Erasmus MC
University Medical Center Rotterdam

Burden of stroke and its vascular risk factors

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Departments of Neurology & Epidemiology, Erasmus MC

The global burden of neurological disorders: translating evidence into policy

Valery L Feigin, Theo Vos, Emma Nichols, Mayowa O Owolabi, William M Carroll, Martin Dichgans, Günther Deuschl, Priya Parmar, Michael Brainin, Christopher Murray

Neurological disorders are the leading cause of disability and the second leading cause of death worldwide. In the past *Lancet Neurol* 2020; 19: 255–65

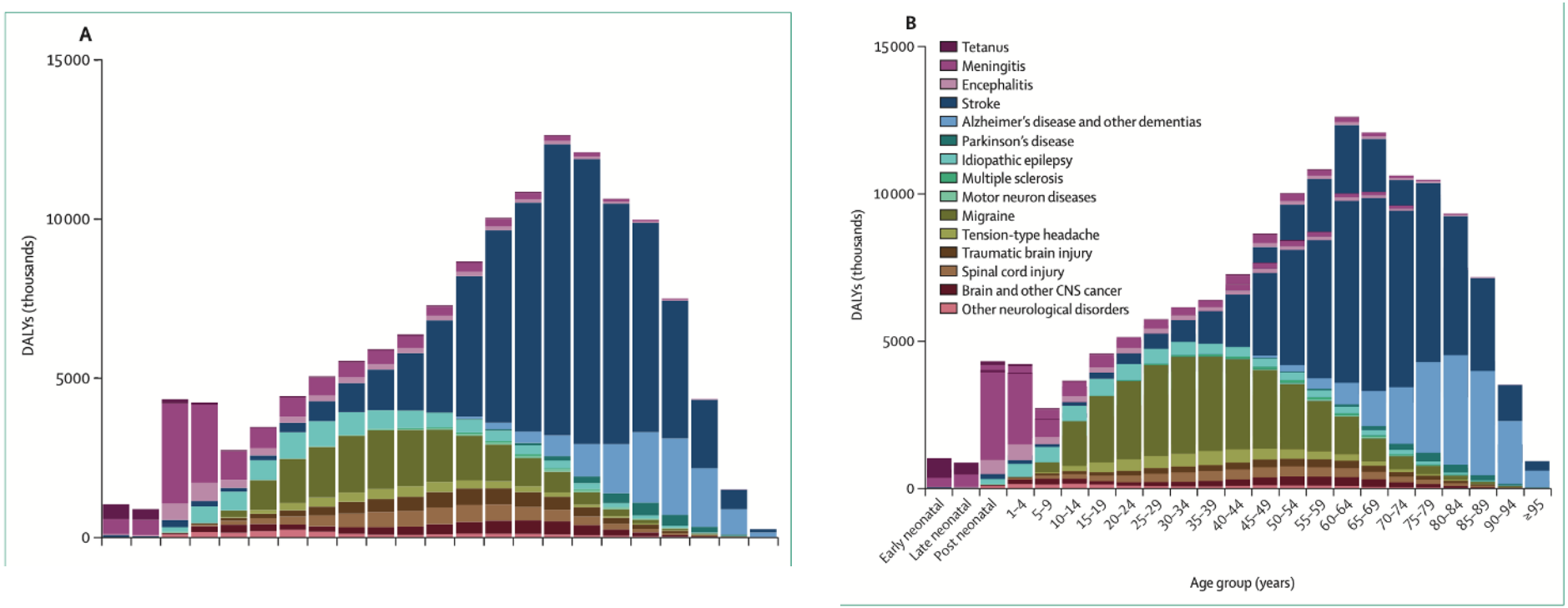


Figure 2: **Global DALYs by age for various neurological disorders in 2016**
Proportions for men (A) and women (B). Early neonatal is 0–7 days; late neonatal is 7–28 days; post-neonatal is 28 days to 1 year. Reproduced from Feigin and colleagues,[1] by permission of Elsevier. DALY=disability-adjusted life-year.

Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019

*GBD 2019 Stroke Collaborators**

Lancet Neurol 2021; 20: 795–820

Summary

Background Regularly updated data on stroke and its pathological types, including data on their incidence, prevalence,

	Incidence (95% UI)		Deaths (95% UI)		Prevalence (95% UI)		DALYs (95% UI)	
	2019	Percentage change, 1990–2019	2019	Percentage change, 1990–2019	2019	Percentage change, 1990–2019	2019	Percentage change, 1990–2019
Ischaemic stroke								
Absolute number, millions	7·63 (6·57 to 8·96)	88·0% (83·0 to 92·0)	3·29 (2·97 to 3·54)	61·0% (46·0 to 75·0)	77·19 (68·86 to 86·46)	95·0% (92·0 to 99·0)	63·48 (57·83 to 68·99)	57·0% (43·0 to 68·0)
Age-standardised rate, per 100 000 people	94·51 (81·9 to 110·76)	−10·0% (−12·0 to −8·0)	43·50 (39·08 to 46·77)	−34·0% (−39·0 to −28·0)	951·0 (849·2 to 1064·1)	−2·0% (−3·0 to 0·0)	798·8 (727·5 to 866·9)	−29·0% (−35·0 to −23·0)
Intracerebral haemorrhage								
Absolute number, millions	3·41 (2·97 to 3·91)	43·0% (41·0 to 45·0)	2·89 (2·64 to 3·10)	37·0% (22·0 to 51·0)	20·66 (18·02 to 23·42)	58·0% (56·0 to 60·0)	68·57 (63·27 to 73·68)	25·0% (12·0 to 36·0)
Age-standardised rate, per 100 000 people	41·81 (36·53 to 47·88)	−29·0% (−30·0 to −28·0)	36·04 (32·98 to 38·67)	−36·0% (−43·0 to −29·0)	248·8 (217·1 to 281·4)	−17·0% (−18·0 to −15·0)	823·8 (769·2 to 894·7)	−37·0% (−43·0 to −31·0)
Subarachnoid haemorrhage								
Absolute number, millions	1·18 (1·01 to 1·39)	61·0% (56·0 to 65·0)	0·37 (0·33 to 0·42)	−12·0% (−25·0 to 26·0)	8·40 (7·19 to 9·83)	65·0% (60·0 to 68·0)	11·18 (9·89 to 12·67)	−14% (−26·0 to 17·0)
Age-standardised rate, per 100 000 people	14·46 (12·33 to 16·94)	−17·0% (−19·0 to −15·0)	4·66 (4·13 to 5·17)	−57·0% (−64·0 to −39·0)	101·6 (87·1 to 118·5)	−37·0% (−43·0 to −31·0)	136·5 (120·8 to 154·7)	−54·0% (−61·0 to −37·0)
Total stroke								
Absolute number, millions	12·22 (11·04 to 13·59)	70·0% (67·0 to 73·0)	6·55 (6·00 to 7·02)	43·0% (31·0 to 55·0)	101·47 (93·21 to 110·53)	85·0% (83·0 to 88·0)	143·23 (133·10 to 153·24)	32·0% (22·0 to 42·0)
Age-standardised rate, per 100 000 people	150·8 (136·5 to 167·5)	−17·0% (−18·0 to −15·0)	84·2 (76·8 to 90·2)	−36·0% (−42·0 to −31·0)	1240·3 (1139·7 to 1353·0)	−6·0% (−7·0 to −5·0)	1768·1 (1640·7 to 1889·4)	−36·0% (−42·0 to −31·0)

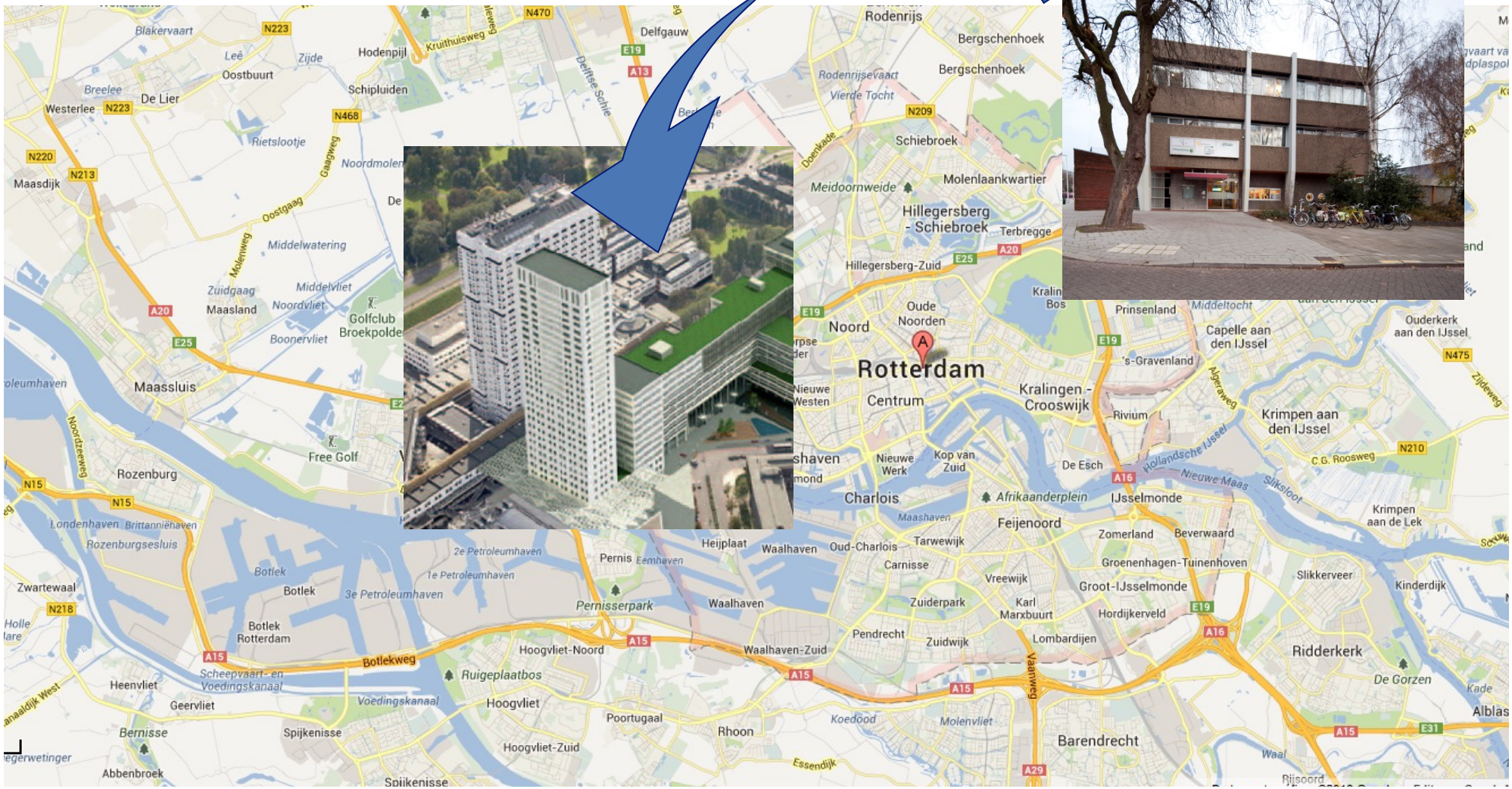
Absolute numbers in millions and age-standardised rates per 100 000 people are presented to two decimal places and percentage change is shown to one decimal place. UI=uncertainty interval. DALY=disability-adjusted life-year.

Table 1: **Absolute number and age-standardised rates per year of incident and prevalent strokes, deaths from stroke and DALYs due to stroke in 2019, and percentage change globally for 1990–2019, by pathological types of stroke**

The Rotterdam Study

- A prospective cohort Study ongoing since 1990

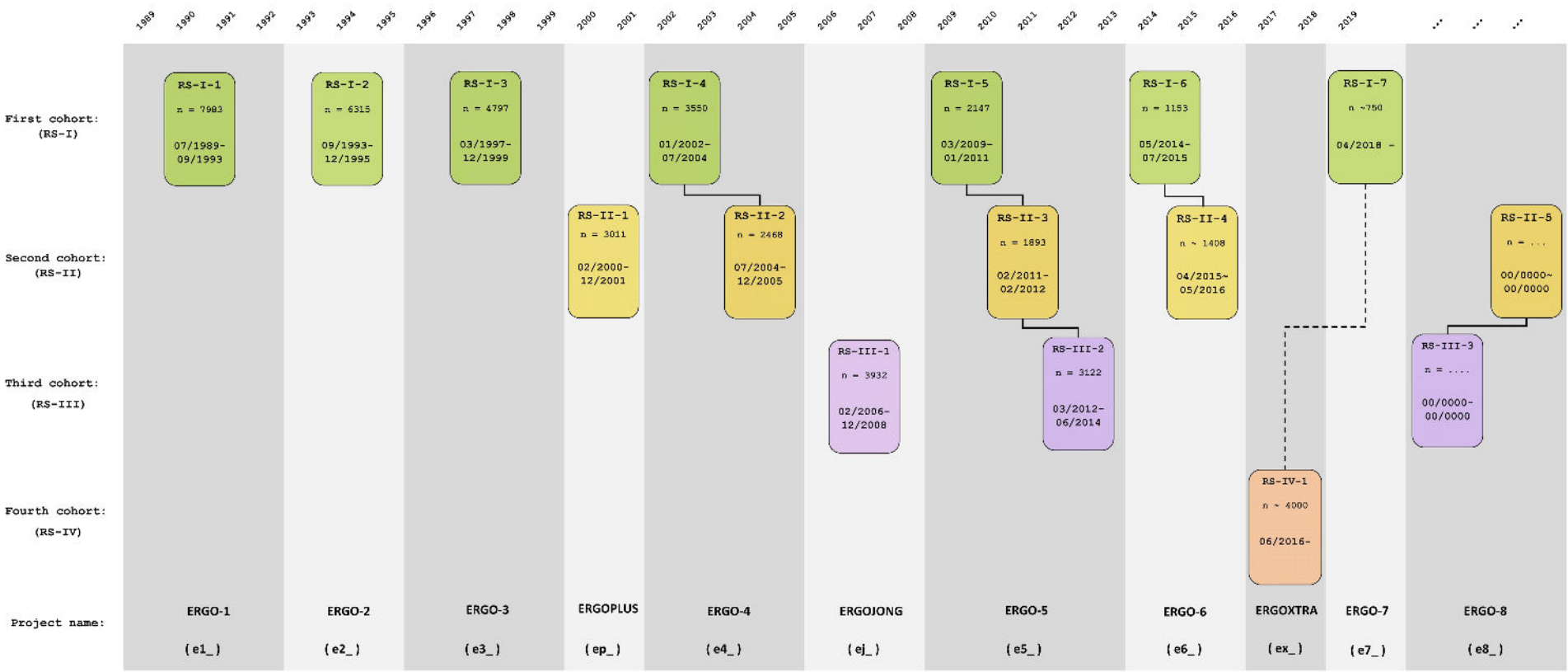
The Rotterdam Study - Erasmus MC



The Rotterdam Study

- Initial aim: focus on cardiovascular, endocrine, ophthalmological and **neurological** diseases.
- Prospective population-based cohort study, on-going since 1990.
- Over the years, both cohort and scope extended.
- Overall response rate ~72%.
- In total ~20.000 subjects, aged > 40 years.

The Rotterdam Study



Measurements

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Cardiovascular

- *Cardiovascular outcomes: HF, AF, CHD, …*
- *Cardiovascular risk factors*
- *Atherosclerosis*
- ***Nutrition** and lifestyle*

Neurological

- *Neurological outcomes: Stroke, Dementia, Parkinson, **Migraine**, Cognition assessment*
- ***Polyneuropathy, EMG, gait***

Dermatology

- ***Full body skin examination***
- ***Skin aging score: wrinkling, pigmentary spots, …***
- ***Hair loss***

Locomotor

- *DXA-based BMD*
- *OA with X-ray*
- ***Muscle strength***

Gastro-intestinal

- ***Abdominal ultrasound***
- ***Steatosis***
- ***Fibrosis***
- ***Gut screening***

Ophthalmic Otolaryngological

- *AMD, myopia, glaucoma*
- *Retinal vessel diameters*
- ***Hearing loss, vestibular function***

Psychiatric

- *Depression, **grief, satisfaction**, Anxiety*
- ***Sleep pattern***

Respiratory

- *COPD, pneumonia, lung asthma, cancer*

*Genetic, **epigenetic, omics***

Imaging

Pharmacology

Clinical endpoints and diagnoses

- Death
- Myocardial infarction
- Heart failure
- Atrial fibrillation
- Diabetes mellitus
- Chronic kidney disease
- NAFLD
- Liver fibrosis
- COPD
- Osteoporosis
- Fractures
- Stroke
- Dementia / Alzheimer
- Cancer
- Thyroid disease
- Glaucoma
- Macular degeneration
- Myopia
- Hearing loss
- Restless legs syndrome
- Polyneuropathy
- Osteoarthritis
- Psoriasis
- Eczema
- Parkinson disease
- Migraine

Neurologic diseases

- Dementia (including Alzheimer's disease)
- Cerebrovascular diseases:
  - ✓ ischemic stroke
  - ✓ intracerebral hemorrhage
  - ✓ TIA/TNA
- Parkinsonism and M. Parkinson
- Migraine
- Polyneuropathy

Diagnostic workflow

- Two approaches:

- 1990 2023

✓ In person assessments at research center

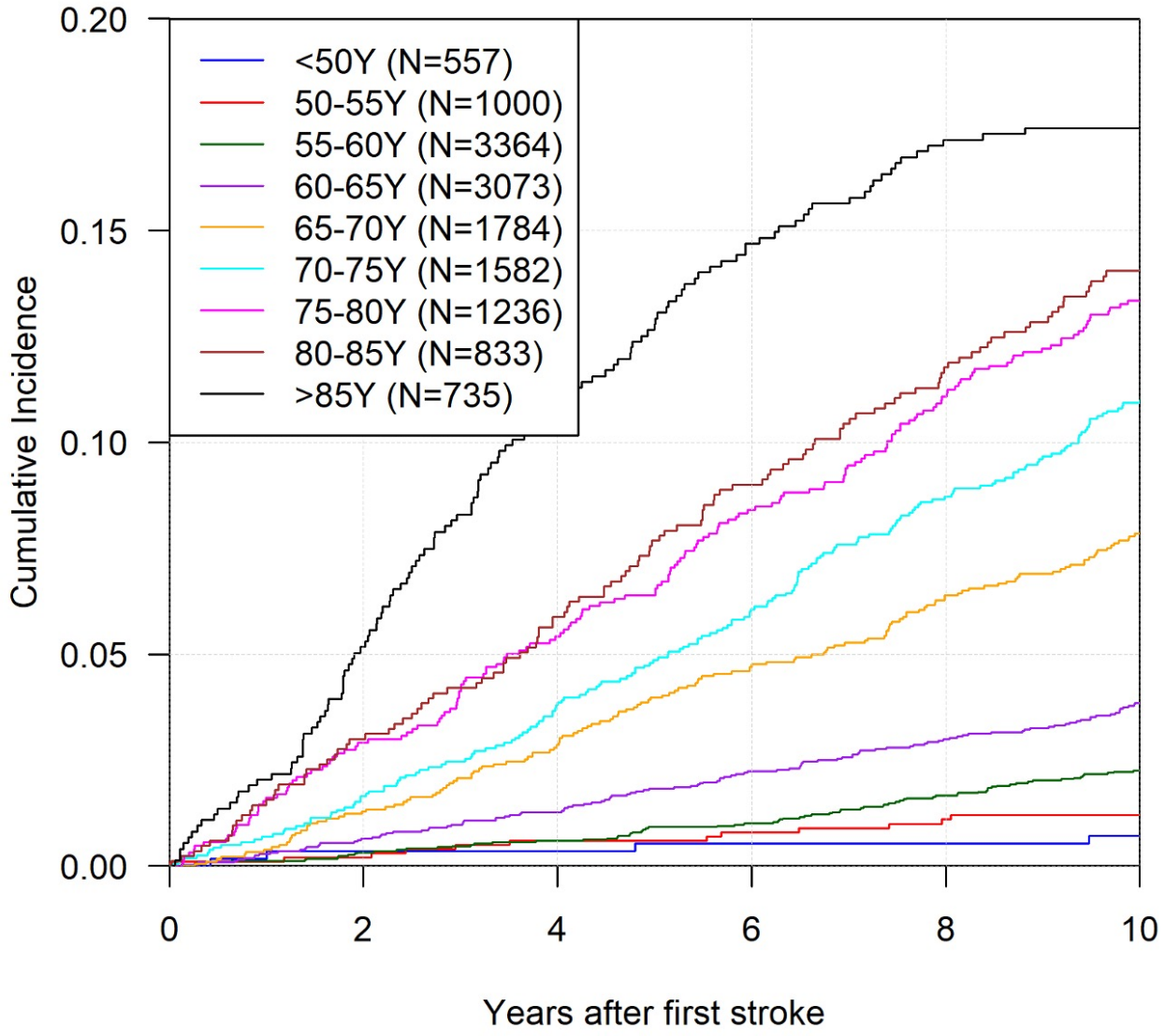
✓ Continuous monitoring through electronic linkage:

- general practitioners: “gate-keeper” function for secondary referral and hospitals report back to them.
- regional institute for outpatient mental health care.

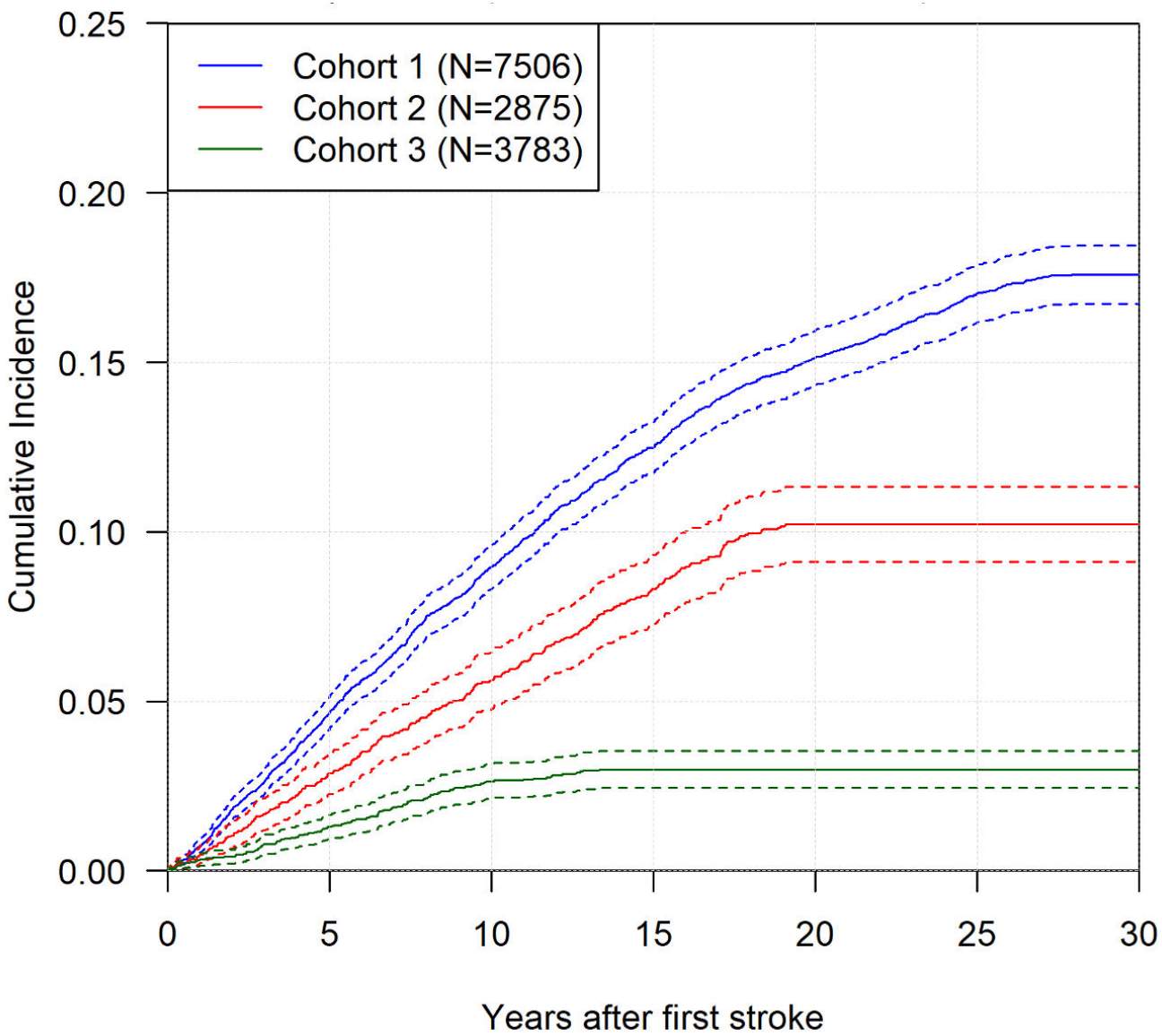
Consensus meetings

- 2-monthly consensus meeting
- Consensus panel: consultant neurologist, research physicians
- After initial diagnosis, subjects are continuously followed.
- Information about subsequent research center visits or clinical disease course used for revision or refinement of prior diagnosis.

Cumulative incidences



Decreasing trend in cumulative incidences



Recent findings from the Rotterdam Study - V

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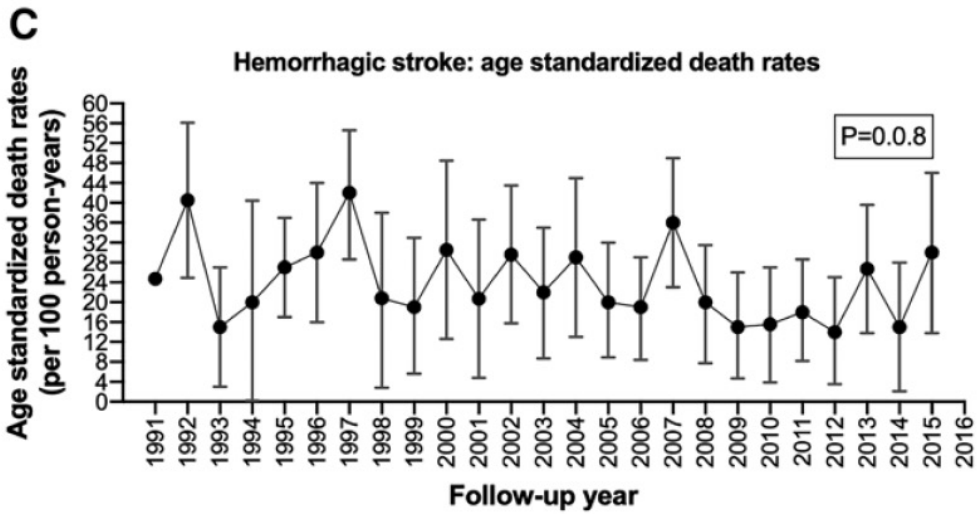
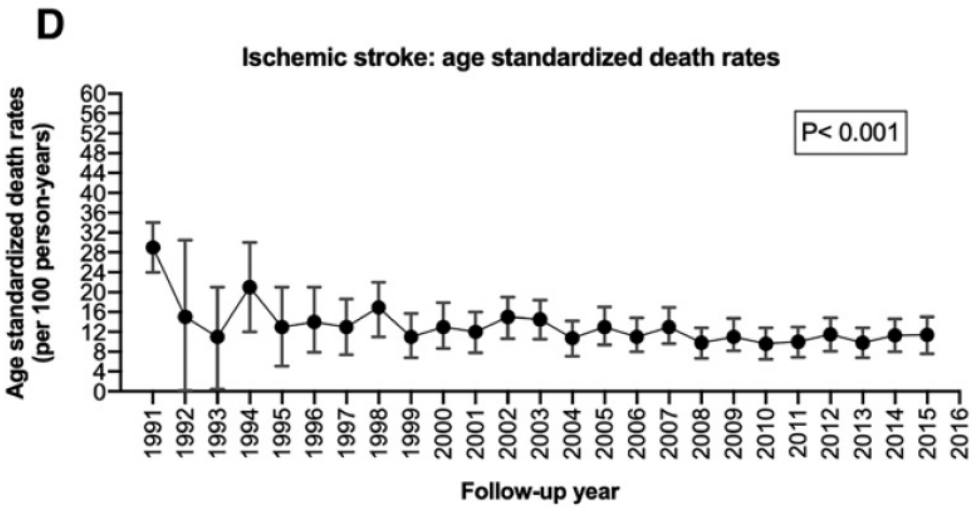
Original Contribution

Time Trends in Survival Following First Hemorrhagic or Ischemic Stroke Between 1991 and 2015 in the Rotterdam Study

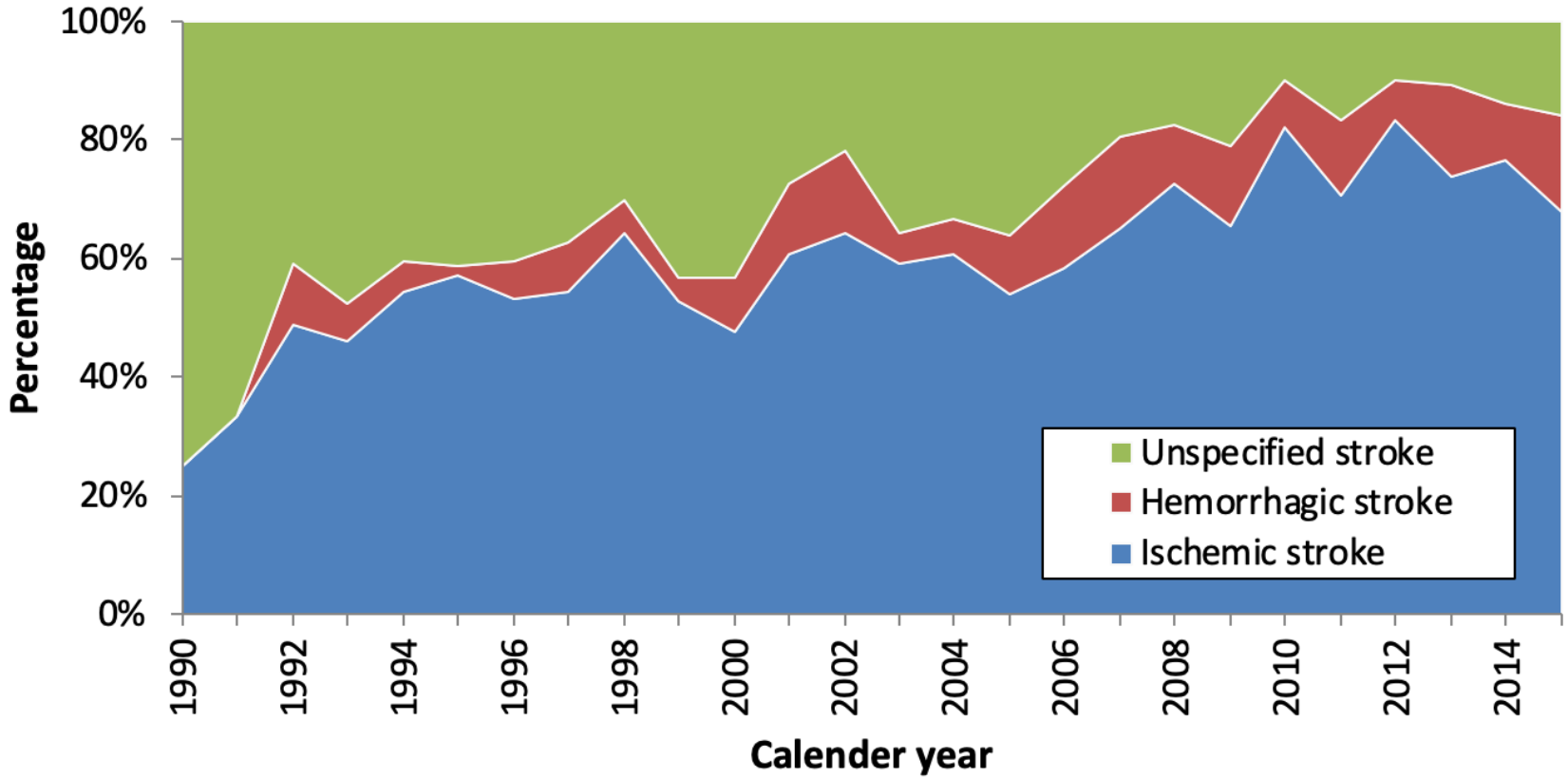
Reem Waziry, MD, PhD; Alis Heshmatollah, MD; Daniel Bos, MD, PhD; Lori B. Chibnik, PhD, MPH; M. Arfan Ikram, MD, PhD; Albert Hofman, MD, PhD; M. Kamran Ikram, MD, PhD



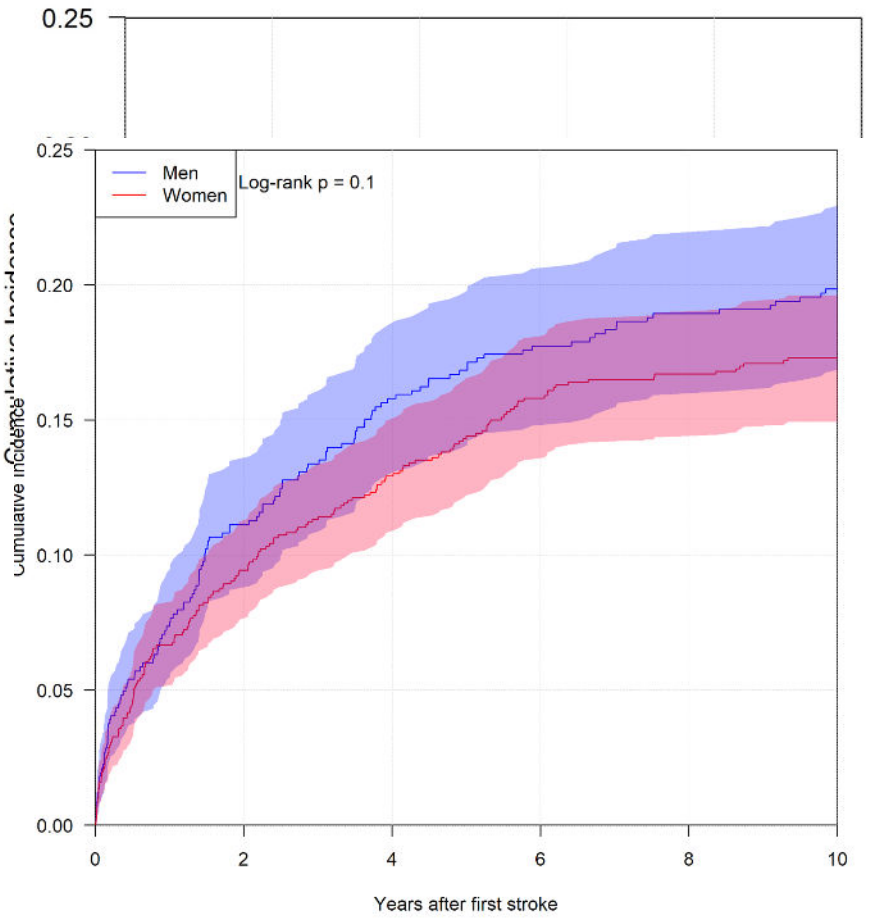


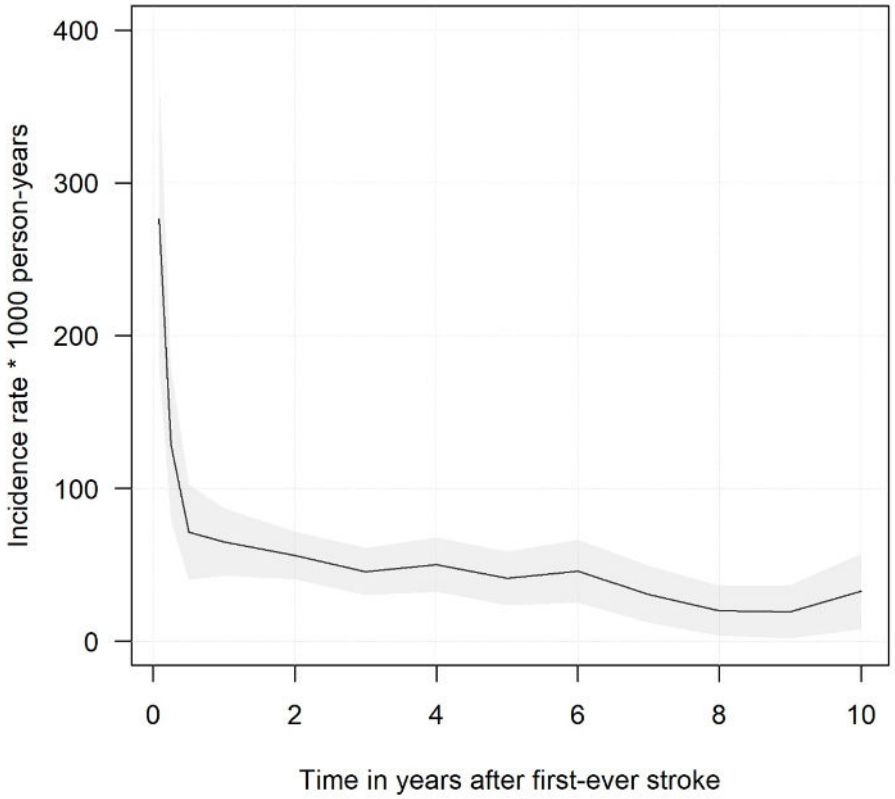
Time trends in unspecified strokes

Figure 1. Time-trends of the proportion of stroke subtypes over calendar years.

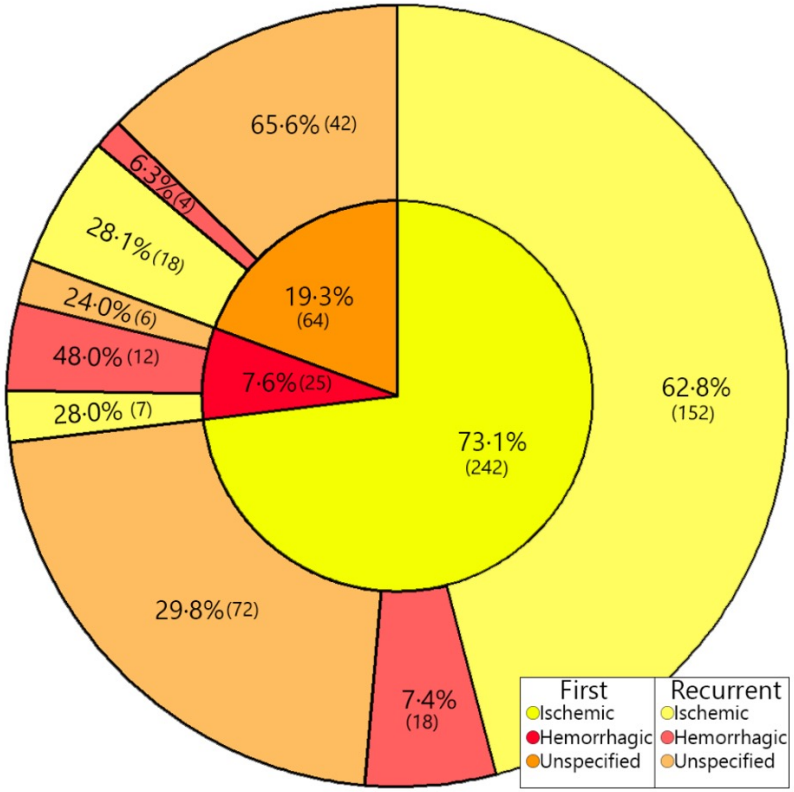


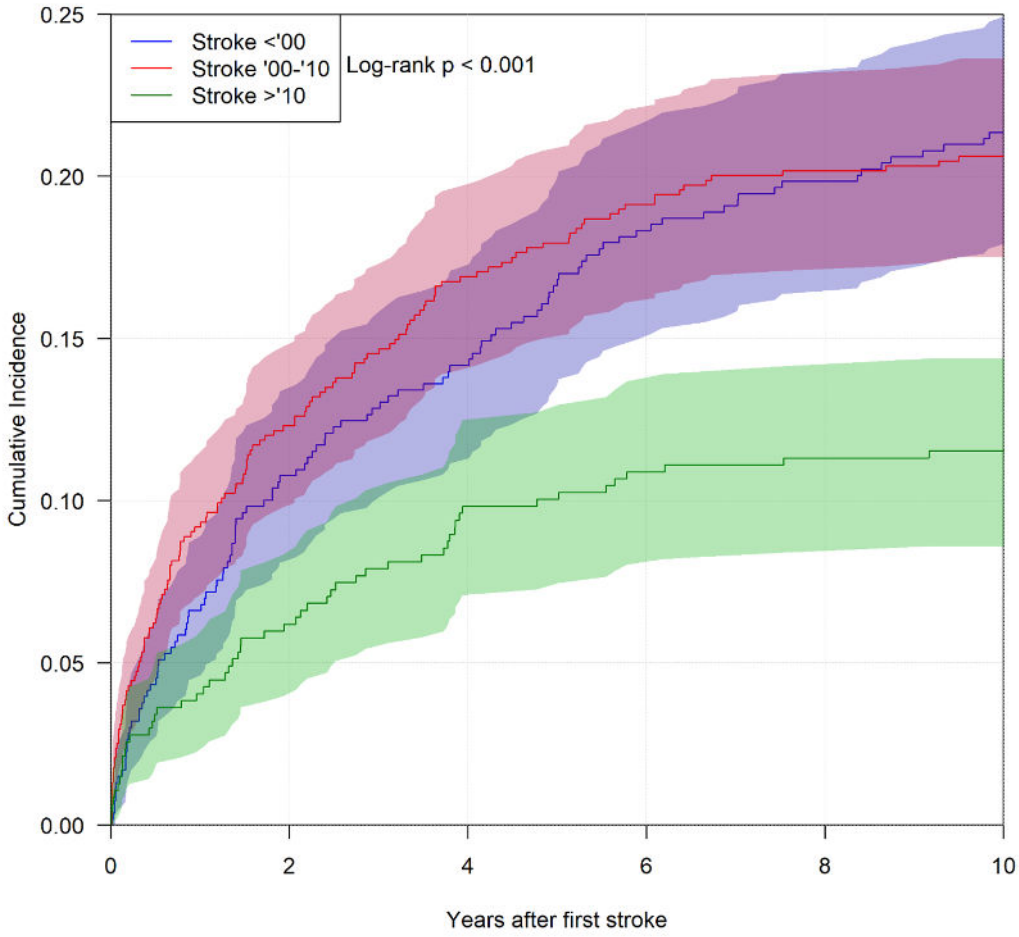
Recurrent strokes





Time trends in recurrent strokes





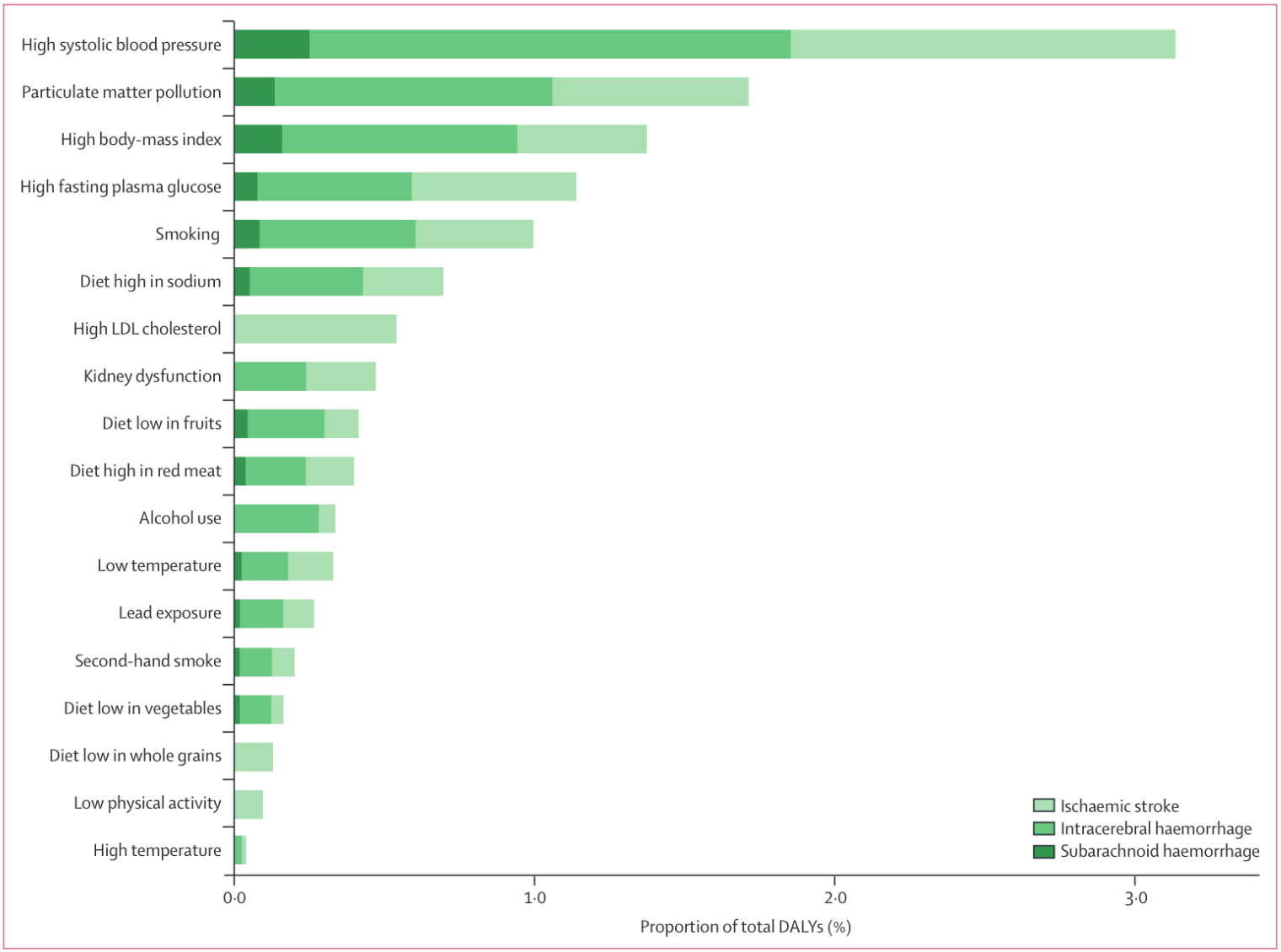


Figure 5: **Proportion of DALYs attributable to risk factors by pathological type of stroke for both sexes combined, 2019**
Proportion of DALYs attributable to household air pollution from solid fuels are not shown in this figure. DALY=disability-adjusted life-year.

A All strokes

	Global	Central Asia	Central Europe	Eastern Europe	High-income Asia Pacific	Australasia	High-income North America	Southern Latin America	Western Europe	Andean Latin America	Caribbean	Central Latin America	Tropical Latin America	North Africa and Middle East	South Asia	East Asia	Oceania	Southeast Asia	Central sub-Saharan Africa	Eastern sub-Saharan Africa	Southern sub-Saharan Africa	Western sub-Saharan Africa
High systolic blood pressure	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
High body-mass index	2	2	2	2	2	4	2	2	2	2	2	2	2	2	4	5	4	2	4	3	2	3
High fasting plasma glucose	3	3	3	5	3	3	3	3	3	4	3	3	3	3	2	6	2	3	3	4	3	4
Ambient particulate matter pollution	4	4	6	7	13	5	12	6	9	3	6	4	7	4	3	2	12	5	5	9	4	5
Smoking	5	5	4	3	6	2	4	4	4	8	4	6	4	6	6	3	5	4	8	7	5	9
Diet high in sodium	6	10	5	12	14	7	11	10	12	9	14	8	8	17	10	4	8	7	14	5	14	11
Household air pollution from solid fuels	7	14	16	19	20	19	20	19	19	11	5	10	15	14	5	12	3	6	2	2	8	2
High LDL cholesterol	8	8	7	4	5	6	6	9	5	5	7	7	6	5	11	8	11	9	10	12	7	8
Kidney dysfunction	9	9	11	8	8	11	8	11	10	7	8	5	9	7	9	11	7	8	9	10	9	7
Diet low in fruits	10	11	12	11	9	8	10	13	11	13	12	11	13	13	7	13	6	11	6	6	6	6
Diet high in red meat	11	7	9	9	4	10	5	5	6	6	13	9	5	15	19	7	10	14	15	14	11	14
Low temperature	12	6	8	6	10	9	7	8	7	10	19	15	19	8	17	9	15	20	16	15	12	20
Alcohol use	13	12	10	10	7	12	9	7	8	15	9	13	10	20	15	10	14	13	11	11	10	10
Lead exposure	14	17	18	18	16	17	18	17	18	16	11	12	16	10	8	14	17	16	12	13	15	13
Second-hand smoke	16	15	13	14	18	14	16	14	17	18	17	17	17	12	14	15	13	15	18	16	16	16
Diet low in vegetables	17	19	19	17	15	18	14	15	16	12	10	14	11	18	12	19	9	12	7	8	13	12
Diet low in whole grains	18	13	14	13	17	16	15	16	15	17	18	18	18	9	18	16	16	17	17	18	19	17
Low physical activity	19	18	17	16	12	15	17	18	14	19	16	19	12	11	20	18	18	18	19	20	17	18
High temperature	20	20	20	20	19	20	19	20	20	20	20	20	20	19	16	20	20	19	20	19	20	15

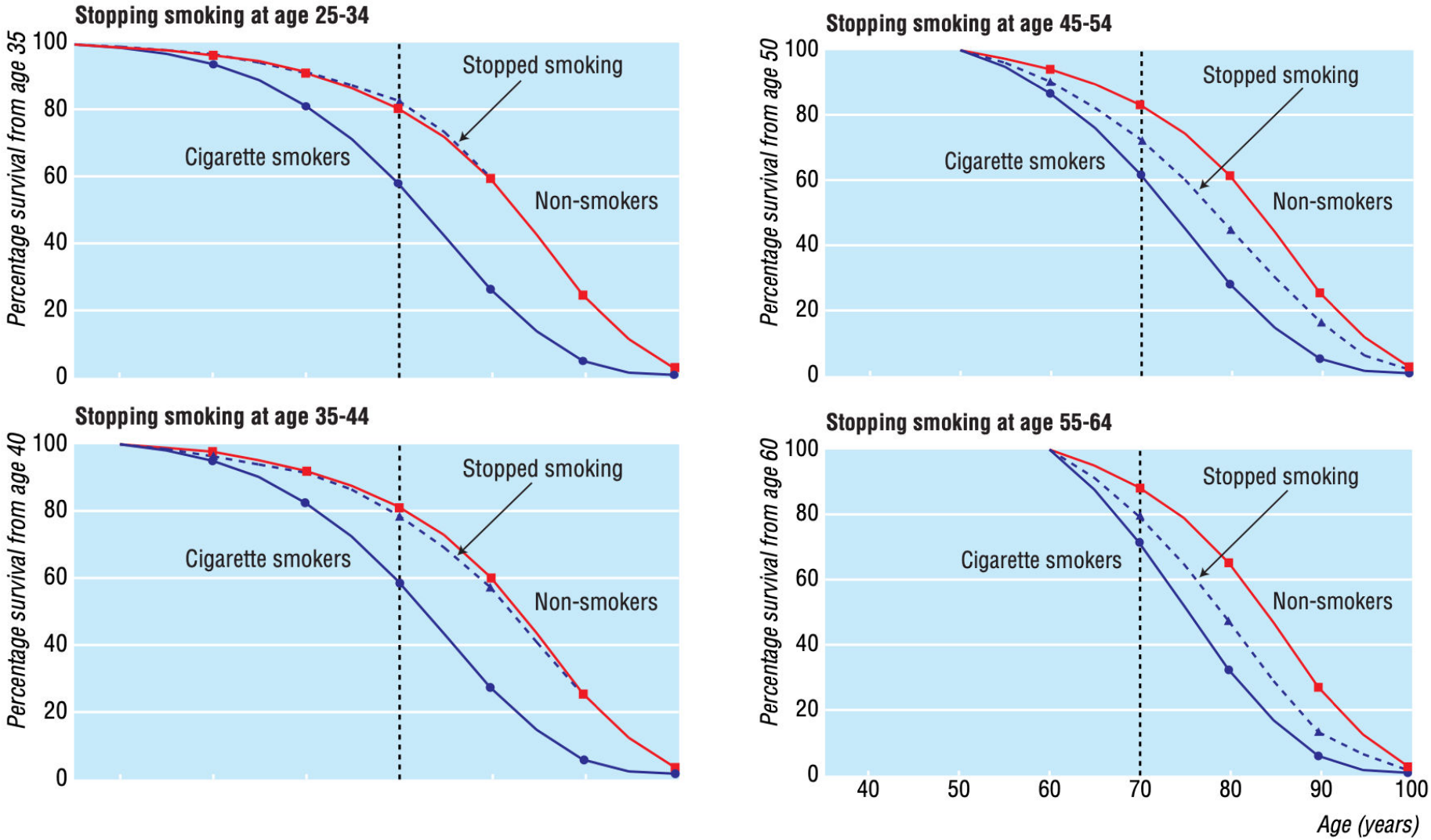
B Ischaemic stroke

High systolic blood pressure	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
High fasting plasma glucose	2	2	2	5	4	3	2	2	2	3	2	2	2	2	2	6	2	2	3	3	2	3
High LDL cholesterol	3	4	4	3	2	2	4	3	3	4	3	3	3	5	4	3	4	3	4	4	4	4
Ambient particulate matter pollution	4	5	7	8	13	5	11	7	8	5	6	5	9	4	3	2	12	5	6	9	5	6
High body-mass index	5	3	3	2	3	6	3	4	4	2	4	4	4	3	6	7	5	6	5	5	3	5
Smoking	6	6	5	4	6	4	5	5	5	9	5	7	5	7	7	4	6	4	9	7	6	11
Diet high in sodium	7	11	6	11	16	7	10	10	13	7	13	8	10	17	11	5	8	8	15	6	15	10
Kidney dysfunction	8	8	9	7	7	8	7	9	9	6	7	6	8	6	8	9	7	9	7	8	7	7
Household air pollution from solid fuels	9	14	17	19	20	19	20	19	19	10	8	10	15	14	5	11	3	7	2	2	8	2
Diet high in red meat	10	10	10	9	5	10	6	6	6	11	12	9	6	13	19	8	11	16	16	15	10	15
Low temperature	11	7	8	6	9	9	8	8	7	8	19	14	18	10	18	10	16	19	17	14	11	20
Diet low in whole grains	12	9	11	10	10	13	9	11	11	12	10	12	11	8	12	13	10	12	10	11	13	8
Diet low in fruits	13	12	12	12	11	11	12	13	14	15	14	13	16	15	10	14	9	11	8	10	9	9
Lead exposure	14	17	18	18	14	17	17	18	17	17	11	11	13	11	9	12	17	17	13	12	16	12
Low physical activity	15	13	13	13	8	12	13	16	10	16	9	16	7	9	14	16	13	13	12	16	12	13
Second-hand smoke	16	15	15	16	19	16	18	15	18	18	17	18	17	12	16	15	15	14	18	18	17	17
Alcohol use	18	18	14	14	15	15	15	14	12	20	18	19	19	20	20	17	20	18	20	19	18	18
Diet low in vegetables	19	19	19	17	17	18	16	17	16	14	15	15	14	19	15	19	14	15	11	13	14	14
High temperature	20	20	20	20	18	20	19	20	20	19	20	20	20	18	17	20	19	20	19	20	20	16

Mortality in relation to smoking: 50 years' observations on male British doctors

Richard Doll, Richard Peto, Jillian Boreham, Isabelle Sutherland

bmj.com



Alcohol Intake as a Risk Factor for Acute Stroke

The INTERSTROKE Study

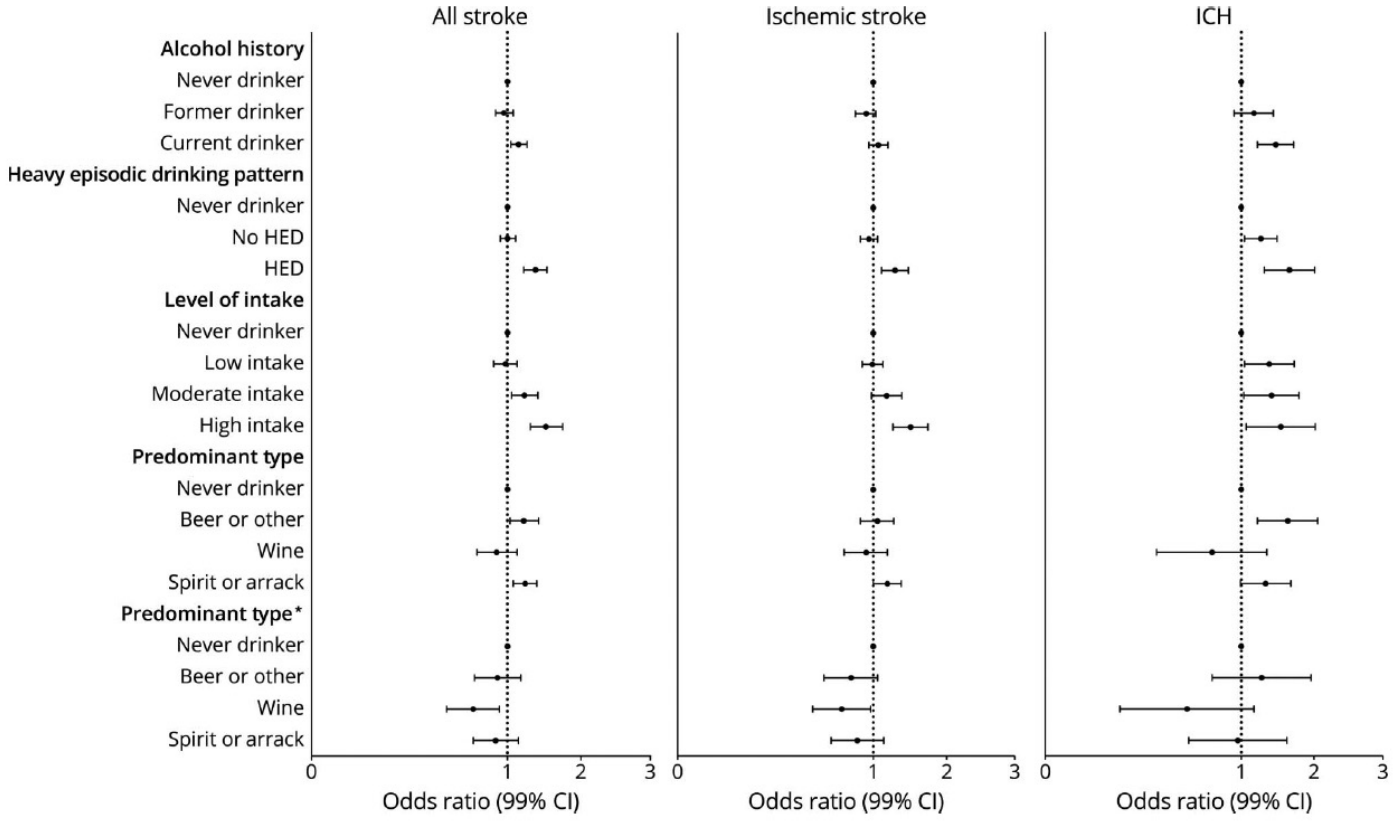
Andrew Smyth, MB BCh, BAO, MSc, PhD, Martin O'Donnell, PhD, Sumathy Rangarajan, MSc, Graeme J. Hankey, MBBS, MD, FRACP, Shahram Oveisgharan, MD, Michelle Canavan, MBBChBAO, PhD, Clodagh McDermott, MB BCh, BAO, MSc, Denis Xavier, MD, Hongye Zhang, MD, Albertino Damasceno, MD, Alvaro Avezum, MD, Nana Pogosova, MD, Aytekin Oguz, MD, Danuta Ryglewicz, MD, PhD, Helle Klingenberg Iversen, MD, Fernando Lanas, MD, Annika Rosengren, MD, Salim Yusuf, DPhil, and Peter Langhorne, PhD, on behalf of the INTERSTROKE Investigators

Neurology® 2023;100:e142-e153. doi:10.1212/WNL.0000000000201388

Methods

INTERSTROKE, a case-control study, is the largest international study of risk factors for acute stroke. Alcohol consumption was self-reported and categorized by drinks/week as low (1–7), moderate (7–14 for females and 7–21 for males), or high (>14 for females and >21 for males). Heavy episodic drinking (HED) was defined as >5 drinks on ≥1 day per month. Multivariable conditional logistic regression was used to determine associations.

Figure 2 Association Between Alcohol Consumption and Stroke



Conditional logistic regression adjusted for hypertension, smoking, AHEI, physical activity, diabetes, cardiac risk factors, ApoB/ApoA, age, stress with pairs matched for age, sex, and region. *Additional adjustment for age, sex, and region. Abbreviation: AEHI = Alternate Healthy Eating Index.

Ambient air pollution and the risk of ischaemic and haemorrhagic stroke

Jamie I Verhoeven, Youssra Allach, Ilonca C H Vaartjes, Catharina J M Klijn, Frank-Erik de Leeuw

Lancet Planet Health 2021; 5: e542–52

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

	Location (study period)	Number of participants; number of cases	Follow-up	Exposure	Results (95% CI)
Ischaemic stroke and haemorrhagic stroke					
Amini et al, 2020[4]	Denmark (1993, 1999–2014)	23 423; 1078	Median 19·45 years	$PM_{2·5}$, PM_{10}, NO_2, NO_x	Ischaemic stroke: HR of 1·12 (1·01–1·25) per 1-year mean 3·9 µg/m³ (IQR) increase of $PM_{2·5}$ concentration, and no significant associations for PM_{10}, NO_x, and NO_2 concentrations; haemorrhagic stroke: no statistically significant associations
Cai et al, 2018[46]	Three cohorts: two from the UK (1993–2008 and 2006–2010) and one from Norway (1995–2013)	355 732; 1845	Mean 14·1, 10·8, and 1·3 years	$PM_{2·5}$	Ischaemic stroke: no statistically significant associations per 1-year mean 4·1 µg/m³ (IQR) increase of $PM_{2·5}$ concentration; haemorrhagic stroke: no statistically significant associations per 1-year mean 4·1 µg/m³ (IQR) increase of $PM_{2·5}$ concentration
Huang et al, 2019[47]	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/m³ increased exposure during a mean 7·5 years follow-up; haemorrhagic stroke: HR of 1·12 (1·05–1·20) per average 10 µg/m³ increased exposure during a mean 7·5 years follow-up
Yuan et al, 2019[48]	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, Russia, and South Africa (1980–2012)	2·2 million; 49 1149	..	$PM_{2·5}$	Ischaemic stroke: no statistically significant association per 5 µg/m³ increase of $PM_{2·5}$ concentration during a 1-year to 4-year period (four studies); haemorrhagic stroke: no statistically significant association per 5 µg/m³ increase of $PM_{2·5}$ concentration during a 1-year to 4-year period (four studies)
Haemorrhagic stroke only					
Noh et al, 2019[49]	Korea (2002–13)	62 676; 521	670 431 person-years	$PM_{2·5}$	Haemorrhagic stroke: HR of 1·43 (1·09–1·88) per average 10 µg/m³ increased exposure of $PM_{2·5}$ concentration during a mean follow-up of 10·7 years

HR=hazard ratio. PM=particulate matter. NO_2=nitrogen dioxide. NO_x=nitrogen oxides. *Recent literature published between Jan 1, 2018, and July 1, 2020.

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

Stroke
Volume 49, Issue 1, January 2018; Pages 255-261
https://doi.org/10.1161/STROKEAHA.117.017838

TOPICAL REVIEWS

Ambient Temperature and Stroke Risk

Evidence Supporting a Short-Term Effect at a Population Level From Acute Environmental Exposures

Pablo M. Lavados, MD, MPH, Verónica V. Olavarría, MD, MSc, and Lorena Hoffmeister, MSc, PhD

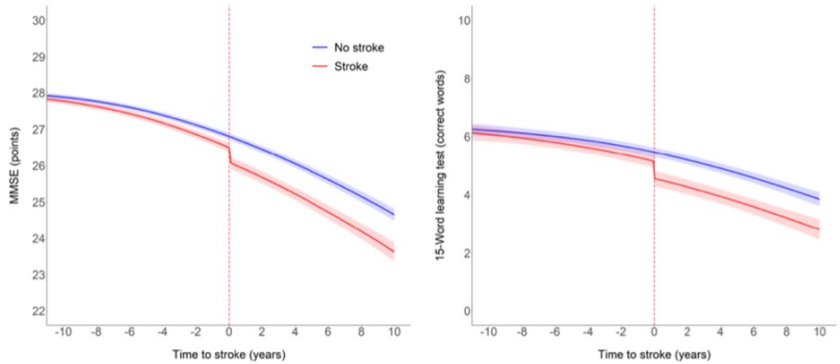
Table. Systematic Reviews and Meta-Analysis of the Effect of Ambient Temperature on Stroke Risk

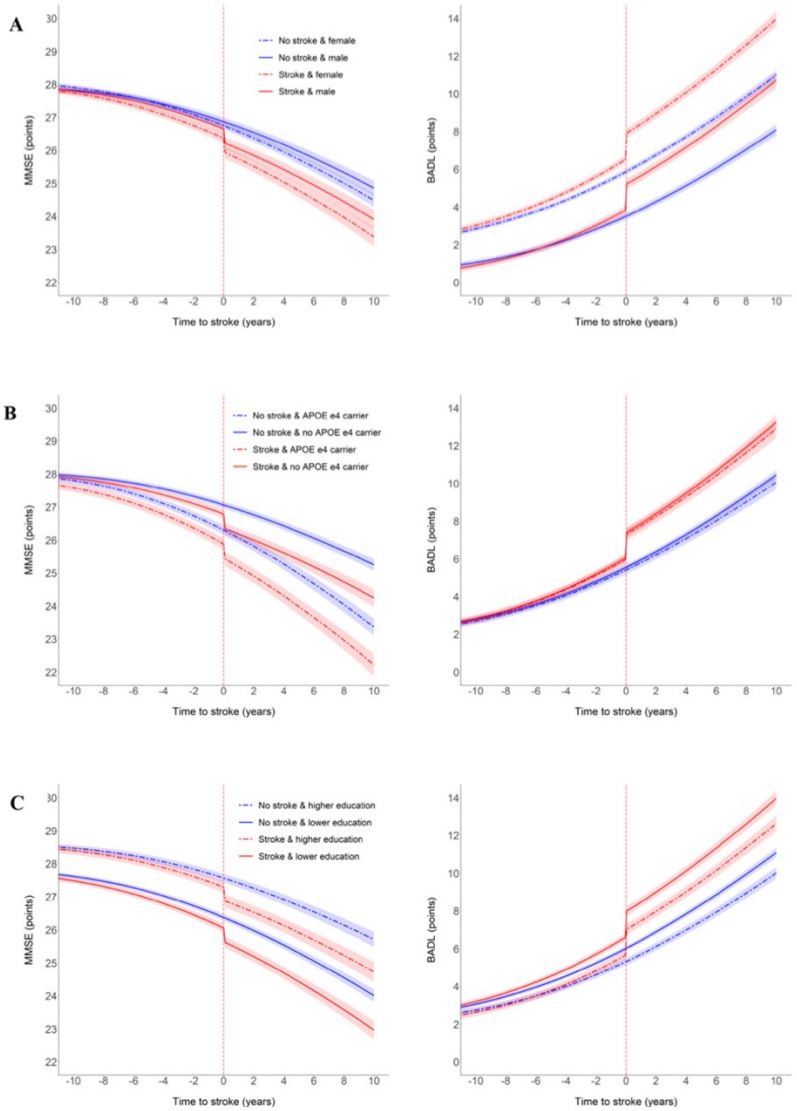
Author, Year	Inception Month and Year	Type of Studies	No. of Included Studies	No. of Patients or Events	Pathological Subtypes	Low Temperature			High Temperature		
						Mortality and Morbidity Combined	Mortality	Incidence	Mortality and Morbidity Combined	Mortality	Incidence
Lian et al, 2015[16]	September 2014	All studies	20	2 070 923	All strokes	Increased risk	Increased risk	Increased risk	Increased risk	Increased risk	Increased risk
					Ischemic	Increased risk			Increased risk		
					ICH	Increased risk			Decreased risk		
					SAH						
Wang et al, 2016[20]	October 2015	Population, community, or hospital registries with consecutive recruitment for at least 1 y	21	476 511	All strokes						
					Ischemic			Increased risk			No increased risk
					ICH			Increased risk			No increased risk
					SAH			No association			No increased risk
Zorrilla-Vaca et al, 2016[17]	December 2015	All studies	26	19 736	All strokes	Increased risk					
					Ischemic	No increased risk					
					ICH	Increased risk					
					SAH	Increased risk					

Original research

Long-term trajectories of decline in cognition and daily functioning before and after stroke

Heshmatollah A, *et al*. *J Neurol Neurosurg Psychiatry* 2021;**0**:1–6. doi:10.1136/jnnp-2021-326043





doi:10.1093/brain/awaa054 BRAIN 2020: 143; 1220–1232 | 1220

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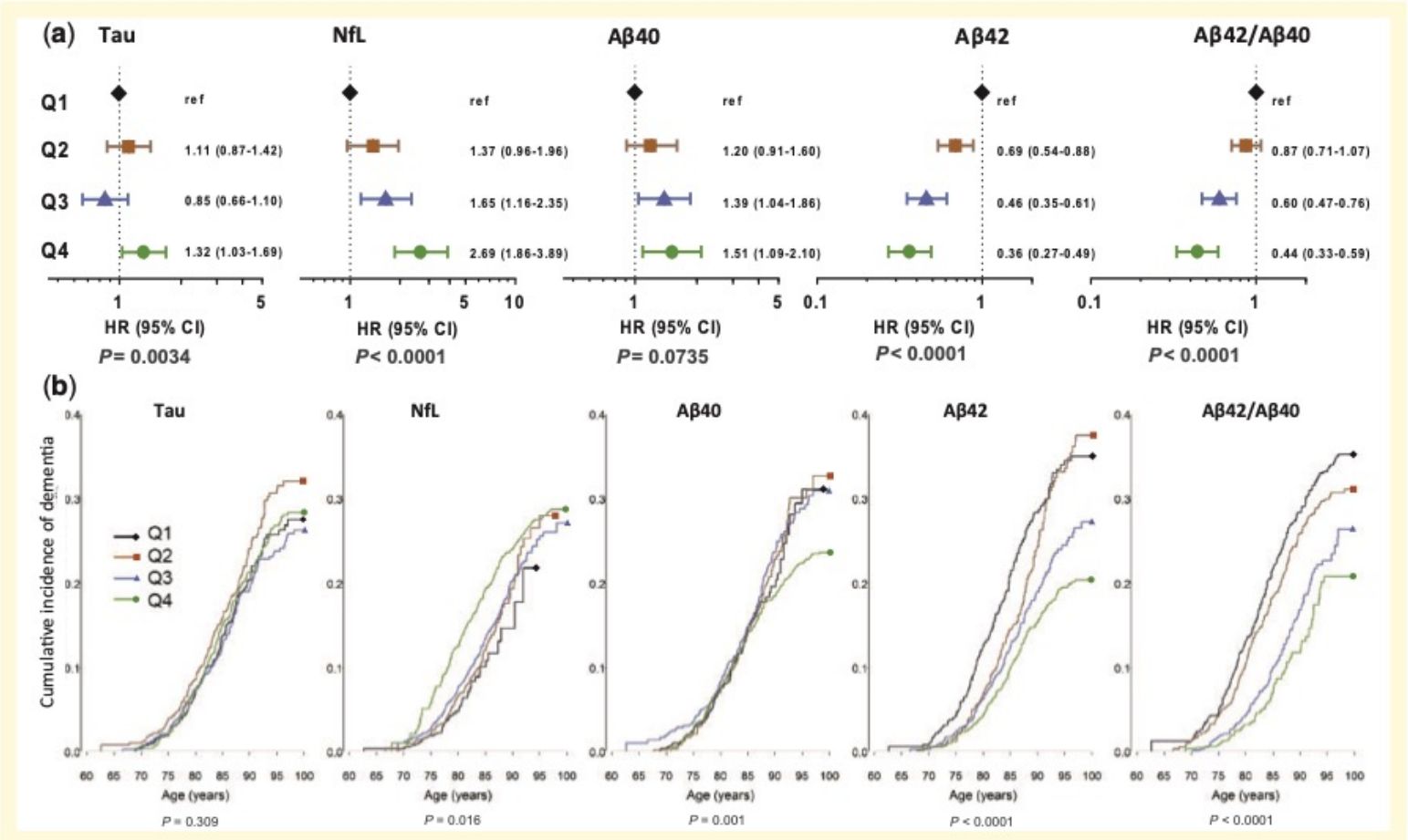
Erasmus MC

Plasma tau, neurofilament light chain and amyloid-β levels and risk of dementia; a population-based cohort study

Frank de Wolf,[1,2,*] Mohsen Ghanbari,[3,4,*] Silvan Licher,[3] Kevin McRae-McKee,[1] Luuk Gras,[2] Gerrit Jan Weverling,[2] Paulien Wermeling,[2] Sanaz Sedaghat,[5] M. Kamran Ikram,[3,6] Reem Waziry,[7] Wouter Koudstaal,[2,8] Jaco Klap,[2] Stefan Kostense,[2] Albert Hofman,[7] Roy Anderson,[1] Jaap Goudsmit[7,9,10] and M. Arfan Ikram[3,7]



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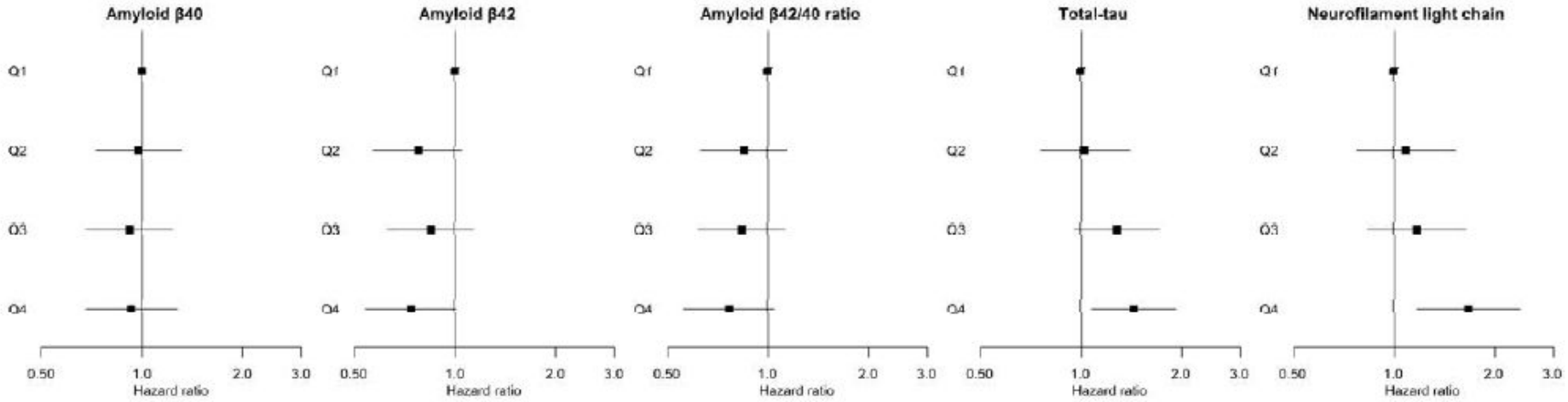
April 26, 2022; 98 (17) RESEARCH ARTICLE

Plasma β-Amyloid, Total-Tau, and Neurofilament Light Chain Levels and the Risk of Stroke

A Prospective Population-Based Study

Alis Heshmatollah, Lana Fani, Peter J. Koudstaal, Mohsen Ghanbari, M. Arfan Ikram, M. Kamran Ikram

Figure 1. Association of plasma amyloid β40, amyloid β42, amyloid β42/40 ratio, total-tau, and neurofilament light chain with risk of stroke.



Final remarks

- Decreasing trends in the incidence of first-ever and recurrent stroke
- Improved survival after cerebral infarction, but not after ICH
- Besides the well-known cardiovascular risk factors, many other factors suggested in large epidemiological studies
- However, hardly any new risk factors!
- Potentially new risk factors overlapping with other neurological (neurodegenerative) diseases