability Adjusted Life Years
DWI	Diffusion Weighted Imaging
DWI+	Diffusion Weighted imaging positive lesions
FLAIR	T1-weighted fluid-attenuated inversion recovery
FUTURE	Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation
GCA	Global cerebral/cortical Atrophy
GRE	T2*gradient-echo
HaNDL	Headache and Neurological Deficit with cerebrospinal fluid Lymphocytosis
HDR	Hospital Discharge Register
HIV	Human Immunodeficiency Virus
ICH	Intracerebral hemorrhage
ICD-9/-10	International classification of Diseases, version 9/10
IKNL	Comprehensive Dutch Cancer Organisation / Integraal Kankercentrum Nederland
INR	International Normalized Ratio

IPSS	International Pediatric Stroke Study
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
JAMA	Journal of the American Medical Association
LAS	Likely atherothrombotic stroke
LAA	Large Artery Atherosclerosis
MELAS	Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke like episodes
MRI	Magnetic Resonance Imaging
mo	Months
MS	Multiple Sclerosis
ND	Not Disclosed
NCR	Netherlands Cancer Registry
NIHSS	National Institutes of Health Stroke Scale
N / n / No	Number
NO2	Nitrogen dioxide
NOx	Nitric Oxides
ODYSSEY	Observational Dutch Young Symptomatic StrokE studY
OR	Odds Ratio
PACNS	Primary angiitis of the central nervous system
PFO	Patent Foramen Ovale
PM	Particulate Matter
PMH	Perimesencephalic hemorrhage
PITCH	Prognosis of InTra-Cerebral Hemorrhage
PROGRESS	Prognosis Research Strategy
PSI	Pollutant Standards Index
R2	R-squared
RCVS	Reversible Cerebral Vasoconstriction Syndrome
SAH	Subarachnoid hemorrhage
SD	Standard Deviation
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SLE	Systemic Lupus Erythematosus
SO2	Sulphur dioxide
SO4-	Sulphate

STOP-trial	Long-term risk of major cardiovascular events after stopping versus continuing antiplatelet therapy in persons under 50 years of age with cryptogenic stroke: a randomized multicenter non-inferiority trial
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient ischemic attack
TTP	Thrombotic Thrombocytopenic Purpura
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UN	United Nations
US	United States
wk	Weeks
WHO	World Health Organisation
y	years
XTC	Ecstasy

*

A II: References

1. 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):113-30.
2. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/ American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. *Stroke*. Jun 2009;40(6):2276-93. doi:10.1161/STROKEAHA.108.192218
3. Singhal AB, Biller J, Elkind MS, et al. Recognition and management of stroke in young adults and adolescents. *Neurology*. 2013;81(23):1089-97.
4. Collaborators GBDS. 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*. Oct 2021;20(10):795-820. doi:10.1016/S1474-4422(21)00252-0
5. 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*. Oct 1 2022;79(10):1036-1048. doi:10.1001/jamaneurol.2022.1520
6. Kissela B, Khoury J, Alwell K, et al. Age at stroke: Temporal trends in stroke incidence in a large, biracial population. *Neurology*. 2012;79(17):1781-1787.
7. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *The Lancet*. 2017;389(10082):1907-1918. doi:10.1016/s0140-6736(17)30505-6
8. 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
9. Putaala J, Metso AJ, Metso TM, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke*. Apr 2009;40(4):1195-203. doi:10.1161/STROKEAHA.108.529883
10. 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*. 01-01-1993 1993;(24):35-41. doi:https://doi.org/10.1161/01.STR.24.1.35
11. van Alebeek ME, Arntz RM, Ekker MS, et al. Risk factors and mechanisms of stroke in young adults: The FUTURE study. *J Cereb Blood Flow Metab*. Sep 2018;38(9):1631-1641. doi:10.1177/0271678X17707138
12. Mackay MT, Wiznitzer M, Benedict SL, et al. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. *Annals of neurology*. Jan 2011;69(1):130-40. doi:10.1002/ana.22224
13. Yitshak Sade M, Novack V, Ifergane G, Horev A, Kloog I. Air Pollution and Ischemic Stroke Among Young Adults. *Stroke*. Dec 2015;46(12):3348-53. doi:10.1161/STROKEAHA.115.010992
14. Shah AS, Lee KK, McAllister DA, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ*. Mar 24 2015;350:h1295. doi:10.1136/bmj.h1295
15. Kulick ER, Kaufman JD, Sack C. Ambient Air Pollution and Stroke: An Updated Review. *Stroke*. Mar 2023;54(3):882-893. doi:10.1161/STROKEAHA.122.035498

16. Lee KK, Miller MR, Shah ASV. Air Pollution and Stroke. *J Stroke*. Jan 2018;20(1):2-11. doi:10.5853/jos.2017.02894

17. Dardiotis E, Aloizou AM, Markoula S, et al. Cancer-associated stroke: Pathophysiology, detection and management (Review). *Int J Oncol*. Mar 2019;54(3):779-796. doi:10.3892/ijo.2019.4669

18. Rioux B, Touma L, Nehme A, Gore G, Keezer MR, Gioia LC. Frequency and predictors of occult cancer in ischemic stroke: A systematic review and meta-analysis. *International journal of stroke: official journal of the International Stroke Society*. Jan 2021;16(1):12-19. doi:10.1177/1747493020971104

19. Selvik HA, Bjerkreim AT, Thomassen L, Waje-Andreassen U, Naess H, Kvistad CE. When to Screen Ischaemic Stroke Patients for Cancer. *Cerebrovascular diseases*. 2018;45(1-2):42-47. doi:10.1159/000484668

20. Navi BB, Iadecola C. Ischemic stroke in cancer patients: A review of an underappreciated pathology. *Annals of neurology*. May 2018;83(5):873-883. doi:10.1002/ana.25227

21. Nouh AM, Staff I, Finelli PF. Three Territory Sign: An MRI marker of malignancy-related ischemic stroke (Trousseau syndrome). *Neurol Clin Pract*. Apr 2019;9(2):124-128. doi:10.1212/CPJ.0000000000000603

22. Rutten-Jacobs LC, Arntz RM, Maaijwee NA, et al. Long term mortality after stroke among adults aged 18 to 50 years. *JAMA*. 2013;309(11):1136-44. doi:10.1001/jama.2013.842

23. Koivunen RJ, Tatlisumak T, Satopaa J, Niemela M, Putaala J. Intracerebral hemorrhage at young age: long-term prognosis. *European journal of neurology*. Jul 2015;22(7):1029-37. doi:10.1111/ene.12704

24. Antithrombotic Trialists' Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849-60. doi:10.1016/S0140-6736(09)60503-1

25. Tillman H, Johnston SC, Farrant M, et al. Risk for Major Hemorrhages in Patients Receiving Clopidogrel and Aspirin Compared With Aspirin Alone After Transient Ischemic Attack or Minor Ischemic Stroke: A Secondary Analysis of the POINT Randomized Clinical Trial. *JAMA Neurol*. Jul 1 2019;76(7):774-782. doi:10.1001/jamaneurol.2019.0932

26. Bath PM, Woodhouse LJ, Appleton JP, et al. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. *The Lancet*. 2018;391(10123):850-859. doi:10.1016/s0140-6736(17)32849-0

27. Li L, Geraghty OC, Mehta Z, Rothwell PM. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *The Lancet*. 2017;390(10093):490-499. doi:10.1016/s0140-6736(17)30770-5

28. Arntz RM, van Alebeek ME, Synhaeve NE, et al. Observational Dutch Young Symptomatic StrokE studY (ODYSSEY): study rationale and protocol of a multicentre prospective cohort study. *BMC Neurology*. 2014;22:14-55.

29. Rutten-Jacobs LC, Maaijwee NA, Arntz RM, et al. Risk factors and prognosis of young stroke. The FUTURE study: a prospective cohort study. Study rationale and protocol. *BMC neurology*. Sep 20 2011;11:109. doi:10.1186/1471-2377-11-109

30. Cordonnier C, Rutgers MP, Dumont F, et al. Intra-cerebral haemorrhages: are there any differences in baseline characteristics and intra-hospital mortality between hospitaland population-based registries? *Journal of neurology*. Feb 2009;256(2):198-202. doi:10.1007/s00415-009-0030-3

31. Vaartjes I, Reitsma JB, de Bruin A, et al. Nationwide incidence of first stroke and TIA in the Netherlands. *European journal of neurology*. Dec 2008;15(12):1315-23. doi:10.1111/j.1468-1331.2008.02309.x
32. van den Brandt PA, Schouten LJ, Goldbohm RA, Dorant E, Hunen PMH. Development of a Record Linkage Protocol for Use in the Dutch Cancer Registry for Epidemiological Research. *International Journal of Epidemiology*. September 1990 1990;19(3):553-558.
33. Organisation WH. Stroke, Cerebrovascular accident. Updated 2017. Accessed 20-10-2017, 2017. http://www.emro.who.int/health-topics/stroke-cerebrovascular-accident/index.html
34. Bejot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in Europe and trends for the 21st century. *Presse medicale*. Nov 2 2016;doi:10.1016/j.lpm.2016.10.003
35. Sultan S, Elkind MS. The growing problem of stroke among young adults. *Current cardiology reports*. Dec 2013;15(12):421. doi:10.1007/s11886-013-0421-z
36. Tibaek M, Dehlendorff C, Jorgensen HS, Forchhammer HB, Johnsen SP, Kammersgaard LP. Increasing Incidence of Hospitalization for Stroke and Transient Ischemic Attack in Young Adults: A Registry-Based Study. *Journal of the American Heart Association*. May 11 2016;5(5)doi:10.1161/JAHA.115.003158
37. George MG, Tong X, Kuklina EV, Labarthe DR. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Annals of neurology*. Nov 2011;70(5):713-21. doi:10.1002/ana.22539
38. Jacobs BS, Boden-Albala B, Lin IF, Sacco RL. Stroke in the Young in the Northern Manhattan Stroke Study. *Stroke*. 2002;33:4. doi:10.1161/01.STR.0000038988.64376.3A
39. Bejot 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. *Journal of neurology, neurosurgery, and psychiatry*. May 2014;85(5):509-13. doi:10.1136/jnnp-2013-306203
40. Medin J, Nordlund A, Ekberg K, Swedish Hospital Discharge R. Increasing stroke incidence in Sweden between 1989 and 2000 among persons aged 30 to 65 years: evidence from the Swedish Hospital Discharge Register. *Stroke*. May 2004;35(5):1047-51. doi:10.1161/01.STR.0000125866.78674.96
41. Diaz-Guzman J, Egido JA, Gabriel-Sanchez R, et al. Stroke and transient ischemic attack incidence rate in Spain: the IBERICTUS study. *Cerebrovascular diseases*. 2012;34(4):272-81. doi:10.1159/000342652
42. Jolink WMT, M. KCJ, Brouwers PJAM, Kappelle LJ, Vaartjes I. Time trends in incidence, case fatality, and mortality of intracerebral hemorrhage. *neurology*. 2015;13(85):1318-24. doi:10.1212/WNL.0000000000002015
43. Tirschwell DL, Longstreth WT. Validating administrative data in stroke research. *Stroke*. 2002;33:2465-2470. doi:10.1161/01.STR.0000032240.28636.BD
44. Fernandes PM, Whiteley WN, Hart SR, Al-Shahi Salman R. Strokes: mimics and chameleons. *Practical neurology*. Feb 2013;13(1):21-8. doi:10.1136/practneurol-2012-000465
45. Nieuwkamp DJ, Vaartjes I, Algra A, Bots ML, Rinkel GJ. Age- and gender-specific time trend in risk of death of patients admitted with aneurysmal subarachnoid hemorrhage in the Netherlands. *International journal of stroke: official journal of the International Stroke Society*. Oct 2013;8 Suppl A100:90-4. doi:10.1111/ijs.12006
46. 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*. Mar 2013;44(3):591-7. doi:10.1161/STROKEAHA.112.677724

47. Bevolking; generatie, geslacht, leeftijd en herkomstgroepering, 1 Januari. CBS Statline. 2017. Available at: statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=37325&D1=0&D2=a&D3=0&D4=a&D5=0&D6=18-21&VW=T. Accessed January 16, 2017.
48. Bejot Y, Delpont B, Giroud M. Rising Stroke Incidence in Young Adults: More Epidemiological Evidence, More Questions to Be Answered. *Journal of the American Heart Association*. May 11 2016;5(5)doi:10.1161/JAHA.116.003661
49. Cabral NL, Freire AT, Conforto AB, et al. Increase of Stroke Incidence in Young Adults in a Middle-Income Country: A 10-Year Population-Based Study. *Stroke*. Nov 2017;48(11):2925-2930. doi:10.1161/STROKEAHA.117.018531
50. Sipila JOT, Posti JP, Ruuskanen JO, Rautava P, Kyto V. Stroke hospitalization trends of the working-aged in Finland. *PloS one*. 2018;13(8):e0201633. doi:10.1371/journal.pone.0201633
51. Maaijwee NA, Rutten-Jacobs LC, Schaapsmeerders P, van Dijk EJ, de Leeuw FE. Ischaemic stroke in young adults: risk factors and long-term consequences. *Nat Rev Neurol*. Jun 2014;10(6):315-25. doi:10.1038/nrneurol.2014.72
52. Putaala J, Curtze S, Hiltunen S, Tolppanen H, Kaste M, Tatlisumak T. Causes of death and predictors of 5-year mortality in young adults after first-ever ischemic stroke: the Helsinki Young Stroke Registry. *Stroke*. Aug 2009;40(8):2698-703. doi:10.1161/STROKEAHA.109.554998
53. Feigin VL, Roth GA, Naghavi M, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*. Aug 2016;15(9):913-924. doi:10.1016/S1474-4422(16)30073-4
54. de los Rios F, Kleindorfer DO, Khoury J, et al. Trends in substance abuse preceding stroke among young adults: a population-based study. *Stroke*. Dec 2012;43(12):3179-83. doi:10.1161/STROKEAHA.112.667808
55. van Rooij AJ, Schoenmakers TM, Van de Mheen D. Nationaal Prevalentie Onderzoek Middelengebruik 2009; kerncijfers 2009. *Rotterdam: IVO*. 2011;
56. Abraham M, Cohen P, Van Til RJ, De Winter M. Licit and Illicit Drug Use in the Netherlands. *Amsterdam: UvA/CBS, CEDRO*. 1999;
57. Gokhale S, Caplan LR, James ML. Sex differences in incidence, pathophysiology, and outcome of primary intracerebral hemorrhage. *Stroke*. Mar 2015;46(3):886-92. doi:10.1161/STROKEAHA.114.007682
58. Giroud M, Delpont B, Daubail B, et al. Temporal Trends in Sex Differences With Regard to Stroke Incidence: The Dijon Stroke Registry (1987-2012). *Stroke*. Apr 2017;48(4):846-849. doi:10.1161/STROKEAHA.116.015913
59. Chau PH, Woo J, Goggins WB, et al. Trends in stroke incidence in Hong Kong differ by stroke subtype. *Cerebrovascular diseases*. 2011;31(2):138-46. doi:10.1159/000321734
60. Putaala J, Haapaniemi E, Metso AJ, et al. Recurrent ischemic events in young adults after first-ever ischemic stroke. *Annals of neurology*. Nov 2010;68(5):661-71. doi:10.1002/ana.22091
61. Boehme AK, Kumar AD, Dorsey AM, et al. Infections Present on Admission Compared with Hospital-Acquired Infections in Acute Ischemic Stroke Patients. *J Stroke Cerebrovasc Dis*. 2013;22(8):582-589. doi:10.1016/j.jstrokecerebrovasdis
62. United Nations Environment Programme. Towards a pollution-free planet: background report. 2017. https://wedocs.unep.org/ bitstream/handle/20.500.11822/21800/UNEA_towardspollution_ long%20version_Web.pdf (accessed July 1, 2020).
63. Stockfelt L, Andersson EM, Molnar P, et al. Long-term effects of total and source-specific particulate air pollution on incident cardiovascular disease in Gothenburg, Sweden. *Environ Res*. Oct 2017;158:61-71. doi:10.1016/j.envres.2017.05.036

64. Amini H, Dehlendorff C, Lim YH, et al. Long-term exposure to air pollution and stroke incidence: A Danish Nurse cohort study. *Environ Int*. Jun-24 2020;142:105891.

65. Barker-Collo S, Bennett DA, Krishnamurthi RV, et al. Sex Differences in Stroke Incidence, Prevalence, Mortality and Disability-Adjusted Life Years: Results from the Global Burden of Disease Study 2013. *Neuroepidemiology*. 2015;45(3):203-14. doi:10.1159/000441103

66. Feigin VL, Nichols E, Alam T, et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*. 2019;18(5):459-480. doi:10.1016/s1474-4422(18)30499-x

67. Tian Y, Liu H, Wu Y, et al. Association between ambient fine particulate pollution and hospital admissions for cause specific cardiovascular disease: time series study in 184 major Chinese cities. *BMJ*. 12 2019;367:l6572.

68. Wellenius GA, Burger MR, Coull BA, et al. Ambient air pollution and the risk of acute ischemic stroke. *Arch Intern Med*. Feb 13 2012;172(3):229-34. doi:10.1001/archinternmed.2011.732

69. Wilker EH, Mostofsky E, Fossa A, et al. Ambient Pollutants and Spontaneous Intracerebral Hemorrhage in Greater Boston. *Stroke*. Oct 18 2018:2764-2766. doi:10.1161/STROKEAHA.118.023128

70. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. *International journal of stroke: official journal of the International Stroke Society*. Jun 2020;15(4):361-364. doi:10.1177/1747493020923472

71. Huang L, Liu Z, Li H, et al. The silver lining of COVID-19: estimation of short-term health impacts due to lockdown in the Yangtze River Delta region, China. *Geohealth*. Jul 7 2020;4(9):e2020GH000272. doi:10.1029/2020GH000272

72. Giani P, Castruccio S, Anav A, Howard D, Hu W, Crippa P. Short-term and long-term health impacts of air pollution reductions from COVID-19 lockdowns in China and Europe: a modelling study. *The Lancet Planetary Health*. 2020;4(10):e474-e482. doi:10.1016/s2542-5196(20)30224-2

73. Zhang K, Batterman S. Air pollution and health risks due to vehicle traffic. *Sci Total Environ*. Apr 15 2013;450-451:307-16. doi:10.1016/j.scitotenv.2013.01.074

74. IQAir. World's most polluted countries 2019 (PM2·5). https:// www.iqair.com/us/world-most-polluted-countries (accessed July 1, 2020).

75. Fisher JA, Puett RC, Laden F, et al. Case-crossover analysis of short-term particulate matter exposures and stroke in the health professionals follow-up study. *Environ Int*. Mar 2019;124:153-160.

76. Gu J, Shi Y, Chen N, Wang H, Chen T. Ambient fine particulate matter and hospital admissions for ischemic and hemorrhagic strokes and transient ischemic attack in 248 Chinese cities. *Sci Total Environ*. May 2020;715:136896.

77. Dong H, Yu Y, Yao S, et al. Acute effects of air pollution on ischaemic stroke onset and deaths: a time-series study in Changzhou, China. *BMJ Open*. Jul-23 2018;8(7):e020425.

78. Chen L, Zhang Y, Zhang W, et al. Short-term effect of PM on hospital admission for ischemic stroke: a multi-city case-crossover study in China. *Environ Pollut*. May 2020;260:113776.

79. Ho AFW, Zheng H, De Silva DA, et al. The Relationship Between Ambient Air Pollution and Acute Ischemic Stroke: A Time-Stratified Case-Crossover Study in a City-State With Seasonal Exposure to the Southeast Asian Haze Problem. *Ann Emerg Med*. Nov 2018;72(5):591-601.

80. Tian Y, Liu H, Zhao Z, et al. Association between ambient air pollution and daily hospital admissions for ischemic stroke: A nationwide time-series analysis. *PLoS Med*. 10 2018;15(10):e1002668.

81. Tian Y, Liu H, Xiang X, et al. Ambient Coarse Particulate Matter and Hospital Admissions for Ischemic Stroke. *Stroke*. Apr 2019;50(4):813-819. doi:10.1161/STROKEAHA.118.022687

82. Qi X, Wang Z, Guo X, et al. Short-term effects of outdoor air pollution on acute ischaemic stroke occurrence: a case-crossover study in Tianjin, China. *Occup Environ Med*. Aug 27 2020;77(12):862-867. doi:10.1136/oemed-2019-106301

83. Wang Z, Peng J, Liu P, et al. Association between short-term exposure to air pollution and ischemic stroke onset: a time-stratified case-crossover analysis using a distributed lag nonlinear model in Shenzhen, China. *Environ Health*. Jan 2 2020;19(1):1. doi:10.1186/s12940-019-0557-4

84. Andersen ZJ, Olsen TS, Andersen KK, Loft S, Ketzel M, Raaschou-Nielsen O. Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen, Denmark. *Eur Heart J*. Aug 2010;31(16):2034-40. doi:10.1093/eurheartj/ehq188

85. Henrotin JB, Besancenot JP, Bejot Y, Giroud M. Short-term effects of ozone air pollution on ischaemic stroke occurrence: a case-crossover analysis from a 10-year population-based study in Dijon, France. *Occup Environ Med*. Jul 2007;64(7):439-45. doi:10.1136/oem.2006.029306

86. Huang F, Luo Y, Guo Y, et al. Particulate Matter and Hospital Admissions for Stroke in Beijing, China: Modification Effects by Ambient Temperature. *Journal of the American Heart Association*. Jul 13 2016;5(7):e003437. doi:10.1161/JAHA.116.003437

87. Lin H, Guo Y, Di Q, et al. Ambient PM2.5 and Stroke: Effect Modifiers and Population Attributable Risk in Six Low- and Middle-Income Countries. *Stroke*. May 2017;48(5):1191-1197. doi:10.1161/STROKEAHA.116.015739

88. Oudin A, Stromberg U, Jakobsson K, Stroh E, Bjork J. Estimation of short-term effects of air pollution on stroke hospital admissions in southern Sweden. *Neuroepidemiology*. 2010;34(3):131-42. doi:10.1159/000274807

89. Tsai SS, Goggins WB, Chiu HF, Yang CY. Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. *Stroke*. Nov 2003;34(11):2612-6.

90. Villeneuve PJ, Johnson JY, Pasichnyk D, Lowes J, Kirkland S, Rowe BH. Short-term effects of ambient air pollution on stroke: who is most vulnerable? *Sci Total Environ*. Jul 15 2012;430:193-201. doi:10.1016/j.scitotenv.2012.05.002

91. Wellenius GA, Schwartz J, Mittleman MA. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among medicare beneficiaries. *Stroke*. Dec 2005;36(12):2549-53. doi:10.1161/01.STR.0000189687.78760.47

92. Chiu HF, Yang CY. Short-term effects of fine particulate air pollution on ischemic stroke occurrence: a case-crossover study. *J Toxicol Environ Health A*. 2013 2013;76(21):1188-97.

93. Guo P, Wang Y, Feng W, et al. Ambient Air Pollution and Risk for Ischemic Stroke: A Short-Term Exposure Assessment in South China. *Int J Environ Res Public Health*. Sep 20 2017;14(9) doi:10.3390/ijerph14091091

94. Maheswaran R, Pearson T, Beevers SD, Campbell MJ, Wolfe CD. Air Pollution and Subtypes, Severity and Vulnerability to Ischemic Stroke-A Population Based Case-Crossover Study. *PloS one*. 2016;11(6):e0158556. doi:10.1371/journal.pone.0158556

95. Matsuo R, Michikawa T, Ueda K, et al. Short-Term Exposure to Fine Particulate Matter and Risk of Ischemic Stroke. *Stroke*. Dec 2016;47(12):3032-3034. doi:10.1161/STROKEAHA.116.015303

96. O'Donnell MJ, Fang J, Mittleman MA, Kapral MK, Wellenius GA, Investigators of the Registry of Canadian Stroke N. Fine particulate air pollution (PM2.5) and the risk of acute ischemic stroke. *Epidemiology*. May 2011;22(3):422-31. doi:10.1097/EDE.0b013e3182126580

97. Byrne CP, Bennett KE, Hickey A, et al. Short-Term Air Pollution as a Risk for Stroke Admission: A Time-Series Analysis. *Cerebrovascular diseases*. 2020;49(4):404-411. doi:10.1159/000510080

98. Sun S, Stewart JD, Eliot MN, et al. Short-term exposure to air pollution and incidence of stroke in the Women's Health Initiative. *Environ Int*. 11 2019;132:105065.

*

99. Vivanco-Hidalgo RM, Wellenius GA, Basagana X, et al. Short-term exposure to traffic-related air pollution and ischemic stroke onset in Barcelona, Spain. *Environ Res*. Apr 2018;162:160-165.
100. Lisabeth LD, Escobar JD, Dvonch JT, et al. Ambient air pollution and risk for ischemic stroke and transient ischemic attack. *Annals of neurology*. Jul 2008;64(1):53-9.
101. Nzwalo H, Guilherme P, Nogueira J, et al. Fine particulate air pollution and occurrence of spontaneous intracerebral hemorrhage in an area of low air pollution. *Clin Neurol Neurosurg*. Jan 2019;176:67-72.
102. Cai Y, Hodgson S, Blangiardo M, et al. Road traffic noise, air pollution and incident cardiovascular disease: A joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. *Environ Int*. May 2018;114:191-201. doi:10.1016/j.envint.2018.02.048
103. Huang K, Liang F, Yang X, et al. Long term exposure to ambient fine particulate matter and incidence of stroke: prospective cohort study from the China-PAR project. *BMJ*. Dec 30 2019;367:l6720. doi:10.1136/bmj.l6720
104. Yuan S, Wang J, Jiang Q, et al. Long-term exposure to PM2.5 and stroke: A systematic review and meta-analysis of cohort studies. *Environ Res*. Oct 2019;177:108587.
105. Noh J, Sohn J, Han M, et al. Long-term Effects of Cumulative Average PM2.5 Exposure on the Risk of Hemorrhagic Stroke. *Epidemiology*. Jul 2019;30:S90-S98.
106. Maheswaran R, Pearson T, Beevers SD, Campbell MJ, Wolfe CD. Outdoor air pollution, subtypes and severity of ischemic stroke--a small-area level ecological study. *Int J Health Geogr*. Jun 17 2014;13:23. doi:10.1186/1476-072X-13-23
107. Adams HP, Bendixen B, Kappelle J, et al. Classification of Subtype of Acute Ischemic Stroke. *Stroke*. January 1993 1993;24(1):35-41.
108. Franchini M, Mannucci PM. Thrombogenicity and cardiovascular effects of ambient air pollution. *Blood*. Sep 1 2011;118(9):2405-12. doi:10.1182/blood-2011-04-343111
109. Tian Y, Xiang X, Wu Y, et al. Fine Particulate Air Pollution and First Hospital Admissions for Ischemic Stroke in Beijing, China. *Sci Rep*. Jun 20 2017;7(1):3897. doi:10.1038/s41598-017-04312-5
110. Sandstrom T, Frew AJ, Svartengren M, Viegi G. The need for a focus on air pollution research in the elderly. *Eur Respir J Suppl*. May 2003;40:92s-95s. doi:10.1183/09031936.03.00403503
111. Xue T, Guan T, Liu Y, et al. A national case-crossover study on ambient ozone pollution and first-ever stroke among Chinese adults: Interpreting a weak association via differential susceptibility. *Sci Total Environ*. Mar-1 2019;654:135-143.
112. Sheel AW, Dominelli PB, Molgat-Seon Y. Revisiting dysanapsis: sex-based differences in airways and the mechanics of breathing during exercise. *Exp Physiol*. Feb 2016;101(2):213-8. doi:10.1113/EP085366
113. Matz CJ, Stieb DM, Davis K, et al. Effects of age, season, gender and urban-rural status on time-activity: CanadianHuman Activity Pattern Survey 2 (CHAPS 2). *Int J Environ Res Public Health*. Feb 19 2014;11(2):2108-24. doi:10.3390/ijerph110202108
114. Guan T, Xue T, Liu Y, et al. Differential Susceptibility in Ambient Particle-Related Risk of First-Ever Stroke: Findings From a National Case-Crossover Study. *American journal of epidemiology*. May 1 2018;187(5):1001-1009. doi:10.1093/aje/kwy007
115. Hahad O, Lelieveld J, Birklein F, Lieb K, Daiber A, Munzel T. Ambient Air Pollution Increases the Risk of Cerebrovascular and Neuropsychiatric Disorders through Induction of Inflammation and Oxidative Stress. *Int J Mol Sci*. Jun 17 2020;21(12)doi:10.3390/ijms21124306
116. Liu H, Tian Y, Xu Y, Zhang J. Ambient Particulate Matter Concentrations and Hospitalization for Stroke in 26 Chinese Cities: A Case-Crossover Study. *Stroke*. Aug 2017;48(8):2052-2059.

117. Chiu HF, Chang CC, Yang CY. Relationship between hemorrhagic stroke hospitalization and exposure to fine particulate air pollution in Taipei, Taiwan. *J Toxicol Environ Health A*. 2014;77(19):1154-63. doi:10.1080/15287394.2014.926801

118. Yorifuji T, Suzuki E, Kashima S. Cardiovascular emergency hospital visits and hourly changes in air pollution. *Stroke*. May 2014;45(5):1264-8.

119. Jolink WMT, Wiegertjes K, Rinkel GJE, Algra A, de Leeuw FE, Klijn CJM. Location-specific risk factors for intracerebral hemorrhage: Systematic review and meta-analysis. *Neurology*. Sep 29 2020;95(13):e1807-e1818. doi:10.1212/WNL.0000000000010418

120. Munzel T, Gori T, Al-Kindi S, et al. Effects of gaseous and solid constituents of air pollution on endothelial function. *Eur Heart J*. Oct 7 2018;39(38):3543-3550. doi:10.1093/eurheartj/ehy481

121. Xu H, Wang T, Liu S, et al. Extreme Levels of Air Pollution Associated With Changes in Biomarkers of Atherosclerotic Plaque Vulnerability and Thrombogenicity in Healthy Adults. *Circ Res*. Mar 2019;124(5):e30-e43. doi:10.1161/CIRCRESAHA.118.313948

122. Kunzli N, Jerrett M, Garcia-Esteban R, et al. Ambient air pollution and the progression of atherosclerosis in adults. *PloS one*. Feb 8 2010;5(2):e9096. doi:10.1371/journal.pone.0009096

123. Li Y, Xu L, Shan Z, Teng W, Han C. Association between air pollution and type 2 diabetes: an updated review of the literature. *Ther Adv Endocrinol Metab*. 2019;10:2042018819897046. doi:10.1177/2042018819897046

124. Ramalle-Gomara E, Ruiz E, Serrano M, Bartulos M, Gonzalez MA, Matute B. Validity of discharge diagnoses in the surveillance of stroke. *Neuroepidemiology*. 2013;41(3-4):185-8. doi:10.1159/000354626

125. Dons E, Laeremans M, Orjuela JP, et al. Wearable Sensors for Personal Monitoring and Estimation of Inhaled Traffic-Related Air Pollution: Evaluation of Methods. *Environ Sci Technol*. Feb 7 2017;51(3):1859-1867. doi:10.1021/acs.est.6b05782

126. Hadley MB, Baumgartner J, Vedanthan R. Developing a Clinical Approach to Air Pollution and Cardiovascular Health. *Circulation*. 02 2018;137(7):725-742.

127. Chapizanis D, Karakitsios S, Gotti A, Sarigiannis DA. Assessing personal exposure using Agent Based Modelling informed by sensors technology. *Environ Res*. Jan 2021;192:110141. doi:10.1016/j.envres.2020.110141

128. Niu Z, Liu F, Yu H, Wu S, Xiang H. Association between exposure to ambient air pollution and hospital admission, incidence, and mortality of stroke: an updated systematic review and meta-analysis of more than 23 million participants. *Environ Health Prev Med*. Jan 26 2021;26(1):15. doi:10.1186/s12199-021-00937-1

129. WHO. Air quality guidelines—global update 2005. 2005. https:// apps.who.int/iris/bitstream/handle/10665/107823/9789289021920eng.pdf?sequence=1&isAllowed=y (accessed July 1, 2020).

130. Diegoli H, Magalhaes PSC, Martins SCO, et al. Decrease in Hospital Admissions for Transient Ischemic Attack, Mild, and Moderate Stroke During the COVID-19 Era. *Stroke*. Aug 2020;51(8):2315-2321. doi:10.1161/STROKEAHA.120.030481

131. Zachary Z, Brianna F, Brianna L, et al. Self-quarantine and weight gain related risk factors during the COVID-19 pandemic. *Obes Res Clin Pract*. May - Jun 2020;14(3):210-216. doi:10.1016/j.orcp.2020.05.004

132. 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*. May 21 2019;92(21):e2444-e2454. doi:10.1212/WNL.0000000000007533

133. 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*. Feb 8 2022;98(6):e573-e588. doi:10.1212/WNL.0000000000013195

134. Maaijwee N, Rutten-Jacobs L, 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.

135. Ferro JM, Massaro AR, Mas J-L. Aetiological diagnosis of ischaemic stroke in young adults. *The Lancet Neurology*. 2010;9(11):1085-1096. doi:10.1016/s1474-4422(10)70251-9

136. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). *Cerebrovascular diseases*. 2013;36(1):1-5. doi:10.1159/000352050

137. Gordon DL, Bendixen BH, Adams HP, Jr., Clarke W, Kappelle LJ, Woolson RF. Interphysician agreement in the diagnosis of subtypes of acute ischemic stroke: implications for clinical trials. The TOAST Investigators. *Neurology*. May 1993;43(5):1021-7. doi:10.1212/wnl.43.5.1021

138. Hennerici MG, Investigators PS. Rationale and design of the Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM) Study. *Cerebrovascular diseases*. 2009;27 Suppl 3:28-32. doi:10.1159/000209263

139. Bousser MG, Amarenco P, Chamorro A, et al. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial. *Lancet*. Jun 11 2011;377(9782):2013-22. doi:10.1016/S0140-6736(11)60600-4

140. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med*. Mar 7 2002;346(10):752-63. doi:10.1056/NEJMra002974

141. Putaala J, Yesilot N, Waje-Andreassen U, et al. Demographic and geographic vascular risk factor differences in European young adults with ischemic stroke: the 15 cities young stroke study. *Stroke*. Oct 2012;43(10):2624-30. doi:10.1161/STROKEAHA.112.662866

142. Adelborg K, Szepligeti SK, Holland-Bill L, et al. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. *BMJ*. Jan 31 2018;360:k96. doi:10.1136/bmj.k96

143. Carlton C, Banks M, Sundararajan S. Oral Contraceptives and Ischemic Stroke Risk. *Stroke*. Apr 2018;49(4):e157-e159. doi:10.1161/STROKEAHA.117.020084

144. Rothman KJ. Causes. *American journal of epidemiology*. Jan 15 1995;141(2):90-5; discussion 89.

145. Vandenbroucke JP, Broadbent A, Pearce N. Causality and causal inference in epidemiology: the need for a pluralistic approach. *Int J Epidemiol*. Dec 1 2016;45(6):1776-1786. doi:10.1093/ije/dyv341

146. Pezzini A, Del Zotto E, Magoni M, et al. Inherited thrombophilic disorders in young adults with ischemic stroke and patent foramen ovale. *Stroke*. Jan 2003;34(1):28-33. doi:10.1161/01.str.0000046457.54037.cc

147. Desai R, Fong HK, Shah K, et al. Rising Trends in Hospitalizations for Cardiovascular Events among Young Cannabis Users (18-39 Years) without Other Substance Abuse. *Medicina (Kaunas)*. Aug 5 2019;55(8)doi:10.3390/medicina55080438

148. Morris JG, Singh S, Fisher M. Testing for inherited thrombophilias in arterial stroke: can it cause more harm than good? *Stroke*. Dec 2010;41(12):2985-90. doi:10.1161/STROKEAHA.110.595199

149. Collaborators GMaCoD. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;8(10053)(388):1459 - 1544.

150. Dearborn JL, Urrutia VC, Zeiler SR. Stroke and Cancer - A Complicated Relationship. *J Neurol Transl Neurosci*. 2014;2(1)

151. Tybjerg AJ, Babore AD, Olsen TS, Andersen KK. Types of occult cancer in stroke and the relation to smoking. *Acta neurologica Scandinavica*. Nov 2020;142(5):486-492. doi:10.1111/ane.13299

152. Vincent L, Leedy D, Masri SC, Cheng RK. Cardiovascular Disease and Cancer: Is There Increasing Overlap? *Curr Oncol Rep*. Apr 6 2019;21(6):47. doi:10.1007/s11912-019-0796-0

153. Aarnio K, Joensuu H, Haapaniemi E, et al. Cancer in young adults with ischemic stroke. *Stroke*. Jun 2015;46(6):1601-6. doi:10.1161/STROKEAHA.115.008694

154. Salazar-Camelo RA, Moreno-Vargas EA, Cardona AF, Bayona-Ortiz HF. Ischemic stroke: A paradoxical manifestation of cancer. *Crit Rev Oncol Hematol*. Jan 2021;157:103181. doi:10.1016/j.critrevonc.2020.103181

155. Netherlands Comprehensive Cancer Organisation (IKNL). NCR data & figures. Updated 2021. Accessed January 4, 2021. https://www.iknl.nl/en/ncr/ncr-data-figures

156. Tybjerg AJ, Skyhoj Olsen T, Andersen KK. Prevalence and risk of occult cancer in stroke. *Acta neurologica Scandinavica*. Mar 2020;141(3):204-211. doi:10.1111/ane.13192

157. Schaapveld M, Aleman BM, van Eggermond AM, et al. Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. *N Engl J Med*. Dec 24 2015;373(26):2499-511. doi:10.1056/NEJMoa1505949

158. Noordzij M, Leffondre K, van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant*. Nov 2013;28(11):2670-7. doi:10.1093/ndt/gft355

159. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. Aug 2007;40(4):381-7. doi:10.1038/sj.bmt.1705727

160. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of Statistics*. 1988;16(3):1141-1154.

161. Selvik HA, Thomassen L, Bjerkreim AT, Naess H. Cancer-Associated Stroke: The Bergen NORSTROKE Study. *Cerebrovascular diseases extra*. Sep-Dec 2015;5(3):107-13. doi:10.1159/000440730

162. Qureshi AI, Malik AA, Saeed O, Adil MM, Rodriguez GJ, Suri MF. Incident cancer in a cohort of 3,247 cancer diagnosis free ischemic stroke patients. *Cerebrovascular diseases*. 2015;39(5-6):262-8. doi:10.1159/000375154

163. Tanislav C, Adarkwah CC, Jakob L, Kostev K. Increased risk for cancer after stroke at a young age: etiological relevance or incidental finding? *J Cancer Res Clin Oncol*. Dec 2019;145(12):3047-3054. doi:10.1007/s00432-019-03022-x

164. Jacob L, Kostev K. Cancer risk in stroke survivors followed for up to 10 years in general practices in Germany. *J Cancer Res Clin Oncol*. Apr 2019;145(4):1013-1020. doi:10.1007/s00432-019-02855-w

165. Rioux B, Gioia LC, Keezer MR. Risk of Cancer Following an Ischemic Stroke in the Canadian Longitudinal Study on Aging. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques*. 2021:1-6. doi:10.1017/cjn.2021.55

166. Ekker MS, Verhoeven JI, Vaartjes I, Jolink WMT, Klijn CJM, de Leeuw FE. Association of Stroke Among Adults Aged 18 to 49 Years With Long-term Mortality. *JAMA*. Jun 4 2019;321(21):2113-2123. doi:10.1001/jama.2019.6560

167. Vondeling GT, Menezes GL, Dvortsin EP, et al. Burden of early, advanced and metastatic breast cancer in The Netherlands. *BMC Cancer*. Mar 7 2018;18(1):262. doi:10.1186/s12885-018-4158-3

168. Lee PN, Forey BA, Coombs KJ. Systematic review with meta-analysis of the epidemiological evidence in the 1900s relating smoking to lung cancer. *BMC Cancer*. 2012;12

169. Akter S, Islam Z, Mizoue T, et al. Smoking and colorectal cancer: A pooled analysis of 10 population-based cohort studies in Japan. *Int J Cancer*. Feb 1 2021;148(3):654-664. doi:10.1002/ijc.33248

*

170. Cocho D, Gendre J, Boltes A, et al. Predictors of occult cancer in acute ischemic stroke patients. *J Stroke Cerebrovasc Dis*. Jun 2015;24(6):1324-8. doi:10.1016/j.jstrokecerebrovasdis.2015.02.006

171. Uemura J, Kimura K, Sibazaki K, Inoue T, Iguchi Y, Yamashita S. Acute stroke patients have occult malignancy more often than expected. *Eur Neurol*. 2010;64(3):140-4. doi:10.1159/000316764

172. Penberthy LT, McClish D, Agovino P. Impact of automated data collection from urology offices: improving incidence and treatment reporting in urological cancers. *J Registry Manag*. 2010;37(4):141-7.

173. Grisold W, Oberndorfer S, Struhal W. Stroke and cancer: a review. *Acta neurologica Scandinavica*. Jan 2009;119(1):1-16. doi:10.1111/j.1600-0404.2008.01059.x

174. Verhoeven JI, Fan B, Broeders MJM, et al. Association of Stroke at Young Age With New Cancer in the Years After Stroke Among Patients in the Netherlands. *JAMA Netw Open*. Mar 1 2023;6(3):e235002. doi:10.1001/jamanetworkopen.2023.5002

175. Navi BB, Reiner AS, Kamel H, et al. Risk of Arterial Thromboembolism in Patients With Cancer. *J Am Coll Cardiol*. Aug 22 2017;70(8):926-938. doi:10.1016/j.jacc.2017.06.047

176. Kwon HM, Kang BS, Yoon BW. Stroke as the first manifestation of concealed cancer. *J Neurol Sci*. Jul 15 2007;258(1-2):80-3. doi:10.1016/j.jns.2007.02.035

177. Kim SJ, Park JH, Lee MJ, Park YG, Ahn MJ, Bang OY. Clues to occult cancer in patients with ischemic stroke. *PloS one*. 2012;7(9):e44959. doi:10.1371/journal.pone.0044959

178. Gon Y, Sakaguchi M, Takasugi J, et al. Plasma D-dimer levels and ischaemic lesions in multiple vascular regions can predict occult cancer in patients with cryptogenic stroke. *European journal of neurology*. Mar 2017;24(3):503-508. doi:10.1111/ene.13234

179. Chen W, He Y, Su Y. Multifocal cerebral infarction as the first manifestation of occult malignancy: Case series of trousseau's syndrome and literature review. *Brain Circ*. Apr-Jun 2018;4(2):65-72. doi:10.4103/bc.bc_1_18

180. Quintas S, Rogado J, Gullon P, et al. Predictors of unknown cancer in patients with ischemic stroke. *J Neurooncol*. May 2018;137(3):551-557. doi:10.1007/s11060-017-2741-0

181. Rosenberg J, Do D, Cucchiara B, Messe SR. D-dimer and Body CT to Identify Occult Malignancy in Acute Ischemic Stroke. *J Stroke Cerebrovasc Dis*. Dec 2020;29(12):105366. doi:10.1016/j.jstrokecerebrovasdis.2020.105366

182. Taccone FS, Jeangette SM, Blecic SA. First-ever stroke as initial presentation of systemic cancer. *J Stroke Cerebrovasc Dis*. Jul-Aug 2008;17(4):169-74. doi:10.1016/j.jstrokecerebrovasdis.2008.01.007

183. Ekker MS, Verhoeven JI, Schellekens MMI, et al. Risk Factors and Causes of Ischemic Stroke in 1322 Young Adults. *Stroke*. Dec 13 2022;doi:10.1161/STROKEAHA.122.040524

184. Halawi R, Moukhadder H, Taher A. Anemia in the elderly: a consequence of aging? *Expert Rev Hematol*. Apr 2017;10(4):327-335. doi:10.1080/17474086.2017.1285695

185. Seystahl K, Gramatzki D, Wanner M, et al. A risk model for prediction of diagnosis of cancer after ischemic stroke. *Sci Rep*. Jan 3 2023;13(1):111. doi:10.1038/s41598-022-26790-y

186. Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. *Circ Res*. Feb 3 2017;120(3):439-448. doi:10.1161/CIRCRESAHA.116.308413

187. (CVDs) WHOCd. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed May 10, 2019.

188. Waje-Andreassen U, Naess H, Thomassen L, Eide GE, Vedeler CA. Long-term mortality among young ischemic stroke patients in western Norway. *Acta neurologica Scandinavica*. Sep 2007;116(3):150-6. doi:10.1111/j.1600-0404.2007.00822.x

189. Naess H, Waje-Andreassen U. Review of long-term mortality and vascular morbidity amongst young adults with cerebral infarction. *European journal of neurology*. Jan 2010;17(1):17-22. doi:10.1111/j.1468-1331.2009.02868.x

190. Koton S, Schneider AL, Rosamond WD, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA*. Jul 16 2014;312(3):259-68. doi:10.1001/jama.2014.7692

191. Marini C, Totaro R, De Santis F, Ciancarelli I, Baldassarre M, Carolei A. Stroke in young adults in the community-based L'Aquila registry: incidence and prognosis. *Stroke*. 2001;32(1):52-56.

192. Giang KW, Bjorck L, Nielsen S, et al. Twenty-year trends in long-term mortality risk in 17,149 survivors of ischemic stroke less than 55 years of age. *Stroke*. Dec 2013;44(12):3338-43. doi:10.1161/STROKEAHA.113.002936

193. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *American journal of epidemiology*. Mar 15 2011;173(6):676-82. doi:10.1093/aje/kwq433

194. Barbieri M, Wilmoth JR, Shkolnikov VM, et al. Data Resource Profile: The Human Mortality Database (HMD). *International Journal of Epidemiology*. 2015;44(5):1549-1556. doi:10.1093/ije/dyv105

195. Harteloh P, de Bruin K, Kardaun J. The reliability of cause-of-death coding in The Netherlands. *European journal of epidemiology*. Aug 2010;25(8):531-8. doi:10.1007/s10654-010-9445-5

196. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *The Lancet Neurology*. 2009;8(4):326-333. doi:10.1016/s1474-4422(09)70047-x

197. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *The Lancet*. 2002;360(9346):1623-1630. doi:10.1016/s0140-6736(02)11600-x

198. Mihaylova B, J E, L B, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *The Lancet*. 2012;380(9841):581-590. doi:10.1016/s0140-6736(12)60367-5

199. Huhtakangas J, Lehto H, Seppa K, et al. Long-Term Excess Mortality After Aneurysmal Subarachnoid Hemorrhage: Patients With Multiple Aneurysms at Risk. *Stroke*. Jul 2015;46(7):1813-8. doi:10.1161/STROKEAHA.115.009288

200. National Agency forWaterways and Public Works. Number of road deaths stable in 2014. https://www.cbs.nl/en-gb/news/2015/18/numberof-road-deaths-stable-in-2014. Published July 5, 2015. Accessed November 14, 2018.

201. Vangen-Lonne AM, Wilsgaard T, Johnsen SH, Carlsson M, Mathiesen EB. Time trends in incidence and case fatality of ischemic stroke: the tromso study 1977-2010. *Stroke*. May 2015;46(5):1173-9. doi:10.1161/STROKEAHA.114.008387

202. Carandang R., Seshadri S., Beiser A., et al. Trends in Incidence, Lifetime Risk, Severity, and 30-Day Mortality of Stroke Over the Past 50 Years. *JAMA*. 2006;296(24):8.

203. Schreuder FH, Sato S, Klijn CJ, Anderson CS. Medical management of intracerebral haemorrhage. *Journal of neurology, neurosurgery, and psychiatry*. Jan 2017;88(1):76-84. doi:10.1136/jnnp-2016-314386

204. Brainin M, Olsen TS, Chamorro A, et al. Organization of stroke care: education, referral, emergency management and imaging, stroke units and rehabilitation. European Stroke Initiative. *Cerebrovascular diseases*. 2004;17 Suppl 2:1-14. doi:10.1159/000074816

*

205. Asadi H, Dowling R, Yan B, Wong S, Mitchell P. Advances in endovascular treatment of acute ischaemic stroke. *Intern Med J*. Aug 2015;45(8):798-805. doi:10.1111/imj.12652

206. 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*. Sep 2014;45(9):2670-6. doi:10.1161/STROKEAHA.114.005648

207. Population; generation, gender, age and origin. Statistics Netherlands. CBS Statline. http://statline.cbs.nl/statweb/publication/?DM= SLNL&PA=37325&D1=0&D2=a&D3=0&D4=a&D6= 18-21&VW=T. Updated July 18, 2017. Accessed January 26, 2017.

208. Rutten-Jacobs LC, Maaijwee NA, Arntz RM, et al. Long-term risk of recurrent vascular events after young stroke: The FUTURE study. *Annals of neurology*. Oct 2013;74(4):592-601. doi:10.1002/ana.23953

209. Tatlisumak T, Cucchiara B, Kuroda S, Kasner SE, Putaala J. Nontraumatic intracerebral haemorrhage in young adults. *Nat Rev Neurol*. Apr 2018;14(4):237-250. doi:10.1038/nrneurol.2018.17

210. van Asch CJJ, Luitse MJA, Rinkel GJE, van der Tweel I, Algra A, Klijn CJM. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *The Lancet Neurology*. 2010;9(2):167-176. doi:10.1016/s1474-4422(09)70340-0

211. Hemphill J, Bonovich D, Besmertis L, Manley G, Johnston S. The ICH Score: A Simple Reliable Grading Scale for Intracerebral Hemorrhage. *Stroke*. 2000;32(4):891-897. doi:10.1161/01.str.32.4.891

212. Koivunen RJ, Satopaa J, Haapaniemi E, et al. Predictors of early mortality in young adults after intracerebral hemorrhage. *Stroke*. Aug 2014;45(8):2454-6. doi:10.1161/STROKEAHA.114.006020

213. Rutten-Jacobs LC, Maaijwee NA, Arntz RM, et al. Clinical characteristics and outcome of intracerebral hemorrhage in young adults. *Journal of neurology*. Nov 2014;261(11):2143-9. doi:10.1007/s00415-014-7469-6

214. Casolla B, Moulin S, Kyheng M, et al. Five-Year Risk of Major Ischemic and Hemorrhagic Events After Intracerebral Hemorrhage. *Stroke*. May 2019;50(5):1100-1107. doi:10.1161/STROKEAHA.118.024449

215. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ*. Feb 5 2013;346:e5595. doi:10.1136/bmj.e5595

216. Casolla B, Dequatre-Ponchelle N, Rossi C, Hénon H, Leys D, Cordonnier C. Heavy alcohol intake and intracerebral hemorrhage: Characteristics and effect on outcome. *Neurology*. 2012;79:1109-1115.

217. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn j. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;(19):604-607.

218. National Institute of Neurogical Disorders and Stroke rtPA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. N Engl J Med 1995; 14: 1581–1587.

219. Moulin S, Labreuche J, Bombois S, et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. *The Lancet Neurology*. 2016;15(8):820-829. doi:10.1016/s1474-4422(16)00130-7

220. Pasquini M, Benedictus MR, Boulouis G, Rossi C, Dequatre-Ponchelle N, Cordonnier C. Incident Cerebral Microbleeds in a Cohort of Intracerebral Hemorrhage. *Stroke*. Mar 2016;47(3):689-94. doi:10.1161/STROKEAHA.115.011843

221. Leys D, Pruvo J, Petit H, Gaudet Y, Clarisse J. Alzheimer's disease. Statistical analysis of CT scanner data. *Rev Neurol (Paris)*. 1989;145(2):134-139.

222. Amin Al Olama A, Wason JMS, Tuladhar AM, et al. Simple MRI score aids prediction of dementia in cerebral small vessel disease. *Neurology*. Mar 24 2020;94(12):e1294-e1302. doi:10.1212/WNL.0000000000009141

223. Pasi M, Casolla B, Kyheng M, et al. Long-term mortality in survivors of spontaneous intracerebral hemorrhage. *International journal of stroke: official journal of the International Stroke Society*. Sep 3 2020:1747493020954946. doi:10.1177/1747493020954946

224. Majhadi L, Leys D, Bodenant M, Henon H, Bordet R, Cordonnier C. Mortality in patients treated by intra-venous thrombolysis for ischaemic stroke. *Journal of neurology*. Jun 2013;260(6):1637-48. doi:10.1007/s00415-013-6847-9

225. Staals J, Makin SDJ, doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology*. 2014;83(14):1228 - 1234.

226. Bernardo F, Rebordao L, Machado S, Salgado V, Pinto AN. In-Hospital and Long-Term Prognosis after Spontaneous Intracerebral Hemorrhage among Young Adults Aged 18-65 Years. *J Stroke Cerebrovasc Dis*. Nov 2019;28(11):104350. doi:10.1016/j.jstrokecerebrovasdis.2019.104350

227. Fonseca AC, Ferro JM. Drug abuse and stroke. *Current neurology and neuroscience reports*. Feb 2013;13(2):325. doi:10.1007/s11910-012-0325-0

228. Ekker MS, Jacob MA, van Dongen MME, et al. Global Outcome Assessment Life-long after stroke in young adults initiative-the GOAL initiative: study protocol and rationale of a multicentre retrospective individual patient data meta-analysis. *BMJ Open*. Nov 14 2019;9(11):e031144. doi:10.1136/bmjopen-2019-031144

229. Antithrombotic Trialists C, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. May 30 2009;373(9678):1849-60. doi:10.1016/S0140-6736(09)60503-1

230. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *The Lancet*. 2004;364(9431):331-337. doi:10.1016/s0140-6736(04)16721-4

231. Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. *Am J Hematol*. Jan 2004;75(1):40-7. doi:10.1002/ajh.10451

232. Easton JD, Aunes M, Albers GW, et al. Risk for Major Bleeding in Patients Receiving Ticagrelor Compared With Aspirin After Transient Ischemic Attack or Acute Ischemic Stroke in the SOCRATES Study (Acute Stroke or Transient Ischemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes). *Circulation*. Sep 5 2017;136(10):907-916. doi:10.1161/CIRCULATIONAHA.117.028566

233. Aarnio K, Siegerink B, Pirinen J, et al. Cardiovascular events after ischemic stroke in young adults. *Neurology*. May 17 2016;86(20):1872-9.

234. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324(7329):71-86. BMJ 2002 Jan 19;324(7330):141. doi:10.1136/bmj.324.7329.71

235. Kasner S, Chalela J, Luciano JM, et al. Reliability and validity of estimating the NIH stroke scale score from medical records. *Stroke*. 1999;30(8):1534-7. doi:10.1161/01.str.30.8.1534

236. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. Jun 14 2011;123(23):2736-47. doi:10.1161/CIRCULATIONAHA.110.009449

237. Arntz RM, van Alebeek ME, Synhaeve NE, et al. The very long-term risk and predictors of recurrent ischaemic events after a stroke at a young age: The FUTURE study. *Eur Stroke J*. Dec 2016;1(4):337-345. doi:10.1177/2396987316673440

*

238. Asberg S, Henriksson KM, Farahmand B, Terent A. Hemorrhage after ischemic stroke - relation to age and previous hemorrhage in a nationwide cohort of 58,868 patients. *International Journal of Stroke*. Feb 2013;8(2):80-6. doi:10.1111/j.1747-4949.2011.00718.x

239. Hilkens NA, Li L, Rothwell PM, Algra A, Greving JP. Refining prediction of major bleeding on antiplatelet treatment after transient ischaemic attack or ischaemic stroke. *Eur Stroke J*. Jun 2020;5(2):130-137. doi:10.1177/2396987319898064

240. van den Brink MJ, Saaltink AL, Groenhof F, et al. Incidence and treatment of heavy menstrual bleeding in general practice. *Fam Pract*. Nov 16 2017;34(6):673-678. doi:10.1093/fampra/cmx050

241. Hilkens N, Algra A, Diener H, et al. Predicting major bleeding in patients with noncardioembolic stroke on antiplatelets: S2TOP-BLEED. *Neurology*. 2017;89(9):936-943. doi:10.1212/WNL.0000000000004289

242. George MG, Tong X, Bowman BA. Prevalence of Cardiovascular Risk Factors and Strokes in Younger Adults. *JAMA Neurol*. Jun 1 2017;74(6):695-703. doi:10.1001/jamaneurol.2017.0020

243. Ekker MS, Verhoeven JI, Rensink KML, et al. Trigger Factors for Stroke in Young Adults: A Case-Crossover Study. *Neurology*. Jan 3 2023;100(1):e49-e61. doi:10.1212/WNL.0000000000201341

244. Ilinca A, Kristoffersson U, Soller M, Lindgren AG. Familial aggregation of stroke amongst young patients in Lund Stroke Register. *European journal of neurology*. Feb 2016;23(2):401-7. doi:10.1111/ene.12881

245. Supanc V, Sonicki Z, Vukasovic I, Solter VV, Zavoreo I, Kes VB. The role of classic risk factors and prothrombotic factor gene mutations in ischemic stroke risk development in young and middle-aged individuals. *J Stroke Cerebrovasc Dis*. Mar 2014;23(3):e171-6. doi:10.1016/j.jstrokecerebrovasdis.2013.09.025

246. MacClellan LR, Giles W, Cole J, et al. Probable migraine with visual aura and risk of ischemic stroke: the stroke prevention in young women study. *Stroke*. Sep 2007;38(9):2438-45. doi:10.1161/STROKEAHA.107.488395

247. Robertson L, Yeoh SE, Broderick C, Stansby G, Agarwal R. Effect of testing for cancer on cancer- or venous thromboembolism (VTE)-related mortality and morbidity in people with unprovoked VTE. *Cochrane Database Syst Rev*. Nov 8 2018;11(11):CD010837. doi:10.1002/14651858.CD010837.pub4

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

249. Mullen MT, Anderson CS. Review of Long-Term Blood Pressure Control After Intracerebral Hemorrhage: Challenges and Opportunities. *Stroke*. Jul 2022;53(7):2142-2151. doi:10.1161/STROKEAHA.121.036885

250. Al-Shahi Salman R, Greenberg SM. Antiplatelet Agent Use After Stroke due to Intracerebral Hemorrhage. *Stroke*. Dec 2023;54(12):3173-3181. doi:10.1161/STROKEAHA.123.036886

251. Schellekens MMI, Springer RCS, Boot EM, et al. Cognitive trajectory in the first year after first-ever ischaemic stroke in young adults: the ODYSSEY study. *Journal of neurology, neurosurgery, and psychiatry*. May 14 2024;95(6):571-579. doi:10.1136/jnnp-2023-332104

252. Edwards JD, Kapoor A, Linkewich E, Swartz RH. Return to work after young stroke: A systematic review. *International journal of stroke: official journal of the International Stroke Society*. Apr 2018;13(3):243-256. doi:10.1177/1747493017743059

253. Verburgt E, Hilkens NA, Ekker MS, et al. Short-Term and Long-Term Risk of Recurrent Vascular Event by Cause After Ischemic Stroke in Young Adults. *JAMA Netw Open*. Feb 5 2024;7(2):e240054. doi:10.1001/jamanetworkopen.2024.0054

A III: Research Data Management

The research presented in this thesis involved human participants and was conducted in accordance with the principles of the declaration of Helsinki and Dutch law for human research (WMO). The handling of data complied with the General Data Protection Regulation 2018 (in Dutch: Algemene Verordening Gegevensbescherming, AVG).

Ethics and privacy

Data presented in **chapter IV, VI,** and **IX** is based on the results from two human studies performed at the Radboudumc Nijmegen. Both studies (ODYSSEY [file number: NL41531.091.12] and FUTURE [NL21086.091.07]) were approved by the local medical ethics committee Region Oost-Nederland (formerly known as Arnhem-Nijmegen) and Informed consent was obtained from all participants (or legal representatives if applicable) to collect and process their data for this research project. Consent was not obtained for sharing the (pseudonymized) data after research. A statement that the studies reported in **chapter VI** and **chapter IX** were not subject to the Dutch Medical Research Involving Human Subjects Act (WMO) and therefore did not require additional informed consent, was obtained from the recognized Medical Ethics Review Committee 'METC Oost-Nederland' (2020-6445, 2020-6443).

The privacy of the participants in these studies was warranted by the use of pseudonymization via a unique subject number assigned to each participant in both the ODYSSEY and FUTURE. The pseudonymization key was stored on the secured department server that was only accessible to members of the project who needed access to it because of their role within the project. The pseudonymization key was stored separately from the research data in a password protected excel file.

Data presented in **chapter VII** is based on the results of a human study performed between 2004 and 2007 at the Lille University Hospital in France. This study (PITCH) was approved by the Internal Review Board of the Lille University Hospital. Informed consent was obtained from all participants (or legal representatives if applicable) to collect and process their data for this research project. Consent was not obtained for sharing the (pseudonymized) data after research.

The pseudonymization key was stored separately from the data at a secured department server of the Lille University Hospital that was only accessible to

members of the project who needed access to it because of their role within the project.

Finally, data presented in **chapter II, V** and **VII** are based on the results of registry-based research. These studies did not include human participants and were performed in accordance to the guidelines of the local medical ethics committee. No ethical review or individual patient consent was required based on the ethical review requirements of the local research ethics committee and due to the use of deidentified data.

Data collection and storage

The data from the ODYSSEY study presented in **chapter IV** and **chapter VI** was collected based on existing health records through electronic Case Report Forms (eCRF) of a prospective data collection in Castor EDC. Data were converged from (electronic) health records or Castor EDC to SPSS (IBM) and R (R Project for Statistical Computing). Data from the FUTURE study was previously gathered from existing health records and study visits between 2010 and 2014.

Study data from the PITCH study described in **chapter VIII** was previously collected and stored on a secured department server of Lille University Hospital. For this study only the pseudonymized data was shared for analyses, which were performed on site in Lille.

Data presented in **chapter II, V** and **VII** were obtained from Statistics Netherlands. The Dutch hospital discharge registry, the Dutch Population Registry and National Cause of Death registry were used, and all analyses were performed in the secured environment of Statistics Netherlands. All output was checked and approved by Statistics Netherlands before public release. All data used for analysis are presented in the tables and supplementary tables of these manuscripts. Pseudonymized data from IKNL was obtained for **chapter VI** and stored on the secured Radboudumc department server.

Processed data and documentation are archived in a Research Documentation Collection (RDC) in the Radboud Data Repository (table 1). These secure storage options safeguard the availability, integrity and confidentiality of the data.

Data sharing according to the FAIR principles

All studies were published with open access.

Research data used in **Chapter II, V** and **VII** are available via Statistics Netherlands (contact: microdata@cbs.nl). Metadata and scripts used for these chapters are available at the Radboud Data Repository (DOI: https://doi.org/10.34973/pr6c-bh78). In **chapter VI** existing and openly available data is used from IKNL (https://iknl.nl/nkr/nkr-cijfers).

Chapter III is a narrative review based on published articles, therefore the data used for this chapter is not published in a data repository.

Chapter IV, VI, and **IX** are based on data from the ODYSSEY (https://www.radboudumc.nl/lopende-onderzoeken/odyssey-onderzoek). The ODYSSEY is still ongoing and therefore data cannot be shared. The metadata and scripts used for these chapters is findable in the Radboud Data Repository; the data is archived with closed access (DOI https://doi.org/10.34973/y1nk-s960).

Research data and scripts from the FUTURE study that are used in **Chapter VII** and **IX**, is archived with closed access (DOI: https://doi.org/10.34973/wa2v-6x07) on the Radboud Data Repository. Raw data cannot be shared because no informed consent was not provided during the duration of this study.

Data from **Chapter VIII** is gathered from the existing PITCH cohort that is owned and managed by Lille University Hospital (https://cheba.unsw.edu.au/consortia/strokog/studies/prognosis-of-intracerebral-haemorrhage-pitch).

Data were made reusable by adding sufficient documentation and by using preferred and sustainable data formats. All data is stored for at least 15 years after completion of the studies and is only accessible for members of the research team or upon reasonable request.

Chapter	RDC	DAC
II, V, VII	Unraveling stroke in the young	Doi: https://doi.org/10.34973/pr6c-bh78
IV, VI, IX		Doi: https://doi.org/10.34973/y1nk-s960
VII, IX		Doi: https://doi.org/10.34973/wa2v-6x07

RDC = Research Documentation Collection, DAC = Data Acquisition Collection

A IV: PhD Portfolio

Abstracts accepted for presentation at international conferences

May 2022	European Stroke Organisation Conference (Lyon, France) Oral presentation: Young stroke: cancer in disguise?
Sept 2021	European Stroke Organisation Conference (Online) Oral presentation: Cryptogenic stroke: Does it really exist?
May 2020	European Stroke Organisation Conference (Online) Oral presentation: The long-term risk of ischemic cardiovascular and bleeding events in young adults after ischemic stroke or transient ischemic attack. Poster: Long-term mortality in young patients with spontaneous intracerebral hemorrhage: predictors and causes of death.
May 2019	European Stroke Organisation Conference (Milan, Italy) Oral presentation: Trends in mortality among young adults with ischemic stroke and intracerebral hemorrhage. Oral presentation: Causes of death following first-ever ischemic stroke or intracerebral hemorrhage in young adults. Poster presentation: Ethnic differences in risk of mortality: The GOAL initiative.
May 2018	European Stroke Organisation Conference (Göteborg, Sweden) Poster presentation: Sex differences in the risk of recurrent vascular events after stroke at young age (Winner of e-poster award)
May 2017	European Stroke Organisation Conference (Prague, Czech Republic) Oral presentation: Long-term risk of mortality after stroke in young adults.

Courses

2023	Statistics for clinical researchers (Nijmegen)
2022	Stroke in the young meeting (Bergen, Norway)
2021	Donders writing week (Nijmegen)
2020	Basiscursus Regelgeving en Organisatie voor Klinische onderzoekers (BROK) (online)

Supervision

2022 – now	Daily supervisor and intended copromotor of Esmée Verburgt, during her PhD-track
2020 – 2022	Daily supervisor of four students (3 medicine students, 1 medical biology) (Anne Mertens, Resa van Lith, Isa Veen and Youssra Allach)

Other research-related activities

June 2024 onwards	Postdoc position working on the multinational ASPIRING trial under supervision of professor Klijn (0.2 FTE)
May 2024	European Stroke Organisation Conference (Basel, Switzerland) Invited speaker in scientific session: Stroke in the young and cancer
2024 onwards	Member of "Externe werkgroep Cijfers Hart & Vaatcijfers" of the Dutch Heart

Foundation

May 2023	European Stroke Organisation Conference (München, Germany) Invited speaker in a teaching course: Air pollution and stroke
2023 onwards	Member of the Editorial Board of the European Journal of Stroke
2022	ESO blog: Verhoeven JI, Casolla B. Contrast-Induced Encephalopathy after endovascular treatment. (eso-stroke.org)
2019	Four week internship at the vascular neurology department of professor Leys at Lille University Hospital (research as well as clinical practice)

A V: Acknowledgements (Dankwoord)

Ik had dit proefschrift nooit alleen kunnen schrijven, hierbij wil ik dan ook iedereen bedanken die een steentje bij heeft gedragen. Een aantal van hen wil ik graag hier in het bijzonder bedanken.

Als eerste wil ik alle patiënten bedanken die vrijwillig hebben deelgenomen aan de ODYSSEY studie, de FUTURE studie en de PITCH (merci à tous). Uiteindelijk is dit proefschrift voor jullie, en dankzij jullie tot stand gekomen.

Beste Frank-Erik / ola FE, met jouw kritische blik en vooral buitengewone en oprechte interesse in het onderzoek "naar de jonkies" ben je altijd motiverend en zorg je dat het beste werk naar boven komt. Ik bewonder vooral jouw grote ideeën, enthousiasme en optimisme binnen de wetenschap. Jij hebt mij, samen met Karin, vanaf dat ik begon als jonge masterstudent veel vertrouwen gegeven en dat vertrouwen ben ik altijd blijven voelen. Jij gaf mij de kans om toen al vol mee te schrijven aan de artikelen met Merel en te blijven werken voor de ODYSSEY tijdens mijn coschappen. Behalve dat ik van jou heb geleerd om wetenschap uit te voeren, heb ik van jou ook geleerd om een wetenschapper te zijn. Jij gaf mij de kans om dingen zelf te doen, zelf een aanvraag te schrijven voor een PhD-beurs, zelf op het grote podium te staan tijdens de 2022 ESOC toen wij waren uitgekozen voor de plenaire sessie, zelf interviews te doen en zelf een postdoc subsidie aan te vragen. En hoewel ik dit alles zelf mocht doen, altijd met jouw hulp, steun en enthousiasme.

Beste Karin, thuis noem ik jou en Frank-Erik ook wel eens mijn werk-mama en -papa. En wat bof ik met dit werk-gezin! Ik weet niet of ik dit ooit verteld heb, maar tijdens mijn sollicitatiegesprek voor de opleiding vroeg Bart aan mij wie mijn voorbeeld was. Ik heb toen zonder twijfel jou genoemd. Ik bewonder jouw toewijding aan het medische vak en de wetenschap en jouw manier van denken en scherpte. Hoeveel tijd er ook tussen zat, als wij weer een meeting hadden, wist jij altijd precies de goede vragen te stellen waardoor ik weer verder kon. Buiten de wetenschap heb je ook veel aandacht voor het persoonlijke: Tijdens de 2023 ESOC was ik je ontzettend dankbaar voor het op sleeptouw nemen bij de Editorial Board meeting van de ESJ en het in mijn handen drukken van een halve liter Weizen bij de conference dinner. Ook in een voor mij best moeilijke periode voelde ik me door jou altijd gehoord en gesteund. Ik ben daarom nog altijd erg blij dat jij mijn tweede promotor bent en erg dankbaar dat ik mijn wetenschapscarrière verder met jou heb mogen voortzetten als postdoc om te werken aan de ASPIRING trial. Ik weet zeker dat ik de komende jaren nog ontzettend veel van je kan gaan leren.

Beste Mireille en Chantal, jullie waren als "outsiders" betrokken bij de aanvraag voor de subsidie voor dit proefschrift en een groot deel van de uitvoering ervan. Het was heel erg leuk en behulpzaam om jullie input te krijgen vanuit de oncologie en epidemiologie/personalized cancer screening. Mireille, zonder ook jouw methodologische kennis waren onze gezamenlijke stukken nooit zo mooi geworden. Stiekem zijn hoofdstuk vijf en zes mijn favorieten in dit proefschrift.

Beste Ilonca, een groot deel van mijn avontuur in de wetenschap begon bij jou met de CBS-data. Ondanks de bloed, zweet en tranen die het heeft gekost om tijdens mijn promotietraject samen met Alicia en Annemarijn het trend-script van SAS naar R te updaten, heb ik er veel profijt van gehad. Jij bent altijd erg behulpzaam geweest met de stukken, zoals toen ik lichte (lees: zware) paniek had over de statistische vragen van de reviewers van de JAMA. Jouw leuke reacties op de manuscripten en onze plannen waren altijd een lichtpuntje. En dan vind ik het ook nog eens ontzettend leuk om nu deel te nemen op jouw voorstel aan de externe werkgroep "Cijfers" van de Hartstichting!

Dear Marco, Barbara and professor Leys (Didier), I had an amazing time during my 4 week visit at Lille University Hospital, and although I absolutely loved the city itself, most of it was due to you three for guiding me and teaching me. Although I could hardly speak any French, I had a great time with Marco at the stroke unit and emergency room. Dear Barbara, thank you for taking me out and about in Lille because you did not want me to feel lonely. Dear professor Leys, thank you for taking the time to work on this research project with us that resulted in chapter VIII of this thesis.

Beste coauteurs, bedankt voor ieders bijdrage aan de dataverzameling, analyse, het meeschrijven en de constructieve commentaren. Mijn speciale dank gaat uit naar de lokale PIs en wetenschapsverpleegkundigen van de ODYSSEY studie zonder wiens deelname we dit bijzondere cohort niet hadden kunnen verzamelen.

De manuscriptcommissie, professor Middeldorp, professor van Herpen en dr Coutinho wil ik bedanken voor het beoordelen van mijn proefschrift en het aanwezig zijn bij de verdediging. Ook Professor van der Worp, Professor Roes, en dr Elias-Smale wil ik bedanken voor het deelnemen aan de promotiecommissie.

Lieve Saskia, Karin en Sharon, dank voor jullie betrokkenheid en moeite bij het bellen van alle deelnemers van de ODYSSEY studie. Altijd als ik bij jullie op de "oude" poli de post voor de ODYSSEY kwam ophalen, kwam ik pas na ruim een

uur weer boven. Bij jullie was het altijd gezellig en een heerlijke afleiding voor als ik toch even geen zin meer had in CRFs invullen of statistische analyses. Sharon, jij verdient speciale dank voor de begeleiding van mijn vader, die niet naar veel mensen luistert, maar gelukkig wel naar jou. Karin, ondanks dat alle vergaderingen met jou erbij twee keer zou lang duren, zijn ze wel ook ruim twee keer gezelliger. Jouw betrokkenheid bij jouw patiënten is bewonderingswaardig en hierbij nogmaals mijn oprechte excuses dat je hoofdstuk 3 uit dit proefschrift moest lezen bij de nonnen tijdens de Engels cursus.

Beste Annet, dank voor al het werk wat jij hebt gedaan voor de ODYSSEY studie, ik denk met plezier terug aan de stapels post die we samen (soms zelfs op zaterdagen) hebben doorgewerkt in mijn student-assistent tijd. Beste Anna, jij was na Annet onze steun en toeverlaat in de ODYSSEY-planning, en met name in de NPO organisatie. Beste Anne en Cato, jullie hebben als geneeskundestudenten met enorm veel enthousiasme en verantwoordelijkheid het stokje van Anna overgenomen.

Lieve Merel en papa, ik had geen twee betere paranimfen kunnen bedenken.

Lieve Merel, dit hele avontuur is bij jou begonnen als wetenschapsstudent in mijn vierde jaar geneeskunde. In de afgelopen jaren hebben we niet alleen veel samengewerkt, aan vele van de hoofdstukken uit dit proefschrift, maar ook een heel goede vriendschap opgebouwd. Ik kijk met veel plezier terug op de wekelijkse werkdate in de COVID tijd waar we samen op zolder in Lent konden werken, ik vaak mocht blijven eten en nog even spelen met Isa en Sophie. Ik keek hier elke week naar uit. Tussen het werken door, bespreken we ook van alles en kan ik altijd al mijn zorgen bij jouw kwijt. Ondanks dat ik initieel student was en jij AIOS en ondertussen ik AIOS ben en jij staflid, heb ik dit nooit zo gevoeld. Dit project voelt echt alsof het van ons beiden is en daarom ben ik superblij dat, nadat ik vorig jaar naast jou mocht staan, je nu als paranimf naast mij staat.

Beste Mayte, Renate en Inge, en beste Loes en Noortje, dank voor het verder mogen werken aan jullie mooie projecten (ODYSSEY en FUTURE), de steun en de gezelligheid op de verschillende ESOCs.

Lieve Mijntje en Esther, samen met Merel en mij vormden wij het team wat de ODYSSEY baseline data compleet ging maken. Samen hebben we de soms eindeloos aanvoelende CRFs ingevuld, door het land gereisd en dossiers doorgespit. Ondanks de gigantische hoeveelheid werk, was het met jullie altijd gezellig! Gelukkig

hebben we in Esmée en Maikel twee heel goeie opvolgers gevonden om verder te werken met de ODYSSEY data.

Ik wil ook al mijn mede-onderzoekers bedanken van de vasculaire onderzoeksgroep die alle werkdagen en congressen leuker hebben gemaakt. Dankjewel Anna, Annemieke, Axel, Bonnie, Esmée, Esther Boot, Esther Janssen, Esther van Leijsen, Floor, Hanna, Hao, Fang, Janneke, Jan Willem, Kim, Lotte, Maaike, Maikel, Marthe, Mayra, Melina, Mengfei, Merel, Mina, Mijntje, Nina, Resa, Sanne en Tessa. Ik ben in deze opsomming vast nog iemand vergeten, waarvoor sorry! Beste Anil en Floris, dank voor de steun en jullie enthousiasme binnen de vasculaire groep! Beste Nina, speciale dank voor jou voor het niet alleen bijdragen aan de ODYSSEY en hoofdstuk VI van dit proefschrift, maar vooral voor jouw interesse, grote kennis van methodologie, statistiek en aandacht voor details. Ik vind het bijzonder en heel erg fijn dat we samen hebben kunnen optrekken in de begeleiding van Esmée. De STOP trial is bij jou in goede handen.

Beste Resa, Youssra, Isa en Anne, ik heb jullie alle vier mogen begeleiden als studenten tijdens mijn promotietraject en ik heb hier enorm van genoten. Jullie waren alle vier enorm gemotiveerd en leergierig, waardoor ik, ondanks ik niet altijd evenveel tijd had, hier altijd energie van kreeg. We hebben samen mooie projecten gedaan, waaronder hoofdstuk III, VI en IX van dit proefschrift.

Lieve Esmée, ik vind het heel bijzonder dat ik jou heb mogen begeleiden tijdens jouw promotietraject en enorm dankbaar dat je dit avontuur met mij hebt aangedurfd en voor het geduld wat hier soms voor nodig was. Het is een waanzinnig proefschrift geworden met prachtige artikelen, die je over niet al te lange tijd zelf ook al mag gaan verdedigen. Samen met Nina en Frank-Erik waren we een mooi team, hoewel het voor jou soms best lastig was als we het niet allemaal met elkaar eens waren;). Ik heb veel van jou geleerd tijdens dit traject, en ik hoop dat je ook wat van mij hebt kunnen leren.

Beste Bas, er zijn twee redenen om jou te noemen in dit dankwoord. Ten eerste, was jouw performance tijdens de grote visite gedurende mijn reguliere neurologie coschap het moment dat ik met zekerheid wist dat ik neuroloog wilde worden. Jouw enorme enthousiasme en hoe jij allerlei reflexen ging testen waar ik nog nooit van gehoord had bij een patiënt op de afdeling, hakte voor mij definitief de knoop door. Ten tweede, was je meteen *on board* toen ik je vroeg om mijn staf-mentor te zijn en ben ik heel dankbaar voor de interesse die je daarbij toont in mij als neuroloog in wording, wetenschapper en mens. Ondanks jouw drukke agenda,

*

neem je altijd de tijd als het belangrijk is, als ik ergens mee zit of om een pitch te oefenen voor een subsidieaanvraag.

Beste Joery en Nicol, ondanks dat ik ondertussen al heel wat jaren bij de vasculaire groep zit, is het uiteindelijk allemaal bij jullie begonnen. Als honours student heb ik bij jullie een fantastische tijd gehad met ons onderzoek naar de ziekte van Brody. Samen de patiënten zien, het wereldwijde contact met de coauteurs van eerdere case reports en natuurlijk de stagetijd in Parijs bij Damien Sternberg en professor Eymard. Het was allemaal geweldig en ik heb nog altijd regelmatig heimwee naar Parijs. Lieve Anouk, wij leerden elkaar kennen in Parijs en waren eigenlijk vanaf dag 1 al onafscheidelijk daar. Lunchen in het park, dansen op de boot bij Concrete en natuurlijk *Grimbergen zondag*, maakte deze stage een groot feest. Ik vind het ontzettend leuk dat je nu ook bent begonnen als AIOS en daarmee ons "masterplan" om samen neuroloog te worden, is uitgekomen.

Lieve Sophie, ik ben echt supertrots op de kaft van dit proefschrift die wij samen hebben gemaakt. Na de middelbare school, waar ik was jou kunst(beeldend) had (wat ik gelukkig meestal kon besteden met tekenen en schilderen) heb ik jarenlang geen kwast meer aangeraakt. Ik ben de creativiteit en de rust die het tekenen gaf best gaan missen in de carrière als arts en wetenschapper. Daarom was ik vastbesloten om de kaft zelf te tekenen en wilde jij mij gelukkig helpen met de vormgeving en het digitaliseren. Enorm bedankt voor al je moeite en hulp!

Lieve Nathalie, Dieuwertje, Laila en Vera, wat begon in de introductie geneeskunde en eerste werkgroepen, groeide al snel uit tot een hechte vriendschap. En wat is er al veel gebeurd. Ik denk met veel plezier terug aan de MFVN feesten, etentjes, wijntjes en tequila, waarbij we eindeloos konden kletsen over de coschappen (sorry Vera, voor alle afkortingen) relaties, gebrek aan relaties en al onze plannen. Ondertussen zien onze werelden er anders uit, maar komen we gelukkig nog steeds samen voor een goeie lunch of borrel en kunnen we nog steeds alle verhalen delen.

Lieve Nathalie, onze band heb ik altijd bijzonder gevonden. We hebben vaak gezegd dat we eigenlijk dezelfde persoon zijn, niemand snapt mijn onzekerheden en gedachtegangen beter dan jij. Je hebt teveel ellende op je bord gekregen en ik vind dat ik er niet altijd genoeg ben geweest voor je. Ik hoop dat het komende jaar er meer zon voor jou gaat schijnen en we nog jaren als twee oude omaatjes samen thee of een wijntje kunnen drinken en kunnen kletsen over van alles en niets.

Lieve Vera, als mede PhDer binnen onze vriendinnengroep hebben we afgelopen jaren veel kunnen delen; frustraties maar ook vreugde. Jij bent altijd optimistisch en staat open naar de wereld, daaraan heb ik me vaak kunnen optrekken. Dank voor alle leuke vrijdagmiddagborrels en vakanties die we samen hebben gehad (Sziget, Friesland, Sevilla en natuurlijk de American roadtrip vanuit Boston). Laten we deze borrels en tripjes zeker weer gaan introduceren.

Lieve N.D.T. (Nimma danst thuis); Anne Fleur, Bobby, Corneel, Frank, Guido, Larissa, Loes, Maikel, Thijs, Tim van Benthem, Tim van Straaten en Tirsa. Wat een stel. Ik kan me nog zo goed herinneren dat Larissa mij voor het eerst naar jullie meenam op koningsdag en ik behalve van de ene verbazing in de andere viel, mij zelden bij anderen zo heb thuis gevoeld. Ondanks dat we elke vrijdagavond samen doorbrachten in de Gouverneur, daar kletsten, wijn dronken en nachten samen dansten in Doornroosje, kwam ik er pas na twee jaar achter dat jullie niet allemaal biologie studeerden maar scheikunde, want daar hadden we het nooit over. Inmiddels kennen we elkaar al tien jaar en hebben we allemaal mindere en betere periodes doorgemaakt, gelukkig zijn we er voor elkaar op een heerlijke soms serieuze en minder serieuze manier.

Lieve Larissa, mijn allerbeste vriendinnetje. Wie had dat gedacht, toen we voor het eerst samen in een werkgroep zaten bij geneeskunde, voor de buitenwereld twee polar opposites. Maar jij had al snel gezien dat wij eigenlijk ook heel veel gemeen hadden en zo ontstond een hele sterke vriendschap; of was het toch vooral voor de samenvattingen…? Jij hebt mij altijd gesteund in mijn ambities en tijdens dit promotietraject, maar hield ook altijd aandacht voor de leuke dingen naast werk en studie. Ik vind het heerlijk om er samen op uit te gaan, maar stiekem het meest om samen op de bank te zitten met een of andere vreselijke reality serie aan en eindeloos te kletsen. Lieve Laris, jij bent zo authentiek en goed zoals je bent, dat je dat maar weet.

Lieve Bart, mijn studiemaatje. Dagen hebben we doorgebracht in de bibliotheek om te studeren voor de bloktoetsen. Jouw eindeloze optimisme en plezier, vrolijkt mij altijd op. Jouw vermogen om tot in de diepe nacht op de tafels te dansen en in de ochtend fris en fruitig in de collegezaal te zitten of in de sportschool te staan, is legendarisch en heeft zelfs een eigen term gekregen “een Bartje doen”. Ik heb ook warme herinneringen aan onze twee weekenden samen tijdens de Honours stage; in Brussel en Parijs. Ik vind het superleuk dat we contact hebben gehouden en nog af en toe samen eten!

*

Lieve Luuk, niet iedereen zal weten dat jij heel veel hebt bijgedragen aan het tot stand komen van dit proefschrift. Menig script is geschreven of op zijn minst verbeterd met jouw eindeloze programmeer skills. Ik kijk met veel plezier terug op onze skype gesprekken waarbij jij mij hielp met een stuk code als ik er niet uit kwam. Voor jou vaak op gekke momenten vanwege het tijdsverschil met Canada, maar je was nooit te beroerd om te helpen. Ik vond het ook heel fijn dat je echt trots op mij was, als ik dan wel zelf iets had geschreven en het werkte. Jij ging mij al voor in het verdedigen van jouw proefschrift in London, Ontario. Luuk, ik ben ook heel trots op jou in alles wat je hebt bereikt en ik hoop dat je snel hier iets vindt waar je mee verder wil.

Lieve papa, ik wist meteen dat jij mijn paranimf moest worden en ik ben heel blij dat jij dit wilde doen. Jij hebt mij zien spreken op mijn eerste congres in Praag, en tot mijn grote horror, terwijl je tussen Frank-Erik en Karin in zat, het hele praatje met jouw telefoon hebt gefilmd. Je was daarbij omdat je mij in twee dagen heen en weer hebt gereden omdat ik niet meer dagen vrij kreeg van coschap. Jij hebt aan een blik genoeg om te weten wat er in mij omgaat. Zelfs zonder blik, maar na enkele woorden aan de telefoon heb je mij altijd feilloos door. Veelal vrij irritant;). Gelukkig werkt dit ondertussen ook andersom, en kan ik er ook af en toe voor jou zijn.

Lieve mama, ik heb het vaak grappend over “familiebedrijf Verhoeven” bij dit proefschrift, met Luuk die hielp met de scripts, papa die mij overal heen bracht en jij die alle stukken nakeek op het Engels. Je staat altijd paraat om te helpen en mee te denken. Ik vind het zo fijn dat we samen over alles kunnen kletsen en dat we nog steeds samen naar de stad gaan om te winkelen en samen eventjes koffie kunnen gaan drinken. Ik weet dat jij altijd trots op mij zal zijn (net als papa), en deze onvoorwaardelijke steun is iets magisch. En hoewel jij niet altijd even trots bent op jezelf, ben ik dat net zo goed onvoorwaardelijk altijd wel.

Liefste Tim, voor jou de laatste plek in dit dankwoord. Jij hebt alles op zijn kop gezet. Bij jou vind ik echte rust, maar jij hebt ook mijn wereld groter gemaakt door jouw optimisme, jouw vrijheid en jouw interesse in zoveel dingen. Ik ben zo trots op het thuis wat we samen gemaakt hebben en het leven waar we samen aan bouwen. Bij jou kan ik helemaal mezelf zijn, bij jou kan ik “pruttelen”, bij jou kan ik huilen, bij jou kan ik lachen en met jou kan ik alles.

A VI: About the author

Jamie was born together with her twin brother Luuk on July 20th 1994 in the Radboud University Medical Center in Nijmegen. She attended the SSgN for her pre-university education (VWO) and graduated cum laude in 2012.

The following year, she moved to Groningen and started studying human movement sciences at the Rijksuniversiteit Groningen. However, after obtaining her propaedeutic exam, she switched to studying Medicine at the Radboud University in Nijmegen and moved back to Nijmegen. During her bachelor degree, she took part in the Honours Programme for Medical Sciences and spent four months at the Institute of Myology in Paris for a research internship. As part of her master degree she did a research internship at the neurovascular research group of Professor Frank-Erik de Leeuw and professor Karin Klijn on the epidemiology of stroke in the young. While doing this internship, she started working on the ODYSSEY as a research-assistant, which she continued during the final years of her master. In 2019 she spent four weeks in Lille for a combined research and clinical visit at the neurovascular department of professor Leys at Lille University hospital. In 2020, she graduated cum laude from her master degree in Medicine.

After obtaining her medical degree and receiving a personal PhD-grant from the Radboud University Medical Center, she started her PhD project on stroke in the young under the supervision of professor Frank-Erik de Leeuw and professor Karin Klijn. In September 2021, she combined her PhD track with a residency in Neurology also at the Radboud University Medical Center. In June 2024 while finishing this thesis, she started as a postdoctoral researcher under supervision of professor Klijn working on the Dutch arm of the multinational ASPIRING trial.

Jamie lives with her fiancé Tim in their house in Nijmegen-Noord.

A VII: List of publications

Publications in this thesis

1. Verhoeven JI, Fan B, Broeders MJM, Driessen CML, Vaartjes ICH, Klijn CJM, de Leeuw FE. *Association of stroke at young age with new cancer in the years after stroke among patients in the Netherlands.* JAMA Network Open. 2023;6(3):e235002.
2. Ekker MS, Verhoeven JI, Schellekens MMI, et al. *Risk Factors and Causes of Ischemic Stroke in 1322 Young Adults*. Stroke. 2023 Feb;54(2):439-447. Epub 2022 Dec 13.
3. Verhoeven JI, van Lith TJ, Ekker MS, Hilkens N, Klijn CJM, de Leeuw FE. *The long-term risk of bleeding- and cardiovascular events in young adults after ischemic stroke or transient ischemic attack.* Neurology. Aug 2022, 99 (6) e549-e559.
4. Verhoeven JI, Allach Y, Vaartjes CH, Klijn CJM, de Leeuw FE. *Ambient air pollution and the risk of ischemic stroke and intracerebral hemorrhage.* Lancet Planetary Health, *5*(8), e542-e552.
5. Verhoeven JI, Pasi M, Casolla B, Hénon H, de Leeuw FE, Leys D, Klijn CJM, Cordonnier C. *Long-term mortality in young patients with spontaneous intracerebral haemorrhage: Predictors and causes of death*. European Stroke Journal 6(2): 185-193.
6. Ekker MS*, Verhoeven JI*, Vaartjes CH, Jolink WMH, Klijn CJM, de Leeuw FE. *Association of Stroke Among Adults Aged 18 to 49 Years With Long Term Mortality.* JAMA. 2019;321(21):2113-2123. *Shared 1st author
7. Ekker MS*, Verhoeven JI*, Vaartjes CH, 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. *Shared 1st author

Articles submitted in this thesis

1. Verhoeven JI, Veen I, Hilkens NA, et al. *Patient- and stroke characteristics in young adults with ischemic stroke or transient ischemic attack associated with underlying cancer*. Submitted.

Publications not in this thesis

Scientific journals

1. Verburgt E, Verhoeven JI, Hilkens NA, Vaartjes I, de Leeuw FE. *Age-Specific Rural-Urban Disparities in the Incidence of Ischemic Stroke in the Netherlands*. Neurology. 2024 Dec 24;103(12):e210102.

2. Schellekens MMI, Li H, Boot EM, Verhoeven JI, et al. *White matter integrity and cognitive performance in the subacute phase after ischemic stroke in young adults.* Neuroimage Clin. 2024 Nov 23:45:103711.
3. Yi H, Jacob MA, Verhoeven JI, Cai M, Duering M, Tuladhar AM, de Leeuw FE. *Baseline and longitudinal MRI Markers Associated With 16-Year Mortality in Patients With Cerebral Small Vessel Disease.* Neurology. 2024 Sep 24:103(6):e209701.
4. Reumers SFI, Schellekens MMI, Lugtmeijer S, Maas RPPWM, Verhoeven JI, et al; ODYSSEY study group. *Cognitive impairment in young adults following cerebellar stroke: Prevalence and longitudinal course.* Cortex. 2024 Sep;178:104-115.
5. Immens MH, Ekker MS, Verburgt E, Verhoeven JI, et al**.** *Trigger factors in patients with a patent foramen ovale-associated stroke: A case-crossover study.* Int J Stroke. 2024 Apr 2:17474930242625
6. Verburgt E, Hilkens NA, Ekkers MS, …, Verhoeven JI*. *Short-Term and Long-Term Risk of Recurrent Vascular Event by Cause After Ischemic Stroke in Young Adults*. JAMA Network Open. 2024;7(2):e240054. *Last author
7. Verhoeven JI, Kramer J, Seeger J, et al. *Brody Disease, an Early Onset Myopathy With Delayed Relaxation and Abnormal Gait: A Case Series of 9 Children.* Neurology. 2024 Mar 12;102(5):e209164
8. Schellekens MMI, Springer RCS, Boot EM, Verhoeven JI, et al. *Cognitive trajectory in the first year after first-ever ischaemic stroke in young adults: the ODYSSEY study*. J Neurol Neurosurg Psychiatry. 2023 Dec:jnnp-2023-332104
9. Ekker MS, Verhoeven JI, Rensink K, et al. *Trigger Factors for Stroke in Young Adults: A Case-Crossover Study*. Neurology Sep 2022, 10.1212/WNL.0000000000020134.
10. Schellekens MMI, Boot EM, Verhoeven JI, et al. *Subacute cognitive impairment after first-ever transient ischemic attack or ischemic stroke in young adults: The ODYSSEY study.* European Stroke Journal. 2022 Epub. October 31, 2022.
11. Verhoeven, JI, Ten Cate, TJF & de Leeuw, FE (2021). Editorial: *The COVID-19 lockdown: a curse or a blessing for acute cardiovascular disease?* Netherlands Heart Journal*, 29*(4), 188-192.
12. van Nieuwenhuizen KM, Vaartjes CH, Verhoeven JI, Rinkel GJ, Kapelle JL, Schreuder FHBM, Klijn CJM. *Long-term prognosis after intracerebral haemorrhage*. European Stroke Journal. 2020; 92(21):e2444-e2454.
13. Molenaar JPF, Verhoeven JI, Rodenburg RJ et al. *Clinical, morphological and genetic characterization of Brody disease: an international study of 40 patients.* Brain. 2020;143(2):452-466.

*

Other publications

14. **ESO Blog:** Verhoeven JI, Casolla B. *Contrast-Induced Encephalopathy after endovascular treatment: An underestimated entity* - European Stroke Organisation (eso-stroke.org)
15. **Book chapter:** Verhoeven JI, Ekker MS, de Leeuw FE. *Stroke in young adults: Chapter 11 Post-stroke Medical Management after ischemic stroke in young adults*. In print
16. **Book chapter:** Verhoeven JI, Richard E. *Het Handboek voor de coassistent: Hoofdstuk 8 Het neurologisch onderzoek (5e druk)*. Amsterdam, Bohn Stafleu van Loghum (BSL). 2021

A VIII: Dissertations of the vascular disorders of movement research group Nijmegen

- Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, 12 March 2010
- Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011
- Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, 30 November 2011
- Rob Gons. Vascular risk factors in cerebral small vessel disease. A diffusion tensor imaging study. Radboud University Nijmegen, 10 December 2012
- Loes C.A. Rutten-Jacobs. Long-term prognosis after stroke in young adults. Radboud University Nijmegen, 14 April 2014
- Noortje A.M.M. Maaijwee. Long-term neuropsychological and social consequences after stroke in young adults. Radboud University Nijmegen, 12 June 2015
- Nathalie E. Synhaeve. Determinants of long-term functional prognosis after stroke in young adults. Radboud University Nijmegen, 28 September 2016
- Anil M. Tuladhar. The disconnected brain: mechanisms of clinical symptoms in small vessel disease. Radboud University Nijmegen, 4 October 2016
- Pauline Schaapsmeerders. Long-term cognitive impairment after first-ever ischemic stroke in young adults: a neuroimaging study. Radboud University Nijmegen, 24 January 2017
- Ingeborg W.M. van Uden. Behavioral consequences of cerebral small vessel disease; an MRI approach. Radboud University Nijmegen, 14 February 2017
- Renate M. Arntz. The long-term risk of vascular disease and epilepsy after stroke in young adults. Radboud University Nijmegen, 16 February 2017
- Helena M. van der Holst. Mind the step in cerebral small vessel disease. Brain changes in motor performance. Radboud University Nijmegen, 5 April 2017
- Joyce Wilbers. Long-term neurovascular complications in cancer patients. Radboud University Nijmegen, 25 September 2017
- Frank G. van Rooij. Transient neurological attacks. Neuroimaging, etiology, and cognitive consequences. Radboud University Nijmegen, 14 June 2018
- Tessa van Middelaar. Memory under pressure: blood pressure management to prevent dementia. Radboud University Nijmegen, 5 November 2018
- Esther M.C. van Leijsen. Unraveling the heterogeneity of cerebral small vessel disease. From local to remote effects. Radboud University Nijmegen, 19 November 2018 366

- Mayte E. van Alebeek. Risk factors and prognosis of stroke in young adults: What to expect? Radboud University Nijmegen, 18 October 2019
- Selma Lugtmeijer. Neurocognitive mechanisms of visual working memory and episodic memory in healthy aging and after stroke. University of Amsterdam, 25 September 2020
- Annemieke ter Telgte. On the origin of cerebral small vessel disease. From in vivo to ex vivo to histopathology. Radboud University Nijmegen, 9 Juni 2020
- Kim Wiegertjes. Ischemic and hemorrhagic MRI markers of cerebral small vessel disease. Two sides of the same coin? Radboud University Nijmegen, 16 September 2021
- Marthe Smedinga. Diseased without symptoms. Radboud University Nijmegen, 5 Oktober 2021.
- Mengfei Cai. Temporal dynamics of cerebral mall vessel disease. A motor perspective. Radboud University Nijmegen, 19 April 2022
- Thijs Landman. Ischemic conditioning and exercise as treatment for cerebrovascular disease. Squeeze the arm to protect the brain? Radboud University Nijmegen, 28 Juni 2022
- Ileana Camerino. White matter tracts associated with executive aspects of language production in small vessel disease and stroke. Radboud University Nijmegen, 27 September 2022
- Merel Ekker. Stroke in the young: From Epidemiology to prognosis. Radboud University Nijmegen, 27 September 2022
- Hanna Abdulrahman. Dementia risk factors and diagnostics. Radboud University Nijmegen, 5 juli 2023
- Anna M. de Kort. Cerebral amyloid angiopathy: novel insights on prevalence and fluid biomarkers. Radboud University Nijmegen, 17 April 2024
- Lotte Sondag. Towards new acute treatments for spontaneous intracerebral hemorrhages. Radboud University Nijmegen, 30 September 2024
- Mayra I. Bergkamp. The clinical spectrum of cerebral small vessel disease. Radboud University Nijmegen, 4 December 2024

*

Donders Graduate School

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 700 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher

education. Others continue in a wide range of positions, such as policy advisors, project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit:

http://www.ru.nl/donders/graduate-school/phd/

DONDERS INSTITUTE

Radboud University

Radboudumc