



# INTERSTROKE

On Behalf of the INTERSTROKE Investigators

Population Health Research Institute, McMaster University, Hamilton, Canada



# INTERSTROKE

## The History of INTERSTROKE

Population Health Research Institute, McMaster University, Hamilton, Canada

# INTERHEART

Population Attributable Risk > 90% for nine easily measured risk factors

Risk factor	Controls (%)	Cases (%)	OR (95% CI)*	PAR (%)
Apo B/A1 ratio <sup>†</sup>	20.0	33.5	3.3 (2.8-3.8)	49.2
Current smoking	26.8	45.2	2.9 (2.6-3.2)	35.7
Psychosocial factors	-	-	2.7 (2.2-3.2)	32.5
Abdominal obesity	33.3	46.3	1.6 (1.5-1.8)	20.1
Hypertension	21.9	39.0	1.9 (1.7-2.1)	17.9
Vegetables and fruit	42.6	32.8	0.7 (0.7-0.8)	13.7
Exercise	19.3	14.3	0.9 (0.8-0.97)	12.2
Diabetes	7.5	18.5	2.4 (2.1-2.7)	9.9
Alcohol intake	24.5	24.0	0.9 (0.8-1.9)	6.7
All risk factors	-	-	129.2 (90-185)	90.4

# WHERE DID INTERSTROKE BEGIN

## March 2006

- Conversation in cafeteria in Hamilton General Hospital
- Denis Xavier (HOPE Scholarship)
- INTERSTROKE Pilot was born (March 2006)
- INTERSTROKE Recruitment started (March 2007)
- Phase 1 completed April 2010, transition to full-scale study

# INTERSTROKE INVESTIGATORS

Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study



Martin J O'Donnell, Denis Xavier, Lisheng Liu, Hongye Zhang, Siu Lim Chin, Purnima Rao-Melacini, Sumathy Rangarajan, Shofiqul Islam, Prem Pais, Matthew J McQueen, Charles Mondo, Albertino Damasceno, Patricio Lopez-Jaramillo, Graeme J Hankey, Antonio L Dans, Khalid Yusoff, Thomas Truelsen, Hans-Christoph Diener, Ralph L Sacco, Danuta Ryglewicz, Anna Czlonkowska, Christian Weimar, Xingyu Wang, Salim Yusuf, on behalf of the INTERSTROKE investigators\*

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American Heart Association 2010

Top 10 Most Important Advance in Stroke Research



# INTERSTROKE

## Overview of Study Rationale

Population Health Research Institute, McMaster University, Hamilton, Canada

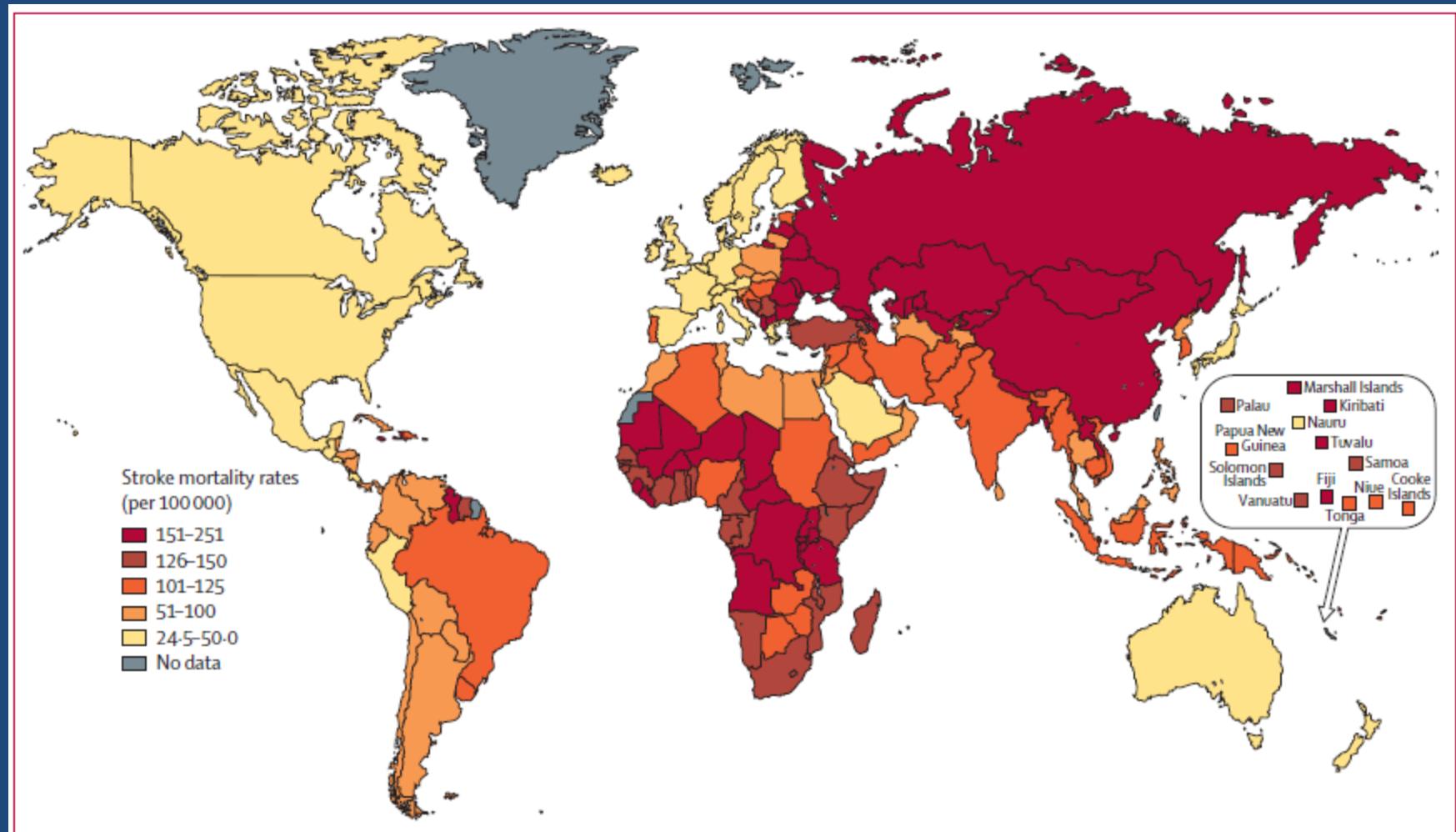
# GLOBAL BURDEN OF STROKE

- Leading cause of acquired adult disability globally
- 2<sup>nd</sup> leading cause of death worldwide
- 5.7 million deaths in 2005 (7.8 million 2030)
  - 87% in low/moderate-income countries

Strong et al *Lancet Neurology* 2007

- Knowledge of stroke epidemiology lags behind CHD
  - Risk factors unstudied in most middle/low-income countries
- O'Donnell and Yusuf *Lancet Neurology* 2009
- Systematic measurement of risk factors for stroke is required for development of population-based prevention programs

# Global Variation in Stroke Mortality



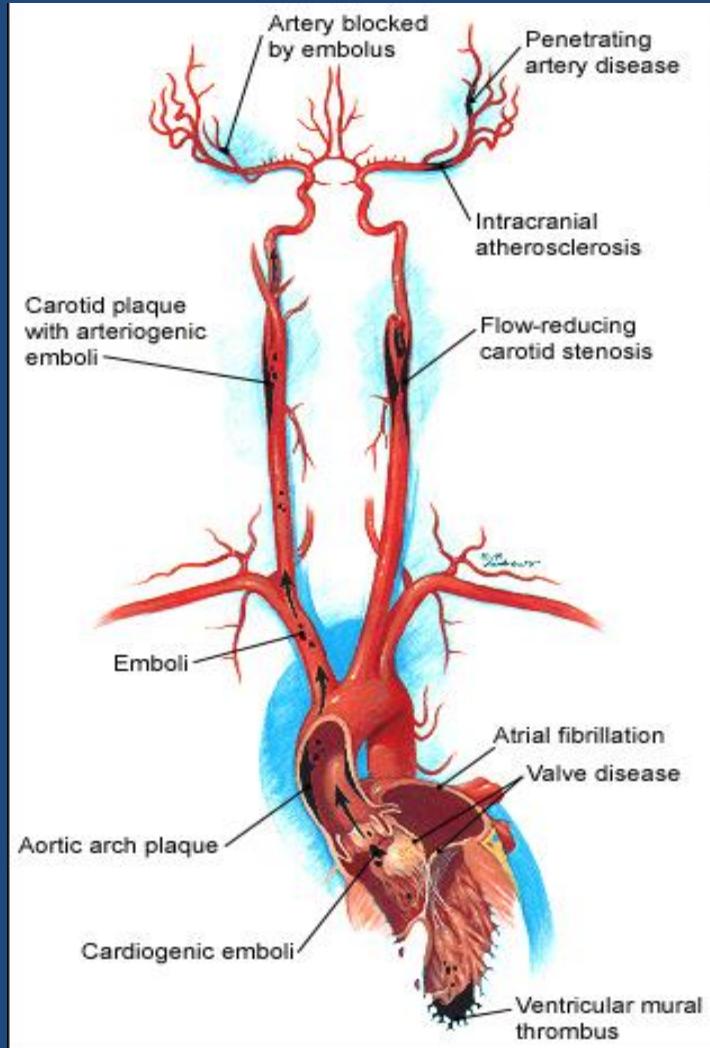
Johnston et al. *Lancet Neurology* 2009

# PREVENTION OF STROKE (POPULATION LEVEL)

- Mandates measurement of importance of common risk factors for stroke within regions
- High, medium and low-income countries
- **Two Options**
  - Large prospective cohort study (Not feasible)
  - Case-control design (Applicable to all income settings)
- To date, case control studies (<1,500 pairs)

## WHY IS A SIMILAR STUDY NEEDED FOR STROKE?

# Heterogeneity of Stroke



**Intracranial hemorrhage**  
**Intracerebral hemorrhage**  
**Subarachnoid hemorrhage**

**Ischemic Stroke**  
**Small vessel disease**  
**Large Vessel (Atherothrombotic)**

- **Intracranial**
- **Extracranial**

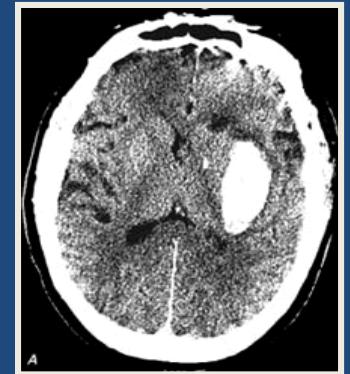
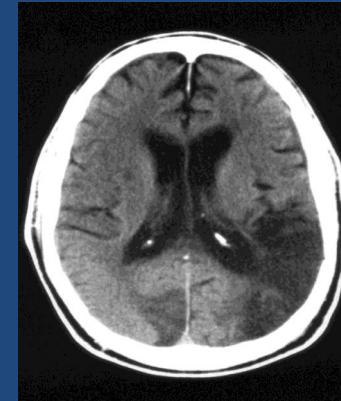
**Cardioembolism**  
**Cryptogenic and Mixed**

# EPIDEMIOLOGY (UNEXPLAINED)

- Considerable regional variation in stroke incidence
  - Unexplained by HTN, Smoking and Diabetes
  - Proposed that 30-40% of stroke is unexplained
- Variation in incidence of individual stroke subtypes by region
- Temporal trends in incidence of MI and Stroke varying by region
- Proposed that traditional vascular risk factors have different magnitude of risk for stroke compared to MI

# CHALLENGES TO STROKE EPIDEMIOLOGY

- All large global epidemiological studies are challenging
  - INTERHEART provided evidence of feasibility
- **Heterogeneity of stroke**
  - Ischemic stroke
  - Intracerebral hemorrhage
  - Subarachnoid hemorrhage
- Requires neuroimaging (CT/MRI)
- **Questionnaire-based research**
  - Neurological deficit (aphasia, severe stroke)
  - Selection bias



# INTERSTROKE-FULL STUDY: OBJECTIVES

- Determine estimates of strength of association between vascular risk factors and stroke
  - Within stroke subtypes
  - Within risk factors
- Determine regional variations in the importance of risk factors for stroke
  - Importance of regional variations in developing prevention programs
- Determine the importance of emerging risk factors, particularly the role of genetics

# FUNDING

Population Health Research Institute

Numerous Local Funding Sources in countries

## PEER-REVIEW

- Canadian Institutes of Health Research (CIHR) X 4
- Heart and Stroke Foundation of Canada (HSFC) X 3
- Canadian Stroke Network (CSN) X 2
- Pfizer Cardiovascular Award
- UK-Chest, Heart and Stroke
- Health Research Board, Ireland
- Swedish Heart and Lung Foundation

## UNRESTRICTED INDUSTRY GRANT

- Merck, Sharp and Dohme
- Boehringer-Ingelheim
- Astra Zeneca



# INTERSTROKE

## Overview of Study Conduct

Population Health Research Institute, McMaster University, Hamilton, Canada



# INTERSTROKE

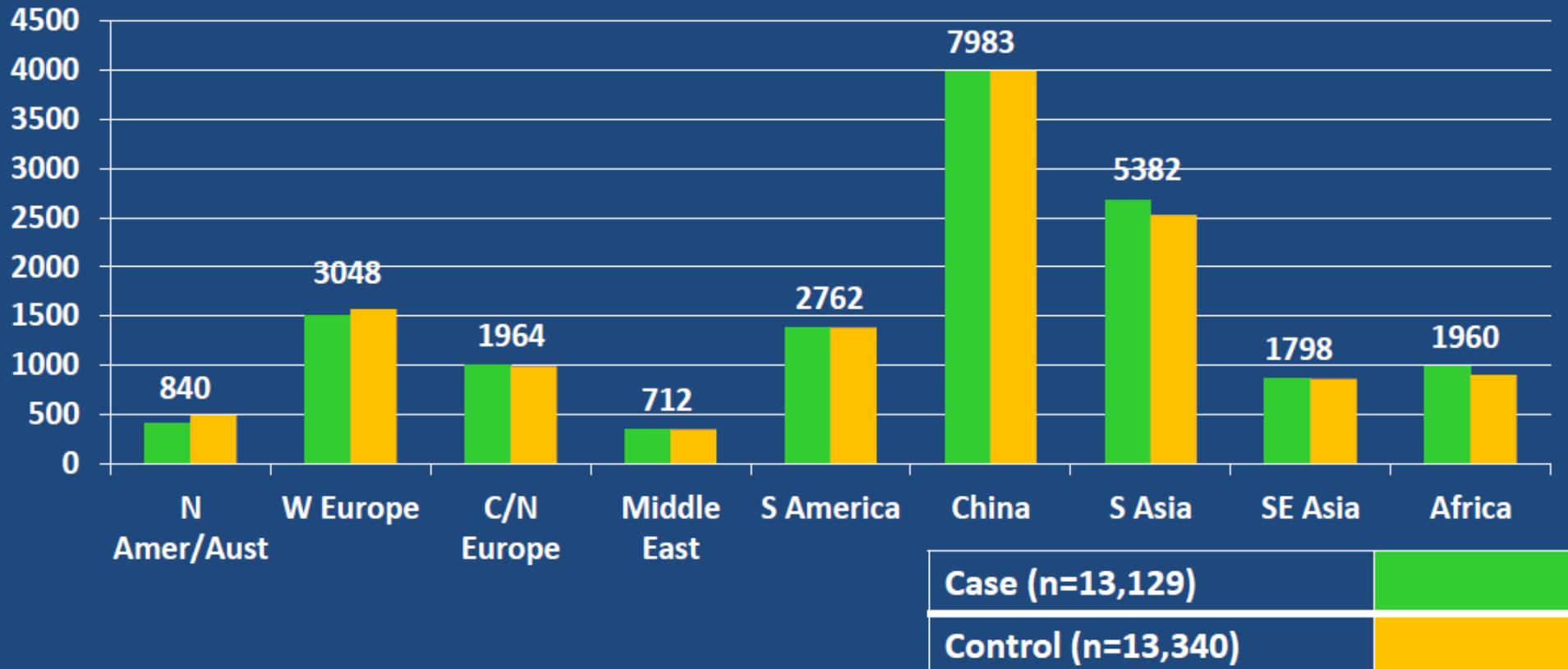
## Overview of Study Population

Population Health Research Institute, McMaster University, Hamilton, Canada

# INTERSTROKE POPULATION

N= 26,469

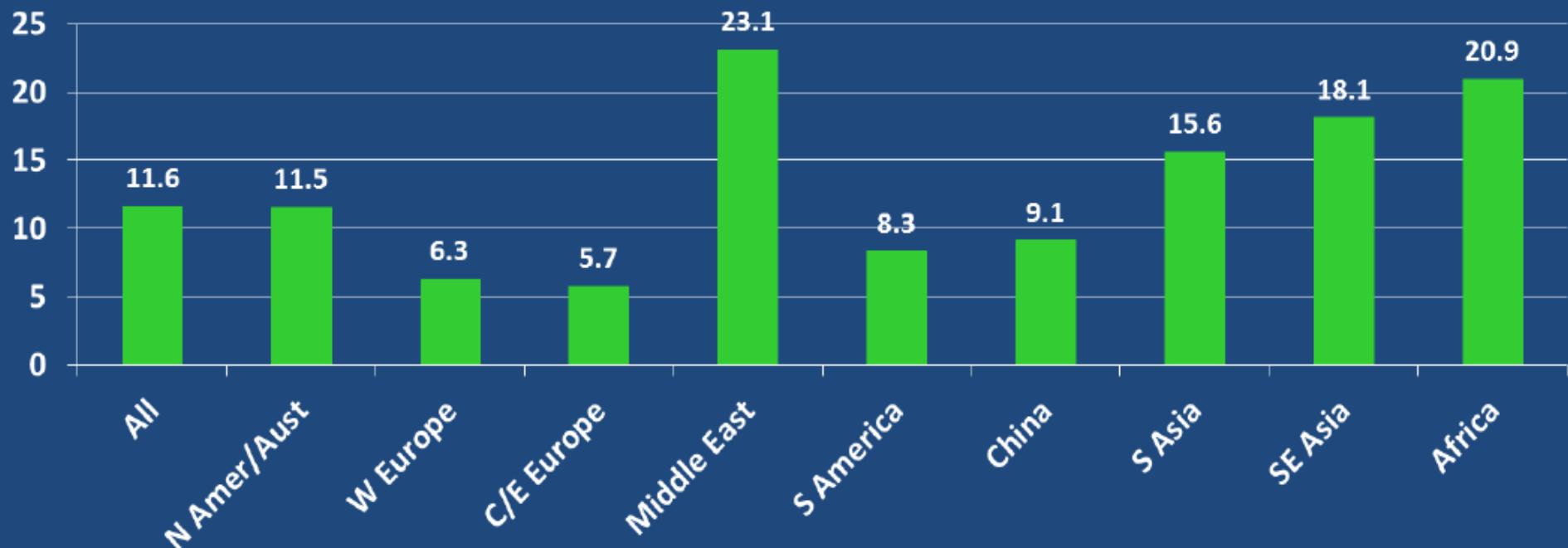
## BY REGION (CASES AND CONTROLS)



# INTERSTROKE POPULATION (CASES) AGE

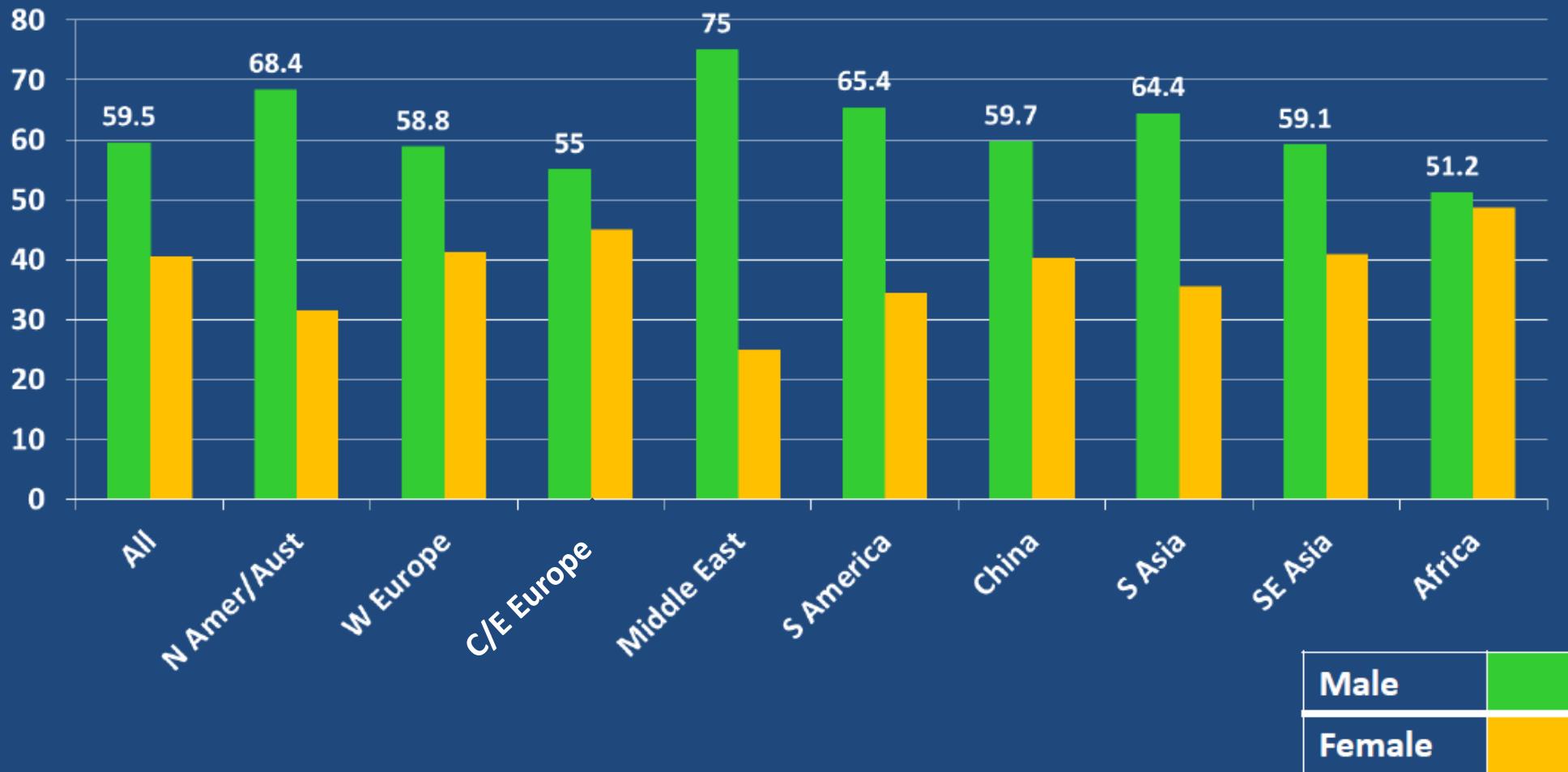
	All	N Amer /Aust	W Europe	C/E Europe	MiddleE ast	South America	China	S Asia	SE Asia	Africa
Age, yrs	<b>62.3</b>	<b>64.5</b>	<b>67.3</b>	<b>66.2</b>	<b>57.6</b>	<b>66.3</b>	<b>61.9</b>	<b>59.6</b>	<b>56.7</b>	<b>58.8</b>
Mean (SD)	(13.6)	(14.5)	(13.2)	(13.1)	(12.5)	(14.6)	(12.5)	(12.8)	(13.0)	(15.3)

**AGE < 45 YEARS (N=1,559)**



# INTERSTROKE POPULATION (CASES)

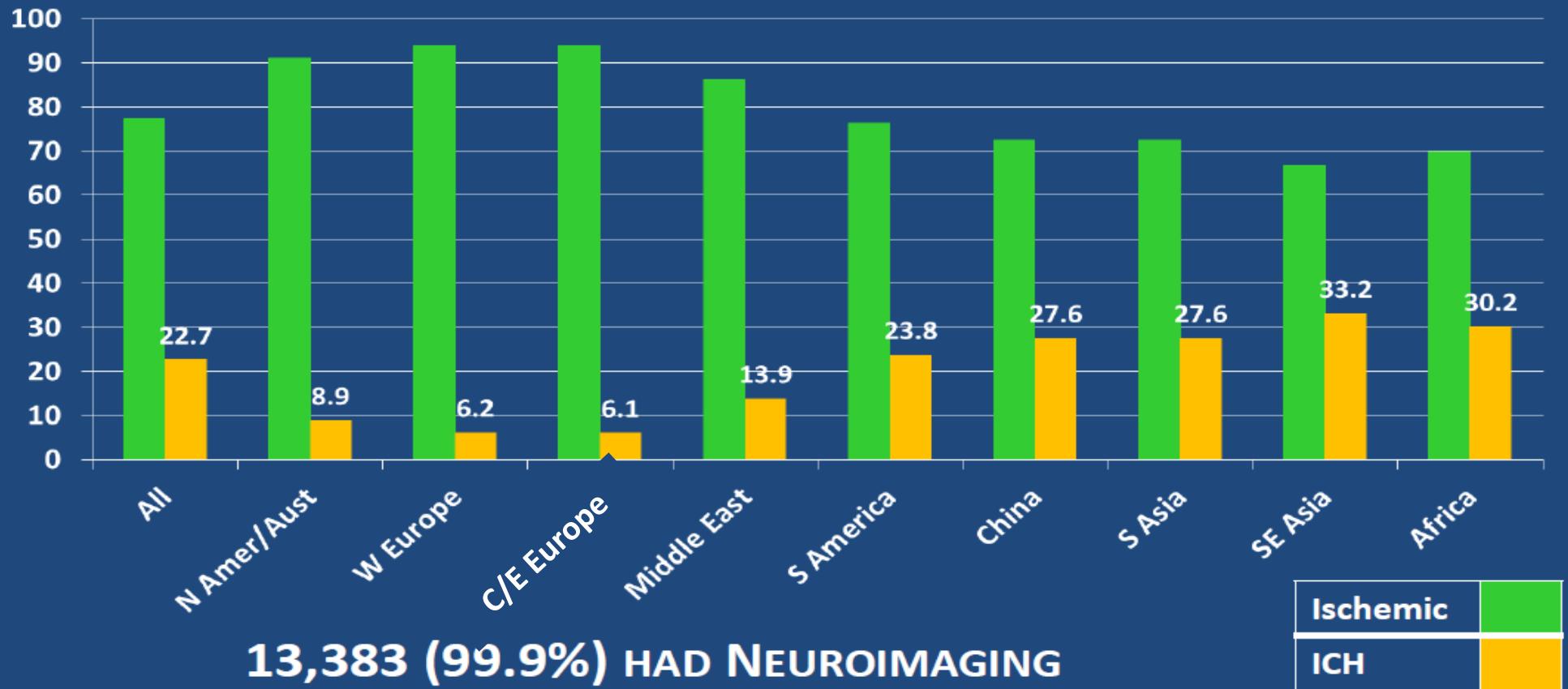
## SEX (MALE/FEMALE BY REGION)



# INTERSTROKE POPULATION (CASES)

## STROKE SUBTYPE (ISCHEMIC AND INTRACEREBRAL HEMORRHAGE)

ISCHEMIC=10,349, ICH=3,039

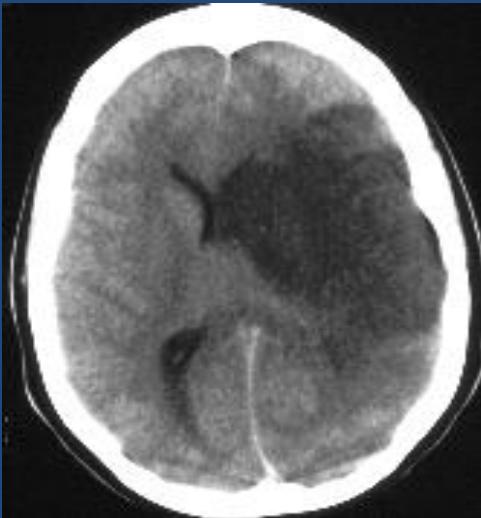


# INTERSTROKE (FULL-SCALE STUDY)

- International standardized case-control study
  - Shared methodology with INTERHEART Yusuf et al INTERHEART *Lancet* 2004
- 32 countries Mar 07-Apr 14
  - N America/Europe: Australia, Canada, Croatia, Denmark, Germany, Ireland, Poland, Russia, Turkey, UK
  - S America: Argentina, Brazil, Chile, Colombia, Ecuador, Peru
  - Asia: China, India, Pakistan, Philippines, Malaysia, Thailand
  - Africa: Mozambique, Nigeria, South Africa, Sudan, Uganda
  - Middle East: Iran, Kuwait, Saudi Arabia, UEA
- Case: First stroke admitted within 5 days of symptom onset
  - Proxy respondents for patients unable to complete Qs
- Control: No history of stroke (Matched for age and gender)
  - Community and hospital-based controls

# OCSP CLASSIFICATION (ISCHEMIC STROKE)

6.5%



Total Anterior Circulation Infarct (TACI)

46.8%



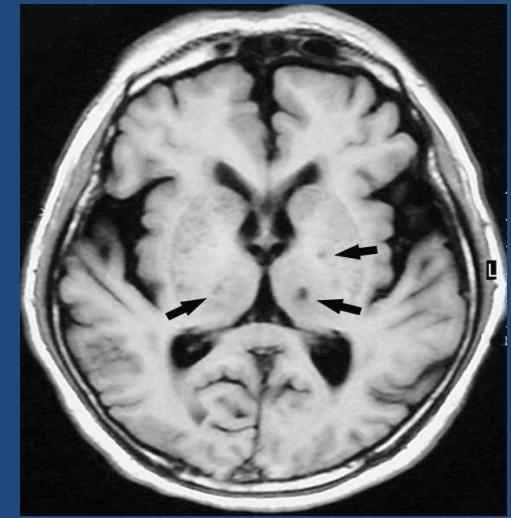
Partial Anterior Circulation Infarct (PACI)

14.6%



Posterior Circulation Infarct (POCI)

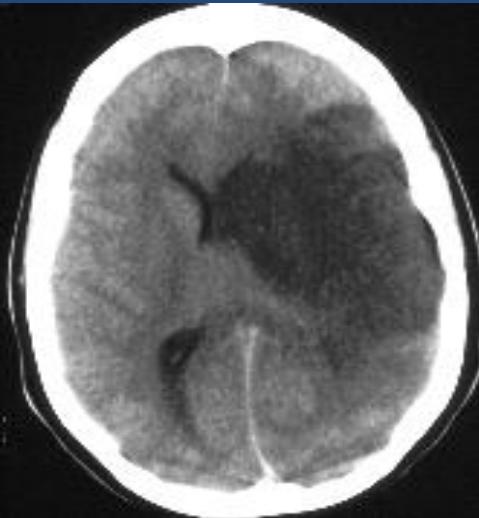
26.9%



Lacunar Infarct (LACI)

# OCSP CLASSIFICATION (ISCHEMIC STROKE)

6.5%  
(8.9%)



Total Anterior  
Circulation Infarct  
(TACI)

46.8%  
(40.9%)



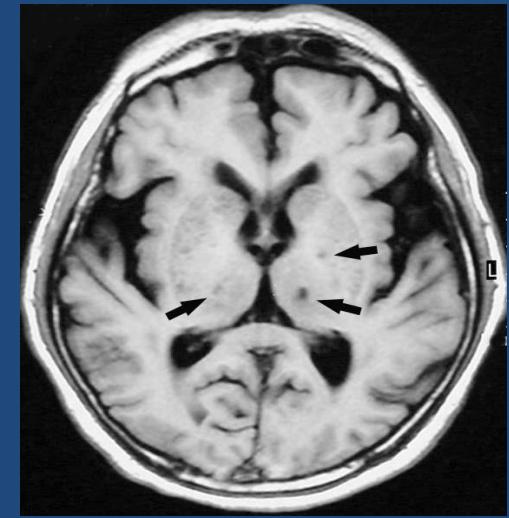
Partial Anterior  
Circulation Infarct  
(PACI)

14.6%  
(26.0%)



Posterior  
Circulation Infarct  
(POCI)

26.9%  
(20%)



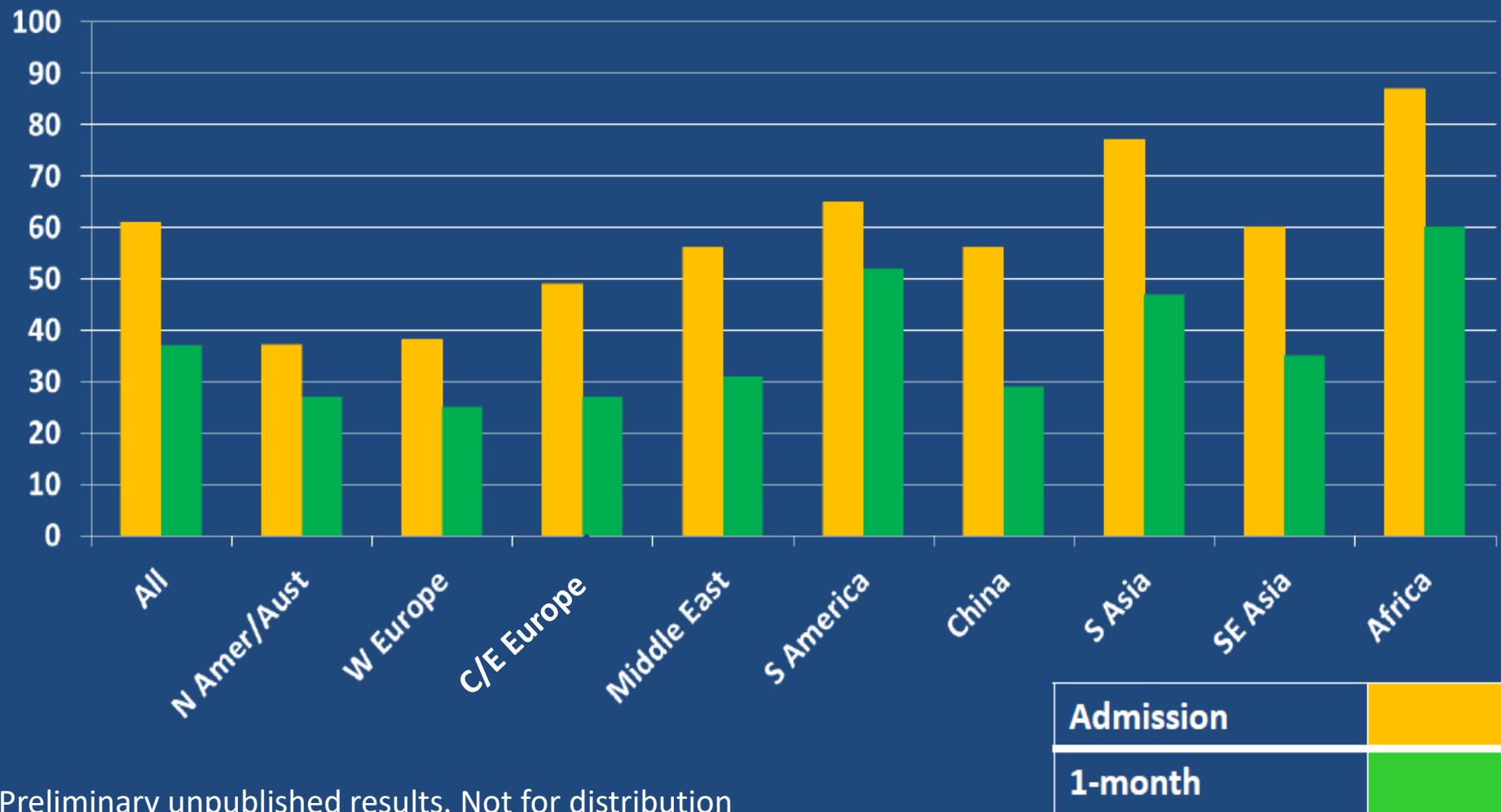
Lacunar Infarct  
(LACI)

# MODIFIED-RANKIN SCORE

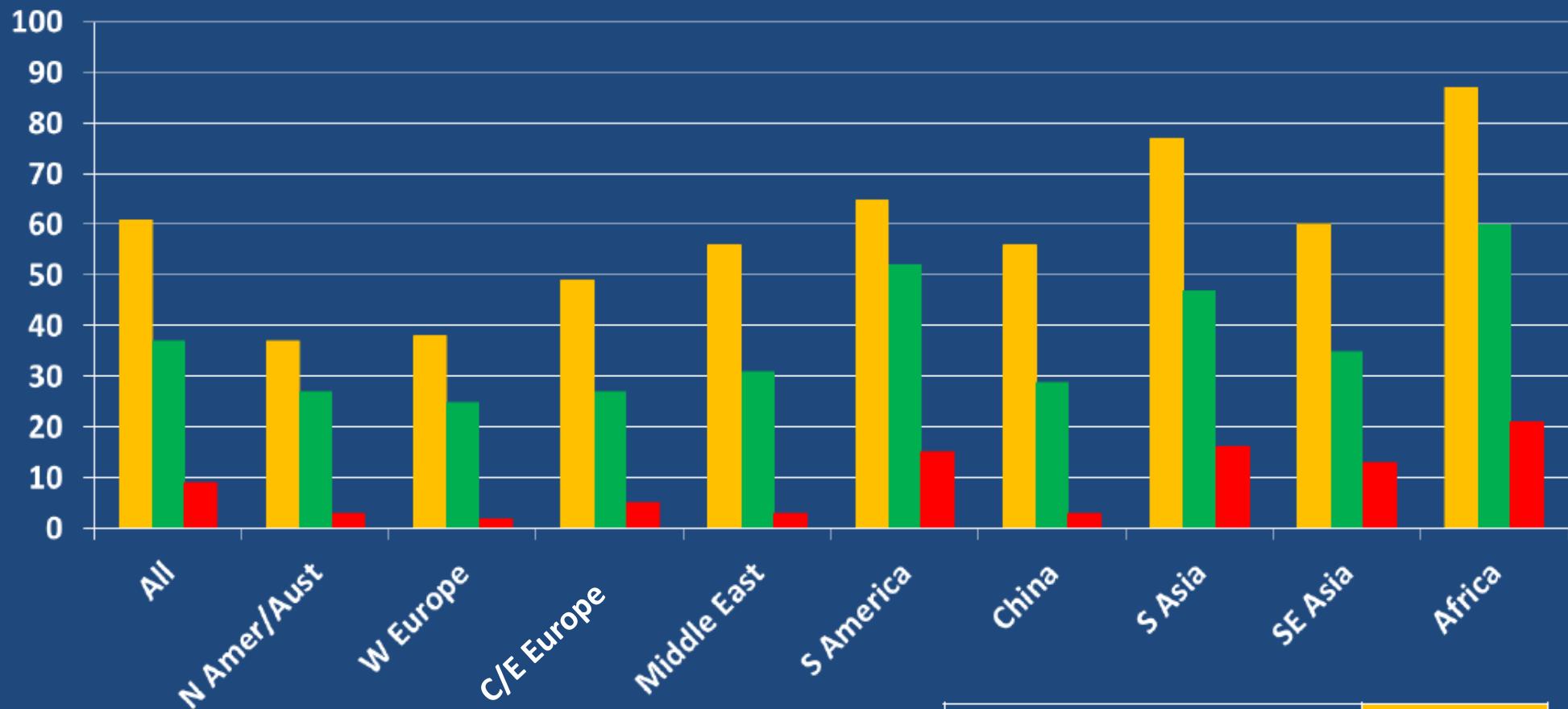
Score	Description
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; <u>requiring some help</u> , but able to walk without assistance
4	Moderately severe disability; <u>unable to walk without assistance</u> and unable to attend to own bodily needs without assistance
5	Severe disability; <u>bedridden</u> , incontinent and requiring constant nursing care and attention
6	Dead

# INTERSTROKE POPULATION (CASES)

STROKE WITH DEPENDENCE OR FATAL (M-RANKIN 3-6)  
(BASELINE TO 1-MONTH FOLLOW-UP)

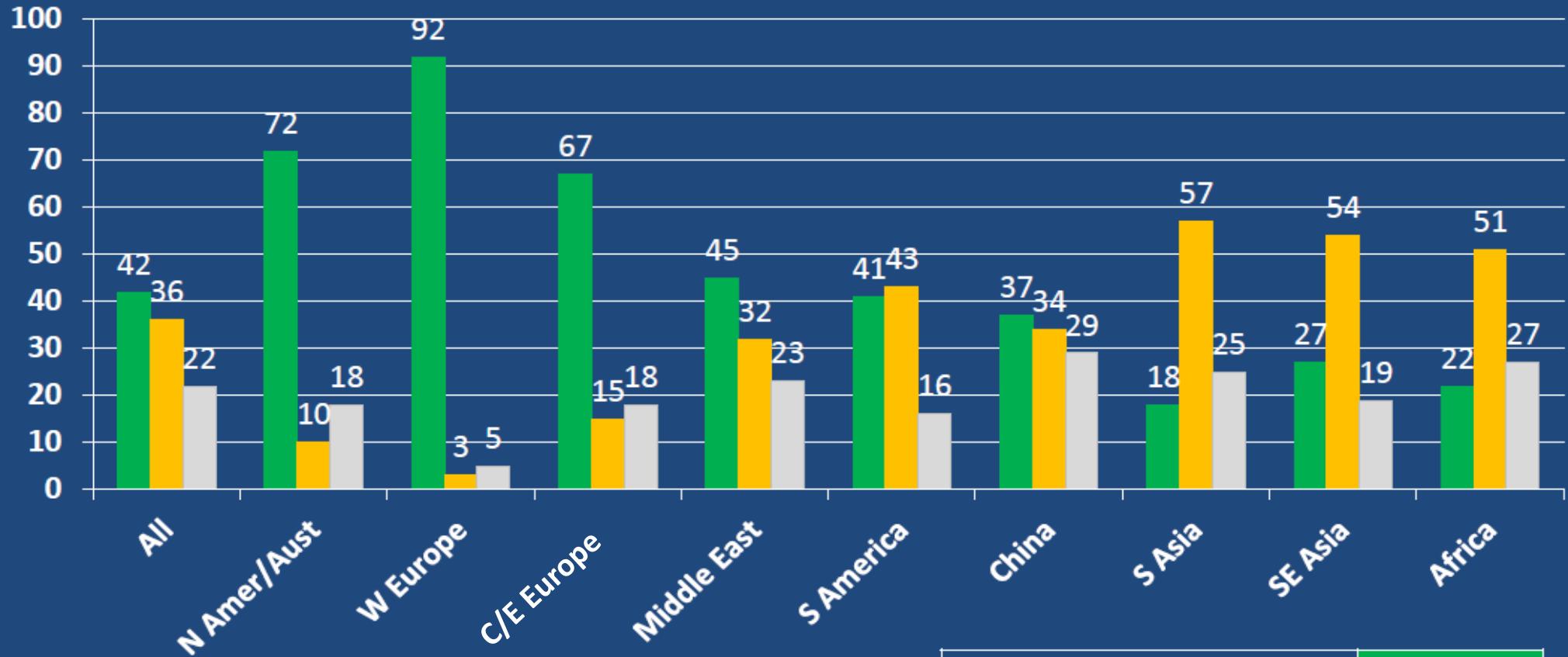


# INTERSTROKE POPULATION (CASES)



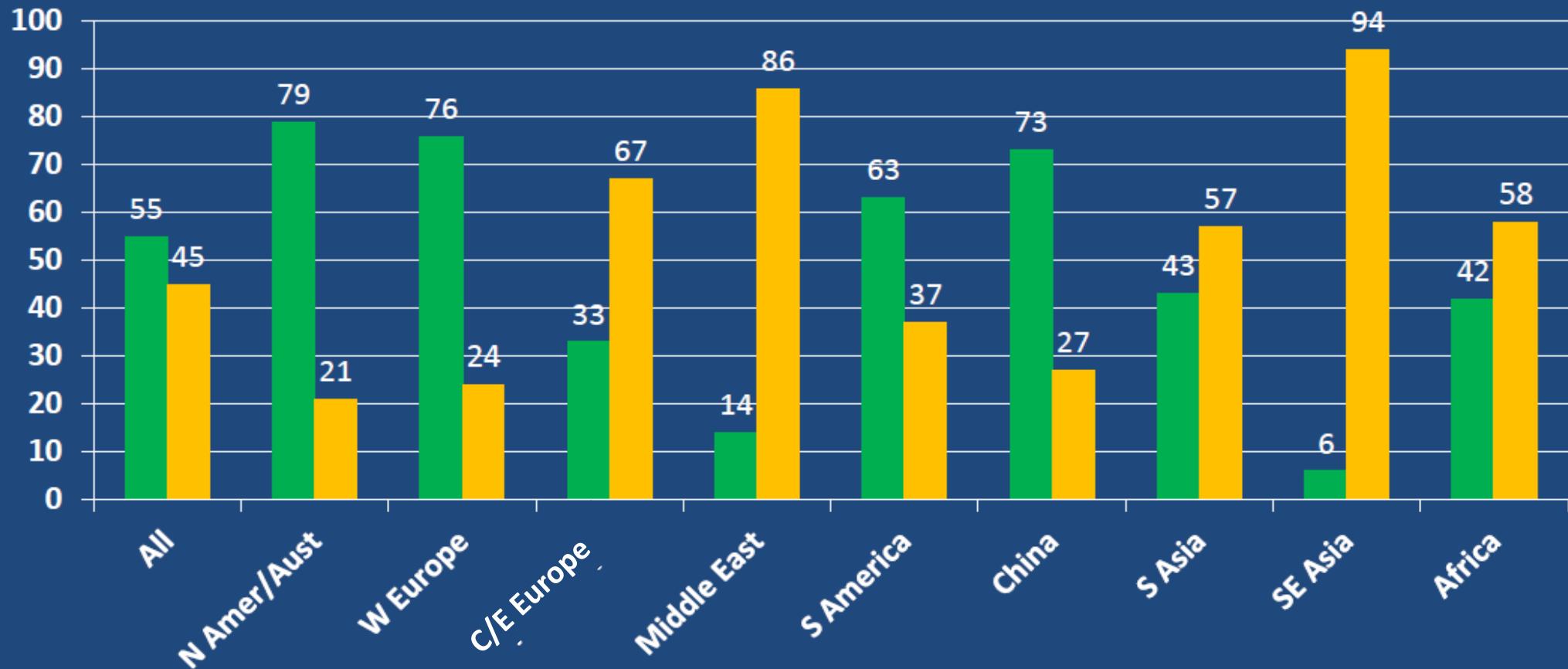
Admission m-R 3-6	
1-month m-R 3-6	
Fatal Stroke	

# SOURCE OF INFORMATION (CASES)



Patient (42%)	
Proxy (36%)	
Both (22%)	

# SOURCE OF INFORMATION (CONTROLS)



Community (55%)	
Hospital (45%)	



# INTERSTROKE

## Risk Factors for Stroke

Population Health Research Institute, McMaster University, Hamilton, Canada

# STATISTICAL ANALYSIS

- Cases
  - All stroke
  - Ischemic stroke
  - ICH
- Controls
  - Optimal use of controls
  - Used all controls, matched for sex, age and site
  - Therefore, able to match ICH with controls 1:4
  - Indirect comparison between ischemic stroke and ICH

# STATISTICAL ANALYSIS

- Conditional and unconditional logistic regression analysis to examine the association between risk factors (OR with 99%CI):
  - All stroke
  - Ischemic stroke
  - ICH
- Estimated population-attributable risk (PAR)
  - Individual risk factors and combination of risk factors
- Multivariable models adjusted for age, sex, region, smoking, WHR, diabetes, physical activity, diet score, alcohol intake, psychosocial factors and cardiac risk factors
  - lipids included in some models
- Continuous variables presented using restricted cubic splines and quantiles (Q1-reference) based on controls

# HYPERTENSION (HISTORY)

## BY REGION (ALL STROKE)

Preliminary unpublished results. Not for distribution

Region	Control (%)	Ischemic (%)	ICH (%)	Odds Ratio (99%CI)	PAR 99%CI
N America	38.0	58.9	54.1	2.15 (1.32-3.52)	27.2 (15-45)
W Europe	37.1	56.5	58.9	1.82 (1.43-2.31)	26.4 (20-35)
E Europe	54.4	71.2	67.2	1.46 (1.03-2.07)	34.8 (24-47)
S America	58.3	70.3	70.7	1.47 (1.13-1.92)	25.7 (16-38)
Middle East	32.2	58.4	58.0	3.02 (1.68-5.42)	34.0 (27-43)
Africa	31.0	51.2	63.5	2.71 (1.93-3.80)	34.0 (27-42)
South Asia	21.7	44.8	41.4	2.55 (2.09-3.10)	26.7 (23-31)
China	28.5	53.2	61.3	3.07 (2.70-3.49)	37.5 (34-41)
SE Asia	43.4	65.3	70.4	3.20 (2.33-4.39)	46.7 (38-56)
<b>Overall PAR</b>					<b>33.6 (32-36)</b>

Following variables included in model, age, sex, region, smoking, WHR, diabetes, physical activity, diet score, alcohol intake, psychosocial factors and cardiac risk factors

# HYPERTENSION (Hx OR BP >140/90 OR 160/90MMHG)

	All Stroke	
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)
BP > 160/90	2.89 (2.61-3.21)	45 (42-48)
BP > 140/90	3.60 (3.29-3.94)	54 (52-57)
BP > 130/80	3.08 (2.73-3.49)	58 (54-62)

	Ischemic Stroke		ICH	
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)	Odds ratio (99%CI)	PAR (99%CI)
BP > 160/90	2.50 (2.22-2.81)	39 (36-44)	5.82 (4.82-7.02)	64 (60-69)
BP > 140/90	2.99 (2.70-3.30)	48 (45-51)	8.13 (6.85-9.65)	74 (71-77)
BP > 130/80	2.59 (2.26-2.97)	51 (46-56)	7.25 (5.60-9.39)	79 (74-83)

# APO B/A AND STROKE (T3 VERSUS T1)

	All Stroke	
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)
Apo B/A (T3)	1.98 (1.74-2.25)	29 (24-34)

	Ischemic Stroke		ICH	
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)	Odds ratio (99%CI)	PAR (99%CI)
Apo B/A (T3)	2.24 (1.94-2.59)	34 (29-40)	1.27 (1.03-1.57)	6 (1-29)

# DIABETES AND STROKE

All Stroke		
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)
Diabetes	1.09 (0.97-1.24)	2 (0.6-7.6)

	Ischemic Stroke		ICH	
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)	Odds ratio (99%CI)	PAR (99%CI)
Diabetes	1.25 (1.09-1.43)	5 (3-9)	0.67 (0.54-0.84)	-

# WHR AND STROKE (T2, T3 VERSUS T1)

All Stroke		
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)
T2	1.19 (1.07-1.32)	
T3	1.38 (1.20-1.59)	13.1 (8-22)

	Ischemic Stroke		ICH	
Risk Factor	Odds Ratio (99%CI)	PAR (99%CI)	Odds ratio (99%CI)	PAR (99%CI)
T2	1.23 (1.09-1.38)		0.99 (0.84-1.17)	
T3	1.40 (1.19-1.64)	16 (9-25)	1.18 (0.94-1.48)	-

# CARDIAC RISK FACTORS BY REGION (ISCHEMIC STROKE)

Region	N	Control (%)	Ischemic (%)	Odds ratio (99%CI)	PAR 99%CI
N America	761	15.0	34.2	2.40 (1.27-4.55)	20.4 (12-32)
Western Europe	2890	12.0	30.0	3.01 (2.20-4.12)	20.2 (16-25)
Eastern Europe	1872	13.5	33.9	2.38 (1.61-3.52)	23.1 (5.1-19)
S America	2352	9.4	22.0	3.73 (2.34-5.95)	13.5 (10-18)
Middle East	619	5.8	13.9	5.17 (1.29-20.7)	10.2 (5-19)
China	5770	1.7	6.5	4.29 (2.72-6.79)	5.0 (4-7)
South Asia	3872	1.5	8.3	5.85 (2.98-11.5)	6.6 (5-9)
SE Asia	1152	3.0	13.7	7.67 (3.14-18.7)	11.4 (8-17)
Africa	1384	3.0	12.4	3.60 (1.38-9.40)	9.8 (7-14)
<b>All Regions</b>					<b>11.0 (10-12)</b>

# ATRIAL FIBRILLATION BY REGION (ISCHEMIC STROKE)

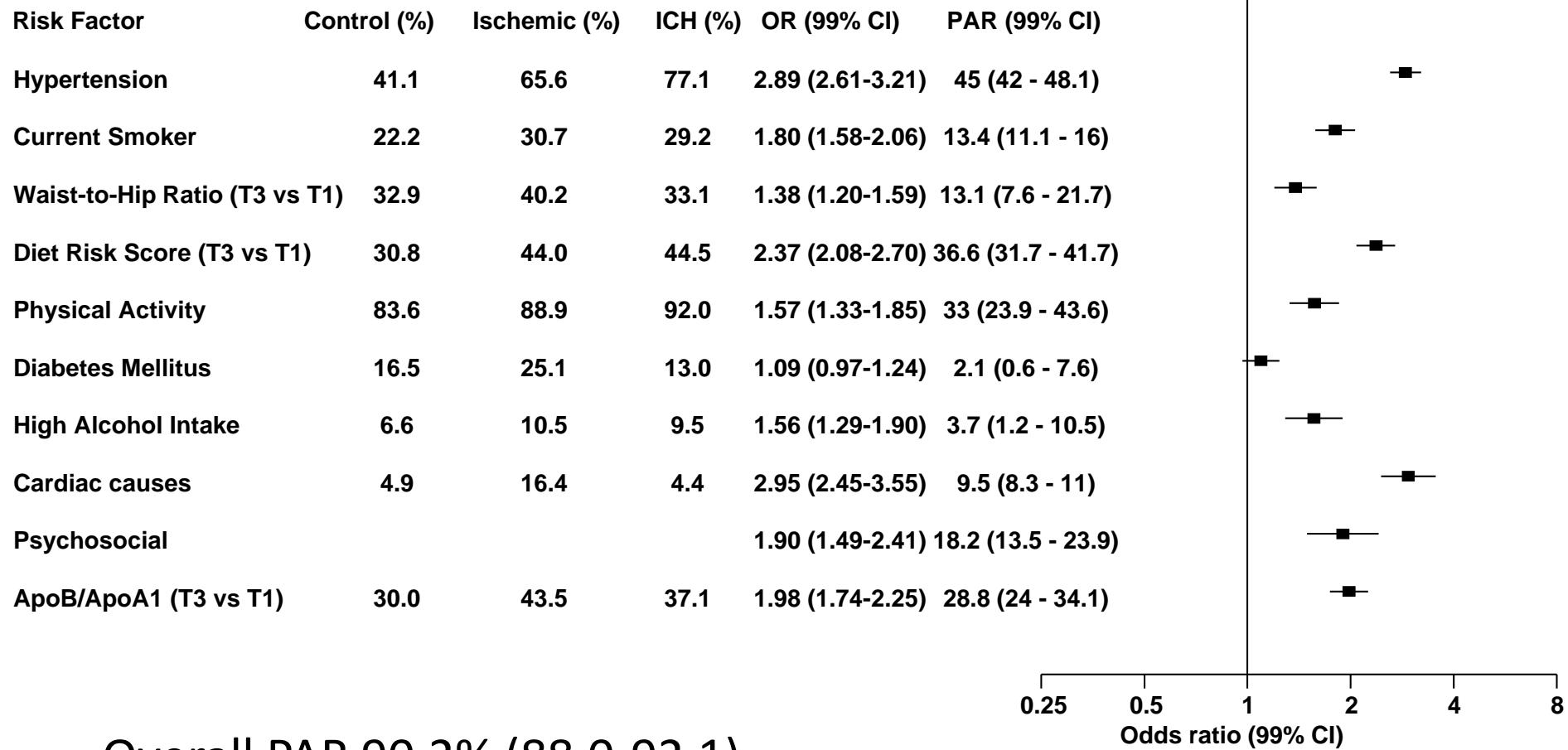
Region	Control (%)	Ischemic (%)	Odds ratio (99%CI)	PAR 99%CI
N America	7.1	24.0	6.86 (2.78-16.9)	19.8 (14-28)
Western Europe	7.4	22.7	3.47 (2.29-5.26)	15.9 (12-21)
Eastern Europe	6.8	24.3	3.77 (2.40-5.93)	17.8 (14-23)
Middle East	1.0	6.0	29.7 (2.04-432)	5.8 (3-11)
S America	4.3	15.5	3.83 (2.22-6.63)	10.9 (8-15)
China	0.9	5.4	6.80 (3.50-13.2)	4.6 (4-6)
South Asia	1.2	4.4	3.25 (1.58-6.66)	3.0 (1.8-5)
SE Asia	1.9	11.1	7.50 (2.60-21.6)	8.8 (6-14)
Africa	2.1	9.4	5.27 (2.15-12.9)	7.6 (5-11.7)
<b>All Regions</b>				

# CURRENT TOBACCO USE BY REGION (ALL STROKE)

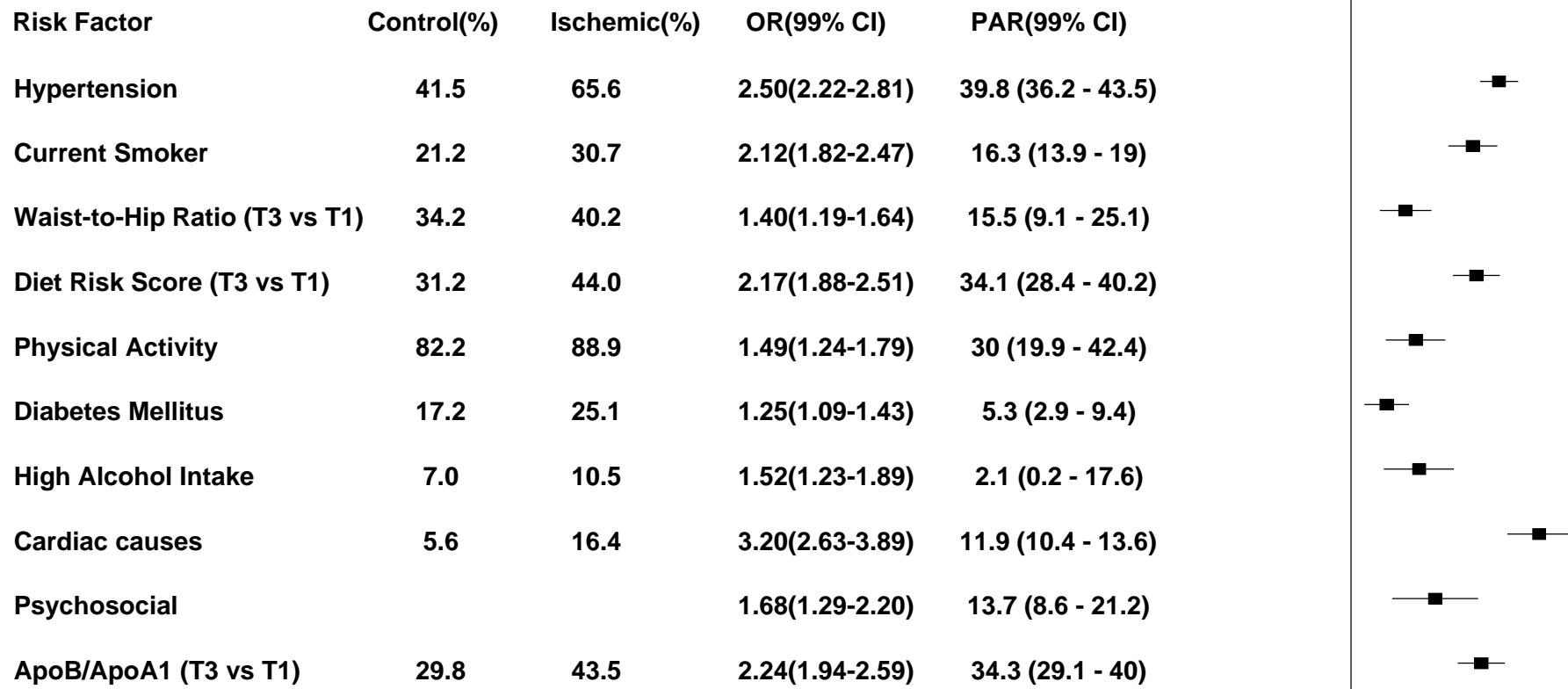
Region	Control (%)	Ischemic (%)	ICH(%)	Odds ratio	PAR
				(99%CI)	99%CI
N America	10.3	27.3	24.3	3.35 (1.76-6.37)	19.1 (13-28)
Western Europe	10.5	27.0	12.6	2.76 (1.97-3.88)	17.5 (14-22)
Eastern Europe	17.8	29.0	19.7	2.21 (1.48-3.29)	15.1 (10-22)
S America	9.5	16.9	12.2	1.56 (1.06-2.30)	6.9 (4-11)
Middle East	20.9	28.1	24.0	1.25 (0.63-2.49)	7.3 (2-30)
Africa	10.4	13.4	12.7	1.61 (0.90-2.85)	3.1 (1-13)
South Asia	30.7	34.9	39.1	1.59 (1.29-1.96)	13.2 (9-19)
China	30.0	40.0	32.9	1.63 (1.38-1.93)	15.3 (12-20)
SE Asia	25.6	30.8	34.5	1.55 (1.06-2.25)	10.3 (5-22)
<b>All Regions</b>				<b>1.80 (1.58-2.06)</b>	<b>13.2 (12-15)</b>

Preliminary unpublished results. Not for distribution

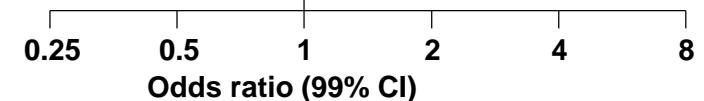
# RISK FACTORS FOR ALL STROKE (ALL REGIONS)



# RISK FACTORS FOR ISCHEMIC STROKE (ALL REGIONS)

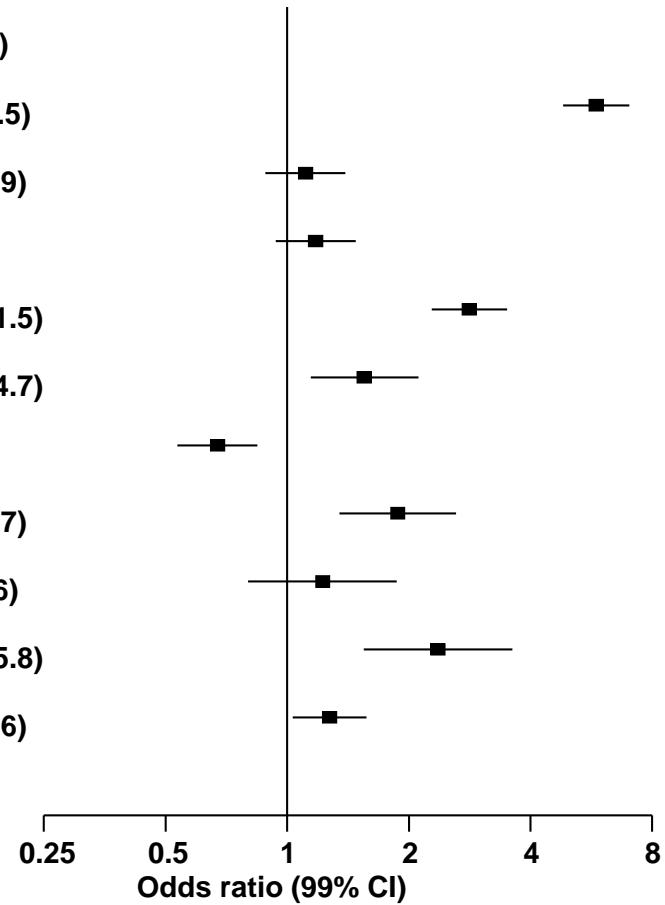


Overall PAR 90.7% (88.2-92.7)



# RISK FACTORS FOR ICH (ALL REGIONS)

Risk Factor	Control(%)	ICH(%)	OR(99% CI)	PAR(99% CI)
Hypertension	39.1	77.1	5.82 (4.82-7.02)	64.4 (60 - 68.5)
Current Smoker	25.3	29.2	1.11 (0.88-1.39)	2.8 (0.4 - 17.9)
Waist-to-Hip Ratio (T3 vs T1)	30.3	33.1	1.18 (0.94-1.48)	-0.1 (N/A)
Diet Risk Score (T3 vs T1)	29.4	44.5	2.82 (2.28-3.50)	43.5 (35.8 - 51.5)
Physical Activity	88.7	92.0	1.55 (1.14-2.11)	32.7 (16.3 - 54.7)
Diabetes Mellitus	14.9	13.0	0.67 (0.54-0.84)	-6.5 (N/A)
High Alcohol Intake	5.2	9.5	1.88 (1.35-2.62)	8.2 (4.1 - 15.7)
Cardiac causes	2.9	4.4	1.22 (0.80-1.87)	0.8 (0.1 - 6.6)
Psychosocial			2.36(1.55-3.61)	26.1 (18.3 - 35.8)
ApoB/ApoA1 (T3 vs T1)	30.3	37.1	1.27 (1.03-1.57)	6.1 (1.1 - 28.6)



Overall PAR 91.2% (86.7-94.2)