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Epidemiology of stroke and its subtypes in Chinese populations

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Declaration

I declare that I composed this thesis by myself, and it is my own original work. The thesis has not been submitted in part or in whole for any other degree or professional qualification except as specified.

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Publications associated with this thesis

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Abstract

Background: Chinese populations have been reported to have a higher stroke incidence as well as different stroke epidemiology compared with white populations. However, reliable comparisons have been precluded by a lack of methodologically robust studies. I aimed to systematically evaluate the incidence of stroke, the distribution of its main types/subtypes, and risk factor distributions among stroke types/subtypes in Chinese, and to compare these with data from white populations.

Methods: I performed a series of systematic reviews and meta-analyses of studies conducted since 1990 which had data on (1) incidence of stroke, (2) pathological types of stroke or ischaemic stroke subtypes, and (3) frequency of risk factors among pathological types of stroke or ischaemic stroke (IS) subtypes in Chinese populations, and in white populations for comparison. I calculated age-standardized stroke incidence and the proportions of each pathological type and ischaemic subtype. For each risk factor, I calculated study-specific and pooled odds ratios (ORs) using a random effects model for intracerebral haemorrhage (ICH) versus IS, for each IS subtype versus other subtypes, and for overall IS patients, comparing findings for Chinese versus Whites.

In addition, I conducted individual patient analyses of data from the National Taiwan University Hospital (NTUH) Stroke Registry, which consecutively recruited 6675 acute stroke patients from 2006-2011, comparing risk factor profiles among stroke types and subtypes and using logistic regression to adjust for potential confounding factors.

Results: From my systematic reviews, I found a younger onset of stroke, a slightly higher overall stroke incidence and higher proportion of ICH in Chinese versus white populations. Although the overall proportion of lacunar infarct appeared higher in Chinese from hospital-based studies than white populations, confirming the different distributions of ischaemic subtypes will need further comparable population-based studies.

In my meta-analyses comparing risk factors for ICH versus IS, in Chinese - but not Whites – hypertension (HTN) and alcohol intake were significantly more frequent, while mean age was lower in ICH than IS. In IS, the overall prevalence of hypertension, diabetes, smoking, and alcohol intake were similar between Chinese and white IS patients, whereas hypercholesterolaemia, ischaemic heart disease (IHD) and atrial fibrillation (AF) were less common in Chinese IS patients. As for IS subtypes, the relative frequencies of risk factors were mostly qualitatively similar (although different in size) in Chinese and white populations. Compared with other ischaemic subtypes: large artery atherosclerosis (LAA) strokes were associated with diabetes; cardioembolic (CE) strokes were associated with AF and IHD; small vessel disease (SVD) strokes or lacunar strokes were associated with hypertension and diabetes.

Analyses of NTUH individual patient data showed that HTN and alcohol intake were independent risk factors for ICH versus IS in a Chinese population in Taiwan, regardless of age, sex, or other risk factors. The results were consistent with my previous risk factor meta-analyses for ICH versus IS. In IS analyses, the prevalence of hypertension, diabetes, AF, and hyperlipidaemia in overall IS patients based in

Taiwan were higher than the pooled results in my risk factor meta-analysis for IS for all Chinese populations including mainland China. In terms of risk factor associations with IS subtypes, the findings after controlling for potential confounders were mostly close to my previous meta-analysis results with the exception of stronger associations of hypertension and diabetes with SVD (lacunar) strokes.

Conclusion: I have shown a younger onset of stroke, a higher overall stroke incidence, an around twofold higher proportion of ICH and different distribution of IS subtypes, as well as some differences in risk factor distributions among pathological types of stroke and IS subtypes in Chinese compared with white populations. My results help to inform us of different stroke mechanisms in different populations, to guide further well-designed research in this area, and to direct better strategies for stroke prevention in Chinese populations.

Abbreviation

AF	Atrial fibrillation
ARIC	Atherosclerosis Risk in Communities
CI	Confidence interval
CE	Cardioembolism
CS	Carotid stenosis
CT	Computed Tomography
DM	Diabetes mellitus
MRI	Magnetic resonance imaging
ECG	Electrocardiography
HC	Hypercholesterolaemia
HTN	Hypertension
ICH	Intracerebral haemorrhage
IHD	Ischaemic heart disease
I^2	Inconsistency
IS	Ischaemic stroke
LAA	Large artery atherosclerosis
LACI	Lacunar infarct
MI	Myocardial infarction
MR	Magnetic resonance
NINDS	National Institute of Neurological Disorders and Stroke
NLAC	Non-lacunar infarct
NTUH	National Taiwan University Hospital
OCSP	Oxfordshire Community Stroke Project
OR	Odds ratio

PACI	Partial anterior circulation infarct
POCI	Posterior circulation infarct
SAH	Subarachnoid haemorrhage
SD	Standard deviation
SVD	Small vessel disease
TACI	Total anterior circulation infarct
TIA	Transient ischaemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
WHO	World Health Organisation

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Section A: Background

Chapter 1: Global stroke epidemiology and the classification of stroke types/subtypes

1.1 Global epidemiology of stroke

Stroke is a major global disease and public health challenge. It is the second commonest cause of death worldwide after ischaemic heart disease (when cancers are counted in different types), and an important global cause of disability (Lopez et al. 2006). According to the World Health Organisation (WHO), it is defined as "rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin" (Hatano et al. 1976; Aho et al. 1980).

1.1.1 Mortality and disability

Stroke caused an estimated 5.7 million deaths worldwide in 2005, and 87% of these deaths happened in developing countries (Strong et al. 2007). The impact of stroke has not decreased in the following years. From a recent report of the Global Burden of Disease Study, stroke was still the second leading cause of death in 2010, accounting for 11% of all causes of death (nearly 5.9 million deaths in worldwide), an increase of 26% since 1990 (Lozano et al. 2012). On top of that, stroke also results in long term disability and is the fourth leading cause of disease burden worldwide (measured in disability-adjusted life years) (Lopez et al 2006).

The mortality and disability of stroke varies substantially between countries (Warlow et al. 2003). There is a ten-fold difference in stroke mortality and disability-adjusted life years [DALY] loss, with the highest rates in affecting most in low income countries in eastern Europe, north Asia, central Africa, and the south Pacific regions (Johnston et al. 2009). Stroke mortality depends on both the incidence of stroke and case fatality. Although it has been declining over recent decades in most countries, it is increasing in eastern Europe (Sarti et al. 2003). However, some areas do not have complete medical records or reliable death certificates, meaning that accurate mortality rates are not available for all countries.

1.1.2 Incidence

Stroke is a non-communicable disease mainly occurring in older people, and the incidence of stroke increases with each decade of life. In a systematic review of worldwide stroke incidence study, more than half of all strokes occur in patients aged 75 years or older (Feigin et al. 2003). The average age affected by stroke was 70 years in men, and 75 years in women. In people aged 55 years or beyond, the overall age-standardised incidence of stroke ranged from 420 to 1180 per 100,000 person-years in population-based studies (Feigin et al. 2003).

Comparing stroke incidence in different countries, regions or populations as well as measuring the trend in incidence needs to use the same definition of stroke, the same methods of case ascertainment and data presentation (Sudlow et al. 1996; Okamoto et al. 2003; Feigin et al. 2003). However, limited numbers of population-based

studies of incidence of stroke have been conducted well enough, using rigorous methods to be comparable. In the 1980s, the WHO MONICA (World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease) project was launched to record the incidence of stroke and myocardial infarction aged 35-64 years and to monitor the trends using uniform methods across many countries, including 16 European and 2 Asian populations. It revealed large geographical variations of all strokes in both incidence and mortality (Thorvaldsen et al. 1995). A later systematic review (without upper age limit for the populations studied) showed that geographical variations in incidence of all strokes combined were modest, smaller than that in the MONICA project, except Ukraine, Russia and Japan (Feigin et al. 2003). Methodological variances including case ascertainment and age limit may partly explain the difference. However, all these data are mostly based on white populations of European origin in developed countries. Few reliable and comparable data are available from other populations around the world or from developing countries, where the stroke burden is high and where there have been rapid changes recently in both economies and lifestyles.

1.1.3 Stroke in the developing world

While stroke incidence has decreased by around 40% in high income countries over the past four decades, it has increased more than 100% in low to middle income countries (Feigin et al. 2009). Nowadays, the overall stroke incidence rates, the incidences and the proportions of intracerebral haemorrhage and subarachnoid

haemorrhage in low to middle income countries are higher than those in high income countries (Feigin et al. 2009). Although the 1 month case fatality of stroke is decreasing in both high and low to middle income countries, the overall 1 month stroke case fatality in low to middle income countries is still 25% higher than that in high income countries (Feigin et al. 2009).

As life expectancy and populations increase, developing countries, especially those with rapid economic and epidemiological transition such as China, will possibly have a major increase of overall burden of stroke (Truelsen et al. 2001; Yusuf et al. 2001; Feigin et al. 2011). Its increasing global impact in the decades ahead is predicted to be greatest in middle income countries, and stroke is expected to be the leading cause of death in 2030, accounting for around 14% of total deaths (Mathers et al. 2006). For intervention and prevention of stroke to be effective with limited resources, it is important to establish reliable and accurate data on stroke epidemiology. Thus, further research using the best possible sources and rigorous methods to study the incidence of stroke and its subtypes, risk factors, and outcome is urgently needed in the developing world including Chinese populations (Sudlow et al. 1996; Truelsen et al. 2001; Okamoto et al. 2003; Feigin et al. 2003; Feigin et al. 2004; Feigin et al. 2011).

1.2 Classification of pathological types of stroke

Stroke is a heterogeneous clinical syndrome. The World Health Organization (WHO) has divided stroke into four pathological types – cerebral infarction (or ischaemic

stroke), intracerebral haemorrhage (blood vessel rupture with bleeding within brain tissue), subarachnoid haemorrhage (blood vessel rupture with bleeding within the subarachnoid space), and type unknown (Aho et al. 1980). For large epidemiological comparisons, all types of stroke have to fulfil the stroke definition of WHO based on clinical manifestations, and appropriately timed brain computed tomography (CT) or magnetic resonance imaging (MRI) is important for differential diagnosis of stroke types (within 30 days of stroke has been suggested though it may be different in clinical practice) (Bamford et al. 1990; Sudlow et al. 1997). Cerebral infarction (or ischaemic stroke) has been suggested to have brain CT (or MRI) scan within 30 days of stroke, which shows infarct or no relevant lesion, or autopsy proof of infarction. Intracerebral haemorrhage (ICH) must have evidence of haemorrhage from brain CT (or MRI) scan within 30 days of stroke or autopsy. Subarachnoid haemorrhage (SAH) must have appropriate clinical history, and subarachnoid blood on brain CT scan or lumbar puncture or source of subarachnoid bleeding from cerebral angiography (Sudlow et al. 1997). Patients who have WHO-defined stroke but do not fulfil the aforementioned criteria for cerebral infarction, ICH or SAH are assigned to unknown type. Among these pathological types of stroke, ischaemic stroke (i.e. cerebral infarction) accounts for the largest proportion of stroke, ranging from 67% to 81% of total stroke cases, while ICH is responsible for 7% to 20%, SAH for 1% to 7%, and unclassified type (i.e. unknown type) for 2% to 15% (Feigin et al. 2003).

1.3 Classification of ischaemic subtypes of stroke

1.3.1 Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification

Ischaemic stroke (IS) can be further classified into several ischaemic subtypes based on presumed aetiology or brain anatomy. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification is the most common used classification system clinically (Adams et al. 1993). Ischaemic strokes are classified into five aetiological subtypes:

1. Large-artery atherosclerosis (LAA)

   Clinical findings include cortical, brain stem or cerebellar dysfunction, and the corresponding infarct lesions are greater than 1.5 cm in diameter on CT or MRI. There is supportive evidence of greater than 50% stenosis of an intracranial or extracranial artery by duplex imaging or arteriography, and potential sources of cardiogenic embolism are excluded.
2. Cardioembolism (CE)

   At least one cardiac source for an embolus, such as atrial fibrillation, should be identified for cardioembolic stroke. Clinical and brain imaging findings are similar to those in large-artery atherosclerosis. The possibility of potential large-artery atherosclerotic thrombosis or embolism should be excluded.
3. Small-vessel occlusion (lacunar, small vessel disease [SVD] strokes)

   Clinical findings of one of the lacunar syndromes should be present, without evidence of cortical dysfunction. The patients should also have a normal or

relevant infarct lesion with a diameter of less than 1.5 cm on brain CT or MRI examination. Potential cardiac sources for embolism and extracranial large artery stenosis more than 50% should be absent. A history of hypertension or diabetes supports the diagnosis.

4. Stroke of other determined aetiology

   Patients with clinical and brain CT or MRI findings of an acute IS are found to have unusual causes of stroke after investigations, such as non-atherosclerotic vasculopathies, hypercoagulation states or haematological disorders. Cardiac embolism and large-artery atherosclerosis should be excluded.

5. Stroke of undetermined aetiology

   Acute IS patients have two or more causes identified, or no identifiable causes of stroke following complete or incomplete evaluation.

Although the TOAST classification is logical, simple and widely used, it has only moderate inter-rater reliability since the interpretation and application of the TOAST classification is likely to vary among stroke physicians (Gordon et al. 1993; Meschia et al. 2006). In addition, TOAST classification is dependent on a range of investigations for possible aetiologies, such as echocardiography, carotid Doppler, transcranial ultrasound, and cerebral angiography. These investigations are not widely available in all hospitals. Thus, differences in diagnostic work-up may lead to substantial variations in the proportion of undetermined IS subtype, which then affect the proportions of other ischaemic subtypes and preclude reliable comparisons across different studies. Moreover, the definition of TOAST classification is somewhat risk-

factor dependent. For instance, patients with atrial fibrillation are more likely to be assigned to cardioembolic subtype directly, irrespective other risk factor investigation results. This could cause a potential classification bias when assessing the associations between risk factors and ischaemic subtypes (Jackson et al. 2005).

1.3.2 Oxfordshire Community Stroke Project (OCSP) classification

In the OCSP classification system, patients with cerebral infarction are classified into four subtypes according to the clinical presentations of stroke patients, corresponding to the arterial territory involved (Bamford et al. 1991):

1. Lacunar infarct (LACI)

   Patients present with a pure motor stroke, pure sensory stroke, sensori-motor stroke, or ataxic hemiparesis.
2. Total anterior circulation infarct (TACI)

   Patients present with combination of new higher cerebral dysfunction (e.g. dysphasia, dyscalculia, visuospatial disorder); homonymous visual field defect, and ipsilateral motor and/or sensory deficits.
3. Partial anterior circulation infarct (PACI)

   Patients present with only two of the three components of the TACI syndrome, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those in LACI.
4. Posterior circulation infarct (POCI)

Patients present with any of the following symptoms/signs: ipsilateral cranial nerve palsy (III-XII) with contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; conjugated eye movement deficit; cerebral dysfunction; or isolated homonymous visual field defect.

It is simple, quick, and practical, and clinically competent stroke physicians can use this method for all ischaemic stroke patients in hospital or in the community. Also, the OCSP classification can predict size and site on brain imaging, functional outcome, mortality and recurrent stroke clinically (Mead et al. 2000; Bamford et al. 1991). In contrast to TOAST classification, the OCSP classification scheme does not rely on clinical investigations beyond a CT or MR brain scan to distinguish ischaemic from haemorrhagic stroke. Thus, differences in diagnostic work-up do not lead to variations in ischaemic subtypes. In addition, it is a risk factor-free classification method, and is recommended for use in comparing the risk factor profiles between lacunar and non-lacunar infarctions (Jackson et al. 2005). The inter-observer reliability of the OCSP classification is moderate to good (Lindley et al. 1993; Dewey et al. 2001). However, the OCSP classification is unlikely to give information of stroke aetiology. Furthermore, it may not have accurate differentiation between small cortical and subcortical infarcts (Asdaghi et al. 2011). Total reliance on clinical stroke syndrome classification may lead to misclassification in some patients, especially in those with less severe clinical presentations and when no lesion is found on brain CT (Asdaghi et al. 2011).

1.3.3 Conclusion

In this chapter, I have reviewed the global epidemiology of stroke. I have also outlined the pathological types and ischaemic subtypes of stroke, and approaches to their classifications in large epidemiological studies. In the following chapters, I systematically aim to assess the incidence of stroke, and distributions of pathological types and ischaemic subtypes of stroke using the TOAST or OCSP classification, and risk factor profiles among pathological and ischaemic subtypes of stroke in Chinese populations, which contribute to the largest number of people in the developing world, and compare these findings with data from white populations. I hope to establish more reliable and accurate analyses of stroke data in Chinese populations, to have better understanding of the characteristics of stroke epidemiology, to provide helpful information to make effective strategies of stroke prevention, and to reduce stroke burden in the years ahead.

Section B: Epidemiology of Stroke in Chinese versus White Populations – Systematic Review

Chapter 2: Incidence of stroke

2.1 Introduction

Compared with white populations, Chinese have been reported to have a higher incidence of overall stroke (Thorvaldsen et al. 1995; Chau et al. 2011; Fuh et al. 2000; Liu et al. 2007; Jeng et al. 2007). However, reliable comparisons have been precluded by a lack of methodologically robust studies of stroke incidence among Chinese populations, and age-standardization of incidence rates in different studies to different standard populations (Feigin et al. 2009; Feigin et al. 2003). Moreover, no previous review of the stroke epidemiology in Chinese populations has taken an explicitly systematic approach.

To clarify what is known and what remains uncertain about the epidemiology of stroke in Chinese populations and differences from white populations, I aimed systematically to evaluate the incidence of stroke in Chinese populations, and to compare this with data from white populations, standardized to the same world population.

2.2 Methods

2.2.1 Search strategy

I comprehensively sought articles published in any language on incidence in populations of Chinese origin. I used electronic searches in Medline and EMBASE

from 1990 (since prior to this, brain imaging with CT or MR was not used widely) to January 2012 (Appendix 1), carried out forward citation searches of relevant reviews (Liu et al. 2007; Feigin et al. 2009) and perused the reference lists of included primary articles and relevant reviews.

2.2.2 Selection criteria for studies of stroke incidence

I adapted inclusion criteria from those proposed for an "ideal" study of stroke incidence (Sudlow et al. 1996; Feigin et al. 2004): standard World Health Organization (WHO, Hatano et al. 1976), National Institute of Neurological Disorders and Stroke (NINDS Ad Hoc Committee. 1990) or Atherosclerosis Risk in Communities (ARIC, Rosamod et al. 1999) definition of stroke; first-ever strokes from a large well-defined population; comprehensive, community-based case ascertainment - including fatal and non-fatal cases not admitted to hospital - using multiple overlapping sources (primary and secondary care clinics, health centres, hospital admissions, death certificates etc.); prospective study design, ideally with "hot pursuit" of cases; lower age limit 45 years or younger; no upper age limit; data collection from 1990 onwards; numbers of first-ever stroke cases per year and of people in the population (or age-specific annual incidence) available in 10 year mid-decade age bands.

I excluded studies with hospital-based design, upper age limit, not first-ever strokes, populations overlapped with another included study, or serious data inconsistencies. I

sought essential information that was unavailable in publication(s) directly from the primary study authors.

2.2.3 Data extraction

From included studies of overall stroke incidence, I extracted information on: geographical area of the study; sources of case ascertainment; study period; size and age range of the population; stroke definition; number of first-ever strokes; mean age and sex distribution of stroke cases; the proportion of CT or MR brain imaging, and admission to hospital; and 1 month case fatality. I extracted or calculated age-specific incidence rate for each 10 year mid-decade age group.

2.2.4 Comparisons with studies in white populations

For comparison, I selected studies performed from 1990 onwards in predominantly white populations from a recent worldwide systematic review of community-based stroke incidence studies (Feigin et al. 2009). I sought relevant additional studies published up to January 2012 through forward citation searches of this review, and perused the reference lists of relevant publications identified. I used the same inclusion criteria as outlined above.

2.2.5 Statistical analysis

For each included study, I calculated age-standardized (to the WHO standard population) incidence of first-ever-in-a-lifetime stroke per 100,000 person years and 95% confidence intervals (CI) (Ahmad et al. 2000; Fay et al. 1997). I standardized for sex to a standard population with equal proportions of males and females in each age stratum. To compare studies, I focused on standardized incidence data for ages 45-74 and 45-75+ years, allowing the most comprehensive inclusion of data from all studies.

2.3 Results

2.3.1 Included studies

Of 3,063 papers describing studies in Chinese populations, 45 were potentially relevant but only six (described in four papers, all published in English) fulfilled the inclusion criteria (Figure 2.1). They included 404,254 people, 2,044,941 person-years and 3,935 first-ever stroke patients (Hu et al. 1992; Chang et al. 1995; Chen et al. 1995; Jiang et al. 2006).

2.3.2 Stroke incidence in Chinese populations

Characteristics of these included studies in Chinese populations are shown in Table 2.1. Four were based in China and two in Taiwan. Mean age of stroke onset was 66-70 years. The proportion of stroke cases with brain imaging varied widely (30-91%, mean [weighted by study size] 76%). Age-standardized stroke incidence rates across

all ages varied widely (92-328 per 100,000 person-years), but are not fully comparable because of the substantial variation in the distribution of ages within the open-ended upper age band and exclusion of people under 35 years from one study. Age-standardized stroke incidence also varied up to fourfold among the seven Chinese cities included in one study, being higher in the north (Harbin) than in the south (Shanghai) of China (Data standardized to the world population were not available separately for the seven cities included in this study, Chen et al. 1995). As expected, age-specific annual incidence increased with age (Figure 2.2). In terms of 1 month case fatality, only one small study reported this around 17% (Hu et al. 1992).

2.3.3 Comparisons with white populations

I compared these results from Chinese populations with those from 10 community-based studies among predominantly white populations, which included 1,333,447 people, 2,162,088 person years, and 4,568 first-ever stroke cases (Giuseppe et al. 1995; Vemmos et al. 1999; Hanne et al. 1997; Kolominsky-Rabas et al. 1998; Steward et al. 1999; Wolfe et al. 2000; Carlo et al. 2003; Thrift et al. 2001; Correia et al. 2004; Appelros et al. 2002). Characteristics of these included studies in predominantly white populations are shown in Table 2.2. Mean age of stroke onset was younger in Chinese populations (range 66-70 versus 72-76 years). Age-standardized annual first-ever stroke incidence was more variable and somewhat higher in Chinese than Whites for ages 45-74 years (range 205-584 versus 170-335 per 100,000) (Figure 2.3). There were similar although less marked Chinese-Whites

differences for ages 45-75+ years. These data included many more incident strokes since all ages over 75 years are included, but were less comparable because of age variation in the open-ended upper age band (Figure 2.4). Additional standardization for sex made no material difference to the results.

2.4 Discussion

To my knowledge, this is the first systematic review of the epidemiology of stroke comparing data from Chinese populations with data from predominantly white populations.

I have shown that, compared with Whites, Chinese populations have a higher age-adjusted incidence of stroke, and a lower mean age of stroke onset. These differences are based on comparisons of methodologically robust, community-based studies, with appropriate age-standardization, avoiding inclusion of an open-ended upper age band. Therefore they are unlikely to be an artefact of variable hospital admission rates or of incomplete adjustment for age. In addition, there is striking variation among Chinese populations in overall stroke incidence.

Earlier studies suggested higher stroke incidence in Chinese versus white populations, and variable stroke incidence rates within China (higher rates in the north with a north-south gradient), but did not include people aged older than 64 years and some comparisons included recurrent as well as first-ever strokes (Thorvaldsen et al. 1995; Wu et al. 2001). My results show reliably that such differences exist after 1990 and

extend previous findings to those aged 65 years or beyond, among whom most strokes occur.

Proposed explanations for Chinese-Whites differences in stroke incidence and the variations among Chinese populations in overall stroke include differences in risk factors, dietary habits (e.g., variable intake of salt and preserved food), smoking, weather, socioeconomic status, and genetic factors (Wu et al. 2001; Yang et al. 2004; Asch et al. 2010). These vary substantially within Chinese populations as well as between Chinese and white populations. In parallel with the north-south gradient in stroke incidence, geographic variations of blood pressure, salt intake, and intracranial atherosclerosis have been also reported - higher rates in the northern and lower in the southern Chinese (Zhao et al. 2004; Pu et al. 2013).

2.4.1 Strengths and limitations

The major strengths of my study are: rigorous, systematic methods, including a comprehensive search strategy for relevant studies published in any language (including Chinese), reducing the selection bias of including only reports published in English; inclusion of Hong Kong and Taiwan as well as mainland China, covering more than 95% of Chinese populations worldwide and including those with highly developed economies; age-standardization of data from Chinese and predominantly white populations to the same world population; and inclusion of data from older people, who were omitted from many previous stroke incidence studies in Chinese populations (Feigin et al. 2004).

An important limitation is that, despite comprehensive searching, I found few community-based studies of incidence of stroke in Chinese populations published up to January 2012, and only one study reported 1 month case fatality. Chinese literature databases were not available to me because I did not have access to the full-text databases. Also, despite including only studies which appeared to fulfil accepted methodological criteria, we could not exclude the possibility of inaccurate or incomplete case ascertainment in some included studies. However, rapid developments and improvements in comprehensive primary health care and centralized health insurance should facilitate future, well-designed epidemiological studies (Liu et al. 2011; Heeley et al. 2009; Wang et al. 2005).

2.4.2 Conclusion

Here, I report a slightly higher overall stroke incidence in Chinese compared with predominantly white populations since 1990, with substantial regional variation among Chinese populations. A better understanding of the reasons for the observed differences in epidemiology of stroke should help us better to predict the potential effects of the rapidly growing economy and changing lifestyles, and contribute to efforts to reduce the stroke burden in Chinese populations.

Tables

Table 2.1 Characteristics of included community-based stroke incidence studies in Chinese populations

Study (first author)	Study area	Case ascertainment	Study period	Population	Person-years	Age range (Y)	Mean age (Y)	Gender (% male)	Stroke definition	First-ever stroke	CT/MR (%)	Case Fatality (one month,%)	Age-adjusted incidence per 100,000 person-years (95%CI)
Hu HH	Taiwan (4 counties)	door to door, local clinic, hospital, death certificate	1986-1990	8562	366389	>35	NR	59%	NINDS	104	65%	17%	328 (268-397)
Chang SF	Taiwan (Ilan)	door to door, hospital, death certificate	1991	184073	184073	All	66	51%	WHO	185	99%	NR	117 (101-135)
Chen XM	China (7 cities)	door to door, health station, home visit, hospital, death report	1986-1990	57914	289570	All	NR	58%	WHO	631	30-60%	NR	201 (185-217)
Jiang B	China (Beijing)	door to door, home visit, hospital, death certificates	1991-2000	50906	509060	All	70	50%	ARIC	1062	91%	NR	150 (141-159)
Jiang B	China-(Shanghai)	door to door, home visit, hospital, death certificates	1991-2000	51972	519720	All	70	49%	ARIC	785	80%	NR	92 (86-99)
Jiang B	China-(Changsha)	door to door, home visit, hospital, death certificates	1991-2000	50827	508270	All	70	56%	ARIC	1168	74%	NR	175 (165-185)

WHO=World Health Organisation; NINDS=National Institute of Neurological Disorders; ARIC=Atherosclerosis Risk in Communities; CT=computed tomography; MR=magnetic resonance imaging; CI=confidence interval; NR=not reported; Y=years.

Table 2.2 Characteristics of included community-based stroke incidence studies in white populations

Study (first author)	Study area	Case ascertainment	Study period	Population	Person-years	Age range (Y)	Mean age of stroke onset (Y)	Gender (% male)	Stroke definition	First-ever stroke	CT/MR (%)	Case fatality (1 month, %)	Age-adjusted incidence per 100,000 person-years (95%CI)
Giuseppe L	Italy (Belluno)	Home visit, clinic recruitment and hospital admission	1992-1993	211389	211389	All	NR	NR	WHO	474	90%	33%	110 (100-121)
Vemmos KN	Greece (Arcadia)	GP notification, hospital admission, health centre, death certificate	1993-1995	80774	161548	>=18	75	56%	WHO	555	90%	27%	133 (120-146)
Hanne E	Norway (Innherred)	GP and nursing home report, hospital admission	1994-1996	69295	138590	>=15	75	46%	WHO	432	87%	19%	154 (138-171)
Kolominsky-Rabas PL	Germany (Erlangen)	Hospital admission, nursing home, ambulance and emergency, GP, death certificate	1994-1996	101450	202900	All	73	41%	WHO	354	95%	19%	85 (76-95)
Stewart JA	UK (London, Whites)	Emergency room, hospital wards, GP, death certificate	1995-1996	167834	335668	All	74	47%	WHO	489	84%	27%	73 (66-81)

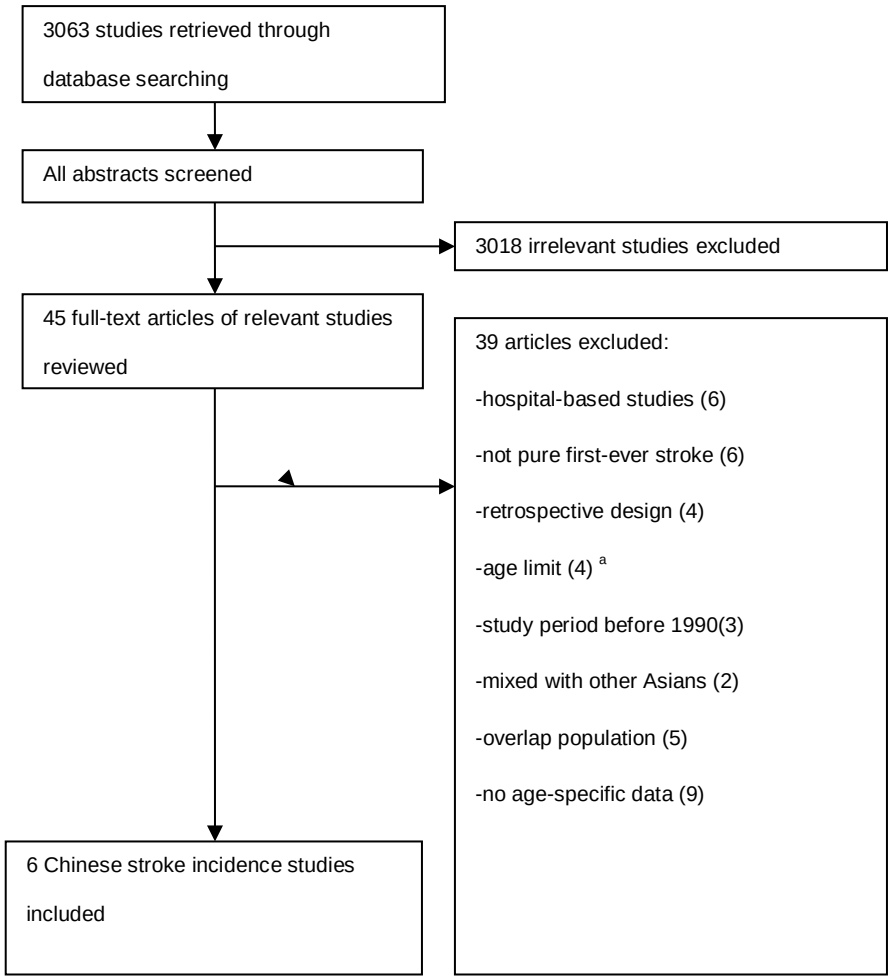
Wolfe CDA	France (Dijon)	Hospitals, nursing home, death certificate and postmortem report	1995-1997	143088	286176	All	NR	48%	WHO	591	89%	15%	67 (48-85)
Carlo AD	Italy (Vibo Valentia)	Hospital admission, emergency, nursing home, GP, and death certificate	1996	179186	179186	All	73	51%	WHO	321	96%	31%	87 (78-97)
Thrift AG	Australia (Melbourne)	Hospital admission, radiology, GP, nursing home, death certificate	1996-1997	133816	133816	All	NR	54%	WHO	276	91%	20%	100 (95-105)
Correia M	Portugal (Porto, rural)	GP, home visit, emergency , health centre, hospital clinic and admission record, death certificate	1998-2000	37089	74178	All	74	48%	WHO	226	96%	15%	261 (249-273)
Correia M	Portugal (Porto, urban)	GP, home visit, emergency service , health centre, hospital clinic and admission record, death certificate	1998-2000	86023	172046	All	72	38%	WHO	462	97%	17%	118 (112-124)

Appelros P	Sweden (Orebro)	Hospital admission, emergency room, GP, nursing home, radiology, pathology, death certificate	1999-2000	123503	123503	All	76	45%	WHO	388	84%	23%	126 (111-140)

WHO=World Health Organisation; GP=general practitioner; CT=computed tomography; MR=magnetic resonance imaging; CI=confidence interval; NR=not reported; Y=years.

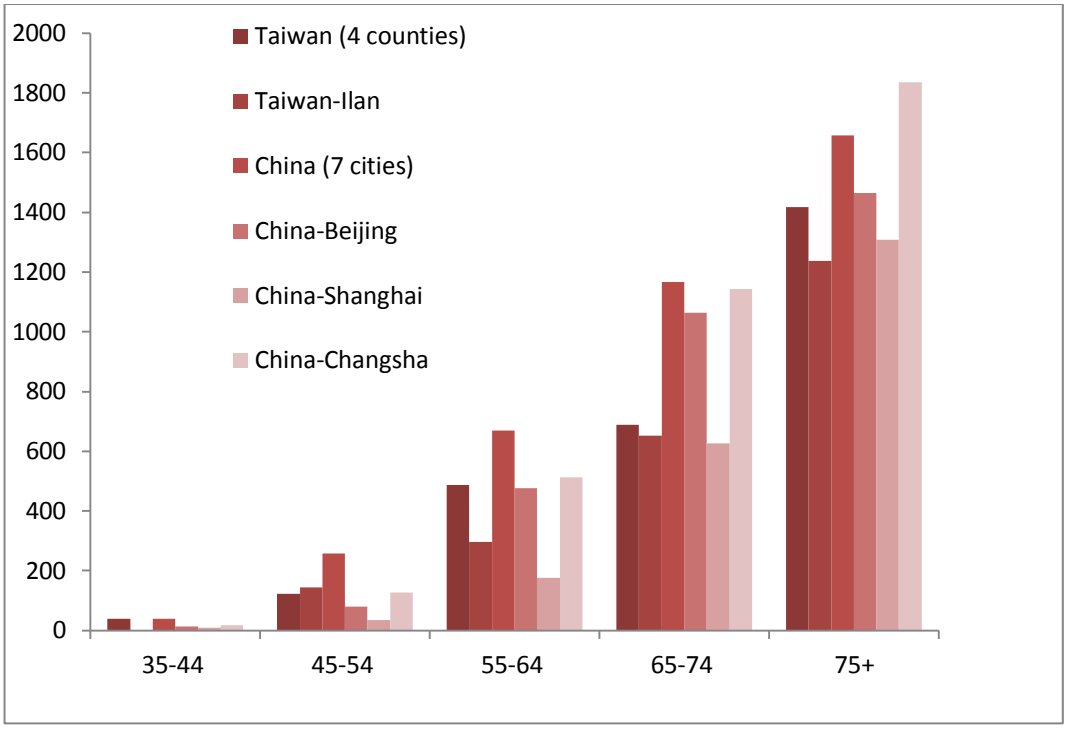
Figures

Figure 2.1 Selection of Chinese stroke incidence studies.



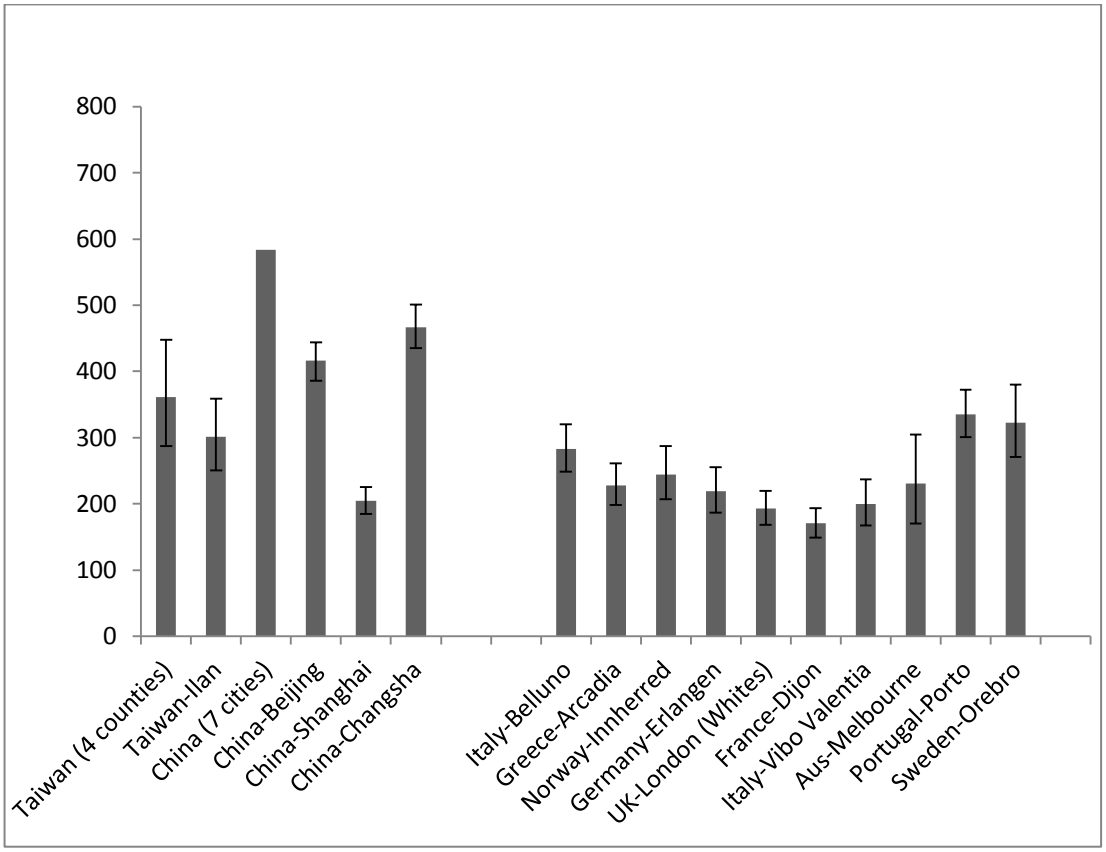
[a] Two studies had age limits of 35 to 64 years, and 25 to 74 years (Thorvaldsen et al. 1995, Zhao et al. 2008), one study included patients aged 35 to 64 years (Wang et al. 2006), and the other included only patients aged 50 years or beyond (Fuh et al. 2000).

Figure 2.2 Age-specific incidence in included studies (per 100,000 person-years).[a]



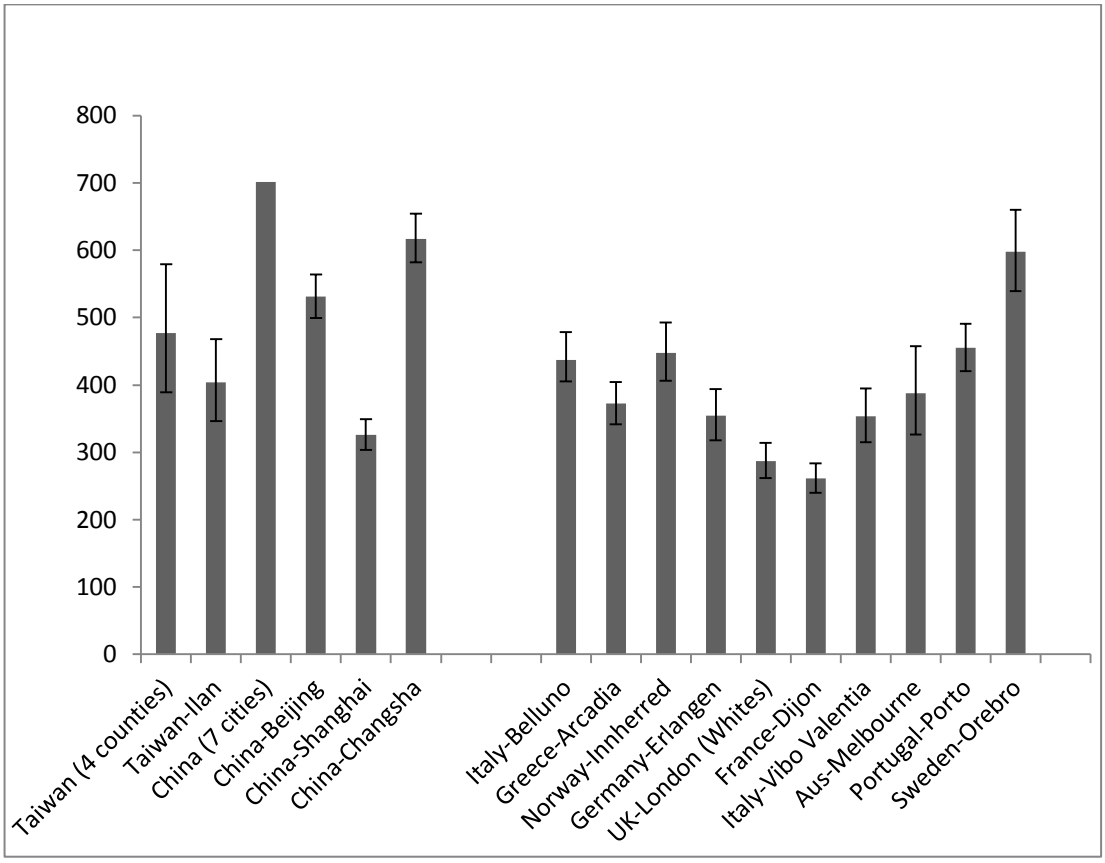
[a] One study did not provide data on incidence in the age band 35-44 years (Chen et al.1995).

Figure 2.3 Age standardized incidence (per 100,000 person-years) for ages 45-74 years in Chinese and in white populations.[b]



[b] Confidence interval could not be calculated in one study because the number of strokes in each age-specific group was not available (Chen et al. 1995).

Figure 2.4 Age standardized incidence (per 100,000 person-years) for ages 45-75+ years in Chinese and in white populations.[c]



[c] Confidence interval could not be calculated in one study because the number of strokes in each age-specific group was not available (Chen et al. 1995)

Chapter 3: Pathological types of stroke

3.1 Introduction

Stroke is a clinical syndrome with three main pathological types (ischaemic stroke [IS], intracerebral haemorrhage [ICH], and subarachnoid haemorrhage [SAH]). Each has several subtypes with different underlying vascular pathologies. Apart from a higher stroke incidence mentioned in Chapter 2, Chinese have been reported to have a higher proportion of ICH in comparison with other populations (Chau et al. 2011; Liu et al. 2007; Jeng et al. 2007). However, few studies provide reliable comparisons due to a lack of robust methods, accurate and consistent classification of stroke types, and systematic approach (Feigin et al. 2009; Feigin et al.2003).

To assess the differences in epidemiology of pathological types of stroke between Chinese and white populations, I aimed to systematically evaluate the distribution of main pathological types of stroke in Chinese populations, and to compare these results with data from white populations.

3.2 Methods

3.2.1 Search strategy

I comprehensively searched for articles published in any language on pathological types of stroke in populations of Chinese origin. I performed electronic searches in Medline and EMBASE from 1990 (since prior to this, brain imaging with CT or MR

was not used widely) to January 2012 (Appendix 2), forward citation searches of relevant reviews (Liu et al. 2007; Feigin et al. 2009), and perusal of the reference lists of included primary articles and relevant reviews.

3.2.2 Selection criteria for studies of pathological types of stroke

The inclusion criteria were: standard World Health Organization (WHO, Hatano et al. 1976) or National Institute of Neurological Disorders and Stroke (NINDS Ad Hoc Committee. 1990) or similar definition of stroke; prospective study design with "hot pursuit" of cases; lower age limit 45 years or younger; no upper age limit; data collection from 1990 onwards. For studies of pathological types of stroke (as compared with those of stroke incidence – see chapter 2), I relaxed the criteria to include both community-based and hospital-based studies of recurrent as well as first-ever strokes, since I expected to find few "ideal" studies. However, for reliable diagnosis and classification of pathological types, I required CT/MR brain imaging (or autopsy) in more than 70% of cases. Strokes had to be classified as IS, ICH, SAH or unknown pathological type (Sudlow et al. 1997).

I excluded studies with retrospective design, highly selected patients, low CT/MR rate, patients overlapped with another included study, unclear classification methods or serious data inconsistencies. I contacted the primary study authors directly to find the essential information that was unavailable in publication(s).

3.2.3 Data extraction

From included studies of pathological types of stroke, I extracted information on: geographical area of the study; sources of case ascertainment; study period; size and age range of the population; stroke definition; number of first-ever and recurrent strokes; mean age and sex distribution of stroke cases; the proportion of CT or MR brain imaging, and admission to hospital; and 1 month case fatality if available. I also extracted data from each study on: whether it was community-based or hospital-based; whether it included recurrent as well as first-ever strokes; stroke type classification method; and case numbers of each pathological type.

3.2.4 Comparison studies in white populations

For comparison, I selected studies conducted from 1990 onwards in predominantly white populations from a recent worldwide systematic review of community-based stroke incidence studies (Feigin et al. 2009). I sought relevant additional studies published up to January 2012 through forward citation searches of this review, and perused the reference lists of relevant publications identified. I used the same inclusion criteria as outlined above, except that no hospital-based studies were included in predominantly white populations.

3.2.5 Statistical analysis

I calculated the proportions of all strokes of each main pathological type. Where possible, I used age-standardized incidence data to obtain the age-adjusted proportion of each pathological type. I compared community-based versus hospital-based Chinese studies, different geographical areas among the Chinese populations, and Chinese versus predominantly white populations, by visual inspection of graphical data. Using StatsDirect software (http://www.statsdirect.com), I computed and compared distributions of pooled proportions of pathological types between Chinese and predominantly white populations. I used random effects meta-analysis because of the substantial heterogeneity of individual study estimates in Chinese and in predominantly white populations (Borenstein et al. 2009).

3.3 Results

3.3.1 Included studies

For stroke pathological types, from 5,160 papers, 43 studies were potentially relevant, and 11 pathological, described in nine papers, met our inclusion criteria (Figure 3.1). Eight were published in English and one was published in Chinese (Chang et al. 1999; Zhang et al. 2003; Wang et al. 2007; Jeng et al. 1998; Yip et al. 2000; Lin et al. 2002; Hsieh et al. 2010; Hao et al. 2011; Wang et al. 2011).

3.3.2 Pathological types of stroke in Chinese populations

Of the 11 pathological type studies, five were community-based and six were hospital-based. Characteristics of these studies are shown in Table 3.1. There were 64,392 first-ever or recurrent stroke cases. Mean age of stroke onset (reported in eight studies) ranged from 63 to 73 years. 74-100% of stroke cases had brain imaging. Only three studies reported 1 month case fatality.

Among included studies, 41-79% of strokes were classified as IS, 17-52% ICH, 1-8% SAH, and 0-10% as unclassified type. I was only able to calculate age-standardized proportions for one study, and found the age-standardized and crude proportions of pathological types to be very similar (Chang et al. 1995). In Chinese populations, there was a greater, more variable proportion of ICH in community-based than hospital-based studies (27-51% versus 17-30%), and in China than Taiwan (range 25-51% versus 17-28%), and (Figure 3.2).

3.3.3 Comparisons with white populations

For comparison, I identified 13 community-based studies in predominantly white populations, including 6,065 first-ever stroke cases (Giuseppe et al. 1995; Vemmos et al. 1999; Hanne et al. 1997; Kolominsky-Rabas et al. 1998; Steward et al. 1999; Wolfe et al. 2000; Carlo et al. 2003; Thrift et al. 2001; Correia et al. 2004; Appelros et al. 2002; Islam et al. 2008; Feigin et al. 2006; Rothwell et al. 2004). Characteristics of these included studies in whites are shown in Table 3.2.

Compared with predominantly white populations, Chinese generally had a higher proportion of ICH (17-51% versus 6-20%). The random effects pooled proportion of

ICH was higher in Chinese than in Whites (28.0% [95% CI 23.6-32.6%] versus 12.4% [95% CI 10.2-14.7%]) while the proportion of unclassified pathological type was lower in Chinese (1.7% [95% CI 0.5-3.6%] versus 7.3% [95% CI 5.2-9.7%]). Considering community-based studies of pathological types only, the pooled proportion of ICH was still, and even higher in Chinese compared with Whites (33.5% [95% CI 24.4-43.1% versus 12.4% [95% CI 10.2-14.7%]), while proportions of unclassified stroke type were similar (5.4% [95% CI 3.2-8.0%] versus 7.3% [95% CI 5.2-9.7%]) (Table 3.3). Heterogeneity between individual studies' proportions was substantial in all comparisons of pooled proportions of pathological types.

3.4 Discussion

The study is the first systematic review of pathological types of stroke comparing data from Chinese populations with that from predominantly predominantly white populations.

I have shown that, compared with white populations, Chinese have a higher proportion of strokes attributable to ICH. The proportion of ICH was generally lower in hospital-based than in community-based studies in Chinese. In addition, there was striking variation among Chinese populations in the proportion of strokes due to ICH.

Although previous studies have reported a higher proportion of ICH in Chinese as compared with white populations, as well as regional variation within mainland China, these have been mostly hospital-based (Wei et al. 2010; Yang et al. 2004).

Immigration studies provide additional relevant data but there are few large studies of stroke types among Chinese and white people living in the same region (Fang et al. 2004; Feigin et al. 2006; Khan et al. 2004). A recent systematic review of population-based studies of ICH found two-fold higher ICH incidence in Asian versus white people, whether living in the same geographical area or in different countries, but included only one study in Chinese and did not consider Chinese populations separately (Asch et al. 2010).

Proposed explanations for Chinese-Whites differences and variations in the proportion of ICH in Chinese populations include differences in hypertension, hyperlipidaemia, diabetes, obesity, dietary habits especially variable salt intake, smoking, alcohol, extreme weather, socio-economic status, and genetic factors (Wei et al. 2010; Yang et al. 2004; Asch et al. 2010; Zhou et al. 2003, He et al. 1999). These vary substantially within Chinese populations as well as between Chinese and white populations (Wei et al. 2010; Wu et al. 2003).

The Sino MONICA community-based stroke study (1987-1993) found a higher proportion of haemorrhagic stroke (ICH and SAH) in Chinese people aged 35-64 years, ranging from 25% to 64% (Wu et al. 2003). The subsequent Sino-MONICA-Beijing community-based stroke study between 1984 and 2004 further showed a 4% increase in total stroke, including 5% increase in IS and 1% decrease in haemorrhagic stroke (ICH and SAH) in Chinese among people aged 25-74 years, with a large reduction in the proportion of incident strokes attributed to haemorrhage (43% in 1984 versus 14% in 2004) (Zhao et al. 2008). Some – but certainly not all - of this change may be explained by overdiagnosis of haemorrhagic stroke in the

1980s when CT brain scan rates were low. These changes occurred during a time of rapid economic development and increasing adoption of Western lifestyles, increased dietary fat and cholesterol intake, increased prevalence of obesity and diabetes, and possibly better hypertension control. My study shows that the higher proportion of haemorrhagic stroke is due to ICH, not SAH, and has persisted in the most recent studies of incident stroke in Chinese populations, even those with highly developed economies, such as Taiwan. However, there are few comparable, community-based data including ages more than 75 years yet available after 2000, since when further economic and lifestyle changes in Chinese populations may have further impact on stroke rates.

3.4.1 Strengths and limitations

The major strengths of my study are: rigorous, systematic methods, including a comprehensive search strategy for relevant studies published in any language (including Chinese), reducing the selection bias of including only reports published in English; inclusion of Hong Kong and Taiwan as well as mainland China, covering more than 95% of Chinese populations worldwide and including those with highly developed economies; and inclusion of data from older people, who were omitted from many previous Chinese stroke studies. Also, for reliable diagnosis and classification of types, I required CT/MR brain imaging (or autopsy) in more than 70% of cases (Sudlow et al. 1997). Actually, most included studies had high brain imaging rates up to 90-100%.

An important limitation is that, despite comprehensive searching, I found few community-based studies of pathological types of stroke in Chinese populations published up to January 2012. Chinese literature databases were not available to me because I did not have access to the full-text databases. Additionally, despite including only studies which appeared to fulfil accepted methodological criteria, I could not exclude the possibility of inaccurate report or incomplete case ascertainment in the included primary studies.

3.4.2 Conclusion

Here I report a higher proportion of ICH in Chinese compared with predominantly white populations since 1990, with substantial regional variation among Chinese populations, which is even more marked in comparisons restricted to community-based studies only. These findings help us realize the different distributions of pathological types of stroke between Chinese and white populations, and shed light on the possibly different stroke mechanisms in different populations.

Tables

Table 3.1 Characteristics of included pathological types of stroke studies in Chinese populations.

Study (first author)	Study area	Study period	Stroke inclusion	Mean age (Y)	Gender (%male)	CT/ MR (%)	Case fatality (1 month %)	Total strokes	SAH %	ICH %	IS %	UC %
Community-based studies												
Chang SF	Taiwan (Ilan)	1991	First- ever	66	51%	99%	NR	185	8.1%	27.6 %	63.8 %	0.5 %
Zhang LF	China (10 communities)	1996-2000	First-ever	66	59%	93%	35%	8268	1.8%	27.5 %	62.4 %	8.3 %
Wang WZ	China (Beijing)	1991-2000	First-ever	69	50%	91%	NR	1062	1.1 %	26.7 %	68.6 %	3.6 %
Wang WZ	China (Shanghai)	1991-2000	First-ever	73	49%	80%	NR	785	0.9 %	34.6 %	54.9 %	9.6 %
Wang WZ	China (Changsha)	1991-2000	First-ever	69	56%	74%	NR	1168	1.3 %	51.5 %	41.4 %	5.8 %

Hospital-based studies												
Jeng JS	Taiwan (Taipei)	1995	First- ever, recurrent	63	57%	100%	11%	954	5.2 %	23.9 %	70.9 %	0.0 %
Yip PK	Taiwan (Taipei)	1997	First-ever, recurrent	NR	NR	100%	NR	598	3.2 %	22.2 %	74.6 %	0.0 %
Lin YT	Taiwan (Kaohsiung)	1999	First- ever, recurrent	67	67%	100%	12%	578	3.8 %	24.6 %	70.6 %	1.0 %
Hsieh FI	Taiwan (39 hospital)	2006-2008	First-ever, recurrent	NR	NR	100%	NR	28546	3.0 %	17.2 %	79.3 %	0.5 %
Hao ZL	China (Chengdu)	2002-2004	First-ever, recurrent	63	60%	97%	NR	1705	4.2 %	30.1 %	65.7 %	0.0 %
Wang Y	China (27 provinces)	2007-2008	First-ever , recurrent	64	61%	100%	NR	20543	3.6 %	25.0 %	69.4 %	0.7 %

SAH=subarachnoid haemorrhage; ICH=intracranial haemorrhage; IS=ischaemic stroke; UC=unclassified; NR=not reported; Y=years.

Table 3.2 Characteristics of included pathological types of stroke studies in white populations.

Study (first author)	Study area	Study period	Stroke inclusion	Mean age (Y)	Gender (%male)	CT/ MR (%)	Case fatality (1 month %)	Total strokes	SAH%	ICH%	IS%	UC%
Community-based studies												
Giuseppe L	Italy (Belluno)	1992-1993	First- ever stroke	NR	NR	90%	33%	474	2.5%	19.6%	67.3%	10.6%
Vemmos KN	Greece (Arcadia)	1993-1995	First- ever stroke	75.4	56%	82%	27%	555	2.5%	13.9%	80.5%	3.1%
Hanne E	Norway-Innherred	1994-1996	First-ever stroke	75.3	46%	88%	19%	432	10.5%	10.4%	74.5%	12.0%
Kolominsky-Rabas PL	Germany (Erlangen)	1994-1996	First-ever stroke	73	41%	96%	19%	354	3.4%	13.6%	78.5%	4.5%
Stewart JA	UK (London, Whites)	1995-1996	First-ever stroke	73.6	49%	88%	27%	489	6.1%	11.0%	70.4%	12.5%
Wolfe CDA	France (Dijon)	1995-1997	First- ever stroke	NR	48%	97%	15%	591	2.0%	6.3%	88.0%	3.7%

Carlo AD	Italy (Vibo Valentia)	1996	First- ever stroke	73	51%	96%	24%	321	3.7%	19.3%	72.9%	4.1%
Thrift AG	Australia (Melbourne)	1996-1997	First-ever stroke	NR	46%	91%	20%	276	4.4%	14.5%	72.5%	8.7%
Correia M	Portugal (Porto)	1998-2000	First-ever stroke	72.7	59%	96%	17%	688	3.3%	15.7%	76.2%	4.8%
Appelros P	Sweden (Orebro)	1999-2000	First-ever stroke	76.3	45%	84%	19%	388	2.8%	11.4%	70.6%	15.9%
Islam MS	Australia (Perth)	2000-2001	First-ever stroke	NR	48%	89%	20%	183	6.6%	10.4%	75.4%	7.7%
Feigin V	New Zealand (Auckland, Whites)	2002-2003	First-ever stroke	74.6	47%	91%	21%	1052	5.9%	10.6%	73.2%	10.4%
Rothwell PM	UK (Oxford)	2002-2004	First-ever stroke	73.6	48%	98%	17%	262	6.1%	6.5%	85.1%	2.3%

SAH=subarachnoid haemorrhage; ICH=intracranial haemorrhage; IS=ischaemic stroke; UC=unclassified; NR=not reported; Y=years.

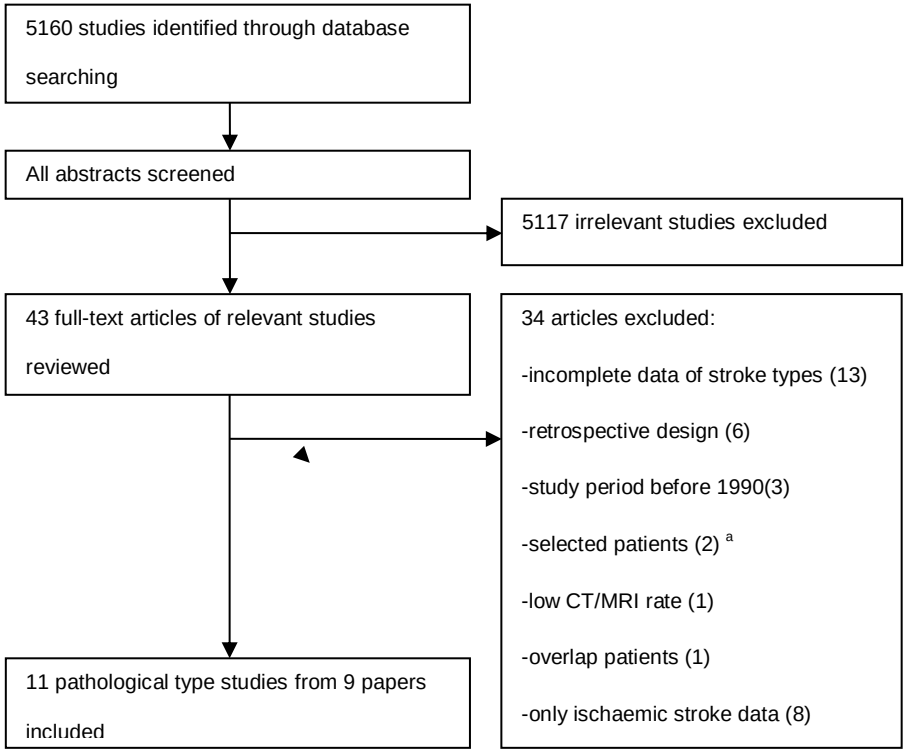
Table 3.3 Comparison of pathological type distributions between Chinese and white populations.

	Stroke patients in Chinese populations			Stroke patients in white populations		
Pathological types	**All community-based and hospital-based studies**			**Community-based studies**		
	Stroke patients (N=62687)	**Random effects pooled proportion (95% CI)**	**Heterogeneity between 11 studies (I^2)**	**Stroke patients (N=6065)**	**Random effects pooled proportion (95% CI)**	**Heterogeneity between 13 studies (I^2)**
SAH % (95% CI)	1951	2.9% (2.2-3.6%)	94%	241	3.9% (3.1-4.8%)	67%
ICH % (95% CI)	14547	28.0% (23.6-32.6%)	99%	755	12.4% (10.2-14.7%)	86%
IS % (95% CI)	46738	66.0% (60.2-71.6%)	99%	4593	76.0% (72.4-79.3%)	90%
UC % (95% CI)	1156	1.7% (0.5-3.6%)	99%	476	7.3% (5.2-9.7%)	91%
Pathological types	**Community-based studies**			**Community-based studies**		
	Stroke patients (N =11468)	**Random effects pooled proportion (95% CI)**	**Heterogeneity between 5 studies (I^2)**	**Stroke patients (N=6065)**	**Random effects pooled proportion (95% CI)**	**Heterogeneity between 13 studies (I^2)**
SAH % (95% CI)	198	1.8% (1.1-2.8%)	85%	241	3.9% (3.1-4.8%)	67%
ICH % (95% CI)	3482	33.5% (24.4-43.1%)	99%	755	12.4% (10.2-14.7%)	87%
IS % (95% CI)	6920	58.2% (49.1-67.1%)	98%	4593	76.0% (72.4-79.3%)	90%
UC % (95% CI)	868	5.4% (3.2-8.0%)	95%	476	7.3% (5.2-9.7%)	91%

SAH=subarachnoid haemorrhage; ICH=intracranial haemorrhage; IS=ischaemic stroke; UC=unclassified; N=total number; I^2=inconsistency

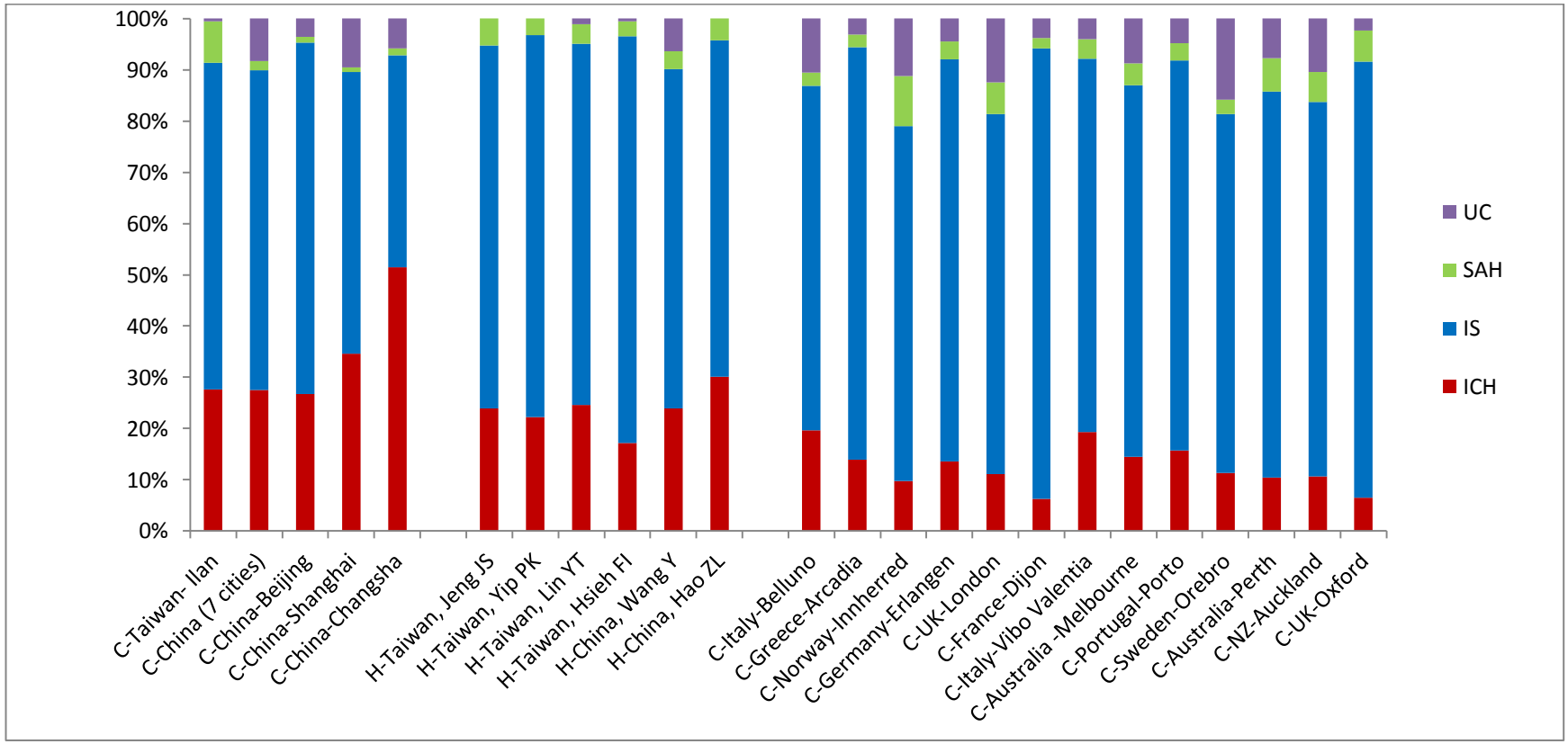
Figures

Figure 3.1 Selection of pathological types of stroke studies in Chinese populations.



[a] One study excluded all patients with suspected cardioembolic stroke (Tan et al. 2005); a second excluded stroke patients with major medical illnesses (Zhang et al. 2009).

Figure 3.2 Distributions of pathological types of stroke in Chinese and in white populations.



C= community-based; H=hospital-based; UC=unclassified; SAH=subarachnoid haemorrhage; IS=ischaemic stroke; ICH=intracerebral haemorrhage; UK=United Kingdom; NZ=New Zealand.

Chapter 4: Ischaemic stroke subtypes

4.1 Introduction

Among pathological types of stroke, ischaemic stroke (IS) is the most common type, accounting for the majority of total strokes (Liu et al. 2007). By contrast with western populations, stroke mortality in Chinese exceeds that of ischaemic heart disease, and some studies claimed a different distribution of IS subtypes in Chinese populations (Wu et al. 2001; Liu et al. 2007; Jeng et al. 2007; Fang et al. 2012). Nonetheless, there are few reliable comparisons using rigorous methods and conducted in a systematic way (Feigin et al. 2009; Feigin et al. 2003).

Herein, I aimed to systematically evaluate the distribution of ischaemic subtypes in Chinese populations, and to compare these results with data from white populations.

4.2 Methods

4.2.1 Search strategy

I comprehensively sought articles published in any language on IS subtypes in populations of Chinese origin. I carried out electronic searches in Medline and EMBASE from 1990 (since prior to this, brain imaging with CT or MR was not used widely) to January 2012 (Appendix 2), forward citation searches of relevant reviews (Liu et al. 2007; Feigin et al. 2009), and perusal of the reference lists of included primary articles and relevant reviews.

4.2.2 Selection criteria for studies of ischaemic stroke subtypes

The selection criteria were: standard World Health Organization (WHO, Hatano et al. 1976) or National Institute of Neurological Disorders and Stroke (NINDS, NINDS Ad Hoc Committee. 1990) or similar definition of stroke; prospective study design, ideally with "hot pursuit" of cases; lower age limit 45 years or younger; no upper age limit; data collection from 1990 onwards. However, for reliable diagnosis and classification of types, I required CT/MR brain imaging (or autopsy) in >70% of cases. Similar to studies of pathological types, for studies of IS subtypes, I relaxed the criteria used to select studies of the stroke incidence in Chapter 2 to include both community-based and hospital-based studies of recurrent as well as first-ever strokes, since I expected to find few "ideal" studies. Ischaemic strokes had to be classified into five aetiological subtypes - large artery atherosclerosis (LAA), cardioembolism (CE), intracranial small vessel occlusion (SVD), other determined aetiology, undetermined aetiology, according to the Trial of Org 10172 in Acute Ischaemic Stroke (TOAST) or NINDS classification schemes, or into the four anatomical subtypes of the Oxfordshire Community Stroke Project (OCSP) classification scheme - lacunar infarct (LACI), total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI) (Adams et al, 1993; Bamford et al.1991; NINDS Ad Hoc Committee, 1990). I excluded studies with retrospective design, highly selected patients, low CT/MR rates, patients overlapped with another included study, unclear classification methods or serious

data inconsistencies. I contacted the primary study authors to acquire essential information that was unavailable in publication(s).

4.2.3 Data extraction

From included studies of IS subtypes, I extracted information on: geographical area of the study; sources of case ascertainment; study period; size and age range of the population; stroke diagnosis and definition; number of first-ever and recurrent strokes; mean age and sex distribution of stroke cases; the proportion of CT or MR brain imaging, and admission to hospital; and 1 month case fatality. I also extracted data on: whether it was community-based or hospital-based; whether it included recurrent as well as first-ever strokes; IS subtype classification method; and numbers of each ischaemic subtype.

4.2.4 Comparison studies in white populations

For comparison, I selected studies performed from 1990 onwards in predominantly white populations from a recent worldwide systematic review of community-based stroke incidence studies (Feigin et al. 2009). Furthermore, I searched for relevant additional studies published up to January 2012 through forward citation searches of this review, and perused reference lists of relevant publications identified. I used the same inclusion criteria as outlined above, except that no hospital-based studies were included in predominantly white populations.

4.2.5 Statistical analysis

For included ischaemic stroke subtype studies, I calculated the proportions of all ischaemic strokes for each ischaemic subtype. I compared the studies in Chinese with those in predominantly white populations, by visual inspection of graphical data. Using StatsDirect software (http://www.statsdirect.com), I calculated the pooled proportions of ischaemic subtypes based on random effects model because of substantial heterogeneity among individual study estimates, and compared the distributions of ischaemic subtypes between Chinese and predominantly white populations (Borenstein et al. 2009).

4.3 Results

4.3.1 Included studies

For IS subtypes, from 5,160 papers, 43 articles were potentially relevant, and 14 studies were included (Figure 4.1). 11 were published in English, and three were published in Chinese (Yip et al. 2000; Lin et al. 2002; Hsieh et al. 2010; Yip et al. 1997; Tan et al. 2001; Wu et al. 2010; Zhou et al. 2004; Liu et al. 2006; Wu et al. 2010; Ma et al. 2010; Lai et al. 2008; Cheung et al. 2001; Li et al. 2008; Zhang et al. 2010).

4.3.2 Ischaemic subtypes in Chinese populations

All 14 ischaemic subtype studies in Chinese populations were hospital-based, ten using the TOAST (or similar) aetiological classification and four using the OCSP anatomical classification. Characteristics of these studies are shown in Table 4.1. In total, they included 33,923 first-ever or recurrent stroke cases. Mean age of stroke onset (reported in ten studies) was 61-69 years. 74-100% of stroke cases had brain imaging. Only three relatively small studies reported 1 month case fatality.

Among studies using the TOAST classification, the proportion of strokes due to LAA ranged from 12-54%; SVD 20-42%; CE 10-26%; and the combination of other specific determined and undetermined etiology subtypes (presented together since not all studies presented data separately for these two subtypes) 4-34%. Among studies using the OCSP classification in Chinese populations, the proportions of different ischaemic subtypes were more consistent than among the TOAST studies: LACI 38-46%; TACI and PACI 40-48%; POCI 10-18%. I could not calculate age-standardized proportions because of no available relevant information from these studies.

4.3.3 Comparison with white populations

For comparison, I identified six community-based studies using the TOAST classification in Whites, including a total of 4,163 ischaemic strokes (Schneider et al. 2004; Kolominsky-Rabas et al, 2001; Hajat et al. 2011; Feigin at al.2006; Schulz et al. 2003; Bejot et al. 2008) (Figure 4.2). Characteristics of these included studies in

predominantly white populations are shown in Table 4.2. In these studies, the proportion of LAA strokes ranged from 6-36%; SVD 11-27%; CE 19-31%; and the combination of other specific determined and undetermined aetiology subtypes 13-54%. I also identified one community-based IS subtype study using OCSP classification in white populations with LACI 32%, TACI and PACI 51%, and POCI 17% (Wolfe et al. 2002).

I compared random effects pooled proportions of ischaemic subtypes from these Chinese studies with those from white studies. In TOAST classification, hospital-based studies in Chinese populations had a higher proportion of SVD stroke (33.1% [95% CI 29.7-36.7%] versus 19.3% [95% CI 14.7-24.3%]) and of LAA stroke (25.4% [95% CI 19.1-32.3%] versus 14.7% [95% CI 9.0-21.4%]), and a lower proportion of CE stroke (15.8% [95% CI 12.8-19.0%] versus 25.7% [95% CI 22.1-29.6%]) and of other/unknown ischaemic stroke (23.2% [95% CI 18.5-29.2%] versus 38.8% [95% CI 28.0-50.1%]) (Figure 4.2, Table 4.3). However, there was substantial variation in the distribution of ischaemic subtypes. Heterogeneity between individual studies' proportions was substantial in all comparisons of pooled proportions of IS subtypes. Furthermore, few studies in Chinese or Whites reported the proportion of patients undergoing various investigations, such as echocardiography and imaging of the extra- or intra-cranial arteries. Where reported, investigation rates were low.

In terms of IS subtype studies using the OCSP classification, comparison of pooled proportions in hospital-based Chinese studies with one available community-based white study showed a relatively higher proportion of LACI (42.1% [95% CI 38.6-

45 .7%] versus 32.2% [95% CI 28.7-35.8%]), and lower proportions of TACI/PACI and POCI in Chinese versus Whites (Wolfe et al. 2002) (Figure 4.3; Table 4.2).

4.4 Discussion

The current study is also the first systematic review of IS subtypes comparing data from Chinese with that from predominantly white populations. My study has shown an apparently different distribution of ischaemic stroke subtypes among Chinese compared with Whites, with a higher proportion of SVD stroke (lacunar infarction), a lower proportion of CE stroke and of other/unknown ischaemic subtype in Chinese.

However, since only hospital-based studies using the TOAST or OCSP classification were available from Chinese populations, different hospital admission rates could contribute to the variations among Chinese studies as well as between the Chinese studies and the community-based studies in Whites (Sudlow et al. 1996; Feigin et al. 2004). In addition, the proportion of strokes in the 'other or undetermined' subtype using the TOAST classification scheme varied widely among the Chinese studies, and was generally lower than among studies in predominantly white populations. This could partly be due to differences in the interpretation and application of aetiological classification systems for ischaemic stroke subtypes (Gordon et al. 1993), or in the proportion of stroke cases with complete investigation, since the higher this proportion, the lower will be the proportion assigned an undetermined subtype (Jackson et al. 2005). The problem of variable investigation rates does not influence the anatomical OCSP classification system, which is based on symptoms and signs,

requiring no investigation results except for a brain scan to exclude haemorrhage. This may explain the more consistent findings among the Chinese studies using the OCSP system, and makes comparisons between studies based on this system more reliable. However, although the OCSP-based Chinese-Whites comparisons still suggest a higher proportion of lacunar strokes in Chinese populations, only comparisons based on community-based studies in both Chinese and white populations will be able to confirm this finding.

4.4.1 Strengths and limitations

The major strengths of our study are: rigorous, systematic methods, including a comprehensive search strategy for relevant studies published in any language (including Chinese), reducing the potential bias of including only reports published in English; inclusion of Hong Kong and Taiwan as well as mainland China, covering more than 95% of Chinese populations worldwide and including those with highly developed economies; and inclusion of data from older people, who were omitted from many previous Chinese stroke studies. Also, for reliable diagnosis and classification of types, I required CT/MR brain imaging (or autopsy) in more than 70% of cases (Sudlow et al. 1997). In fact, most included studies had high performance rates of brain imaging over 80%.

An important limitation is that, despite comprehensive searching, I found no community-based studies of IS subtypes in Chinese populations published up to January 2012. Chinese literature databases were not available to me because I did not

have access to the full-text databases. In addition, despite including only studies which appeared to fulfill accepted methodological criteria, I could not exclude the possibility of inaccurate information or incomplete case ascertainment in some included studies.

4.4.2 Conclusion

Here I report a different distribution of IS subtypes, with an overall higher proportion of lacunar stroke in Chinese compared with predominantly white populations since 1990, with substantial regional variation among Chinese populations. Confirming variation in the distribution of ischaemic subtypes will require comparable population-based studies with consistent definitions and interpretations of the classification method in Chinese populations.

Tables

Table 4.1 Characteristics of included ischaemic stroke subtype studies using the TOAST and OCSP classifications in Chinese populations.

Study (first author)	Study area	Study period	Stroke inclusion	Mean age (Y)	Gender (% male)	CT/MR (%)	Case fatality (1 month, %)	Total IS	Ischaemic stroke subtypes (%)			
TOAST classification									**SVD (%)**	**LAA (%)**	**CE (%)**	**O and U (%)**
Yip PK	Taiwan (Taipei)	1995	First- ever and recurrent	NR	57%	100%	6%	676	28.8%	16.7%	19.7%	34.8%
Yip PK	Taiwan (Taipei)	1997	First-ever and recurrent	NR	NR	100%	NR	446	33.6%	11.9%	21.5%	33.0%
Tan TY	Taiwan (Kaohsiung)	1998-1999	First-ever	64	56%	100%	NR	219	29.2%	21.9%	17.4%	31.5%
Lin YT *	Taiwan (Kaohsiung)	1999	First- ever and recurrent	67	67%	100%	12%	408	37.5%	44.9%	14.0%	3.7%
Hsieh FI	Taiwan (39 hospitals)	2006-2008	First-ever and recurrent	NR	NR	100%	NR	22642	37.7%	27.7%	10.9%	23.7%
Wu CY	Taiwan (Taoyane)	2007-2008	First-ever and recurrent	66	63%	100%	NR	1161	39.4%	14.6%	12.0%	34.1%
Zhou H	China (Beijing)	2002-2003	First-ever	62	64%	>80%	NR	300	31.3%	40.0%	12.3%	16.3%
Liu X	China (Nanjing)	2002-2003	First-ever	67	66%	98%	14%	610	20.2%	19.7%	26.2%	33.9%
Wu B	China (Chengdu)	2002-2007	First-ever	65	59%	74%	NR	3905	42.3%	14.0%	16.2%	27.6%

Ma Y	China (Beijing)	2007-2008	First-ever and recurrent	61	75%	86%	NR	377	29.7%	53.9%	10.3%	6.1%
OCSP classification									**LACI (%)**	**TACI and PACI (%)**		**POCI (%)**
Lai SL	Taiwan (Chiayi)	2003-2005	First-ever	NR	53%	100%	NR	424	41.5%	40.1%		18.4%
Cheung RTF	Hong Kong	1996-1999	First-ever and recurrent	69	56%	NR**	NR	672	45.7%	42.0%		12.4%
Li W	China (Chengdu)	2002-2005	First-ever and recurrent	64	57%	98%	NR	1314	38.2%	47.6%		14.2%
Zhang XY	China (Xinjiang)	2005-2009	First-ever	67	59%	100%	NR	769	43.4%	46.0%		10.5%

IS= ischaemic stroke; TOAST=Trial of Org 10172 in Acute Ischaemic Stroke; LAA=large artery atherosclerosis; SVD=small vessel disease; CE=cardioembolism; O=other determined aetiology; U=undetermined etiology; NR=not reported; OCSP= Oxfordshire Community Stroke Project; LACI= lacunar infarct; TACI=total anterior circulation infarct; PACI=partial anterior circulation infarct; POCI= posterior circulation infarct; Y=years; *NINDS classification= National Institute of Neurological Disorders and Stroke classification; **presumably high percentage.

Table 4.2 Characteristics of included ischaemic stroke subtype studies using the TOAST and OCSP classifications in white populations.

Study (first author)	Study area	Study period	Stroke inclusion	Mean age (Y)	Gender (% male)	CT/MR (%)	Case fatality (1 month %)	Total IS	Ischaemic stroke subtypes (%)			
TOAST classification									**SVD (%)**	**LAA (%)**	**CE (%)**	**O and U (%)**
Schneider AT	USA (Cincinnati, Whites)	1993-1994	First-ever stroke	73	44%	NR	NR	1594	15.3%	12.2%	21.6%	50.9%
Kolominsky-Rabas PL	Germany (Erlangen)	1994-1998	First-ever stroke	73	44%	100%	NR	531	22.6%	13.4%	26.9%	37.1%
Hajat C	UK (London, Whites)	1999-2005	First-ever stroke	74	48%	NR	NR	834	22.4%	9.7%	30.8%	37.1%
Feigin V	New Zealand (Auckland, Whites)	2002-2003	First-ever stroke	75	NR	91%	NR	770	11.0%	6.4%	29.1%	53.5%
Schulz UGR	UK (Oxford)	2002	First-ever stroke	NR	51%	98%	NR	102	19.6%	16.7%	18.6%	45.1%
Bejot Y	France (Dijon)	2005-2006	First-ever stroke	74	45%	100%	NR	332	26.8%	35.8%	24.4%	13.0%
OCSP classification									**LACI (%)**	**TACI and PACI (%)**		**POCI (%)**

Wolfe CDA	UK (London, Whites)	1995-1998	First-ever stroke	74	NR	88%	NR	696	32.2%	51.0%	16.8%

IS= ischaemic stroke; TOAST=Trial of Org 10172 in Acute Ischaemic Stroke; LAA=large artery atherosclerosis; SVD=small vessel disease; CE=cardioembolism; O=other determined aetiology; U=undetermined etiology; NR=not reported; OCSP= Oxfordshire Community Stroke Project; LACI= lacunar infarct; TACI=total anterior circulation infarct; PACI=partial anterior circulation infarct; POCI= posterior circulation infarct; Y= years.

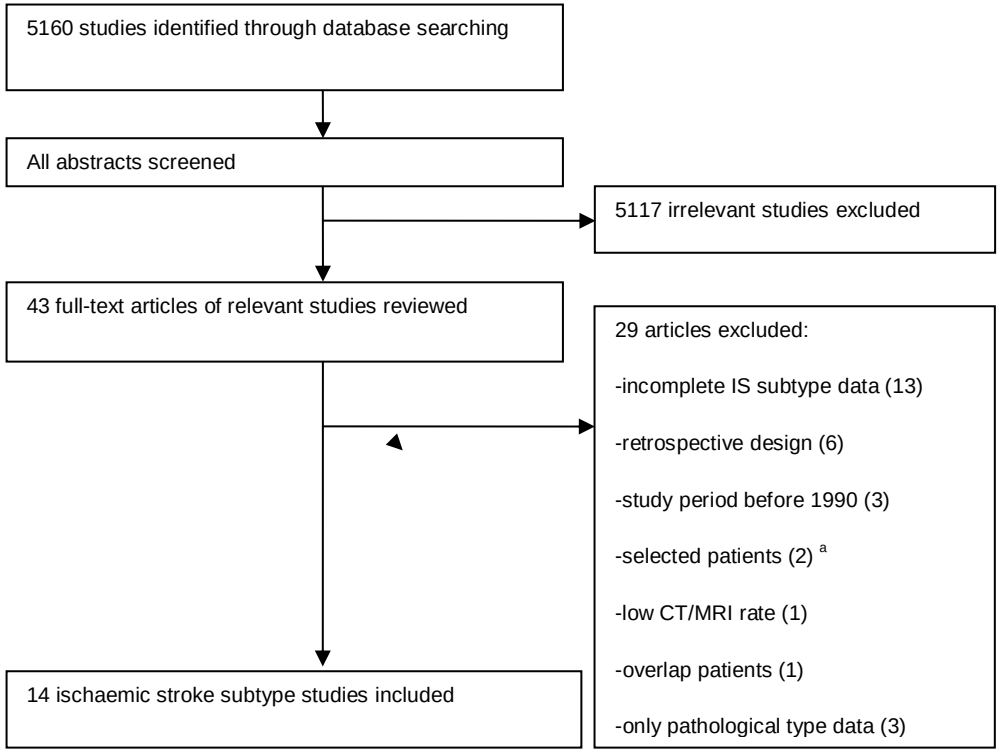
Table 4.3 Comparison of ischaemic subtype distributions between Chinese and white populations.

	Ischaemic stroke patients in Chinese populations			Ischaemic stroke patients in European populations		
Ischaemic subtypes (TOAST)	**Hospital-based studies**			**Community-based studies**		
	IS patients (N=30744)	**Random effects pooled proportion (95% CI)**	**Heterogeneity between 10 studies (I^2)**	**IS patients (N=4163)**	**Random effects pooled proportion (95% CI)**	**Heterogeneity between 6 studies(I^2)**
LAA% (95% CI)	7827	25.4% (19.1-32.3%)	99%	531	14.7% (9.0-21.4%)	97%
SVD% (95% CI)	11539	33.1% (29.7-36.7%)	95%	745	19.3% (14.7-24.3%)	93%
CE% (95% CI)	3795	15.8% (12.8-19.0%)	96%	1068	25.7% (22.1-29.6%)	85%
O and U% (95% CI)	7583	23.2% (18.5-28.2%)	98%	1819	38.8% (28.0-50.1%)	98%
Ischaemic subtypes (OCSP)	**Hospital-based studies**			**Community-based studies**		
	IS patients (N=3179)	**Random effects pooled proportion (95% CI)**	**Heterogeneity between 4 studies (I^2)**	**IS patients (N=696)**	**Random effects pooled proportion (95% CI)**	**Heterogeneity (I^2)**
LACI% (95% CI)	1319	42.1% (38.6-45.7%)	75%	224	32.2% (28.7-35.8%)	NA
TACI or PACI% (95% CI)	1432	44.3% (40.1-47.6%)	72%	355	51.0% (47.2-54.8%)	NA
POCI% (95% CI)	428	13.7% (11.0-16.6%)	80%	117	16.8% (14.1-19.8%)	NA

IS=ischaemic stroke; N=total number; TOAST=Trial of Org 10172 in Acute Ischaemic Stroke; LAA=large artery atherosclerosis; SVD=small vessel disease; CE=cardioembolism; O=other determined etiology; U=undetermined etiology; OCSP= Oxfordshire Community Stroke Project; LACI= lacunar infarct; TACI=total anterior circulation infarct; PACI=partial anterior circulation infarct, POCI= posterior circulation infarction; I^2=inconsistency; NA=not applicable because of only one study.

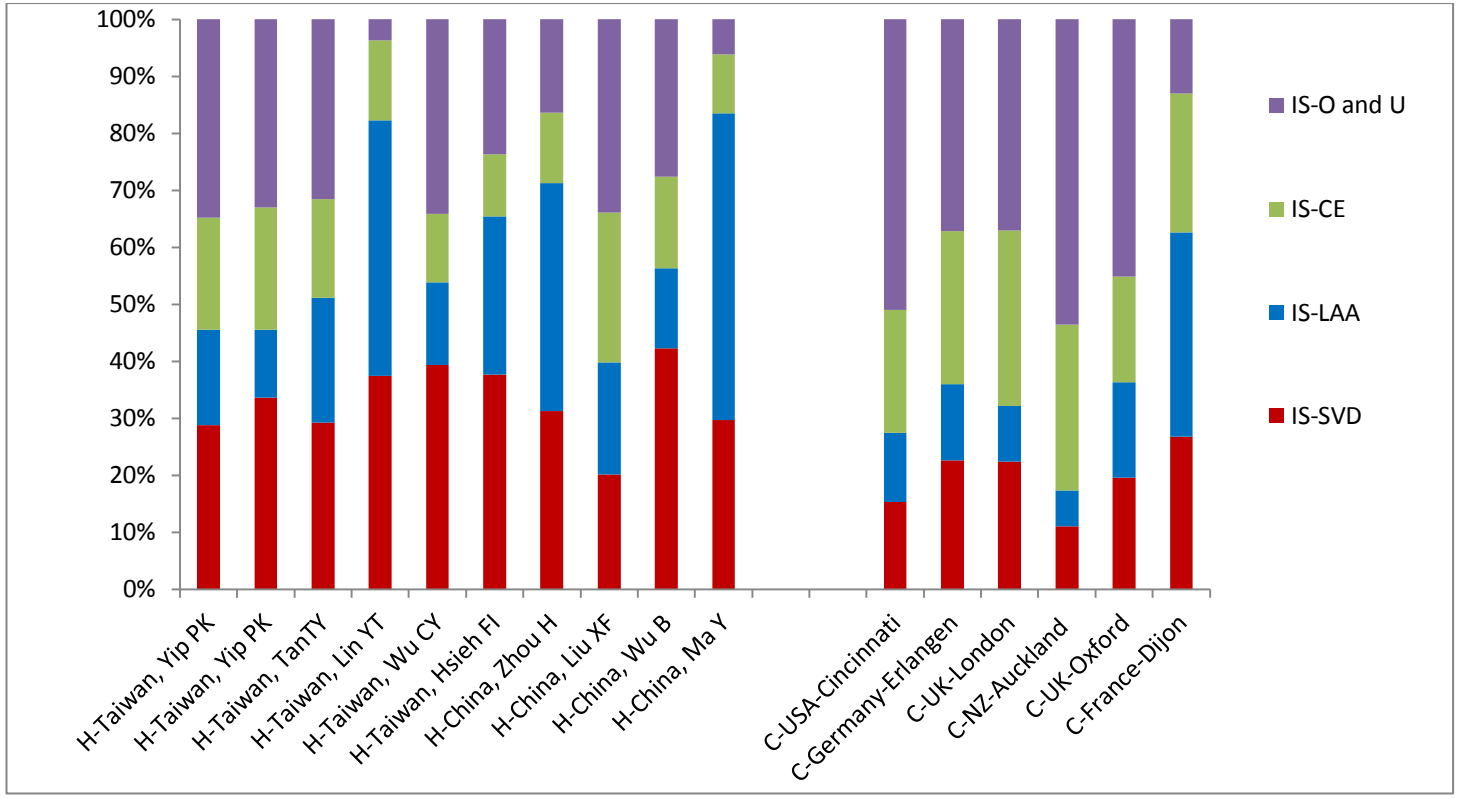
Figures

Figure 4.1 Selection of ischaemic stroke subtype studies.



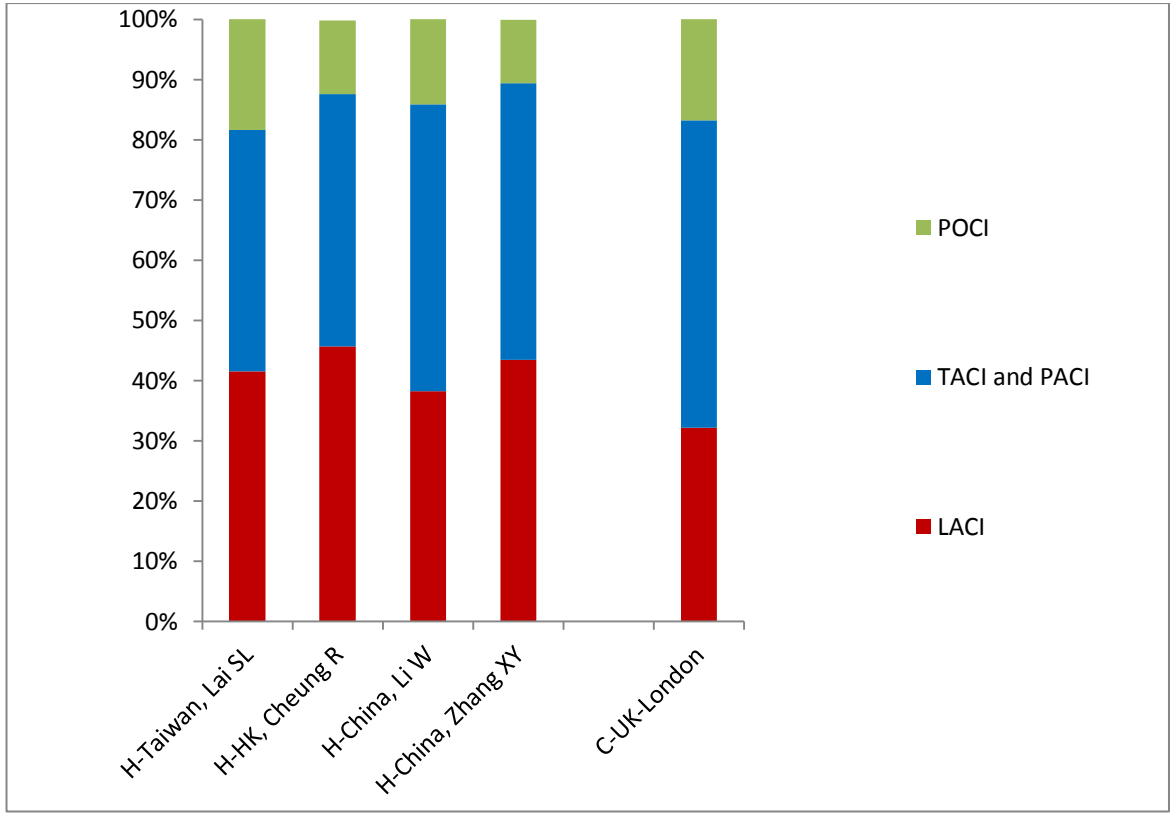
[a] One study excluded all patients with suspected cardioembolic stroke (Tan et al. 2005); a second excluded stroke patients with major medical illnesses (Zhang et al. 2009).

Figure 4.2 Distributions of ischaemic stroke subtypes by the TOAST classification in Chinese and in white populations.



TOAST=Trial of Org 10172 in Acute Ischaemic Stroke; C= community-based; H=hospital-based; IS=ischaemic stroke; O=other determined aetiology; U=undetermined aetiology; CE=cardioembolism; L=large artery atherosclerosis; S=small vessel occlusion; UK=United Kingdom.

Figure 4.3 Distributions of ischaemic stroke subtypes by the OCSP classification in Chinese and in white populations.



OCSP= Oxfordshire Community Stroke Project; LACI=lacunar infarct; TACI=total anterior circulation infarct; PACI=partial anterior circulation infarct; POCI=posterior circulation infarct; C= community-based; H=hospital-based; HK=Hong Kong; UK=United Kingdom.

Section C: Risk Factors for Stroke in Chinese versus White Populations – Systematic Review and Meta-Analysis

Chapter 5: Risk factor meta-analyses in pathological types of stroke – intracerebral haemorrhage versus ischaemic stroke

5.1 Introduction

The distribution of pathological types of stroke may vary in different populations. Asians (including Chinese) were reported to have a higher incidence of intracerebral haemorrhage (ICH) versus white populations (Asch et al. 2010). My systematic reviews in Chapter 2 and 3 also found a relatively higher stroke incidence, younger age of onset, an approximately twofold higher proportion of ICH and a lower proportion of ischaemic stroke (IS) in Chinese versus predominantly white populations of European origin (Tsai et al. 2013). The reasons for the difference in relative frequency of the main pathological types of stroke between Chinese and white populations are not fully understood. They may relate to differences in the prevalence of risk factors (both genetic and environmental) in the different populations, as well as to differences in the associations between stroke risk factors and different pathological types of stroke (O'Donnell et al. 2010; Woodward et al. Asia Pacific Cohort Studies Collaboration 2005; Tzourio et al. 2008; Wu et al. 2009).

To further explore the possible causes for a higher proportion of ICH and a lower proportion of IS in Chinese populations, and to test the hypothesis that the associations of risk factors with ICH versus IS vary in different populations, I systematically assessed the evidence for differences in the vascular risk factor

profiles between ICH and ischaemic stroke (IS) in Chinese and compared these results with data from predominantly white populations.

5.2 Methods

5.2.1 Search strategy

I searched Medline and EMBASE for studies published in any language that compared the frequency of risk factors among different pathological types of stroke in Chinese populations (Appendix 2). For comparison, I sought similar studies in predominantly white populations with Medline and EMBASE searches that aimed to identify existing systematic reviews and meta-analyses of risk factors for pathological types of stroke (Appendix 3). I also conducted citation searches of key relevant reviews and perused the reference lists of included primary articles and relevant reviews (Feigin et al. 2009; Liu et al. 2007; Ariesen et al. 2003).

5.2.2 Selection criteria for risk factor studies of pathological types of stroke

I included community-based or hospital-based studies published by August 2012, with prospective collection of stroke cases, standard World Health Organization (WHO, Hatano et al. 1976) or National Institute of Neurological Disorders and Stroke (NINDS Ad Hoc Committee. 1990) or similar definition of stroke definition

of stroke, and data collection from 1990 onwards since brain imaging with computer tomography (CT) or magnetic resonance (MR) were not used widely before this. Strokes had to be classified as ischaemic stroke (IS), intracerebral haemorrhage (ICH), subarachnoid haemorrhage (SAH])or unknown pathological type, with CT or MR brain imaging in >70% of cases (Sudlow et al. 1997). I excluded studies with retrospective case ascertainment, unclear definitions of stroke or its pathological types, highly selected patients, traumatic ICH, only one unusual risk factor studied, low CT/MR rate, stroke cases overlapping with those in another included study, or serious data inconsistencies. I contacted original study authors directly for essential information not available in publication(s).

5.2.3 Data extraction

I extracted information from included studies on: the geographical area and time period of the study; sources of case ascertainment; whether or not recurrent as well as first-ever strokes were included; definitions of stroke and its pathological types; the proportion of cases with CT or MR brain imaging; mean age and sex distribution of stroke cases; risk factor definitions; and numbers of cases with each risk factor for each pathological type.

5.2.4 Statistical analysis

For each risk factor, I calculated study-specific odds ratios (ORs) with 95% confidence intervals (CIs) for ICH versus IS. Where data were available from more than one study, I performed meta-analyses, calculating pooled ORs for each risk factor for Chinese and predominantly white populations, and for Chinese populations in Taiwan and mainland China separately.

I assessed heterogeneity among studies with I^2 and Cochrane Q chi-square statistics, and adapted a random-effects model since there was evidence of statistically significant heterogeneity, obtaining within-group heterogeneity (Higgins et al. 2003; Ryan R, Cochrane Consumers and Communication Review Group. 2013). To assess whether pooled ORs for each risk factor comparison differed between Chinese and white groups, and also between populations in Taiwan versus mainland China, I treated ethnic groups or geographical subgroups within Chinese populations as if they were studies and performed a test for heterogeneity, using the within-group pooled estimates, standard errors and chi-square statistics to test for statistical significance (Borenstein et al. 2009; Ryan R, Cochrane Consumers and Communication Review Group. 2013; Sedgwick P. 2013). A probability value of less than 0.10 was regarded significant because heterogeneity tests were typically used in a conservative manner for meta-analysis (Petitti et al. 2001). I performed analyses with StatsDirect (http://www.statsdirect.com).

5.3 Results

5.3.1 Characteristics of included studies

My search for studies in Chinese populations retrieved 5810 publications. From these, I identified 48 potentially relevant publications for full text review, eventually including six eligible studies with a total of 36190 patients, of whom 35294 had an IS or ICH (Hsu et al. 1997; Hsu et al. 1996; Jeng et al. 1998; Liu et al. 2006; Hsieh et al. 2010; Hao et al. 2011) (Figure 5.1). From 3051 articles retrieved through my search for studies in white populations, I reviewed 15 potentially relevant full text publications and eventually included five eligible studies (Figure 5.2) with 47885 patients, of whom 47671 had IS or ICH (Marti-Vilalta. 1999; Vemmos et al. 2000; Silvestrelli et al. 2006; Feigin et al. 2006; Andersen et al. 2009).

Characteristics of these included studies are shown in Table 5.1. All Chinese studies were hospital-based - two in China, four in Taiwan – with around 80% of the cases from one large multicentre study in Taiwan (Hsieh et al. 2010). Of the five white studies, one was a community-based study from New Zealand, while the others were hospital-based studies from European countries. Around 80% of the cases were from a large, multicentre, Danish, hospital-based study (Andersen et al. 2009). Stroke diagnoses in both Chinese and predominantly white populations were based on WHO, NINDS or similar criteria in all studies and all had CT or MR brain imaging in >90% of cases. White stroke patients were older and less often male than Chinese (overall mean age 72 versus 68 years, males 52% versus 61%). Chinese ICH patients were younger and more often male than IS patients (mean age 62 versus 69 years, males 65% versus 60%, male/female OR, 1.22 [95% CI 1.09-1.37], $p<0.001$), while mean age and gender distribution in the white ICH and IS groups was the same (mean age 72 versus 72 years, males 51% versus 52%, male/female OR, 1.03 [95% CI 0.87-

1.22], p=0.099). All studies had risk factor data for ICH and IS, but only two reported such data for SAH. Therefore I restricted my meta-analyses of risk factors to ICH versus IS. Risk factors analysed were those with data available from more than one study in both Chinese and white stroke patients: hypertension, diabetes, atrial fibrillation (AF), ischaemic heart disease (IHD), hypercholesterolaemia, alcohol intake and smoking. Study risk factor definitions are summarised in Table 5.2.

5.3.2 Risk factor comparisons for ICH versus IS

For hypertension, all Chinese and white studies (Chinese: 6470 ICH and 28824 IS patients; Whites: 5001 ICH and 40255 IS) had relevant data. All gave definitions of hypertension, mainly based on a history of raised blood pressure with anti-hypertensive treatment before stroke, and on elevated blood pressure recorded after stroke (Table 5.2). Although there was substantial heterogeneity within Chinese and white studies (Chinese I^2=61%; whites I^2=93%; Figure 5.3), ICH patients had consistently higher frequency of hypertension than IS in Chinese populations, yielding a pooled OR for ICH versus IS of 1.38 (95% CI [1.18 to 1.62]; Figure 5.3). By contrast, there was no significant difference in frequency of hypertension between ICH and IS in white stroke studies (OR 1.15, 95% CI 0.84 to 1.57). However, the results did not differ significantly between Chinese and Whites (heterogeneity between Chinese and whites studies: p=0.308; Figure 5.10).

All Chinese and white studies also had data on diabetes, with definitions based on history of diabetes before stroke or fasting plasma glucose levels (> 7.0 mmol/L after stroke in Chinese; >6.0 mmol/L before or after stroke in Whites, Table 5.2). With the exception of one relatively small study (Liu et al. 2006), all Chinese and white studies reported a lower prevalence of diabetes in ICH than in IS patients, with similar pooled ORs for ICH versus IS among Chinese and whites studies but substantial heterogeneity among individual studies (Chinese pooled OR 0.55, 95% CI 0.39 to 0.75, I^2=87%; Whites pooled OR 0.67, 95% CI 0.54 to 0.83, I^2=69%; no significant heterogeneity between ORs for Chinese versus Whites: p=0.336; Figures 5.4 and 5.10).

Four Chinese studies (6165 ICH, 28051 IS) and three white studies (4239 ICH, 35843 ICH) provided data on AF, although only four (two Chinese, two white studies) gave clear definitions (history of AF before stroke or electrocardiographic documentation after stroke; Table 5.2). AF prevalence was consistently lower in ICH than in IS patients, with substantial heterogeneity among both Chinese and white studies. (Chinese pooled OR 0.26, 95% CI 0.18 to 0.40, I^2=66%; Whites pooled OR 0.35, 95% CI 0.16 to 0.77, I^2=96%; heterogeneity between Chinese and white subgroups p=0.515; Figures 5.5 and 5.10).

Four Chinese studies (6165 ICH, 28051 IS) and two white studies (3586 ICH, 33701 ICH) provided data on IHD, although only three (two Chinese, one white) provided a definition (usually history of angina or myocardial infarction; Table 5.2). IHD prevalence was lower in ICH than IS, much more so among Chinese than white studies, with substantial heterogeneity among Chinese and white studies (Chinese

pooled OR 0.46, 95% CI 0.42 to 0.51, I^2=91%; Whites pooled OR 0.70, 95% CI 0.62 to 0.80, I^2=86%; Chinese-Whites heterogeneity: p<0.001; Figures 5.6 and 5.10).

For hypercholesterolaemia, four Chinese studies (1322 ICH, 3526 IS) and three white studies (936 ICH, 3674 IS) provided relevant data. Definitions were based on medical history or raised cholesterol after stroke, with threshold cholesterol levels varying between studies (Table 5.2). Pooled results showed a lower prevalence of hypercholesterolaemia in ICH versus IS, but this was statistically significant only in white studies (Chinese pooled OR 0.76, 95% CI 0.38 to 1.52; Whites pooled OR 0.52, 95% CI 0.38 to 0.72; Chinese-Whites heterogeneity: p=0.428; Figures 5.7 and 5.10). There was also substantial heterogeneity among Chinese studies (I^2=85%) and moderate heterogeneity among white studies (I^2=49%).

For smoking, all six Chinese and five white studies presented relevant information, generally defining smoking as current or former smoking (Table 5.2). Overall, prevalence of smoking was similar among Chinese ICH and IS patients, but less prevalent among white ICH versus IS patients, and heterogeneity among individual Chinese and white studies was moderate to substantial (Chinese pooled OR 0.94, 95% CI 0.82 to 1.08, I^2=45%; Whites pooled OR 0.71, 95% CI 0.52 to 0.97, I^2=92%; heterogeneity between Chinese and white subgroups p=0.103; Figures 5.8 and 5.10). Five Chinese studies (1557 ICH, 4129 IS) and two white studies (3415 ICH, 31417 IS) presented data on alcohol intake, but only three Chinese and one white study provided clear (yet different) definitions (Table 5.2). Meta-analysis showed a significant excess of regular alcohol intake in ICH versus IS patients in Chinese but not in predominantly white populations, and substantial heterogeneity among

individual Chinese and white studies (Chinese pooled OR 1.46, 95% CI 1.12 to 1.91, I^2=62%; Whites pooled OR 0.82, 95% CI 0.37 to 1.85, I^2=94%; Chinese-Whites heterogeneity p=0.182; Figures 5.9 and 5.10).

5.3.3 Subgroup analysis in Chinese populations

When studies from Taiwan and mainland China were considered separately, heterogeneity remained substantial within both Chinese population subgroups for all risk factors except hypertension (Figures 5.11 to 5.17). The OR of hypertension for ICH versus IS appeared more marked in Taiwan (Taiwan pooled OR 1.49, 95% CI 1.38 to 1.61; mainland China pooled OR 1.12, 95% CI 0.97 to 1.30; heterogeneity between Taiwan and mainland China: p<0.001), and heterogeneity among studies within the Taiwan and China subgroups was markedly reduced (Taiwan I^2=0%; mainland China I^2=0%; Figure 5.18).

5.4 Discussion

My results in this study showed that the relative frequencies of risk factors in ICH versus IS were generally of similar direction in stroke patients from both Chinese and predominantly white populations, but varied in size and significance. Diabetes, AF and IHD were significantly less common in ICH in both ethnic groups. Both hypertension and alcohol intake were significantly more frequent in ICH versus IS in Chinese but not in white stroke patients, while both hypercholesterolaemia and

smoking were significantly less frequent in ICH versus IS in white but not Chinese stroke patients. However, the risk factor associations with ICH versus IS did not differ significantly between Chinese and Whites except for IHD, which had a stronger association with IS versus ICH in Chinese than predominantly white populations. These results should be interpreted with caution since individual studies varied substantially beyond the differences in ethnicity (including variation in risk factor definitions). Furthermore, other confounding factors, for which we could not adjust, may partly explain the observed differences, in particular the finding that Chinese ICH were younger and more often male than IS patients, while mean age and gender distribution were similar in white ICH and IS patients.

My systematic search revealed few studies and no previous systematic reviews comparing risk factors in ICH versus IS, in either Chinese or white populations. Recently, a large international case-control study (the INTERSTROKE study) in 22 countries (including low, middle and high income countries) reported on risk factors for all stroke, IS and ICH among 3000 cases of stroke and 3000 controls (O'Donnell et al. 2010). Around a third of the cases were from Southeast Asia (including China) and India, with less than a sixth from high income (predominantly Whites) countries. 22% of cases had ICH. Hypertension was more strongly associated with ICH than IS. Cardiac causes (including atrial fibrillation, ischaemic heart disease and valvular heart disease) were associated with IS but not ICH. For smoking, associations appeared stronger with IS than ICH. Risk of ICH increased with increasing alcohol intake, while for IS, modest alcohol intake (up to around one drink per day) was protective, but heavier alcohol intake increased risk. However, risk factor

associations for IS and ICH were not provided separately for the different ethnic groups.

Immigration studies have demonstrated different risk factor distributions between Chinese and white stroke patients living within the same area but there are no published comparisons of risk factor distributions for ICH versus IS in these different ethnic groups (Fang et al. 2004; Shen et al. 2011).

The contrasts in the strength and significance of several risk factor associations with ICH versus IS in our study could be due – at least in part - to differences in distributions of ICH and IS subtypes in Chinese compared with white stroke patients, as well as to differences in the prevalence of these risk factors in Chinese and white populations. For example, a higher proportion of strokes in Chinese compared with Whites may be due to deep ICH (predominantly associated with hypertension) and lacunar ischaemic stroke among ICH and IS respectively, with a lower proportion due to lobar ICH (predominantly associated with amyloid angiopathy) and non-lacunar subtypes, reflecting a different combination of genetic and non-genetic exposures. (Wang et al. 2012; Woo et al. 2002; Chen et al. 2010).

Meta-analyses of data from prospective studies among predominantly eastern Asian (Chinese and Japanese) populations and among predominantly white populations of European origin suggest a stronger association of blood pressure with stroke among eastern Asian than predominantly white populations (44% versus 27% increase in stroke risk per 5mm Hg higher diastolic blood pressure) (Eastern Stroke and Coronary Heart Disease Collaborative Research Group.1998; Prospective Studies

Collaboration. 1995). Furthermore, among the predominantly eastern Asian populations, associations of BP with haemorrhagic stroke appeared stronger than with IS (Eastern Stroke and Coronary Heart Disease Collaborative Research Group.1998), while such differences have not been demonstrated for predominantly white populations (Prospective Studies Collaboration. 1995).These findings are consistent with my results and suggest that the effect of BP reduction may be particularly greater in eastern Asian populations including Chinese.

Similar meta-analyses of data from prospective studies among eastern Asian and predominantly white populations have shown that the associations of cholesterol with stroke and its pathological types are complex. There seems to be a positive association of increasing cholesterol with IS and a negative association with haemorrhagic stroke (Zhang et al. Asia Pacific Cohort Studies Collaboration 2003). However, the strength of these associations is probably influenced by age, blood pressure and cholesterol level (Asia Pacific Cohort Studies Collaboration 2005; Suzuki et al. 2011). Since Chinese stroke patients are younger on average than white ones, and average cholesterol levels are lower in Chinese than in predominantly white populations, these can affect the strength of associations with stroke and its pathological types between populations.

Previous studies have suggested that alcohol has a dose-dependent relationship with haemorrhagic stroke, but a curvilinear relationship with ischaemic stroke - a protective effect for low to moderate intake and increased risk for high consumption (O'Donnell et al. 2010; Patra et al. 2010). Different definitions of alcohol intake in the Chinese and white studies included in our review, combined with different shapes

of the relationship of alcohol with ICH and IS, could partly explain why we observed a higher prevalence of alcohol consumption in ICH versus IS in Chinese but not white stroke studies.

5.4.1 Strengths and limitations

My study has several major strengths. First, I used a comprehensive search strategy to identify all relevant studies published in any language (including Chinese), reducing the potential bias of including only English language publications. Second, I included only studies using a standard definition of stroke and reliable classification of its pathological types. Third, I documented carefully the characteristics, methodology and risk factor definitions used in each included study, and carried out rigorous meta-analyses between Chinese and predominantly white populations and subgroup analyses within Chinese studies to explore potential explanations for some of the substantial statistical heterogeneity encountered.

There were some limitations. First, despite a comprehensive literature search, I found only a limited number of studies in either Chinese or predominantly white populations which fulfilled our inclusion criteria (Chinese literature databases were not available to me because I did not have access to the full-text databases). Most included studies were hospital-based rather than community-based, and so will not have included all stroke patients in the relevant geographical area irrespective of admission to hospital (Sudlow et al. 1996; Feigin et al. 2004). Prevalence of risk factors and stroke subtypes may have some differences between hospitalized and

non-hospitalized patients (Schulz et al. 2003). Second, there was substantial statistical heterogeneity among studies, which could arise from differences in age and sex distributions, methodological differences (e.g., case ascertainment methods), variable risk factor definitions, differences between geographical areas, as well as genuine differences in risk factor associations between ethnic groups. Third, because my study was based on published data, I did not have individual patient data to adjust for potential confounders, especially age. Finally, some included studies were limited by collection of data about risk factors prior to stroke occurrence (which may be subject to recall biases), while others defined risk factor status based on measures made after stroke, raising the possibility of apparent associations arising due to reverse causality.

5.4.2 Conclusion

Here I report several differences between Chinese and predominantly white populations in the strength and significance of associations of several risk factors with ICH versus IS. These differences raise interesting possibilities about varying mechanisms of pathological types of stroke in different ethnic groups with different genetic and environmental exposures. Further analyses to adjust for possible confounding factors in large prospective studies are needed.

Tables

Table 5.1 Clinical characteristics of included risk factors studies for intracerebral haemorrhage versus ischaemic stroke in Chinese and White populations.

Author (First)	Region	Study period (Year)	Patient recruitment	Stroke inclusion	Mean age (Year)	Gender (male%)	CT/MR (%)	Total stroke	Risk factors reported
Chinese populations									
Hsu LC	Taiwan, Taipei	1990-1991	Hospital-based, consecutive admission	First-ever	64	76%	100%	240	HTN, DM, HD, CS, HC, HTG, age, gender
Hsu WC	Taiwan, Taoyuan	1993-1995	Hospital-based, admission	First-ever and recurrent	64	57%	100%	838	HTN, DM, HD,CS, HL, smoking, alcohol, obesity, previous stroke, HU, age, gender
Jeng JS	Taiwan, Taipei	1995	Hospital-based, consecutive admission	First-ever and recurrent	63	58%	100%	954	HTN, DM, AF, IHD, LVH, CS, HC, HTG, smoking, alcohol, previous stroke age, gender,
Liu XF	China, Nanjing	2002-2003	Hospital-based, admission	First-ever	67.	66%	98%	752	HTN, DM, AF, IHD, HL, smoking, alcohol, age, gender
Hsieh FI *	Taiwan, multicentre	2006-2008	Hospital-based, admission	First-ever and recurrent	68	60%	100%	30454	HTN, DM, AF, IHD, CS, HL, smoking, obesity, previous stroke, age, gender

Hao ZL	China, Chengdu	2002-2006	Hospital-based, consecutive admission	First-ever and recurrent	64	61%	97%	2952	HTN, DM, AF, IHD, HC, smoking, alcohol, previous stroke, age, gender
White populations									
Marti-Vilalta JL	Spain, Barcelona	1977-1994	Hospital-based, consecutive admission	First-ever	66	57%	100%	3577	HTN, DM, HD, HL, smoking, PAD, TIA, age, gender
Vemmos KN	Greece, Athens	1992-1997	Hospital-based, consecutive admission	First-ever	70	59%	100%	1042	HTN, DM, AF, IHD, HC, smoking, TIA, age, gender
Silvestrelli G	Italy, Perugia	1998-2002	Hospital-based, consecutive admission	First-ever	73	52%	100%	2359	HTN, DM, HD, HL, HC, HTG, smoking, alcohol, obesity, TIA, age, gender,
Feigin V	New Zealand, Auckland	2002-2003	Community-based with multiple sources	First-ever	72	47	91%	1423	HTN, DM, HD, HC, smoking, obesity, age, gender,
Andersen KK	Denmark, multicentre	2002-2003	Hospital-based, admission (multicentre)	First-ever and recurrent	73	52%	100	39484	HTN, DM, AF, smoking, alcohol, PAD, previous MI, previous stroke, age, gender

CT=Computed tomography; MR=Magnetic resonance; HTN=Hypertension; DM=Diabetes mellitus; HD=Heart disease; AF=Atrial fibrillation; IHD=ischaemic heart disease; LVH=Left ventricular hypertrophy; CS=Carotid stenosis; HL=Hyperlipidaemia; HC=Hypercholesterolaemia; HTG=Hypertriglyceridaemia; HU=Hyperuricemia; PAD=peripheral artery disease; TIA=transient ischaemic attack. *This study contained 8% TIA data.

Table 5.2 Definitions of risk factors among included studies in Chinese and white populations

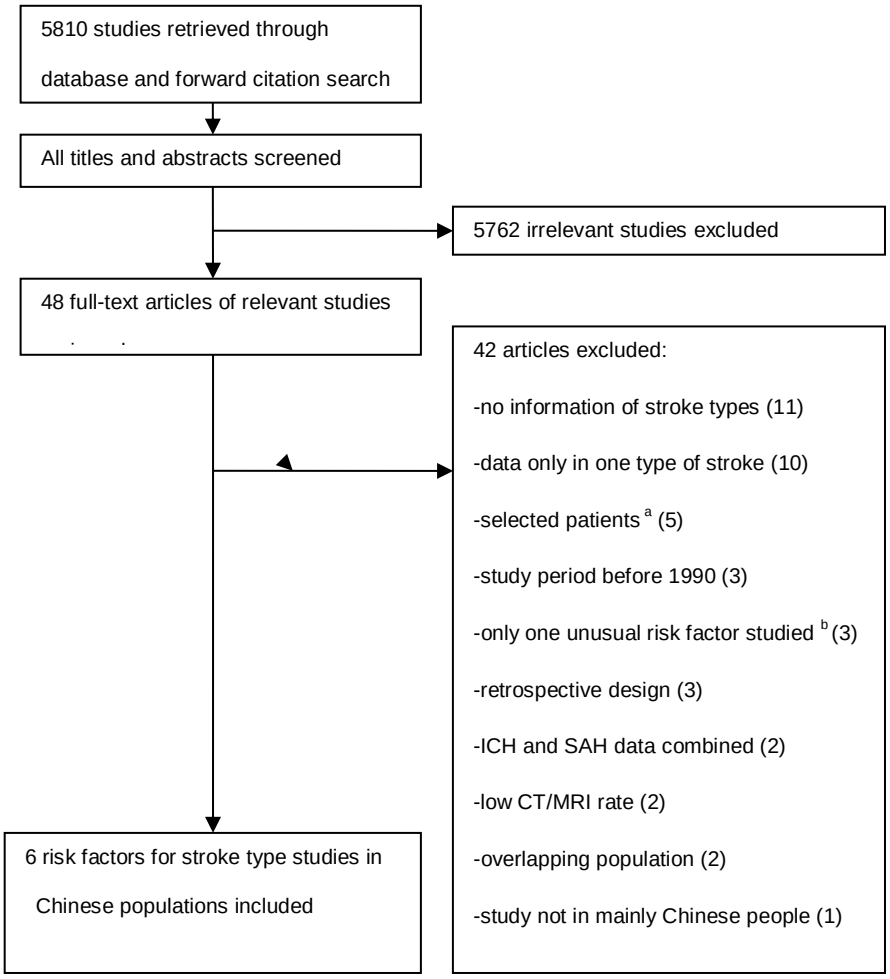
Study (First author)	HTN	DM	AF	IHD	HC	Smoking	Alcohol
Hao ZL	> 140/90 mmHg or use of antihypertensive medication	Fasting serum glucose ≥ 7.0 mmol/L or use of anti-diabetic medication	NR	NR	Fasting serum TC ≥ 5.7 mmol/L or use of lipid –lowering agents	Current smoking ≥ 1/day for at least 1 year	≥ 50 ml/day for more than one year
Hsu LC	≥ 160/95 mmHg, or HTN history with anti-HTN drugs	DM history with drugs	--	--	NR	≥ 1/day for the preceding 3 months or more	NR
Hsu WC	History of HTN and/or clinical workup	History of DM and/or clinical workup	--	--	--	NR	NR
Hsieh FI	≥ 140/90 mm/Hg 7 days after stroke, or HTN history with anti-HTN drugs	Fasting plasma glucose > 7.0 mmol/L, or DM history with medication	ECG	History of angina or MI	--	Current daily smoking for more than half a year or past daily smoking	Daily drinking for more than one year
Jeng JS	History of HTN	History of DM	History of AF or ECG proof	History of angina or MI	TC ≥ 5.2 mmol/L	≥ 10/day for more 10 years	Habit drinking ≥ once per week
Liu XF	> 160/95 mm/Hg or HTN history with anti-HTN drugs	Fasting serum glucose > 7.0 mmol/L or DM history with medication	NR	NR	TC> 5.7 mmol/L, or hyperlipidaemia history with drugs	NR	NR

Andersen KK	History of HTN or diagnosed at admission	History of DM or diagnosed at admission	History of AF or diagnosed at admission	--	--	Current daily or former smoking	>14 drinks per week in women and >21 drinks per week in men
Feigin V	History of HTN or on HTN drugs	History of DM or on DM drugs	--	--	NR	Current or former smoker	--
Marti-Vilalta JL	History of > 160/95 mm/Hg, or evidence of HTN related end organ damage	History of DM or glucose > 6.1 mmol/L at admission	--	--	--	History of smoking within 5 years	--
Silvestrelli G	History of > 160/95 mm/Hg	History of DM drug use or fasting glucose > 6.0 mmol/L before stroke	--	--	History or cholesterol > 6.5 mmol/L at admission	Current daily smoking or within previous year	NR
Vemmos KN	History of >160/95 mm/Hg	History of DM drugs use or fasting glucose > 6.0 mmol/L before stroke	By ECG	History of MI, angina or CHF	History or cholesterol > 6.5 mmol/L at admission	Current daily smoking or within previous year	--

HTN=Hypertension; DM=Diabetes mellitus; AF=Atrial fibrillation; IHD=ischaemic heart disease; MI=myocardial infarct; CHF=congestive heart failure; ECG=electrocardiography; CUS=carotid ultrasound; HC=Hypercholesterolaemia; TC=Total cholesterol; HTG=Hypertriglyceridaemia; --=no data - the risk factor was not studied or unavailable from the publication; NR=not reported; risk factor was studied but definition not reported

Figures

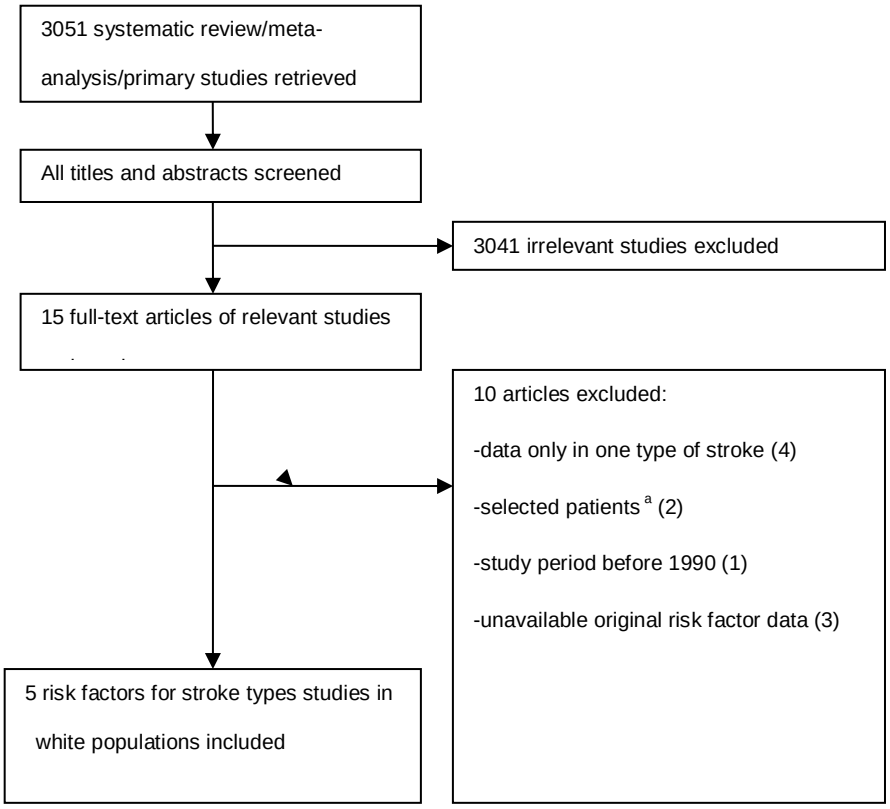
Figure 5.1 Selection of studies in Chinese populations.



[a] Excluding patients with cardiogenic emboli (Zhao et al. 2008); excluding patients with cardiogenic emboli, or with arteriovenous malformation, or using anticoagulants, or mixed types of stroke (Tan et al. 2005); excluding patients with other major medical illness (e.g., cancer, anaemia, thyroid dysfunction, etc.; Zhang et al. 2009); data only in men (Zhang et al. 2004); data only in patients aged 35-64 years (Wang et al. 2006).

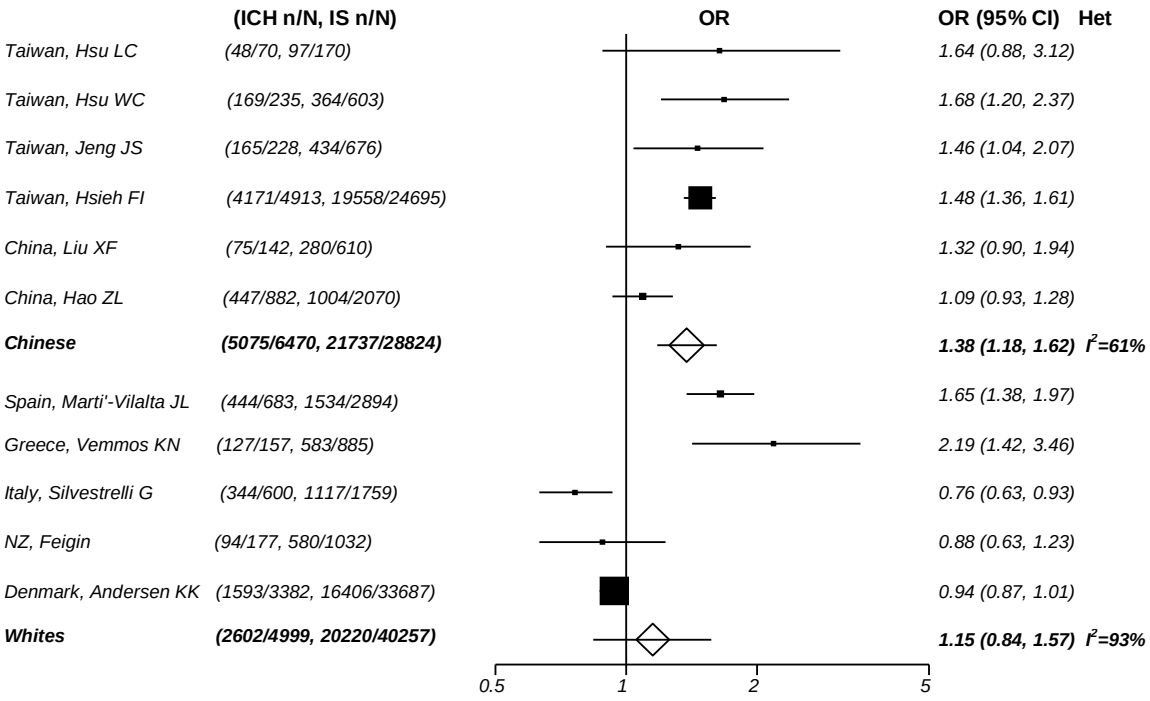
[b] Weather (Chen et al. 1995), circadian variation of stroke onset (Cheung et al. 2001), and dietary pattern (Li et al. 2011).

Figure 5.2 Selection of studies in white populations.



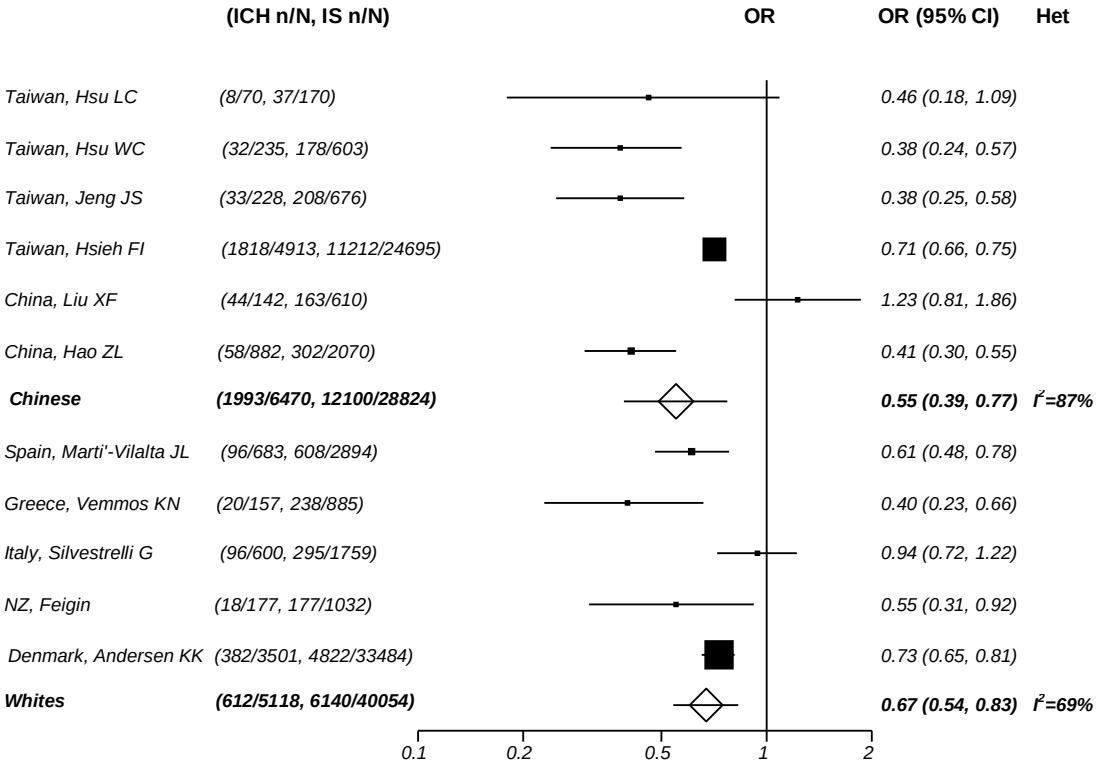
[a] Excluding patients IS due to cardiogenic emboli, or haemorrhage due to amyloid angiopathy (Schmal et al. 1998); data only in men (Leppala et al. 1999).

Figure 5.3 Hypertension meta-analysis for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



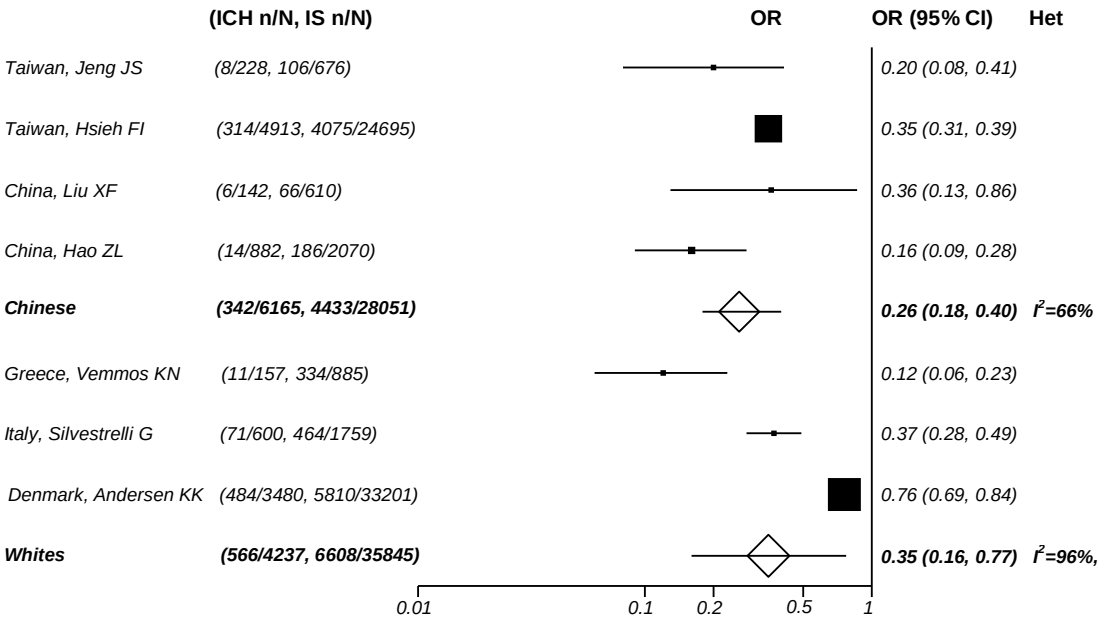
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.4 Diabetes meta-analysis for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



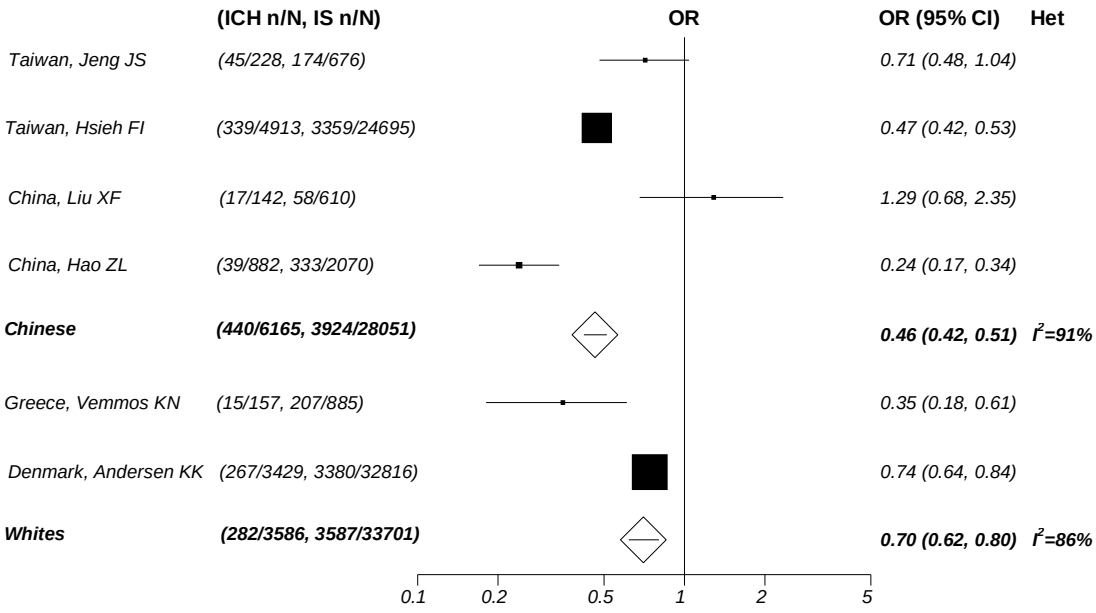
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.5 Atrial fibrillation meta-analysis for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



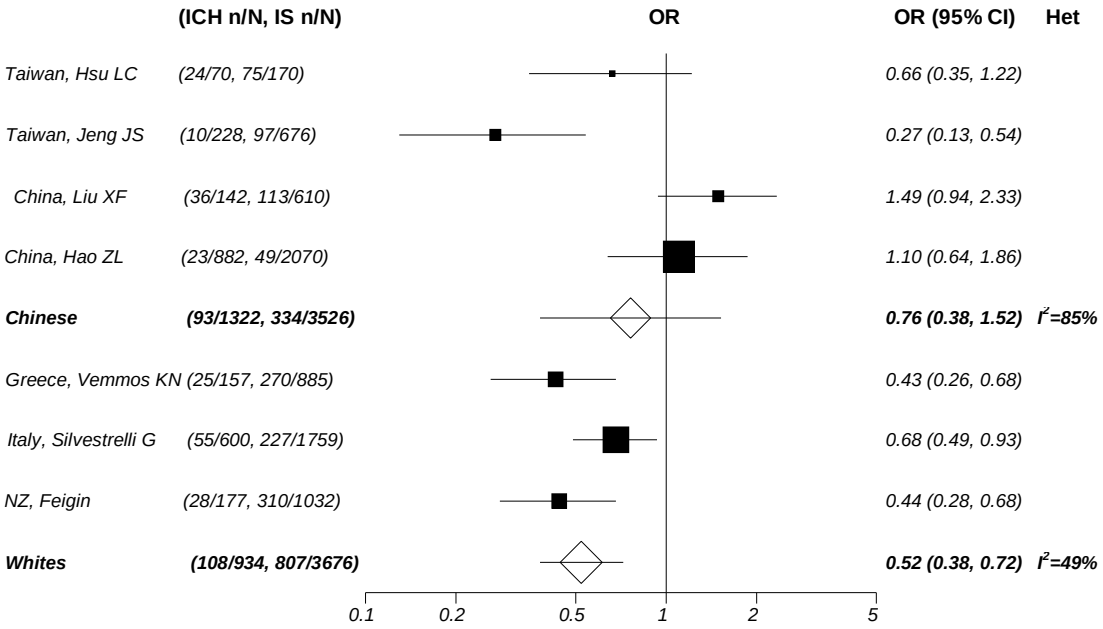
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.6 Ischaemic heart disease meta-analysis for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



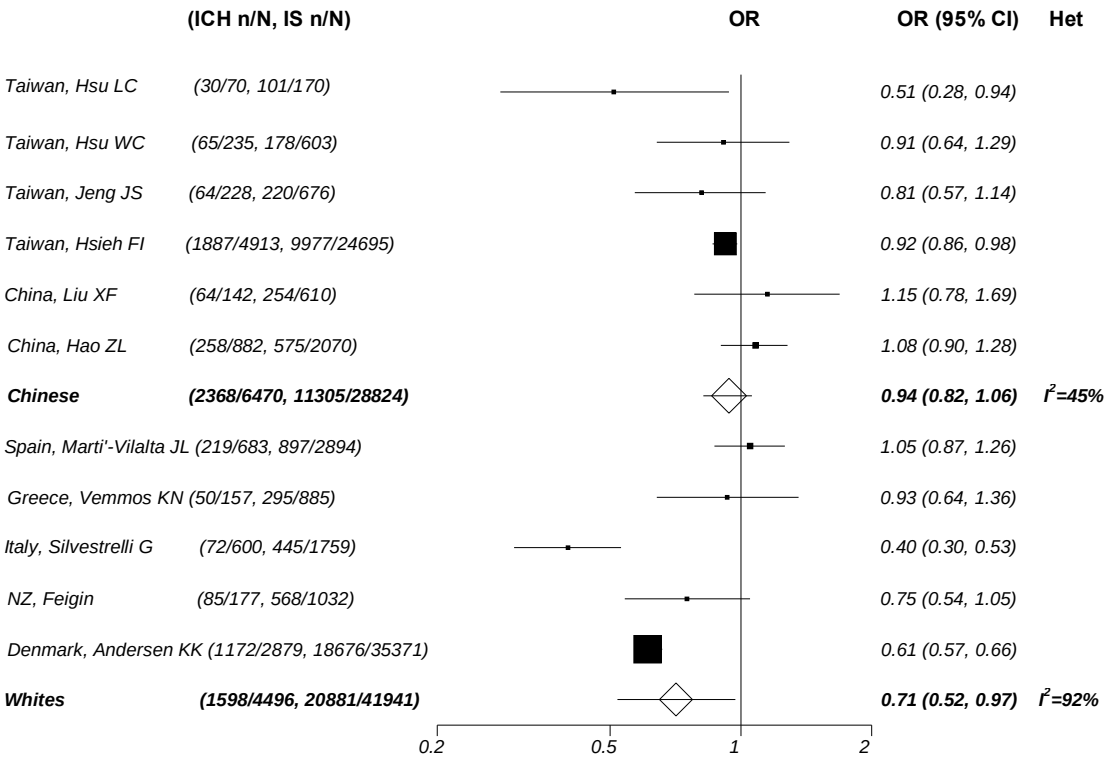
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.7 Hypercholesterolaemia meta-analysis for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



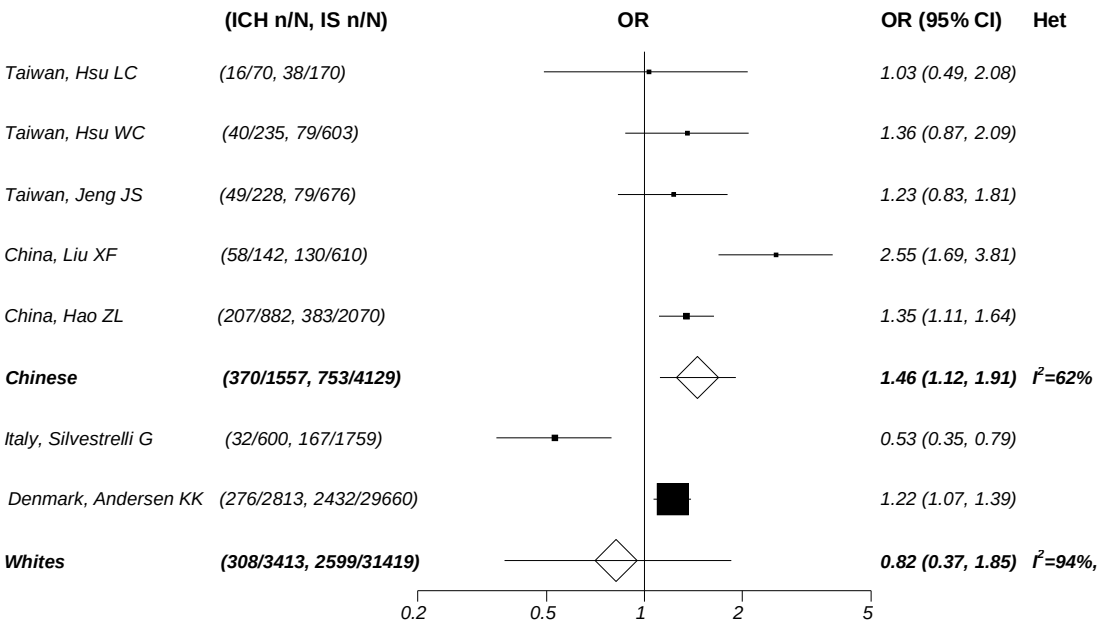
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.8 Smoking meta-analysis for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



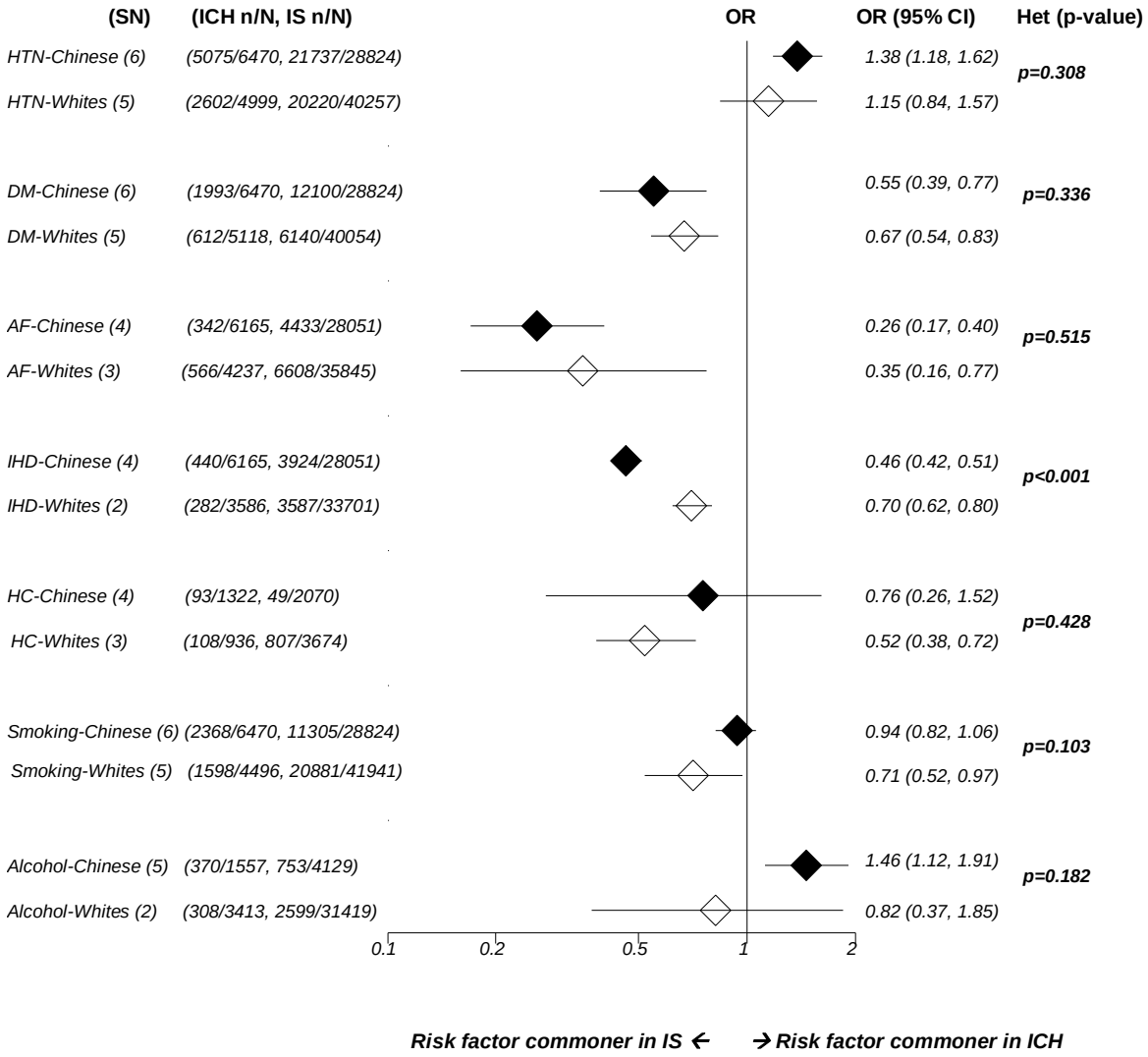
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.9 Alcohol meta-analysis for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



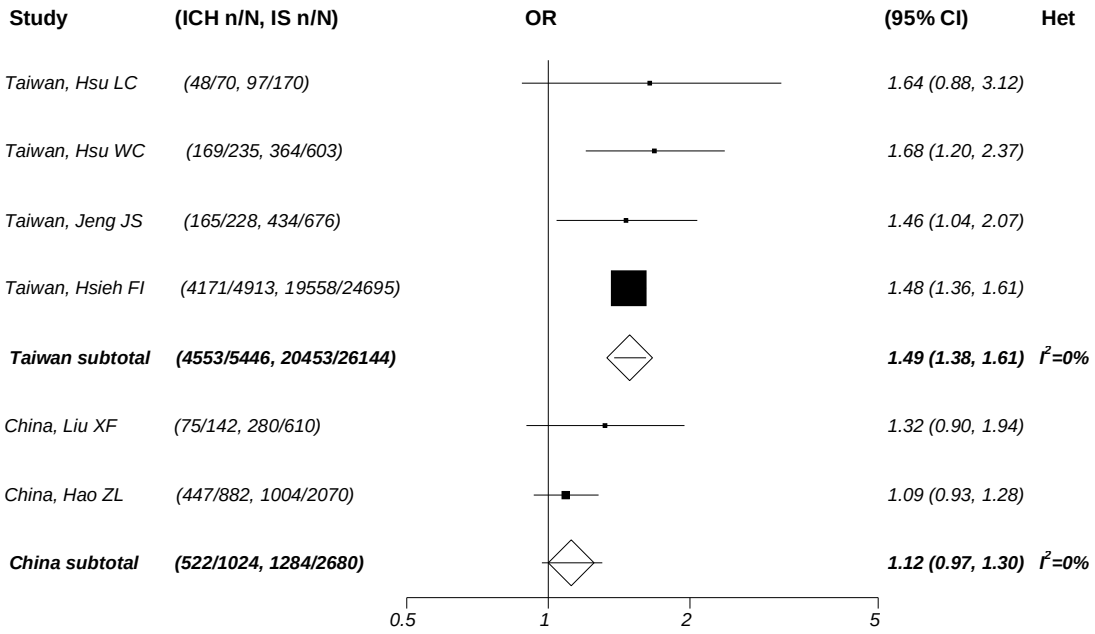
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.10 Summary of risk factor comparisons for intracerebral haemorrhage versus ischaemic stroke in Chinese and white populations.



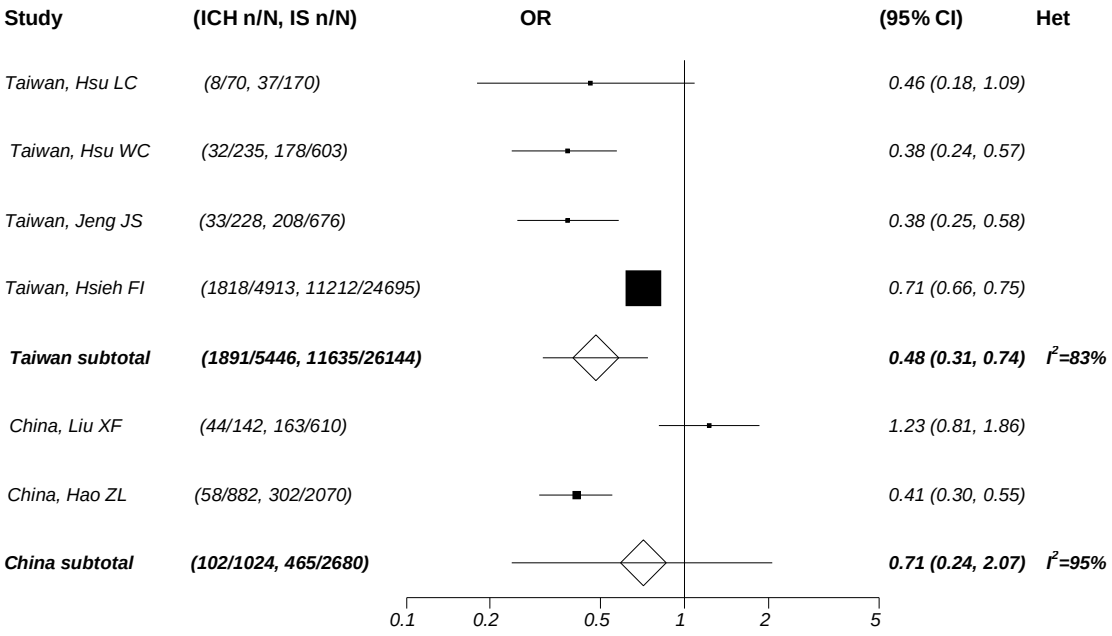
SN=study number; ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=Between-group heterogeneity; HTN=Hypertension; DM=Diabetes Mellitus; AF=Atrial fibrillation; IHD= Ischaemic heart disease; HC=Hypercholesterolaemia. Diamonds represent pooled ORs. Horizontal lines represent 95% CIs.

Figure 5.11 Subgroup analysis of hypertension for intracerebral haemorrhage versus ischaemic stroke by different geographical regions in Chinese populations.



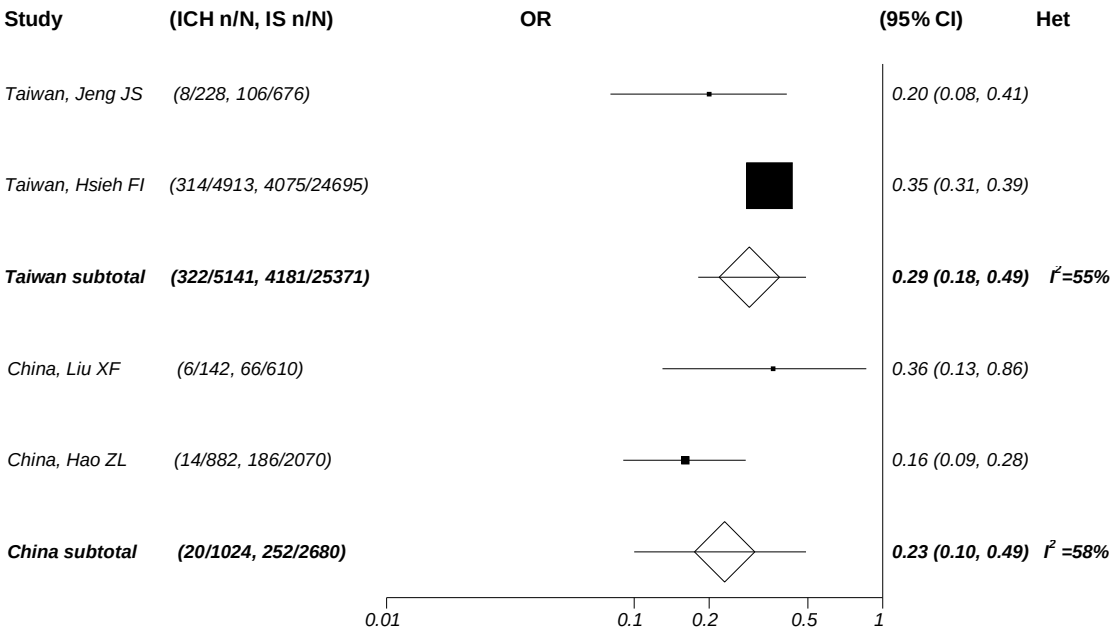
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.12 Subgroup analysis of diabetes for intracerebral haemorrhage versus ischaemic stroke by different geographical regions in Chinese populations.



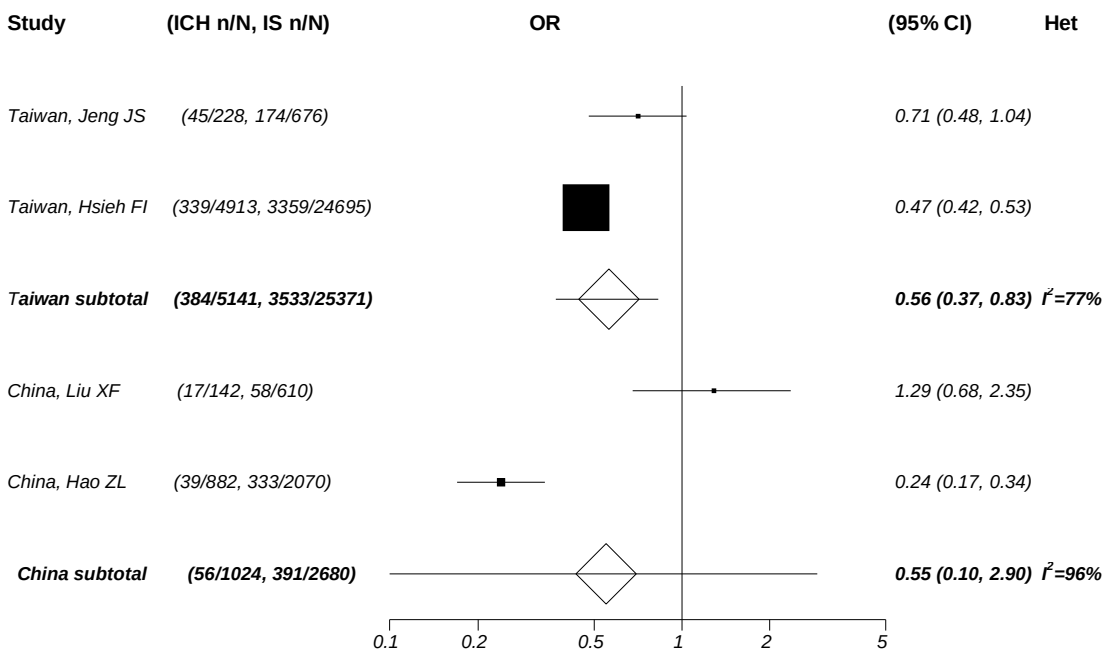
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.13 Subgroup analysis of atrial fibrillation for intracerebral haemorrhage versus ischaemic stroke by different geographical regions in Chinese populations.



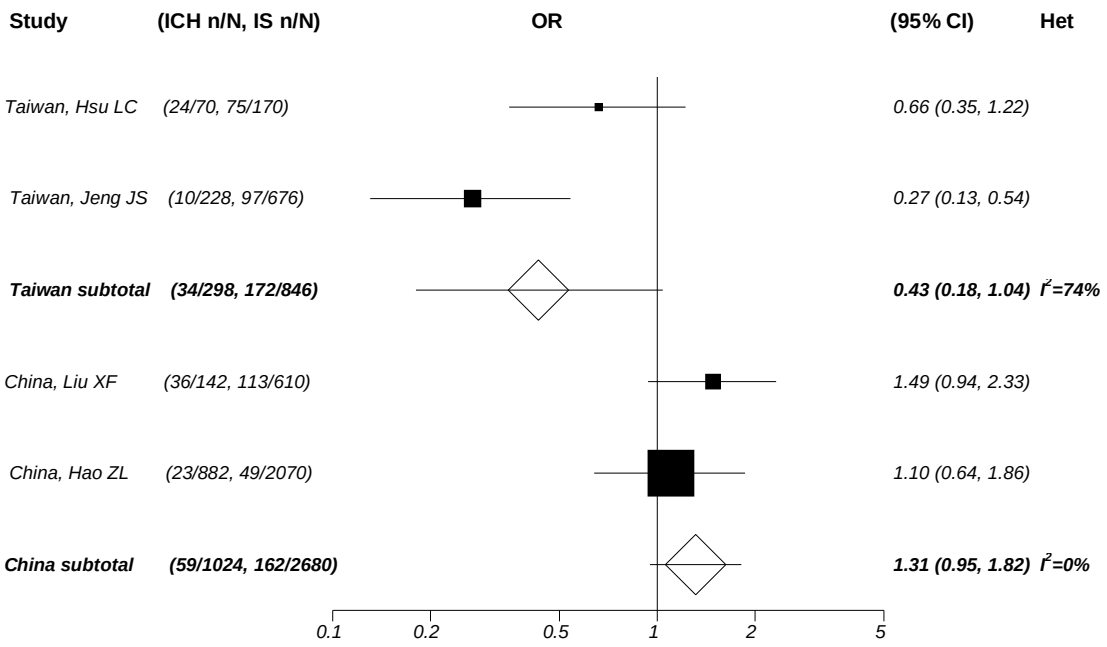
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.14 Subgroup analysis of ischaemic heart disease for intracerebral haemorrhage versus ischaemic stroke by different geographical regions in Chinese populations.



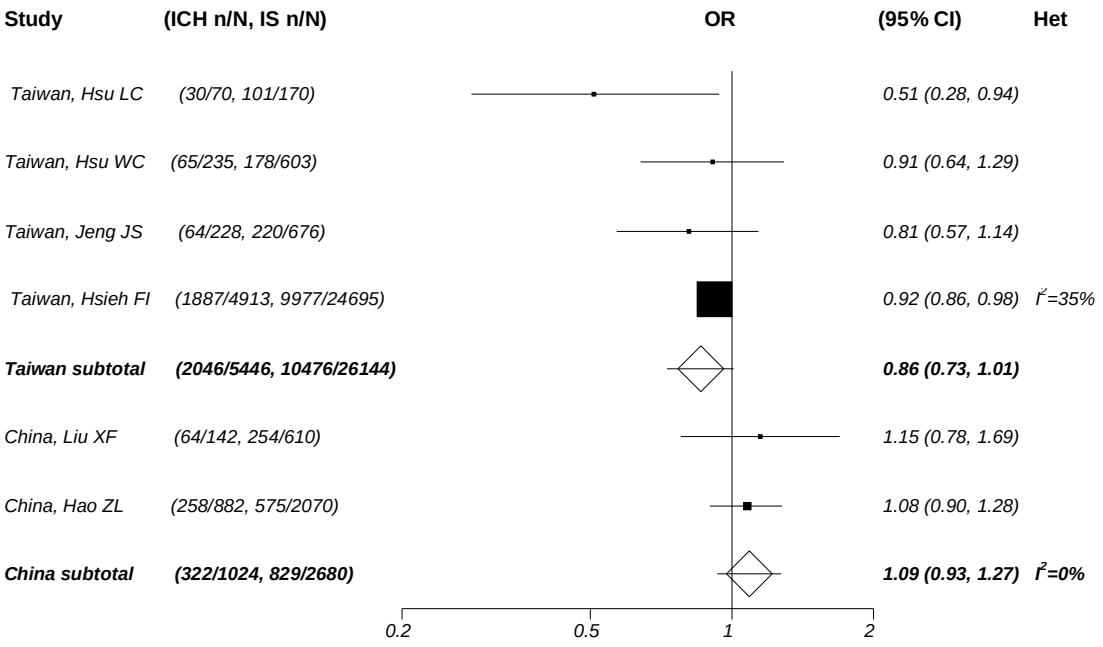
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.15 Subgroup analysis of hypercholesterolaemia for intracerebral haemorrhage versus ischaemic stroke by different geographical regions in Chinese populations.



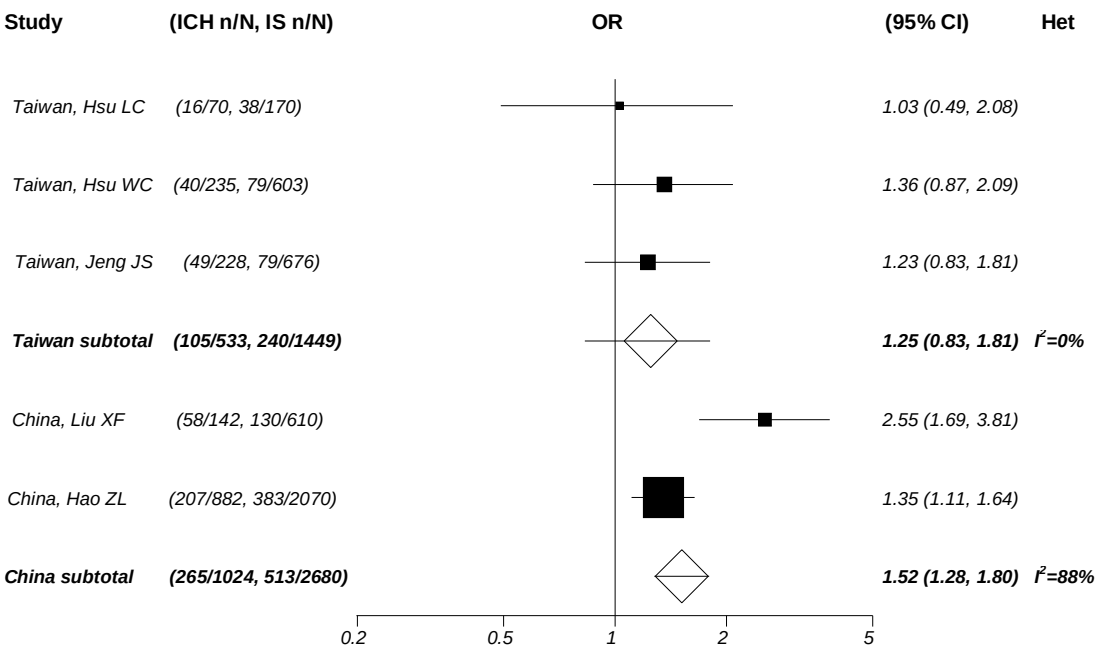
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.16 Subgroup analysis of smoking for intracerebral haemorrhage versus ischaemic stroke by different geographical regions in Chinese populations.



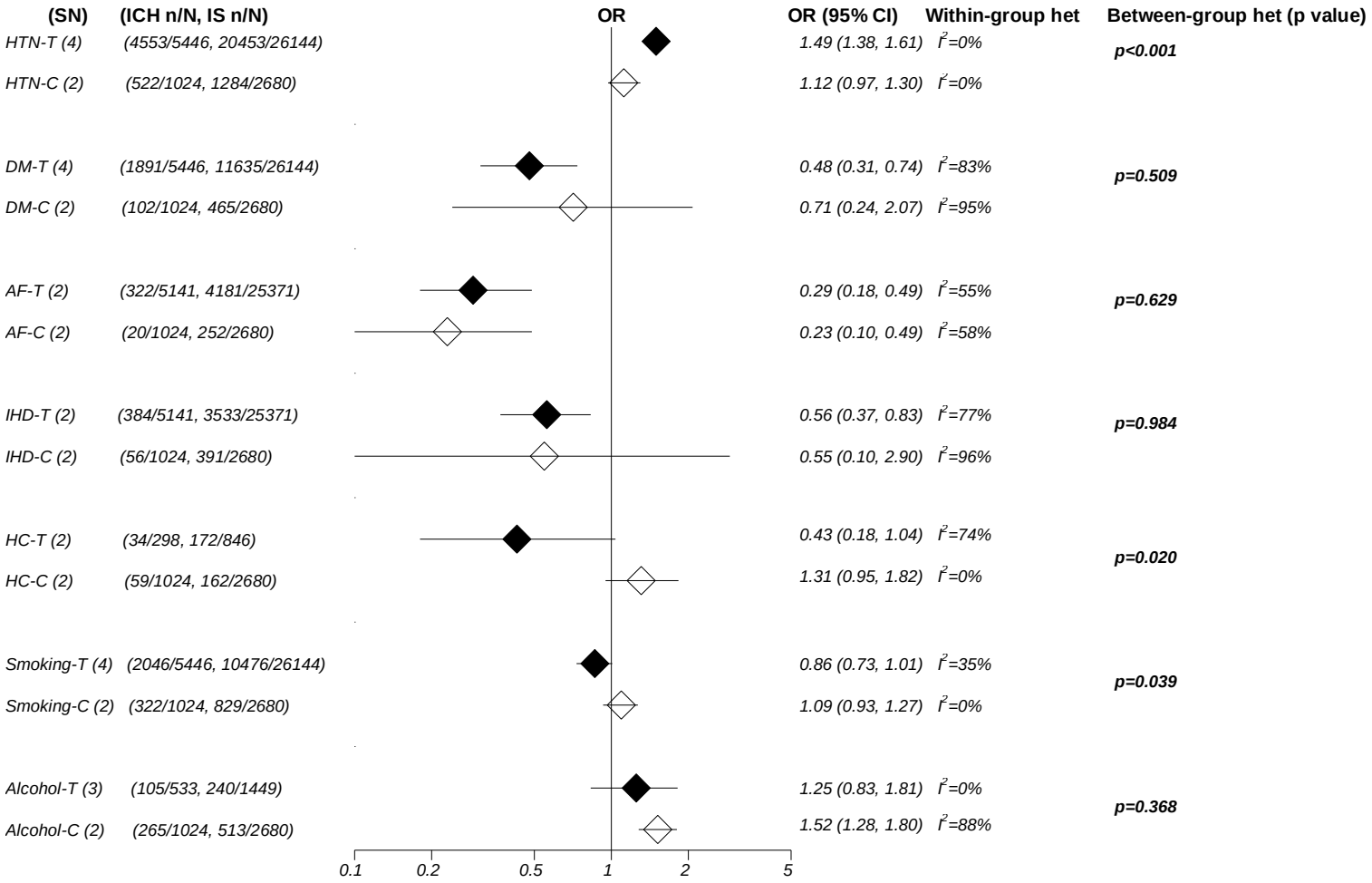
ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.17 Subgroup analysis of alcohol intake for intracerebral haemorrhage versus ischaemic stroke by different geographical regions in Chinese populations.



ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 5.18 Summary for subgroup analyses of risk factor comparisons for ICH versus IS by different geographical regions in Chinese populations.



SN=study number; ICH=intracerebral haemorrhage; IS=ischaemic stroke; n=number of patients with certain risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; het=heterogeneity; I=inconsistency; T=Taiwan; C=mainland China; HTN=Hypertension; DM=Diabetes mellitus; AF=Atrial fibrillation; IHD=Ischaemic heart disease; HC=hypercholesterolaemia. Diamonds represent pooled ORs. Horizontal lines represent 95% CIs.

Chapter 6: Risk factor meta-analyses in ischaemic stroke subtypes – the TOAST and OCSP classifications

6.1 Introduction

My systematic review for ischaemic stroke (IS) subtypes using the Trial of Org 10172 in Acute Ischaemic Stroke (TOAST) or the Oxfordshire Community Stroke Project (OCSP) classification in Chapter 4, and another recent community-based study using Atherosclerosis Risk in Communities (ARIC) classification scheme showed evidence to suggest a different distribution of ischaemic stroke (IS) subtypes, with a higher proportion of lacunar strokes in Chinese versus white populations (Tsai et al. 2013; Fang et al. 2012).

However, the reasons for the difference in distribution of IS subtypes between Chinese and white populations are not clear. It may relate to differences in the prevalence of vascular risk factors and their associations with IS subtypes, and/or different genetic risk factors (Schulz et al. 2003; Jackson et al. 2005; Traylor et al. International Stroke Genetics Consortium. 2012). To test the hypothesis that the distributions of risk factors among IS subtypes vary in different populations, I conducted a systematic review and meta-analysis to evaluate differences in the prevalence of risk factors in overall IS and their associations with IS subtypes in Chinese compared with white patients with IS.

6.2 Methods

6.2.1 Search strategy

I used comprehensive strategies to identify articles comparing the frequency of risk factors among IS subtypes in Chinese populations from electronic databases Medline and EMBASE (Appendix 2). For comparison, I sought similar studies in predominantly white populations with Medline and EMBASE searches that aimed to identify existing systematic reviews and meta-analyses of risk factors for IS subtypes (Appendix 3). I also conducted citation searches of key relevant reviews and perused the reference lists of included primary articles and relevant reviews in both populations (Feigin et al. 2009; Liu et al. 2007; Schulz et al. 2003; Jackson et al. 2005).

6.2.2 Selection criteria for risk factor studies of IS subtypes

I included studies with prospective design, standard World Health Organization (WHO, Hatano et al. 1976) or National Institute of Neurological Disorders and Stroke (NINDS Ad Hoc Committee. 1990) or similar definition of stroke definition of stroke, and data collection from 1990 onwards since brain imaging with computer tomography (CT) or magnetic resonance (MR) were not used widely before this. I included both community-based and hospital-based studies of recurrent as well as first-ever strokes. For reliable stroke diagnosis and classification, I required CT/MR

brain imaging (or autopsy) in >70% of cases. IS had to be classified into five aetiological subtypes - large artery atherosclerosis (LAA), cardioembolism (CE), intracranial small vessel disease (SVD), other determined aetiology, or undetermined aetiology according to the Trial of Org 10172 in Acute Ischaemic Stroke (TOAST) classification scheme or similar, or into the four anatomical subtypes of the Oxfordshire Community Stroke Project (OCSP) classification scheme - lacunar infarct (LACI), total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), posterior circulation infarct (POCI) (Adams et al. 1993; Bamford et al. 1991). I excluded studies with retrospective design, unclear stroke definition or IS classification, incomplete risk factor information for separate IS subtypes, IS classification other than TOAST or OCSP, low CT/MR rate, or highly selected patients (e.g. confined to a particular subgroup). I contacted study authors directly for essential information which was not available in their original publication(s).

6.2.3 Data extraction

From each included IS study, I extracted available information on: the geographical area of the study; sources of case ascertainment; whether it included only first-ever or first-ever and recurrent strokes; study period; stroke definition; stroke subtype classification method; the proportion with CT or MR brain imaging; time from symptom onset to brain imaging; numbers of total IS and of each IS subtype; mean age and sex distribution of stroke cases; risk factor definitions; number of cases with each risk factor for separate IS subtypes using the TOAST or OCSP classification.

6.2.4 Statistical analysis

I calculated pooled proportions of each risk factor in all IS patients in Chinese and predominantly white populations separately. For each risk factor, I calculated study-specific odds ratio (OR) with 95% confidence interval (CI) for each IS subtype versus all others in the TOAST classification in Chinese and in predominantly white populations. If there was more than one study, I used a random effects model to compute pooled ORs with 95% CI because of the substantial heterogeneity among individual studies. In IS using the OCSP classification, I categorized subtypes into lacunar and non-lacunar groups, and used the same methods.

I assessed heterogeneity among Chinese studies and among white studies with both I^2 and Cochrane Q chi-square statistics, obtaining within-group heterogeneity (Higgins et al. 2003; Ryan R, Cochrane Consumers and Communication Review Group. 2013). To assess whether pooled ORs for each risk factor comparison differed significantly between Chinese and white patients, I treated ethnic groups as if they were studies and performed a test for heterogeneity, using the within-group pooled estimates, standard errors and chi-square statistics to test for statistical significance (Borenstein et al. 2009; Ryan R. 2013; Sedgwick P. 2013). A probability value of less than 0.10 was regarded significant because heterogeneity tests were typically used in a conservative manner for meta-analysis (Petitti et al. 2001). I performed analyses with StatsDirect software (http://www.statsdirect.com).

6.3 Results

6.3.1 Characteristics of included studies

I retrieved 5817 articles from my research for studies in Chinese populations. From these, 45 potentially relevant studies were identified for full text review, finally including eight studies (four using TOAST, four OCSP) with a total of 16199 patients with a first-ever or recurrent stroke (Yip et al. 1997; Lin et al. 2002; Liu et al. 2006; Wang et al. 2013.; Li et al. 2003; Li et al. 2008; Jia et al. 2011; Yang et al. 2011). In white (or predominantly white) populations, I identified 11 studies (eight TOAST, three OCSP) in a total of 16187 white (or predominantly white) IS patients (Adams et al. 1993; Marti-Vilalta et al. 1999; Vemmos et al. 2000; Kolominsky-Rabas et al. 2001; Grau et al. 2001; Silvestrelli et al. 2006; Hajat et al. 2011; Bejot et al. 2008; Lindgren et al. 1994; Carlo et al. 2006; Hajat et al. 2001). Study selection and reasons for exclusions are shown in Figures 6.1 and 6.2.

The characteristics of these included studies are displayed in Tables 6.1 and 6.2. Generally, the brain imaging rates were high (range 98 to 100%). In Chinese populations, all were hospital-based. I could not find any community-based study using the TOAST or OCSP even after comprehensive search. Two studies provided risk factor information in both TOAST and OCSP in the same population (Wang et al. 2013; Jia et al. 2011). Patients in the Chinese studies had younger onset of stroke compared with whites (Chinese: mean age 66, range 61 to 69; Whites: mean age 71, range 66 to 74).

6.3.2 Risk factor prevalence for overall IS patients

Risk factors studied were hypertension, diabetes, atrial fibrillation (AF), ischaemic heart disease (IHD), hypercholesterolaemia, smoking and alcohol intake. The definitions of each risk factor reported in original studies are summarised in Tables 6.3 and 6.4. Definitions were not always given, and where they were, there were some differences between studies. Compared with Whites, Chinese IS patients had similar pooled prevalence of hypertension (pooled proportions both 59%), diabetes (25% versus 21%), smoking (38% versus 30%) and alcohol intake (21% versus 15%), as well as lower prevalence of AF (11% versus 27%), IHD (11% versus 20%) and hypercholesterolaemia (9%, versus 30%) (Figure 6.3). However, heterogeneity within Chinese and white studies was substantial and there were some differences in risk factor definitions between Chinese and predominantly white populations such as hypertension. (e.g., Most Chinese studies used 140/90 mmHg as the cut-off point to define hypertension, while most white studies used 160/95 mmHg).

6.3.3 Risk factor associations with IS subtypes

Comparisons of risk factors among IS subtypes showed generally very similar directions of results between Chinese and white IS patients, although the size of the differences were sometimes different. Nevertheless, Chinese stroke patients had younger age onset of stroke versus white patients across major IS subtypes (mean age of onset: LAA 66 versus 68 years, CE 69 versus 76 years, SVD 65 versus 69 years, lacunar 65 versus 71 years), while the proportion of male gender was higher in

Chinese SVD or lacunar IS subtypes as compared with Whites (LAA: 64% versus 62%, p=0.123; CE 45% versus 47%, p=0.202; SVD 64% versus 58%, p<0.001; lacunar 62% versus 56%, P=0.015).

Among studies using the TOAST classification, comparing LAA versus other IS subtypes, in both Chinese and Whites, diabetes was slightly but significantly more common in LAA stroke (ORs 1.34 and 1.42 for Chinese and whites respectively, Figure 6.5) and AF substantially and significantly less common (ORs 0.27 and 0.19, Figure 6.6). Smoking appeared slightly commoner in LAA stroke (significantly in Chinese, but non-significantly in whites) (Figure 6.8). Otherwise there were no significant risk factor differences between subtypes, with the exception of alcohol consumption, which appeared commoner in LAA versus other subtypes in Chinese but not in whites, possibly accounted for – at least in part - by different definitions of alcohol consumption (Figures 6.4 to 6.9; Tables 6.3 and 6.4). Overall, there was no significant difference in any risk factor association between Chinese and Whites (Figure 6.10).

Comparing CE versus other stroke subtypes, there were consistent, significant, strongly positive associations with AF (ORs 71.4 and 36.8 in Chinese and Whites respectively) and significantly positive associations with IHD (ORs 3.62 and 1.31, Figures 6.13 and 6.14). Both associations were significantly more marked in Chinese (heterogeneity between Chinese and white studies for AF: p<0.001, for IHD: p=0.021; Figure 6.17). Hypertension, diabetes, smoking and alcohol were all less common in CE versus other subtypes in both populations (Figures 6.11, 6.12, 6.15, and 6.16). The negative association with diabetes was non-significant in Whites, but

statistically significant in Chinese, while the negative associations with smoking and alcohol were non-significant in Chinese but statistically significant in Whites (between-group heterogeneity for diabetes: p=0.079, for smoking: p=0.011, for alcohol: p=0.028; Figure 6.17).

Comparing SVD versus other stroke subtypes showed, in both Chinese and Whites, significantly positive associations with hypertension and diabetes, and negative associations with AF and IHD (Figures 6.18 to 21). The negative association with IHD was significant in Chinese, but not in Whites (Figure 6.21). These associations were all similar in Chinese and Whites, without between-group heterogeneity (hypertension ORs 1.78 versus 1.93; diabetes ORs 1.17 versus 1.50; AF ORs 0.15 in versus 0.14; IHD ORs 0.55 versus 0.52; Figure 6.24). Neither smoking nor alcohol consumption differed significantly between SVD and other ischemic subtypes in either Chinese or Whites (Figures 6.22 and 23).

Among studies using the OCSP classification scheme and comparing lacunar IS versus others subtypes (Figures 6.25 to 31), the direction of risk factor associations was very similar to that for the comparison between TOAST SVD stroke versus other subtypes (Figures 6.18 to 24), but the pooled estimates were less extreme and differences were less marked. Only AF differed significantly between lacunar stroke and other subtypes for both Chinese and white stroke patients, and the difference was similar for both groups (OR in Chinese 0.40, OR in Whites 0.49; between-group heterogeneity: p=0.568). No risk factors showed significant Chinese-White between-group differences (Figure 6.31).

6.4 Discussion

My results showed that, compared with Whites, Chinese IS patients had younger onset of stroke, a similar prevalence of hypertension, diabetes, smoking and alcohol, and a significantly lower prevalence of AF, IHD and hypercholesterolaemia than white IS patients although there was substantial heterogeneity in either Chinese or white studies. In addition, I found that the risk factor associations with IS subtypes using the TOAST or OCSP classifications were mostly similar in direction (though different in size) in both Chinese and white IS patients. Compared with all other ischaemic subtypes, diabetes was slightly more common in LAA, AF and IHD in CE, and hypertension and diabetes in SVD. However, the small albeit significant associations with lacunar stroke became less so in the OCSP classification scheme.

In my study, the pooled proportion of overall IS revealed a significant lower prevalence of AF, IHD and hypercholesterolaemia in Chinese stroke patients than Whites. My findings were consistent with other reports, which were probably related to the relatively lower prevalence of these risk factors in Chinese populations as compared with Whites (Zhang et al. 2004; Chien et al. 2010; Wu et al. 2001). In addition, I found the prevalence of diabetes in overall Chinese IS patients (which included more than 80% of patients after 2000) was comparable to, and even a bit higher than that in white patients, while the prevalence of hypertension is similar between the groups. This result differed from the report of lower prevalence of diabetes in Chinese stroke patients from an earlier study (Zhang et al. 2004). The difference could possibly reflect around 300% increase of prevalence of pre-diabetes

and diabetes in the recent two decades due to the rapid growing economy and the westernized lifestyle of China (Yang et al. 2012). As for smoking and alcohol, my results showed a relatively higher prevalence (though statistically non-significant) of smoking and alcohol in Chinese than white IS patients. Actually, smoking and alcohol are increasingly common in Chinese, and China is the world's largest consumer of tobacco (Yang et al. 1999). There was a strong and dose-dependent association between cigarette smoking and IS, while alcohol has a curvilinear relationship with IS - a protective effect for low to moderate intake and increased risk for high consumption (Kelly et al. 2008; Patra et al. 2010).

In terms of risk factor associations with ischaemic subtypes, my study showed that LAA had a positive association with diabetes in both Chinese and Whites. Diabetes is a well-known risk factor for ischaemic stroke, especially for large vessel and small vessel diseases (WHO Diabetes Drafting Group, 1985). My finding was in agreement with previous studies (Rincon et al. 2009; Arenillas et al. 2004). Diabetes is an independent risk factor for intracranial large artery atherosclerosis (Arenillas et al. 2004). Compared with extracranial atherosclerosis or non-atherosclerosis (lacunar, cardioembolic and cryptogenic), Diabetes was a more important determinant for intracranial atherosclerosis related stroke (Rincon et al. 2009). Although there were slight excess, but less consistent associations with smoking and with alcohol intake in Chinese, these findings did not appear significantly in whites. Different definitions in Chinese and white studies might partly explain the difference.

In my meta-analysis, CE subtype was strongly associated with AF and IHD in both ethnic groups, more in Chinese. In literature, non-valvular AF and myocardial

infarction are the leading causes of cardioembolism (Arboix et al. 2012, Ferro et al 2003). However, there may be different interpretations of the TOAST classification system among stroke physicians, such that IS patients with AF are more likely to be assigned to CE stroke than other subtypes, irrespective of other risk factors and investigation results (Jackson et al. 2005).

In terms of SVD using the TOAST classification, there was a slight excess in hypertension as well as diabetes when compared with other IS subtypes in both Chinese and whites. By contrast, it was negatively associated with AF and IHD, without significant differences between ethnic groups. Nevertheless, in IS subtype studies using the OCSP classification scheme, the slightly positive associations with hypertension and diabetes for lacunar versus non-lacunar infarctions became less so. My findings are in agreement with the earlier systematic review (Jackson et al. 2005). The associations with risk factors for lacunar versus non-lacunar infarcts are less extreme when using the OCSP classification – a risk factor-free classification. Although my systematic review in Chapter 4 showed a higher proportion of lacunar stroke from hospital-based studies in Chinese than Whites, and recently another community-based study using the Atherosclerosis Risk in Communities (ARIC) classification also reported a higher incidence rate of lacunar infarction in Chinese, there seemed to be no evidence of significant difference in the risk factor distributions in lacunar stroke between these two ethnic groups (Tsai et al. 2013; Fang et al. 2012). Nevertheless, the results could be possibly confounded by different population structures such as age and gender, along with other risk factors. Further

studies using individual patient data in large stroke registries to adjust for possible confounders and further genetic studies for IS subtypes are necessary.

6.4.1 Strengths and limitations

My study is the first systematic review and meta-analysis comparing risk factor distributions among IS subtypes in Chinese compared with predominantly white populations. It has several major strengths. First, I used a comprehensive search strategy including backward and forward tracking to identify all relevant studies published in any language (including Chinese), reducing the potential bias of including only English language publications. Second, I included only studies using a standard definition of stroke and the TOAST or OCSP classification of ischaemic subtypes with a high brain imaging rate. Third, I carefully documented the characteristics, methodology and risk factor definitions used in each included study, and carried out rigorous meta-analyses to assess within-group and between-group heterogeneity among Chinese and predominantly white populations for each IS subtype versus others.

There were some limitations. First, despite a comprehensive literature search, I found only a limited number of studies in either Chinese or predominantly white populations which fulfilled our inclusion criteria (Chinese literature databases were not available to me because I did not have access to the full-text databases). I could only find hospital-based studies based on TOAST or OCSP classifications in Chinese and few community-based studies in predominantly white populations, whereas an

ideal study population should be community-based, including all stroke patients in a geographical area, irrespective of hospital admission rate (Sudlow et al. 1996; Feigin et al. 2004). Prevalence of risk factors and stroke subtypes may differ between hospitalized and non-hospitalized patients (Schulz et al. 2003). Second, there was substantial statistical heterogeneity among both Chinese and white studies. This is likely to have arisen from differences in age and sex distributions, methodological differences (e.g., case ascertainment methods), variation in classification of IS subtypes, variation in investigation rates affecting ability to assign a determined subtype with the TOAST classification, different risk factor definitions, differences between geographical areas, as well as genuine differences in risk factors associations between ethnic groups. Third, because my study was based on published data, I did not have individual patient data to allow adjustment for possible confounding factors such as age. Finally, although I included only studies which ascertained stroke cases prospectively, definitions of risk factors in some studies were limited by the need to collect information prior to stroke occurrence (which might have recall biases) while others were based on the measures made after stroke, raising the possibility of reverse causality.

6.4.2 Conclusion

My study results illustrated and compared that the overall prevalence of risk factors in IS and the risk factor associations with IS subtypes in a substantial number of Chinese and white IS patients. These findings help us understand the similarities and

differences in contributions of modifiable risk factors for IS and its subtypes in different populations, which also highlight the need for high quality community-based studies, and provide directions for future research. Further analyses of large stroke registry data to adjust for possible confounding factors are mandatory.

Tables

Table 6.1 Clinical characteristics of included risk factors studies among ischaemic stroke subtypes in Chinese populations.

Author (First)	Region	Study period (Year)	Patient recruitment	Stroke inclusion	Mean age of IS (years)	Gender (male%)	CT/MR (%)	IS patients (n)	Risk factors reported
TOAST classification									
Yip PK	Taiwan, Taipei	1995	Hospital-based, consecutive admission	First-ever and recurrent	65	57%	100%	676	HTN, DM, AF, IHD, CS, HC, HTG, smoking, alcohol, previous stroke, age, gender
Lin YT *	Taiwan, Kaohsiung	1999	Hospital-based, consecutive admission	First-ever and recurrent	69	NR	100%	408	HTN, DM, AF, IHD, CS, HL, smoking
Liu XF	China, Nanjing	2002-2003	Hospital-based, consecutive admission	First-ever stroke	68	66%	98%	610	HTN, DM, AF, IHD, HL, smoking, alcohol, age, gender
Wang Y	China, multicentre	2007-2008	Hospital-based, consecutive admission	First-ever and recurrent	66	62%	100%	11560	HTN, DM, AF, IHD, DL, smoking, alcohol, previous stroke, age, gender
OCSP classification									

Li H	China, Hong Kong	1997-1998	Hospital-based, consecutive admission	First-ever and recurrent	68	58%	NR **	699	HTN, DM, AF, IHD, smoking, previous stroke, age, gender
Li W	China, Chengdu	2002-2005	Hospital-based, consecutive admission	First-ever and recurrent	65	54%	100%	1314	HTN, DM, AF, HL, smoking, alcohol, previous stroke, age, gender
Jian Q	China, multicentre	2007-2008	Hospital-based, consecutive admission	First-ever and recurrent	67	62%	100%	11657	DM
Yang P	China, Yinchuan	2009-2010	Hospital-based, consecutive admission	First-ever and recurrent	61	69%	100%	932	HTN, DM, AF, HL, smoking, alcohol, age, gender

CT=Computed tomography; MR=Magnetic resonance; IS=ischaemic stroke; n=number; HTN=Hypertension; DM=Diabetes mellitus; HD=Heart disease; AF=Atrial fibrillation; IHD=Ischaemic heart disease; LVH=Left ventricular hypertrophy; CS=Carotid stenosis; DL=Dyslipidaemia; HL=Hyperlipidaemia; HC=Hypercholesterolaemia; HTG=Hypertriglyceridaemia; HU=Hyperuricemia; *NINDS classification= National Institute of Neurological Disorders and Stroke classification; **presumably high percentage.

The order of studies was ranked according to study period in TOAST and OCSP classifications respectively.

Table 6.2 Clinical characteristics of included risk factors studies among ischaemic stroke subtypes in white populations.

Author (First)	Region	Study period (Year)	Patient recruitment	Stroke inclusion	Mean age of IS (years)	Gender (male%)	CT/MR (%)	IS patients (n)	Risk factors reported
TOAST classification									
Marti-Vilalta JL	Spain, Barcelona	1977-1994	Hospital-based, consecutive admission	First-ever	66	57%	100%	2894	HTN, DM, HD, HL, smoking, PAD, TIA, age, gender
Vemmos KN	Greece, Athens	1992-1997	Hospital-based, consecutive admission	First-ever	70	59%	100%	885	HTN, DM, AF, IHD, HC, smoking, TIA, age, gender
Kolominsky-Rabas PL	Germany, Erlangen	1999	Community-based with multiple sources	First-ever	73	42%	100%	531	HTN, DM, HD, smoking
Grau AJ	Germany, multicentre	1998-1999	Hospital-based, admission (multicentre)	First-ever and recurrent	66	58%	100%	5017	HTN, DM, Arrhythmia, IHD, HC, smoking, alcohol, PAD, TIA, age, gender
Silvestrelli G	Italy, Perugia	1998-2002	Hospital-based, consecutive admission	First-ever	73	52%	100%	1759	HTN, DM, EHD, HL, HC, HTG, smoking, alcohol, obesity, TIA, age, gender,

Schulz UGR	UK, Oxford	2002	Community-based with multiple sources	First-ever and recurrent	NR	51%	98%	102	HTN, DM, smoking, TIA, age, gender
Hajat C [a]	UK, London	1999-2005	Community-based with multiple sources	First-ever	71	49%	NR	1169	HTN, DM, smoking, TIA, age, gender
Bejot Y	France, Dijon	2005-2006	Community-based with multiple sources	First-ever stroke	74	45%	100%	332	HTN, DM, HC, smoking, TIA, age, gender
OCSP classification									
Lindgren A	Sweden, Lund	1991-1992	Hospital-based, consecutive admission	First-ever	73	55%	100%	166	AF, CS
Carlo AD	Europe, multinational	1993-1994	Hospital-based, admission	First-ever	71	53%	NR	2472	HTN, DM, AF, IHD, smoking, alcohol, TIA, age, gender
Hajat C [b]	UK, London	1995-1998	Community-based with multiple sources	First-ever	72	48%	NR	862	HTN, DM, AF, IHD, smoking, alcohol, TIA

CT=Computed tomography; MR=Magnetic resonance; IS=ischaemic stroke; n=number; HTN=Hypertension; DM=Diabetes mellitus; HD=Heart disease; AF=Atrial fibrillation; IHD=Ischaemic heart disease; LVH=Left ventricular hypertrophy; CS=Carotid stenosis; EHD=Embolic heart disease;

HD=Heart disease; HL=Hyperlipidaemia; HC=Hypercholesterolaemia; HTG=Hypertriglyceridaemia; PAD=peripheral artery disease; TIA=transient ischaemic attack.

[a] TOAST classification; [b] OCSP classification.

The order of studies was ranked according to study period in TOAST and OCSP classifications respectively.

Table 6.3 Definitions of risk factors among included studies in Chinese populations

Study (First author)	HTN	DM	AF	IHD	HC	Smoking	Alcohol
Jian Q **	--	DM history or taking DM drugs	--	--	--	--	--
Li H	NR	NR	NR	NR	--	NR	--
Lin YT	>140/90 mm/Hg or taking anti-HTN drugs	Fasting >7.0 mmol/L	NR	By coronary arteriogram	TC>5.2 mmol/L	NR	NR
Liu XF	>160/95 mm/Hg or HTN history with anti-HTN drugs	Fasting >7.0 mmol/L or DM history with medication	NR	NR	TC> 5.7 mmol/L, or hyperlipidaemia history with drugs	NR	NR
Li W	>140/90 mm/Hg or HTN history with anti-HTN drugs	Fasting>7.8 mmol/L or DM history with drugs	NR	NR	TC>5.8mmol/L or hyperlipidaemia history with drugs	NR	NR
Yang P	>=140/90 mm/Hg or taking anti-HTN drugs	Fasting>=7.0 mmol/L or taking DM medication	ECG proof before or after stroke	--	TC>=5.2 or LDL >=2.6 or HDL,<=1.0 mmol/L	Frequent or long term smoking >=20/day	Frequent or long term drinking>=50 ml/day
Yip PK	History of HTN	History of DM	History of AF or ECG proof before or after stroke	History of angina or MI	>=5.2 mmol/L	>=10/day for more 10 years	Habit drinking >= once per week
Wang Y	>=140/90 mm/Hg during	Fasting>=6.7 mg/dl or use of	History of AF or ECG in hospital	History of MI, or a diagnosis of MI at	--	current or previous smoker	moderate or heavy drinking

	hospitalization or on HTN antihypertensive medication	antidiabetic drugs	discharge

HTN=Hypertension; DM=Diabetes mellitus; AF=Atrial fibrillation; IHD=Ischaemic heart disease; ECG=electrocardiography; CUS=carotid ultrasound; HC=Hypercholesterolaemia; HTG=Hypertriglyceridaemia; --=no data - the risk factor was not studied or unavailable from the publication; NR=not reported; risk factor was studied but definition not reported; ** =no data in each subtype.

The order of studies was ranked according to the alphabet initials of first author.

Table 6.4 Definitions of risk factors among included studies in white populations

Study (First author)	HTN	DM	AF	IHD	HC	Smoking	Alcohol
Bejot Y	History of HTN, or >=160/95 mm/Hg	History of fasting sugar >=7.8 mmol/L or at stroke, or on DM drugs	--	--	TC>=5.7mmol/L or on lipid-lower drugs	Current smoking>1 cigarette/day or former smoking	--
Carlo AD	History of HTN, on HTN drugs, or >=160/90 mm/Hg	History of DM, on DM drugs, or fasting >=7.8 mmol/L	History of AF, or by ECG at admission	History of MI	--	Current or former smoking	Specified as average units per day
Grau AJ	History of >160/90 mm/Hg or on HTN drugs	History of elevated blood glucose, or on DM drugs, or elevated Haemoglobin A1c at admission	--	NR	History of TC> 5.7 mmol/L or on lipid-lowering drugs	Current smoking	Daily consumption
Hajat C [a]	>140/90 mm/Hg from GP or hospital records	Self-reported	--	--	--	NR	--
Hajat C [b]	History of HTN on treatment, or prestroke records >160/95 mm/Hg from GP or	History of DM from GP or hospital records	Prestroke ECG records at outpatient clinic or at hospital	History of angina or MI	--	Ever smoked	>14 units per week in women and >21 units per week in men

	hospital records						
Kolominsky-Rabas PL	History of HTN, on HTN drugs, or >160/95 mm/Hg	History of DM, on DM drugs, or fasting > 6.7 mmol/L	--	--	--	Current smoking	--
Lindgren A	--	--	ECG proof after stroke	--	--	--	--
Marti-Vilalta JL	History of >160/95 mm/Hg, or evidence of HTN related end organ damage	History of DM or glucose >6.1 mmol/L at admission	--	--	--	History of smoking within 5 years	--
Schulz UGR	History of HTN, on HTN drugs, or >160/95 mm/Hg before stroke	History of DM or on DM drugs	--	--	--	Current smoking	Daily consumption
Vemmos KN	History of >160/95 mm/Hg	History of DM drugs use or fasting >6.0 mmol/L before	By ECG	History of MI, angina or CHF	History or cholesterol >6.5 mmol/L at admission	Current daily smoking or within previous year	--
Silvestrelli G	History of >160/95 mm/Hg	History of DM drug use or fasting >6.0 mmol/L before	NR	--	History or cholesterol >6.5 mmol/L at admission	Current daily smoking or within previous year	NR

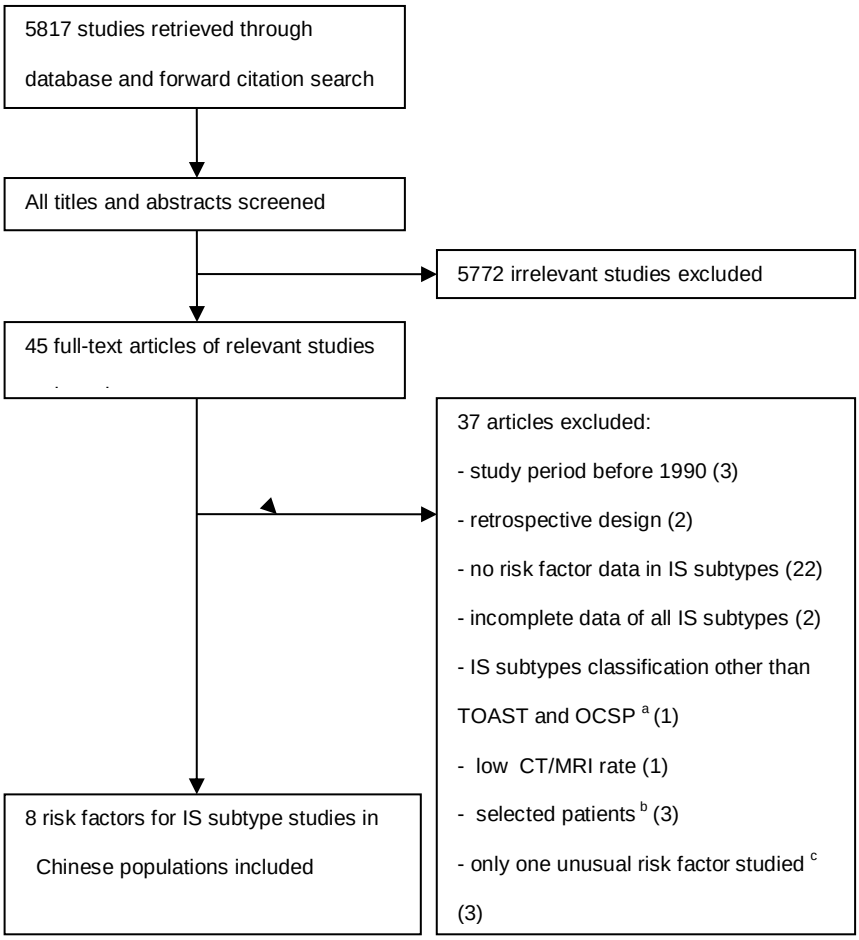
HTN=Hypertension; DM=Diabetes mellitus; AF=Atrial fibrillation; IHD=Ischaemic heart disease; MI=myocardial infarct; CHF=congestive heart failure; ECG=electrocardiography; CUS=carotid ultrasound; HC=Hypercholesterolaemia; HTG=Hypertriglyceridaemia; --=no data - the risk factor was not

studied or unavailable from the publication; NR=not reported; risk factor was studied but definition not reported; GP=general practice; Hajat C [a]=TOAST classification; Hajat C [b]=OCSP classification.

The order of studies was ranked according to the alphabet initials of first author.

Figures

Figure 6.1 Selection of studies of risk factors for ischaemic stroke subtypes in Chinese populations.

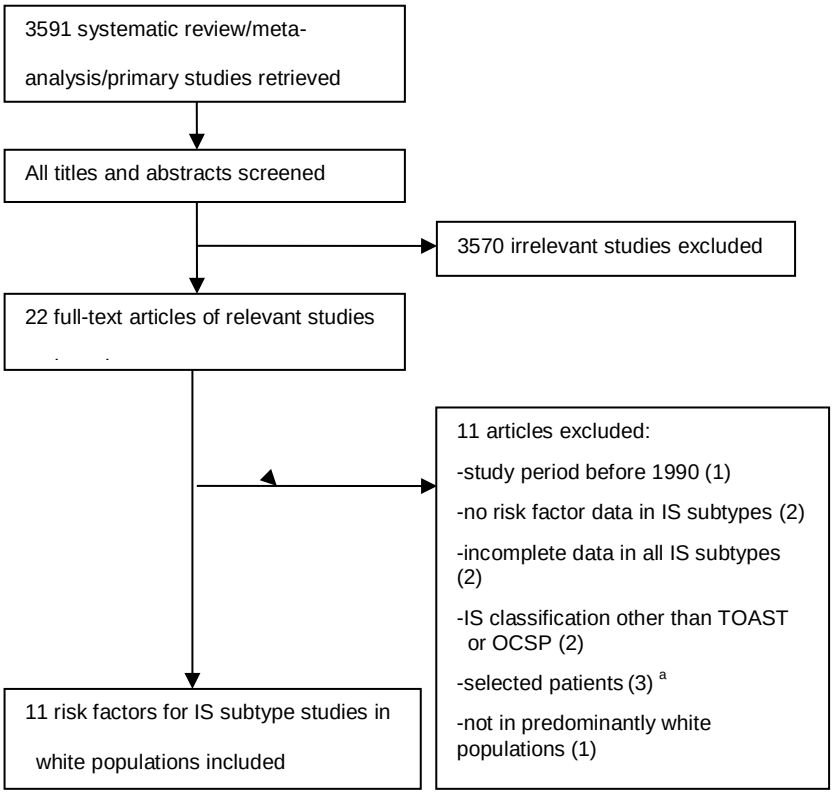


[a] IS subtypes using the Atherosclerosis Risk in Communities (ARIC) classification (Fang et al. 2012).

[b] Excluding patients with cardiogenic emboli (Zhao et al. 2008); excluding patients with other major medical illness (e.g., cancer, anaemia, thyroid dysfunction, etc.; Zhang et al. 2009); data only in men (Zhang et al. 2004).

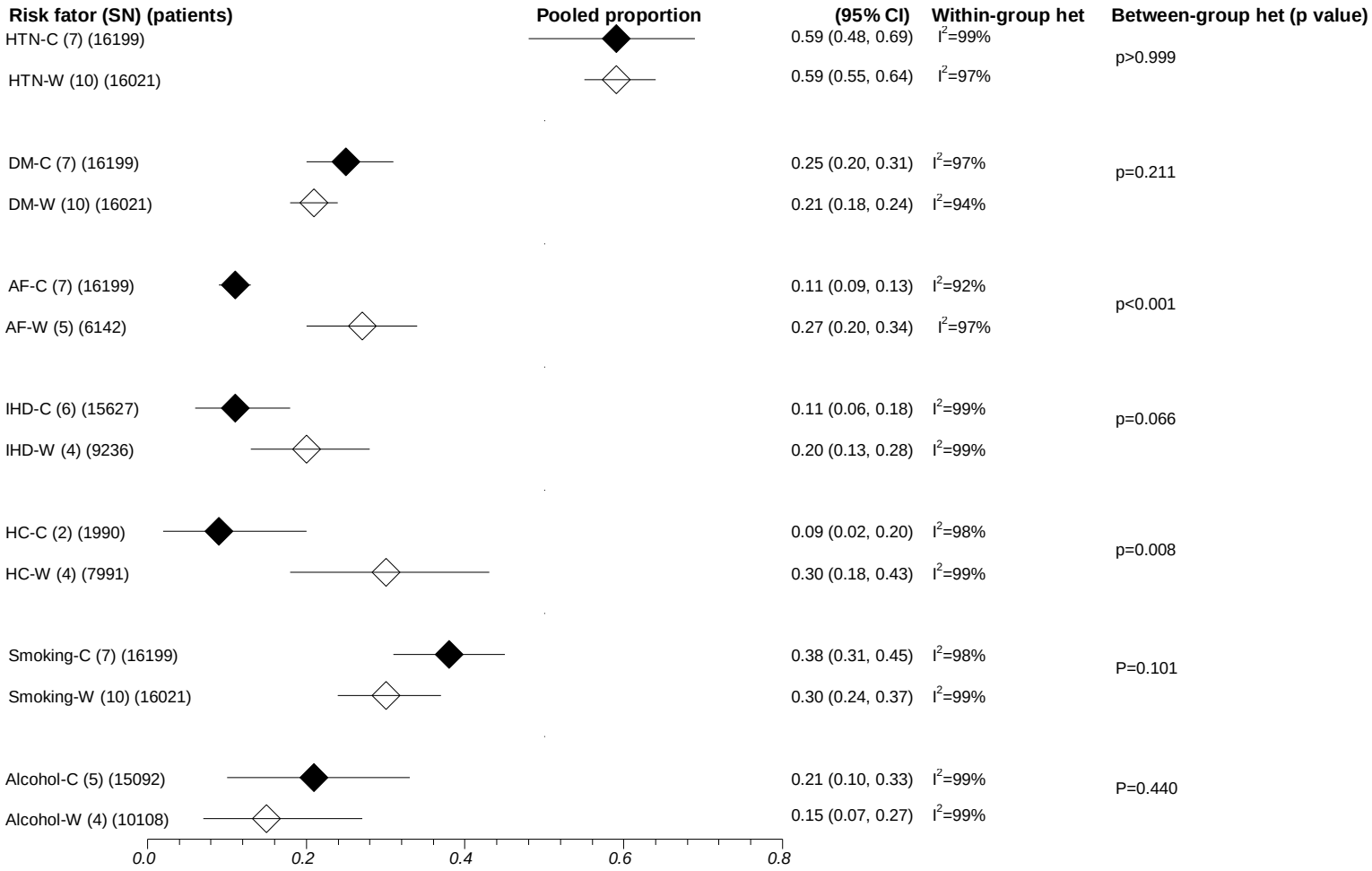
[c] Weather (Chen et al. 1995), circadian variation of stroke onset (Cheung et al. 2001),and homocysteine (Ma et al. 2010).

Figure 6.2 Selection of studies of risk factors for ischaemic stroke subtypes in white populations.



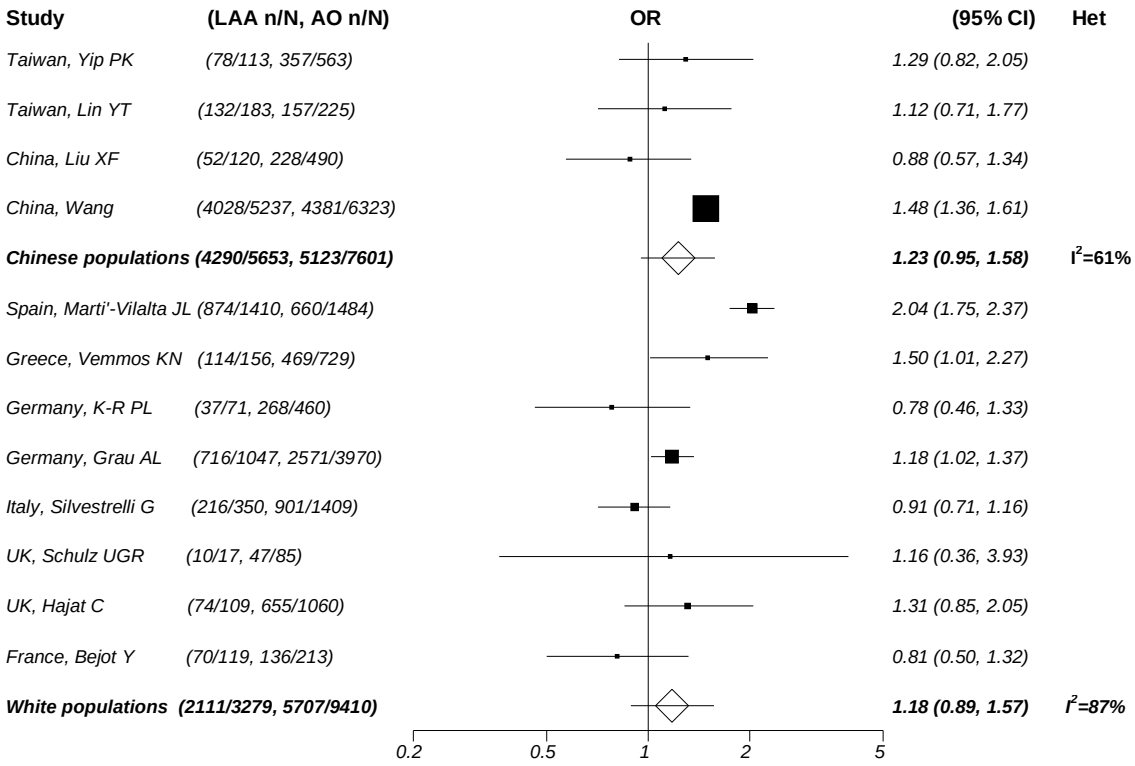
[a] One study excluded IS patients of posterior circulation infarction, or with uncertain subtype, or with unusual cause (e.g. arterial dissection; Jackson et al. 2009), one excluded IS patients due to cardiogenic emboli (Schmal et al. 1998), and the other included data only in men (Leppala JM et al. 1999).

Figure 6.3 Meta-analyses of prevalence of risk factors among ischaemic stroke patients in Chinese and Whites.



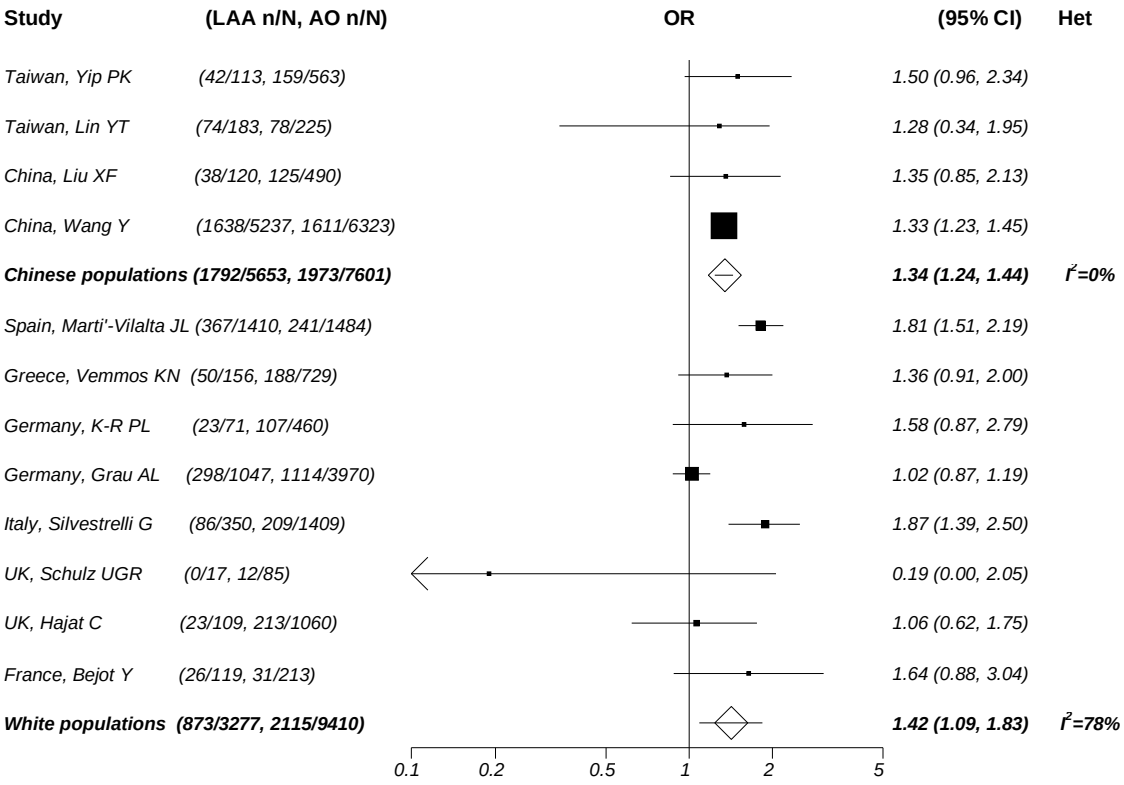
SN=study number; CI=confidence interval; Het=heterogeneity; I=inconsistency; HTN=Hypertension; DM=Diabetes Mellitus; AF= Atrial fibrillation; IHD=Ischaemic heart disease; HC=Hypercholesterolaemia. Horizontal lines represent 95% CIs. Diamonds represent pooled proportion.

Figure 6.4 Meta-analysis of hypertension for LAA versus others ischaemic subtypes in Chinese and Whites.



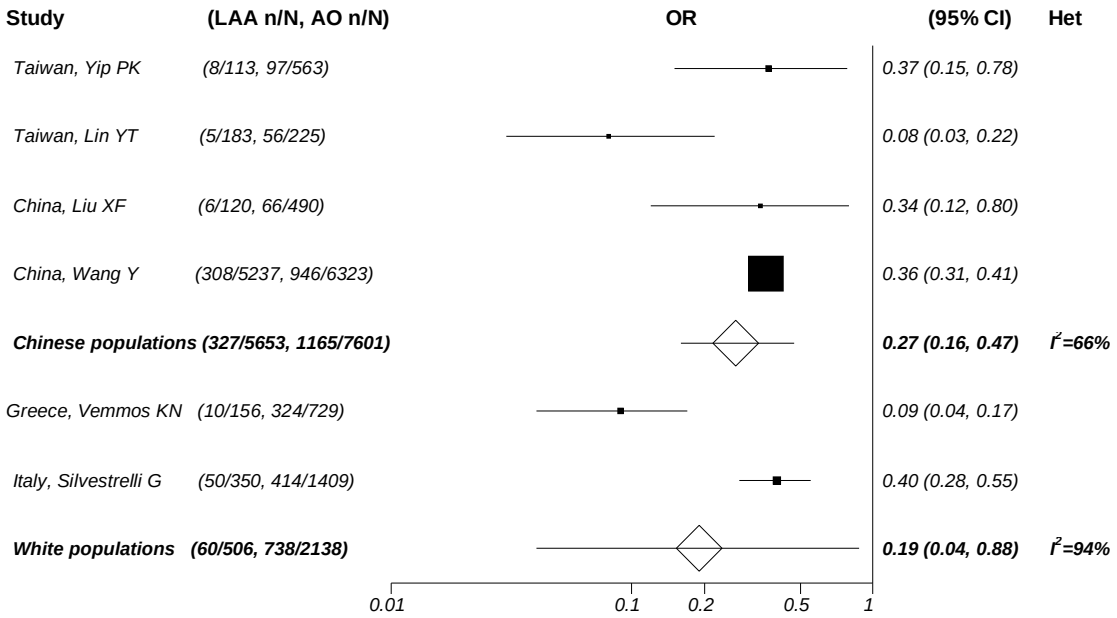
LAA=Large artery atherosclerosis; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.5 Meta-analysis of diabetes for LAA versus other ischaemic subtypes in Chinese and Whites.



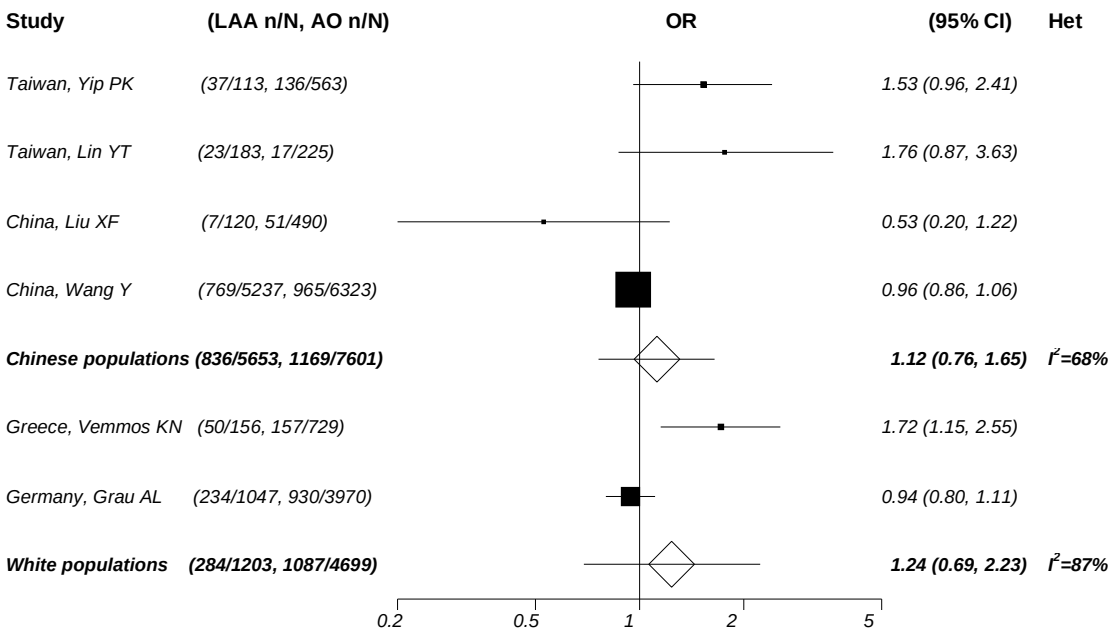
LAA=Large artery atherosclerosis; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.6 Meta-analysis of atrial fibrillation for LAA versus other ischaemic subtypes in Chinese and Whites.



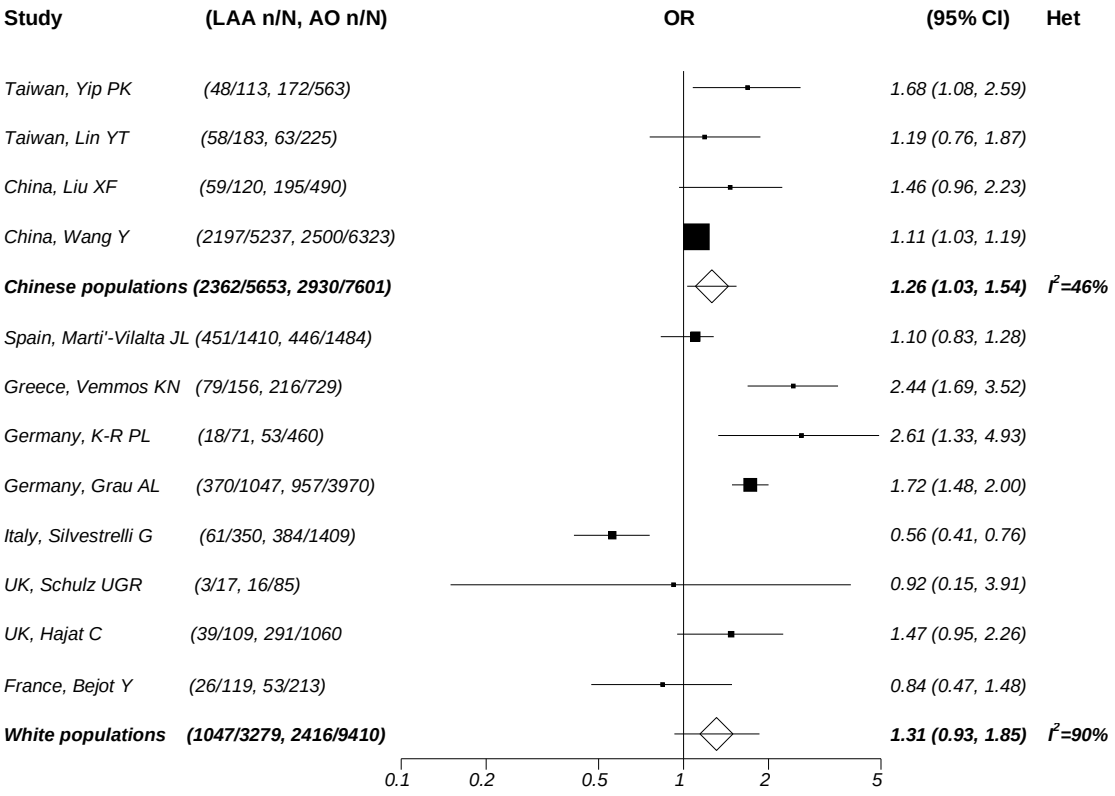
LAA=Large artery atherosclerosis; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.7 Meta-analysis of ischaemic heart disease for LAA versus other ischaemic subtypes in Chinese and Whites.



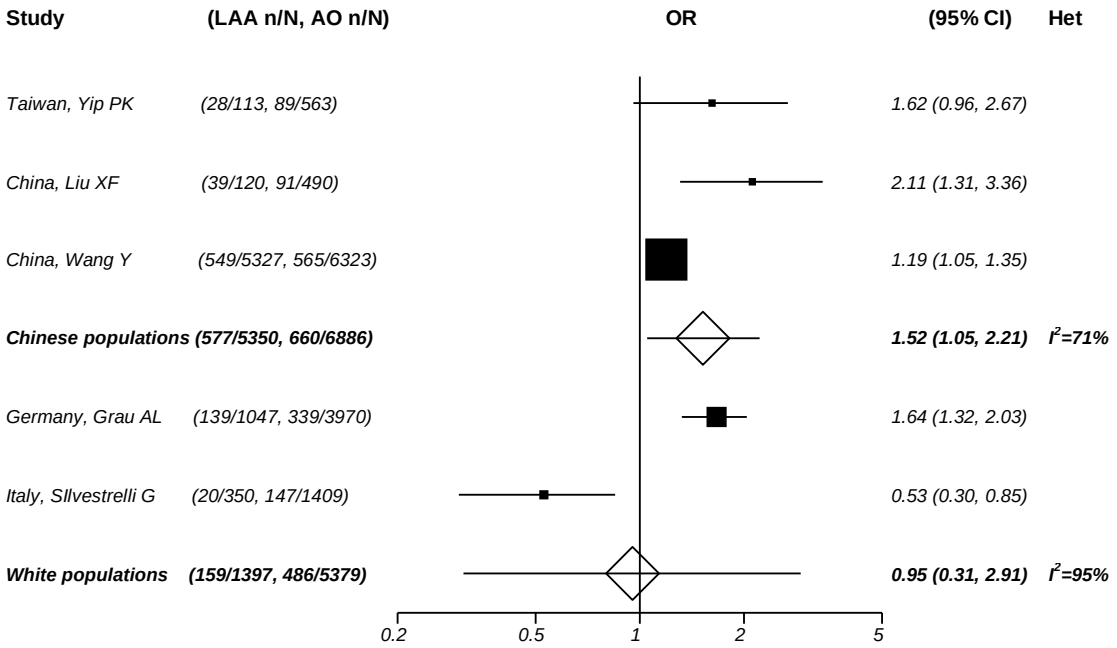
LAA=Large artery atherosclerosis; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.8 Meta-analysis of smoking for LAA versus other ischaemic subtypes in Chinese and Whites.



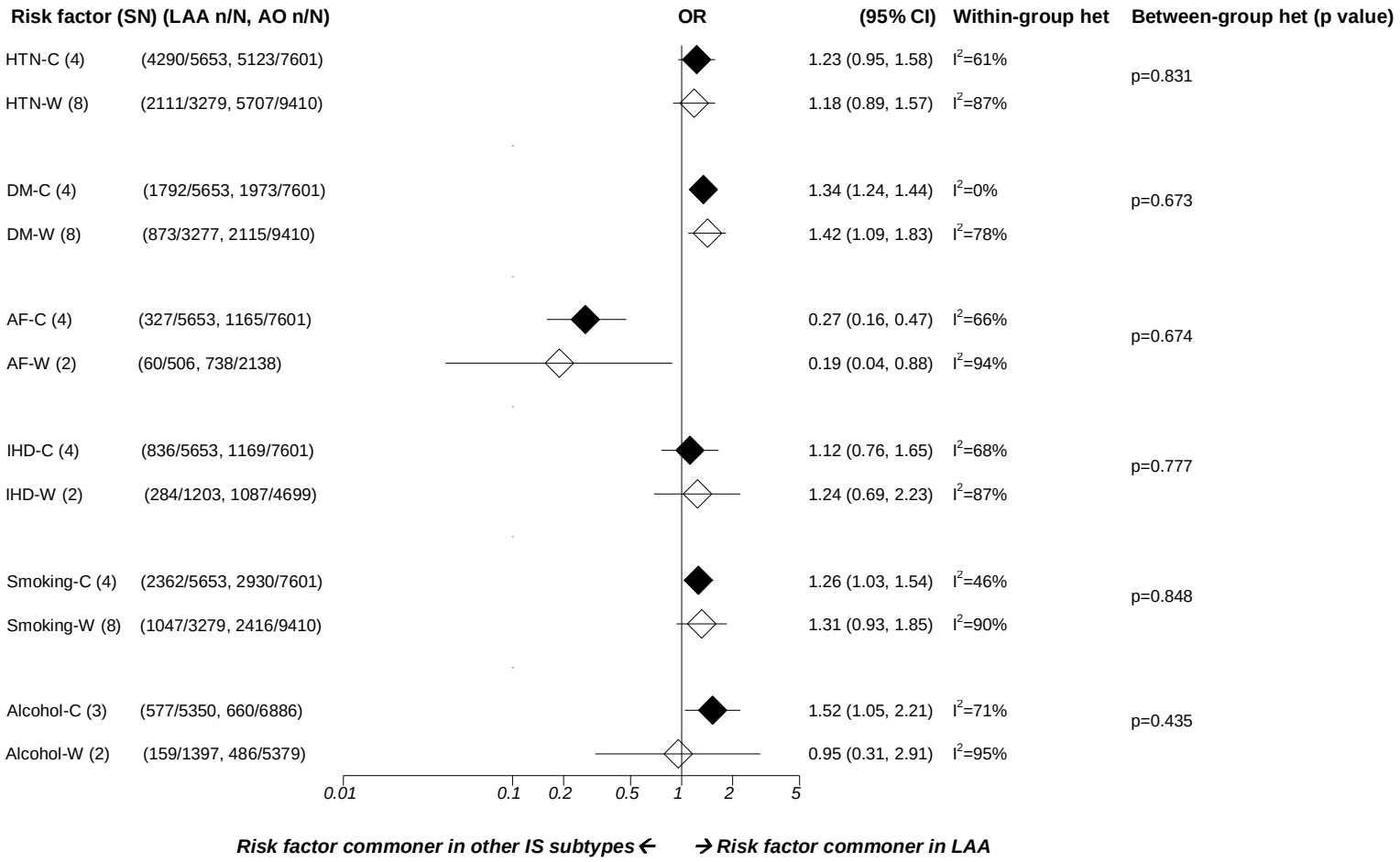
LAA=Large artery atherosclerosis; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.9 Meta-analysis of alcohol intake for LAA versus other ischaemic subtypes in Chinese and Whites.



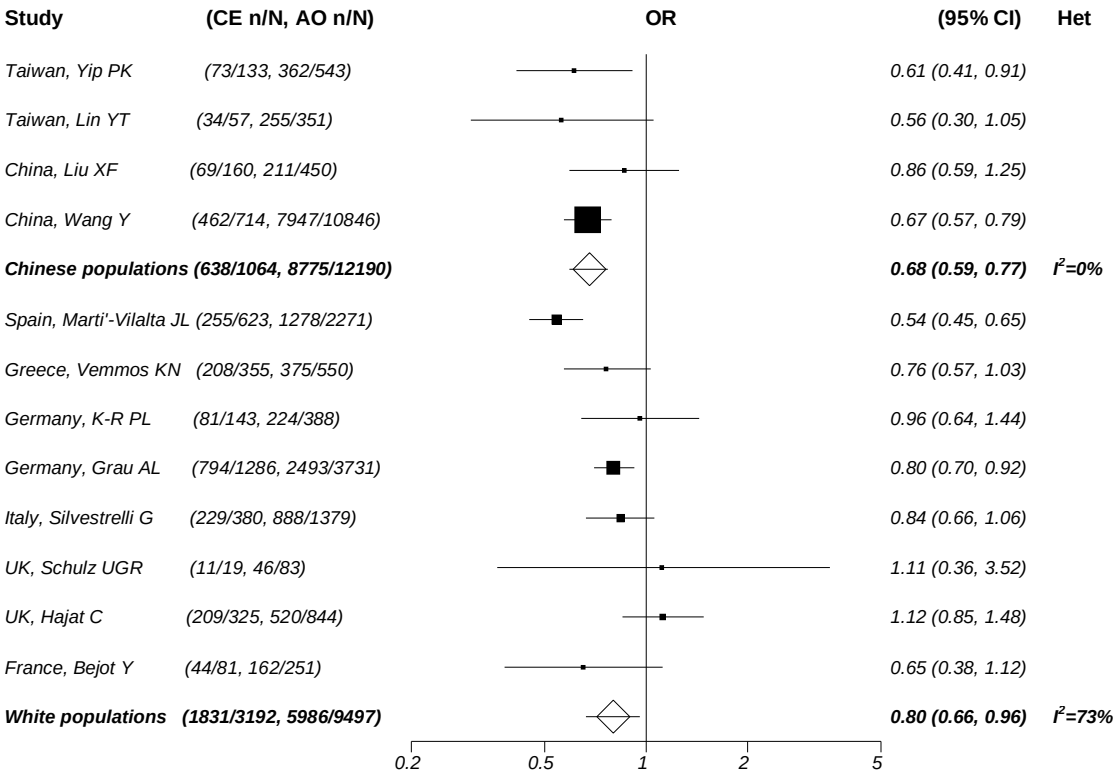
LAA=Large artery atherosclerosis; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.10 Summary of risk factor meta-analyses for LAA versus all others (TOAST) in Chinese and Whites.



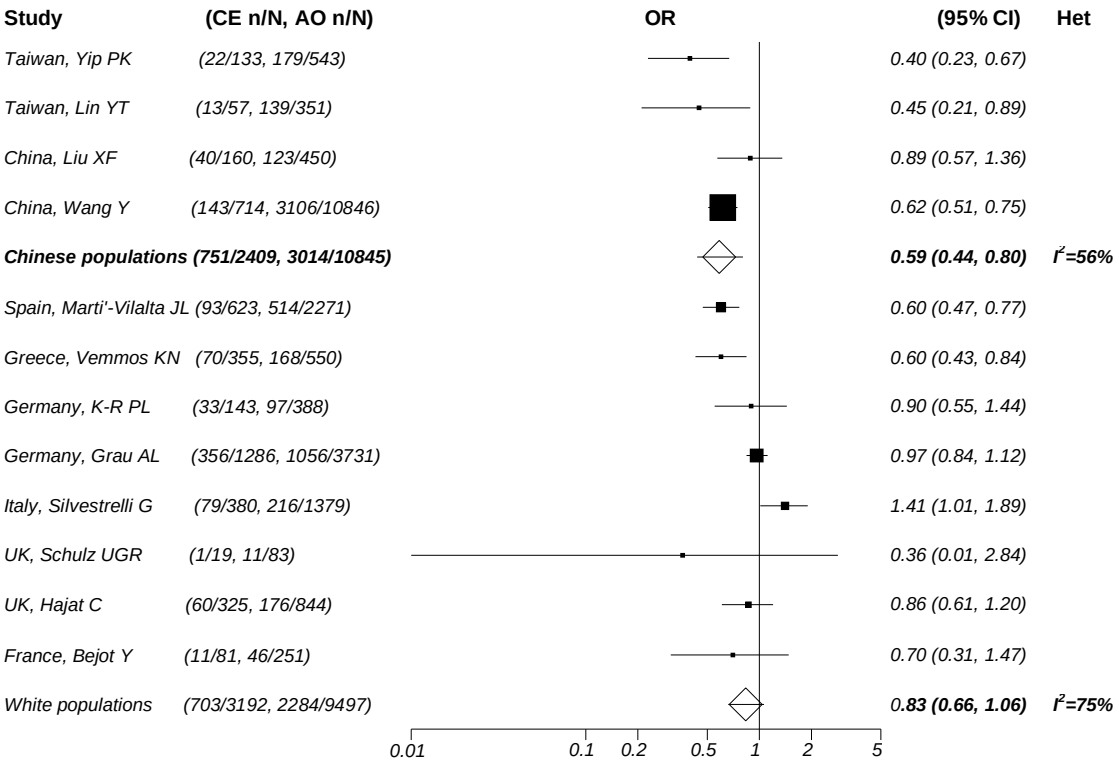
SN=study number; LAA=Large artery atherosclerosis; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; HTN=Hypertension; DM=Diabetes mellitus; AF=Atrial fibrillation; IHD=Ischaemic heart disease; C=Chinese; W=Whites; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.11 Meta-analysis of hypertension for CE versus other ischaemic subtypes in Chinese and Whites.



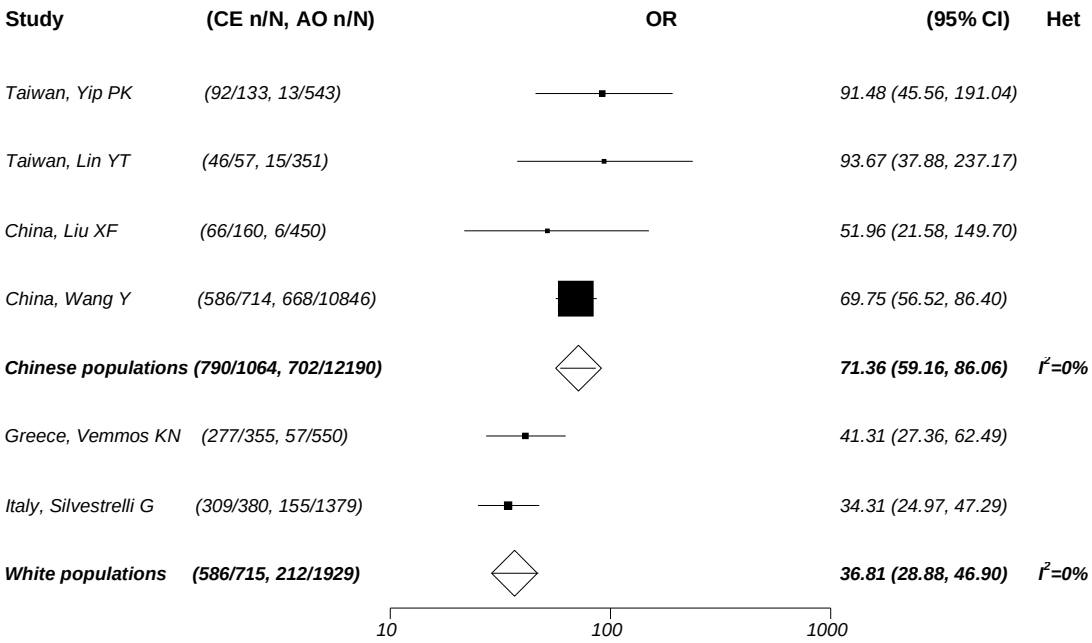
CE=cardioembolism; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.12 Meta-analysis of diabetes for CE versus other ischaemic subtypes in Chinese and Whites.



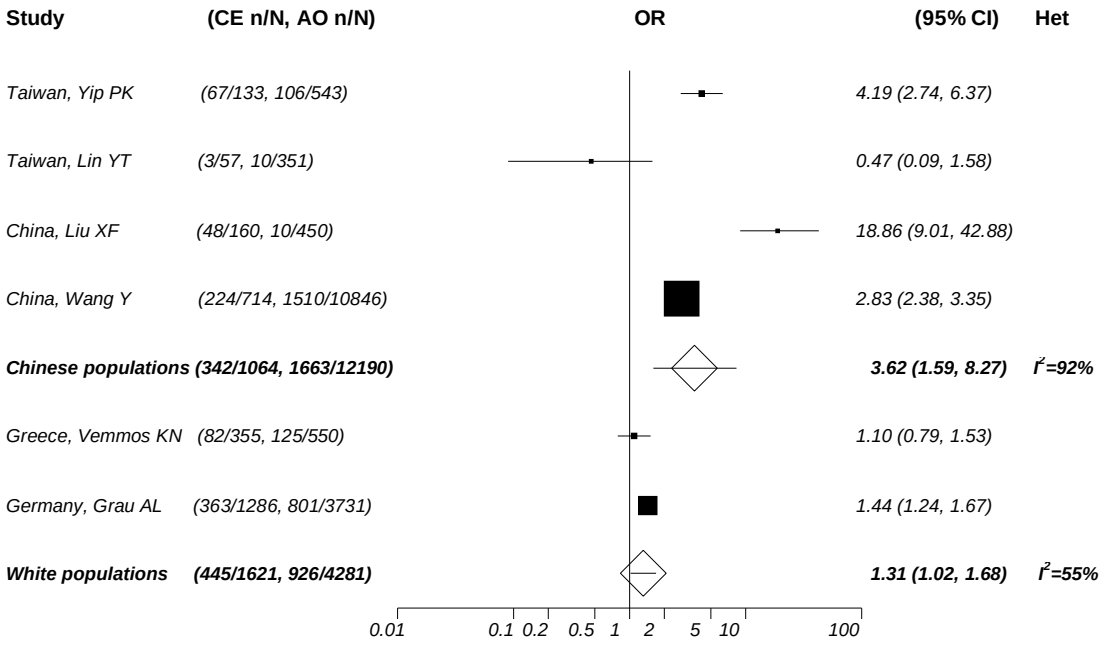
CE=cardioembolism; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.13 Meta-analysis of atrial fibrillation for CE versus other ischaemic subtypes in Chinese and Whites.



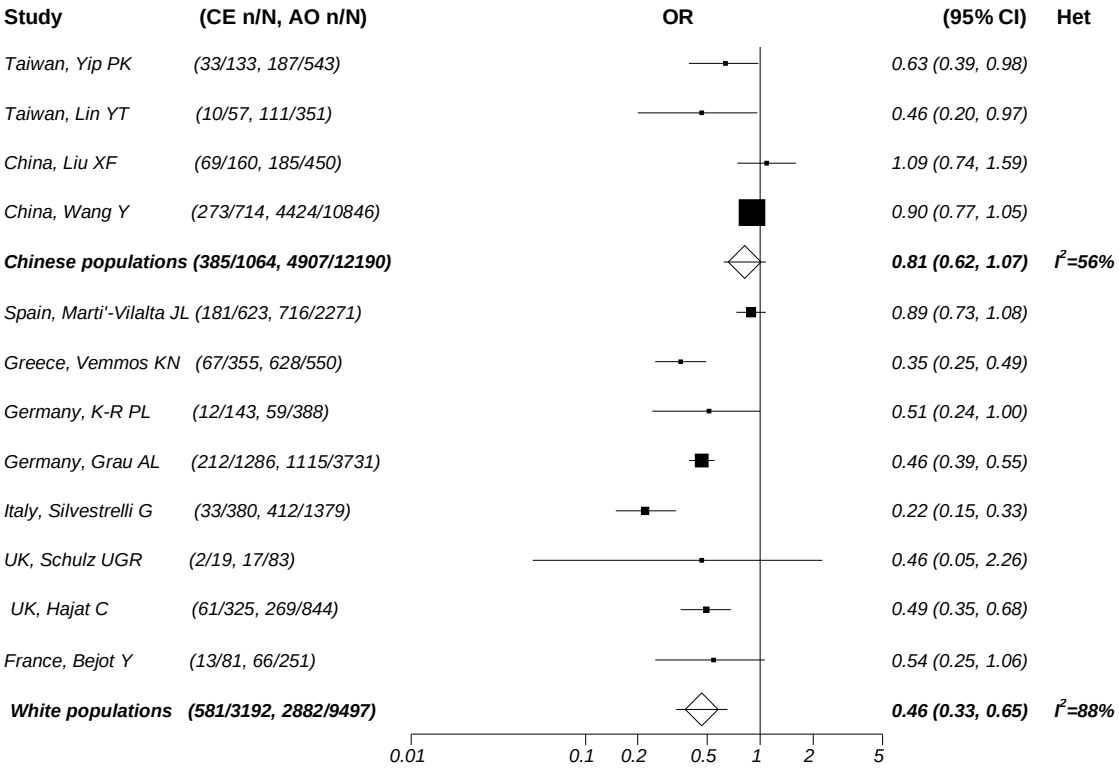
CE=cardioembolism; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.14 Meta-analysis of ischaemic heart disease for CE versus other ischaemic subtypes in Chinese and Whites.



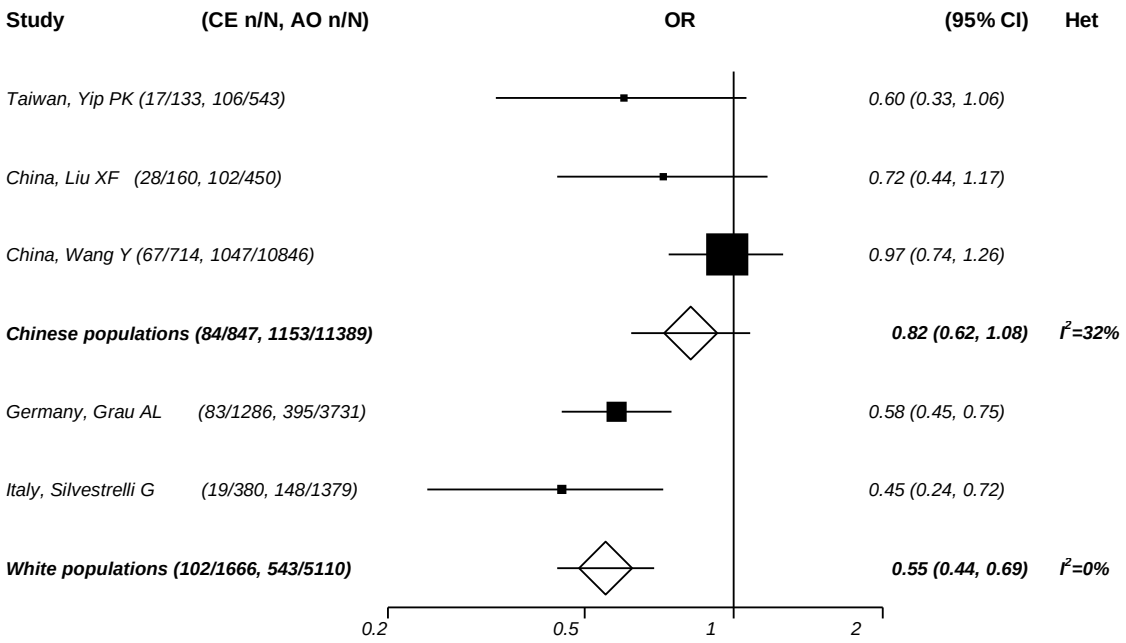
CE=cardioembolism; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.15 Meta-analysis of smoking for CE versus other ischaemic subtypes in Chinese and Whites.



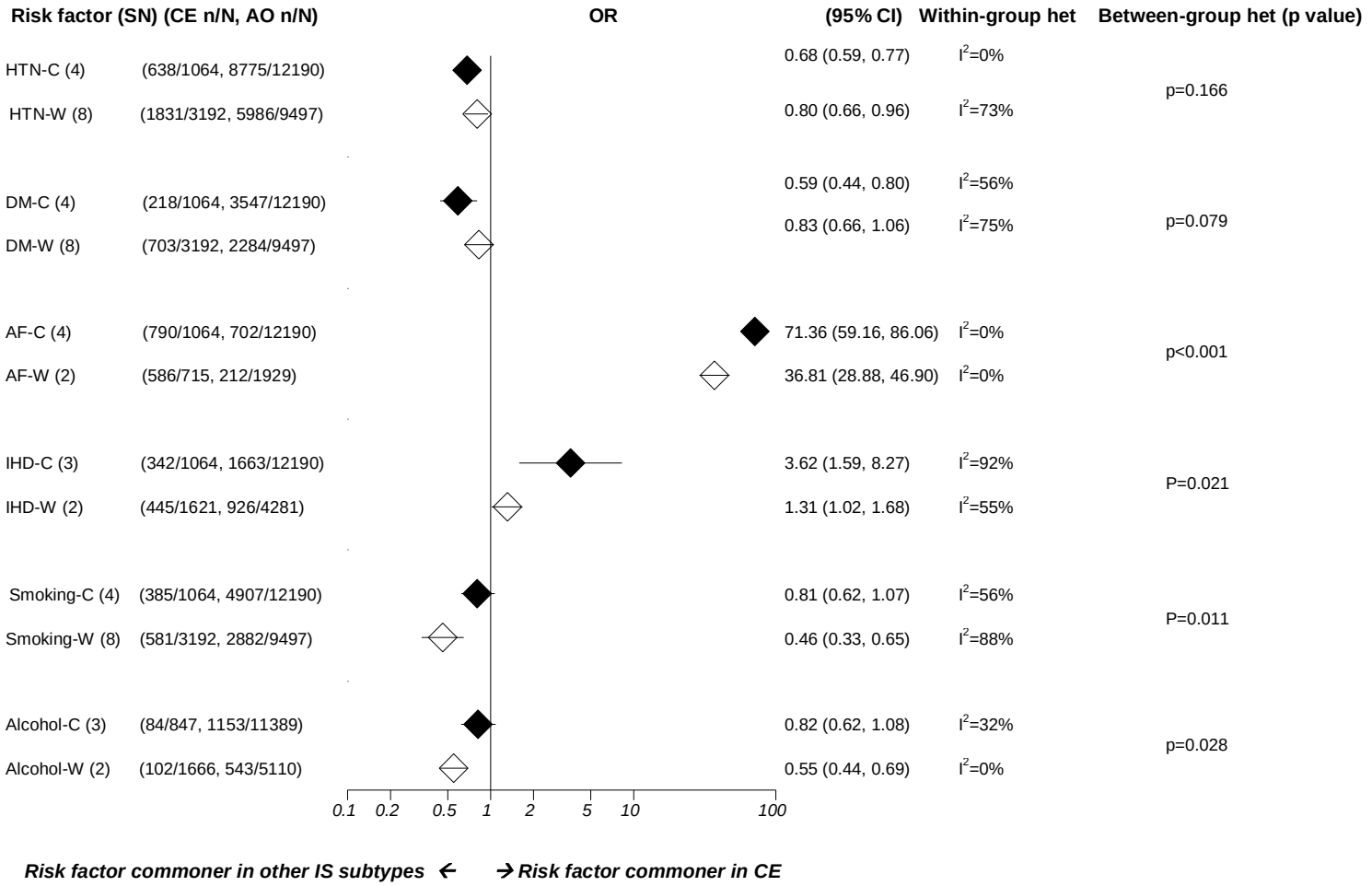
CE=cardioembolism; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.16 Meta-analysis of alcohol intake for CE versus other ischaemic subtypes in Chinese and Whites.



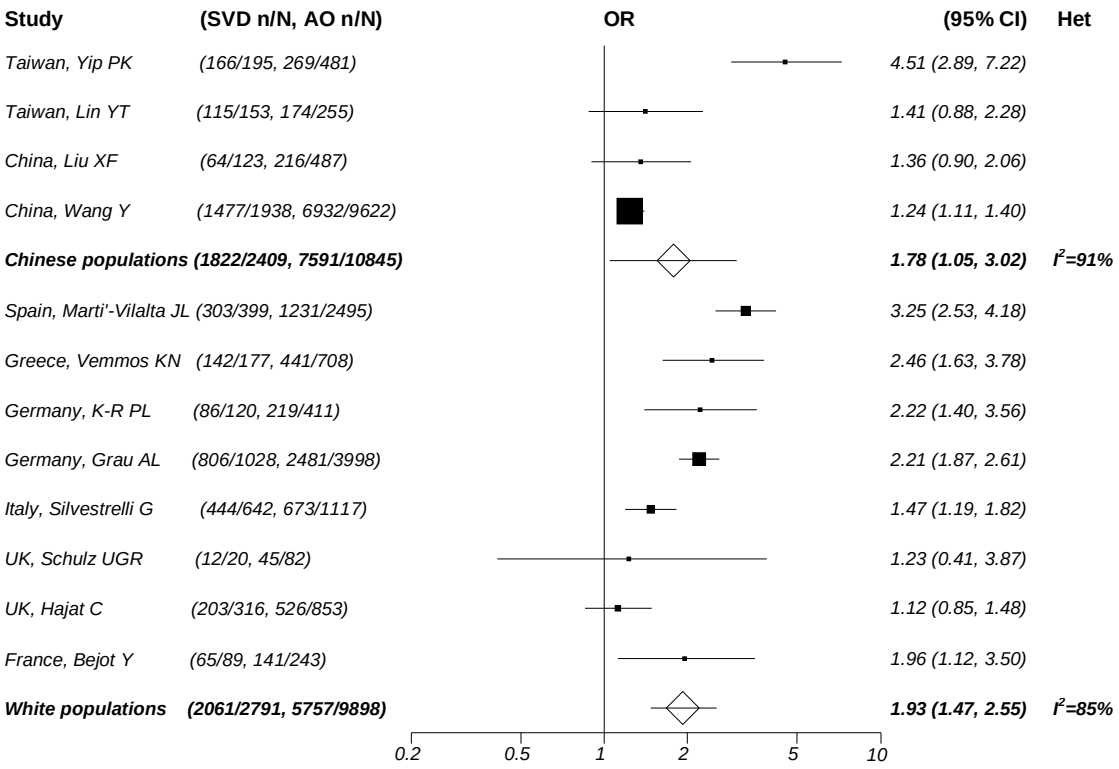
CE=cardioembolism; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.17 Summary of risk factor meta-analyses for CE versus all others (TOAST) in Chinese and Whites.



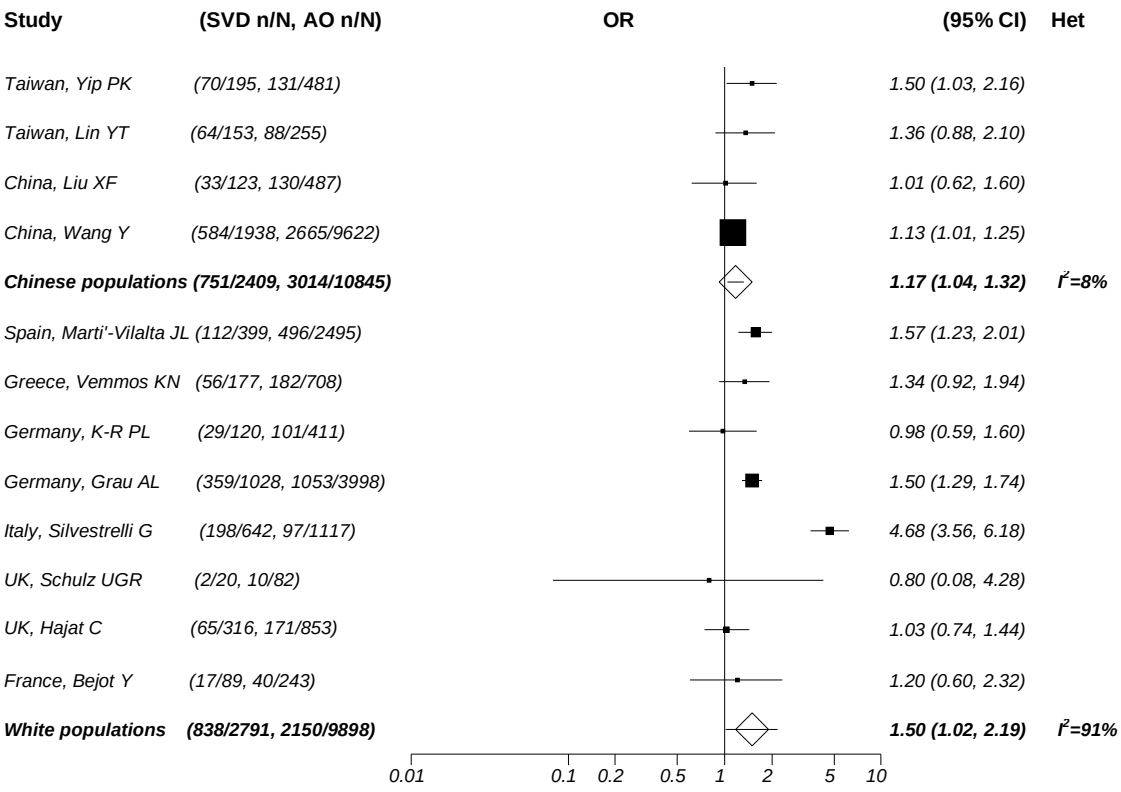
SN=study number; CE= cardioembolism; AO=Any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; HTN=Hypertension; DM=Diabetes mellitus; IHD=Ischaemic heart disease; C=Chinese; W=Whites; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.18 Meta-analysis of hypertension for SVD versus other ischaemic subtypes in Chinese and Whites.



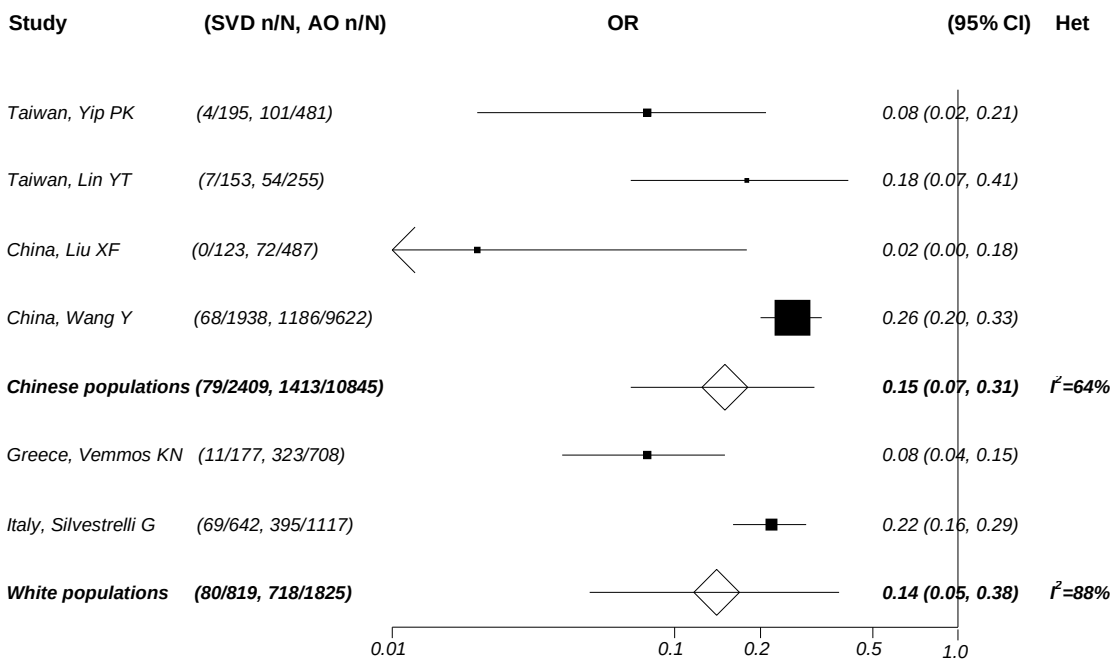
SVD=small vessel disease; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.19 Meta-analysis of diabetes for SVD versus other ischaemic subtypes in Chinese and Whites.



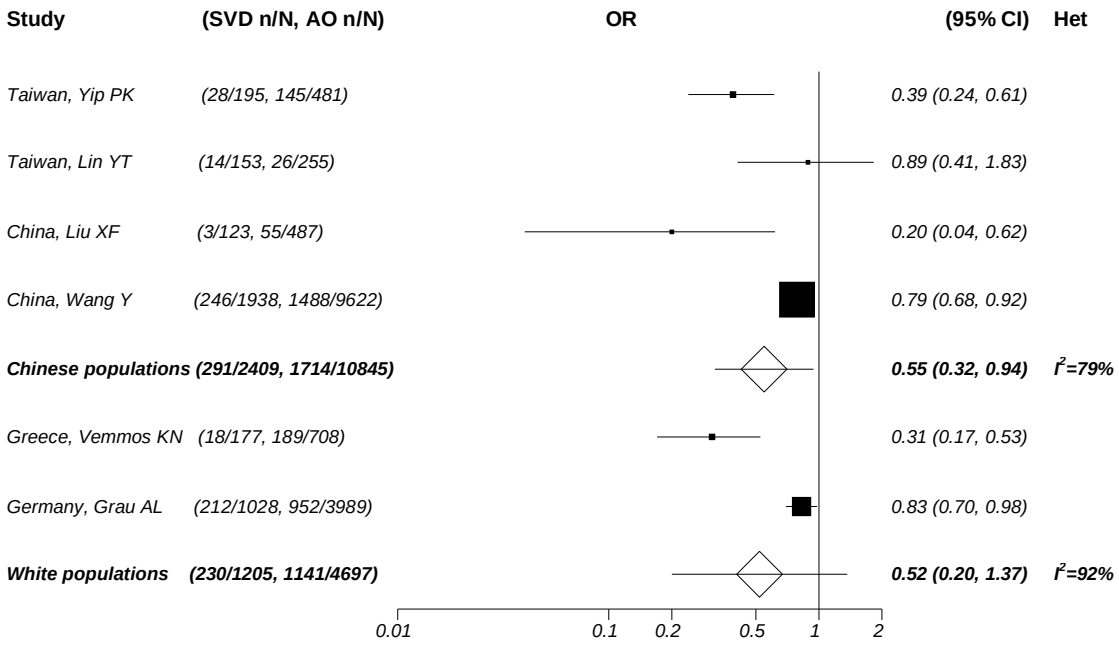
SVD=small vessel disease; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.20 Meta-analysis of atrial fibrillation for SVD versus other ischaemic subtypes in Chinese and Whites.



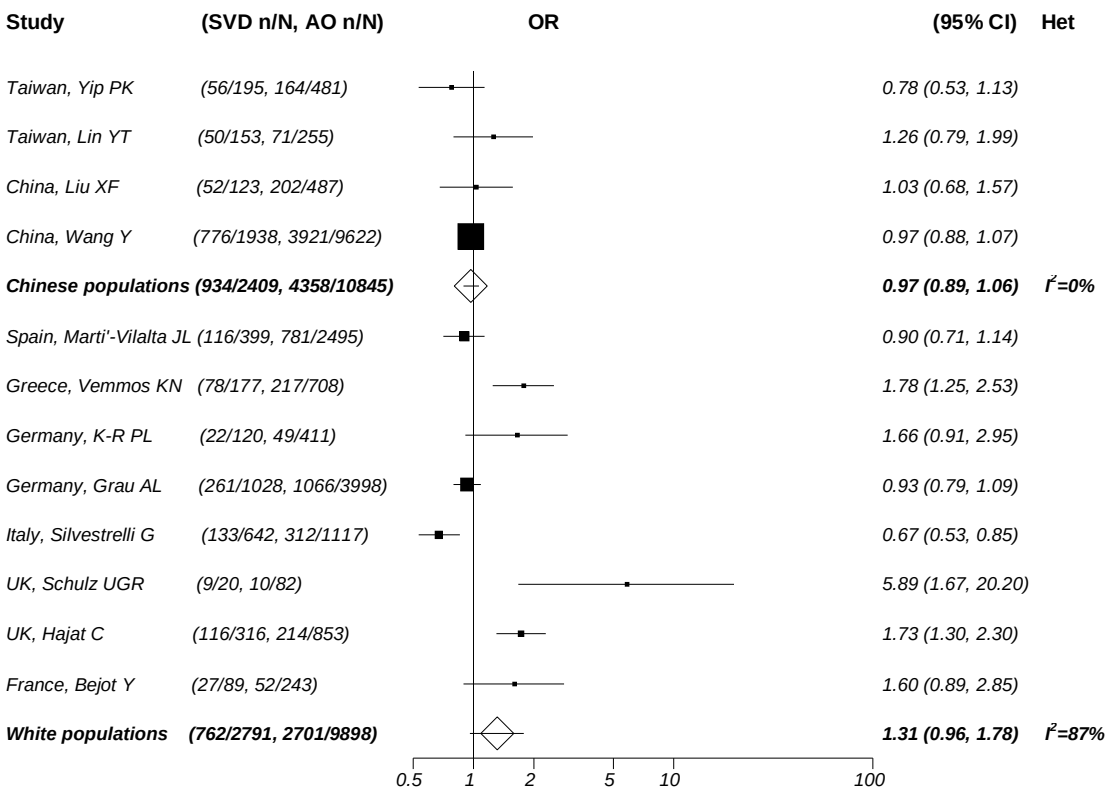
SVD=small vessel disease; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.21 Meta-analysis of ischaemic heart disease for SVD versus other ischaemic subtypes in Chinese and Whites.



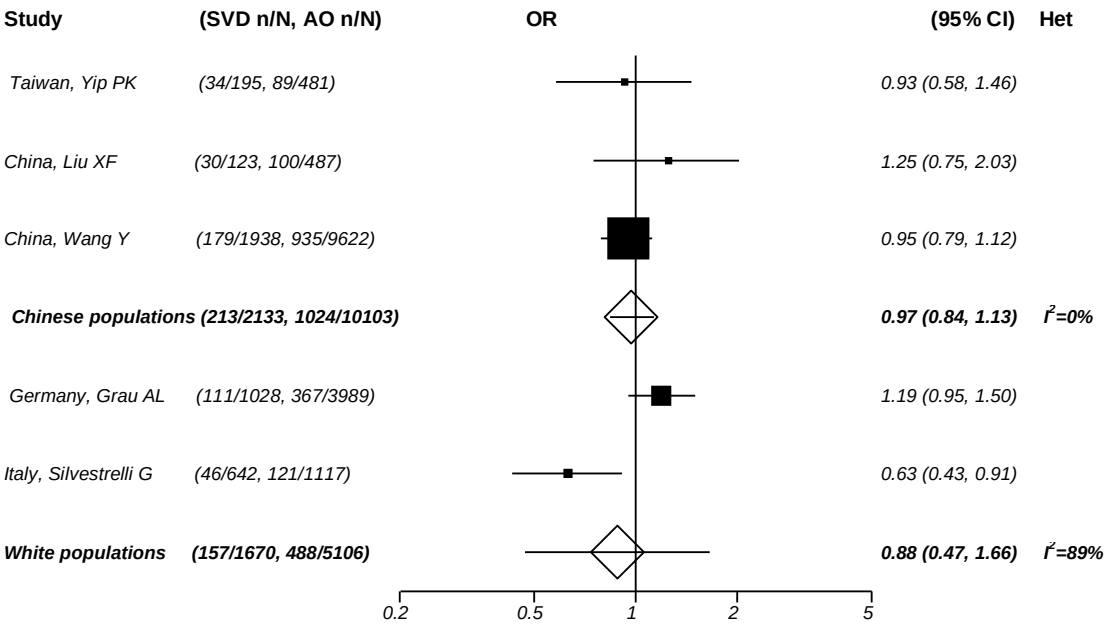
SVD=small vessel disease; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.22 Meta-analysis of smoking for SVD versus other ischaemic subtypes in Chinese and Whites.



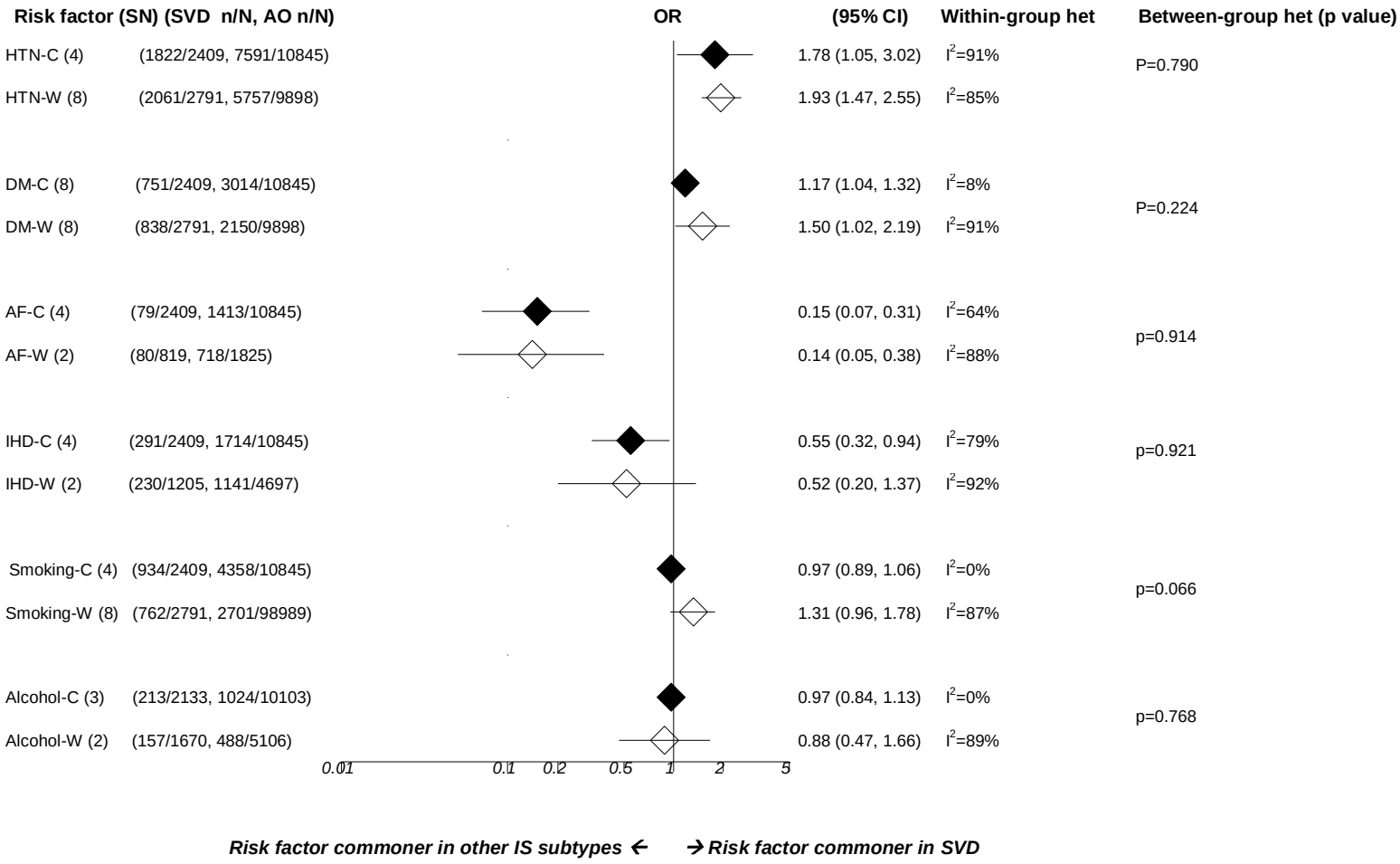
SVD=small vessel disease; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.23 Meta-analysis of alcohol intake for SVD versus other ischaemic subtypes in Chinese and Whites.



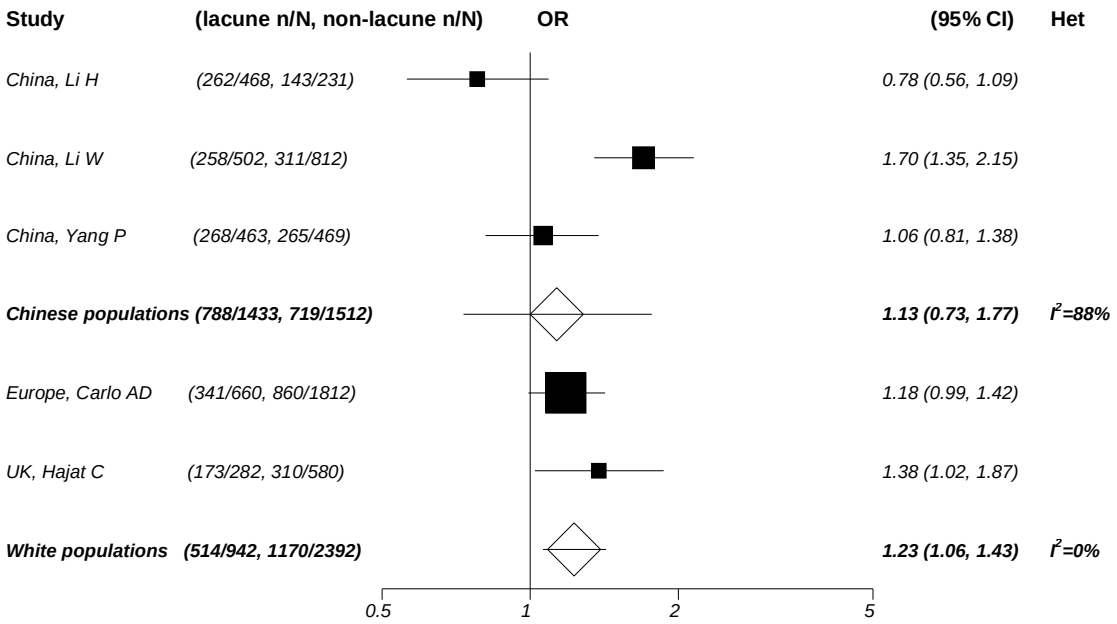
SVD=small vessel disease; AO=any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.24 Summary of risk factor meta-analyses for SVD versus all others (TOAST) in Chinese and Whites.



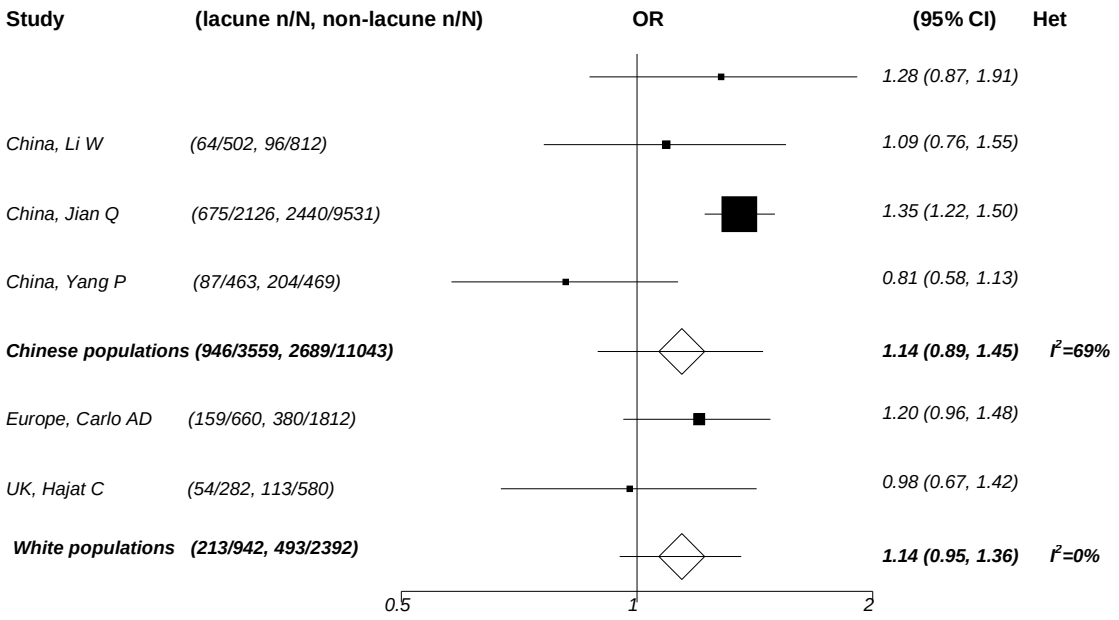
SN=study number; SVD= Small vessel disease; AO=Any other subtypes; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; HTN=Hypertension; DM=Diabetes mellitus; IHD=Ischaemic heart disease; C=Chinese; W=Whites; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.25 Meta-analysis of hypertension for lacunar versus non-lacunar infarcts in Chinese and Whites.



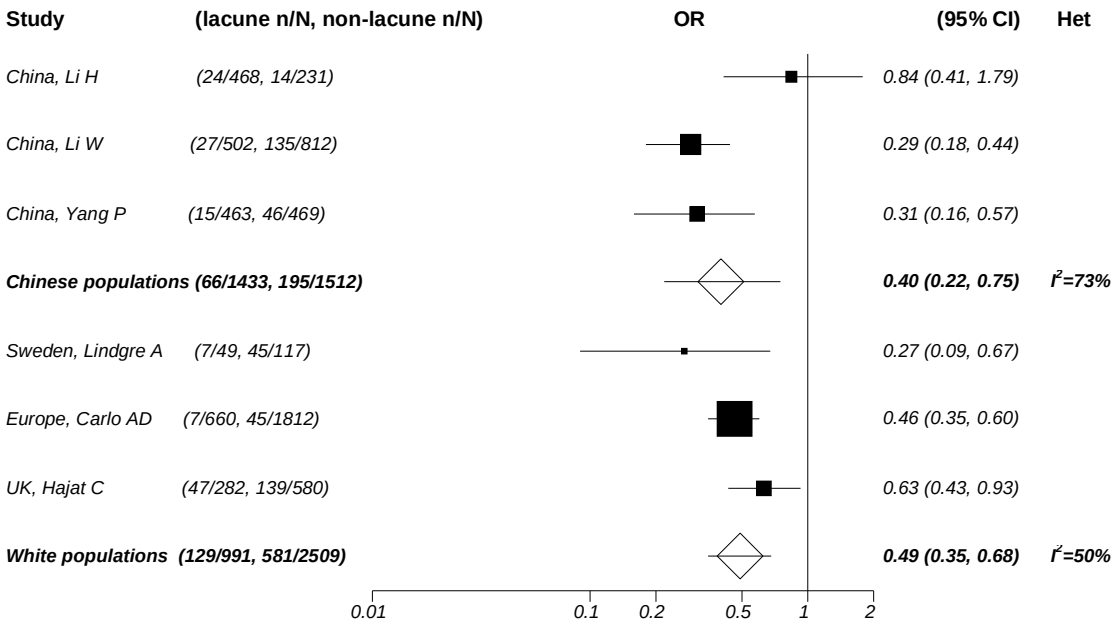
n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.26 Meta-analysis of diabetes for lacunar versus non-lacunar infarcts in Chinese and Whites.



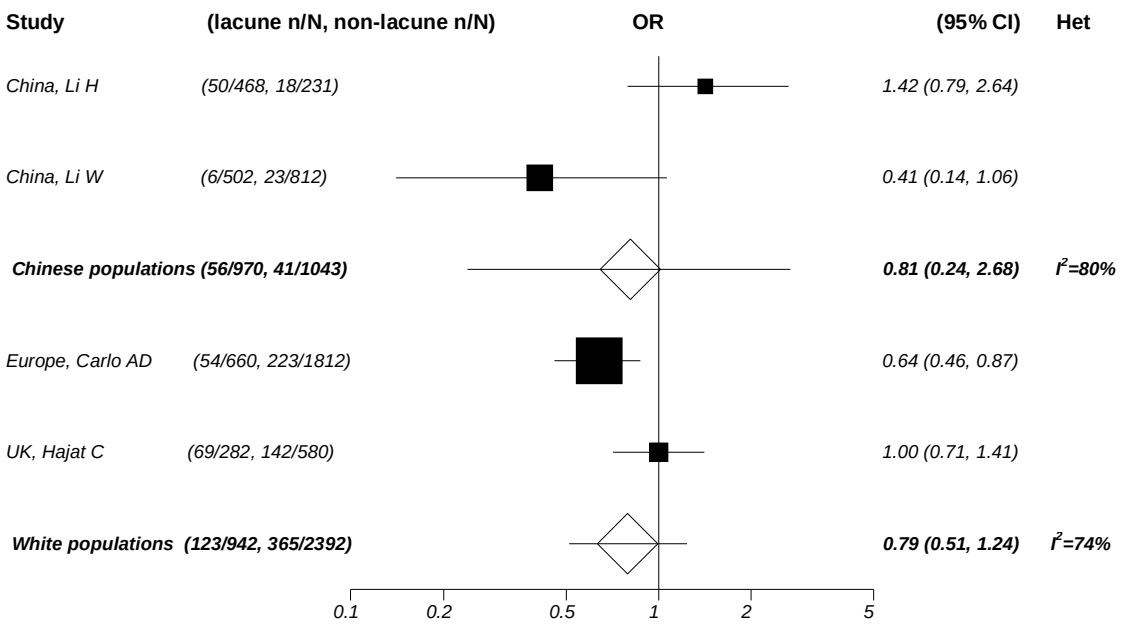
n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.27 Meta-analysis of atrial fibrillation for lacunar versus non-lacunar infarcts in Chinese and Whites.



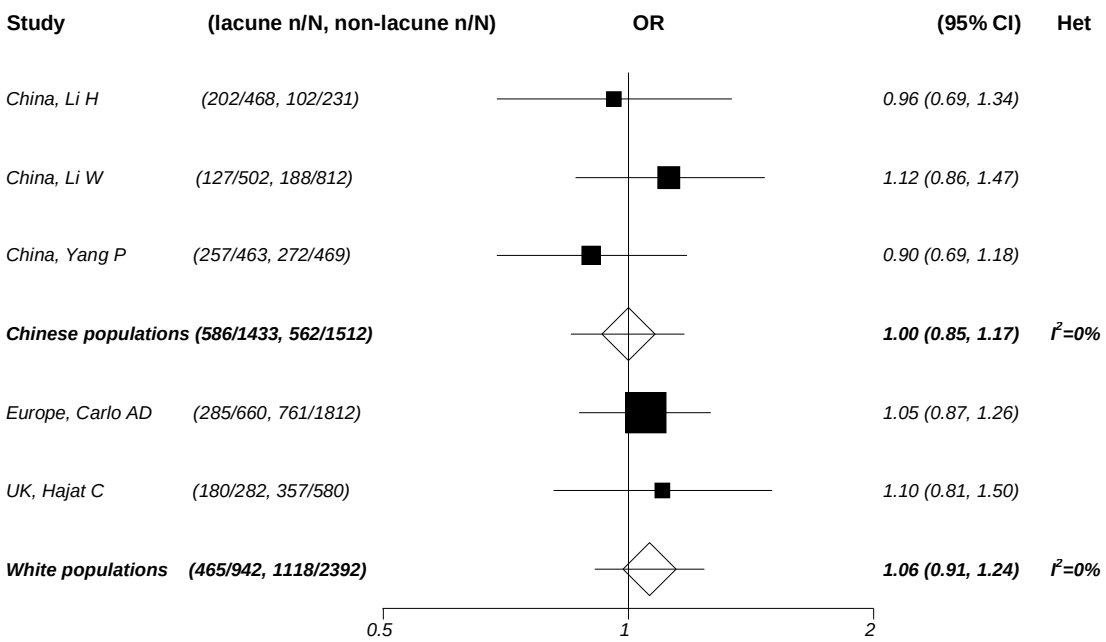
n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.28 Meta-analysis of ischaemic heart disease for lacunar versus non-lacunar infarcts in Chinese and Whites.



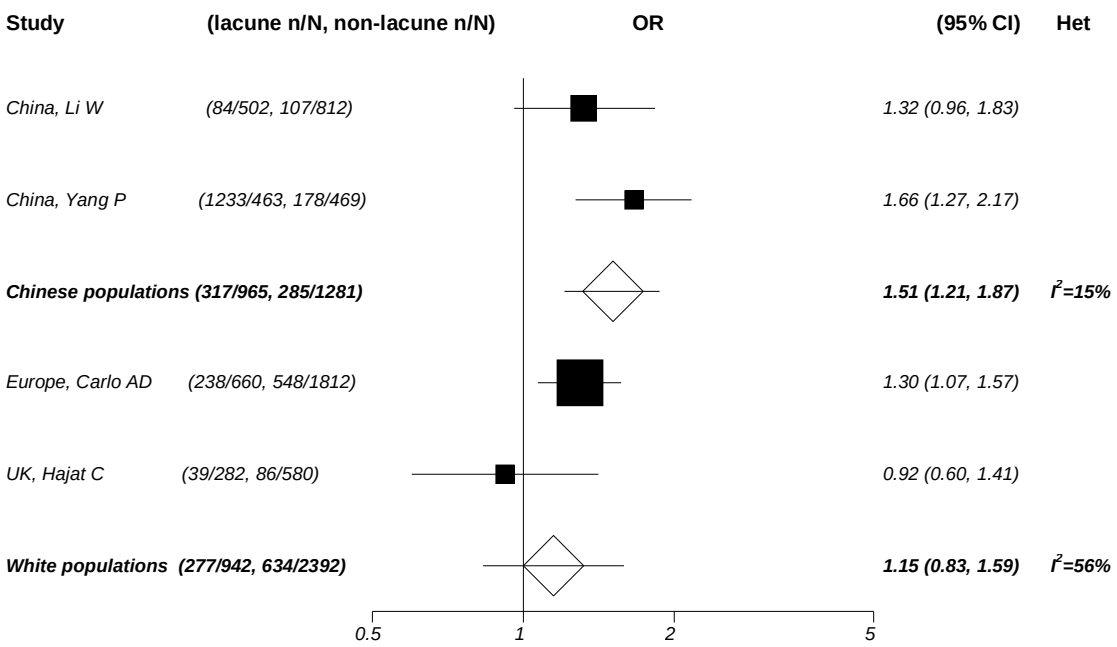
n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.29 Meta-analysis of smoking for lacunar versus non-lacunar infarcts in Chinese and Whites.



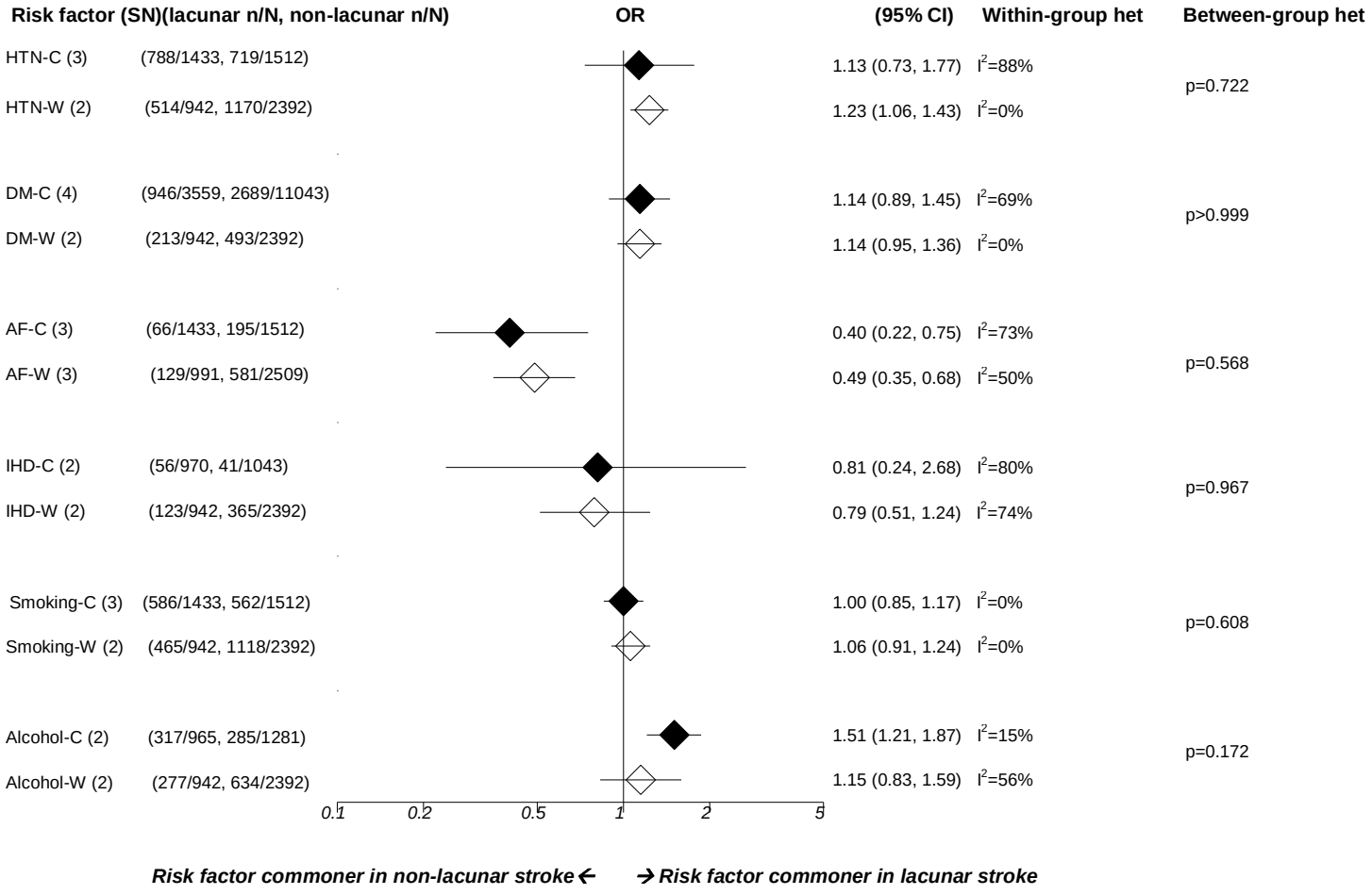
n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.30 Meta-analysis of alcohol intake for lacunar versus non-lacunar infarcts in Chinese and Whites.



n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 6.31 Summary of risk factor meta-analyses for lacunar versus non-lacunar (OCSP) in Chinese and Whites.



SN=study number; n=number of patients with risk factor; N=total number of patients; OR=odds ratio; CI=confidence interval; Het=heterogeneity; I=inconsistency; HTN=Hypertension; DM=Diabetes mellitus; IHD=Ischaemic heart disease; C=Chinese; W=Whites; Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Section D: Risk Factors in Chinese Populations – Individual Patient Analysis from National Taiwan University Hospital (NTUH) Stroke Registry 2006-2011

Chapter 7: Risk factor analyses for intracerebral haemorrhage versus ischaemic stroke in NTUH patients

7.1 Introduction

Intracerebral haemorrhage (ICH) is the most devastating pathological type of stroke, with a high case-fatality, and poor functional outcome (Balami et al. 2012; Ash et al. 2010). It accounts for 10-20% of total strokes in western populations, while the incidence and proportion of ICH are higher in eastern Asians (Feigin et al. 2009; Ash et al. 2010). Although knowledge of stroke, availability of brain imaging, and medical care have improved in the past two decades, the incidence and mortality of ICH have not decreased (Ash et al. 2010; Qureshi et al. 2009).

My systematic reviews in Chapter 3 reported that Chinese populations had a twofold higher proportion of ICH, and a lower proportion of ischaemic stroke (IS) among all strokes as compared with predominantly white populations (Tsai et al. 2013). My subsequent meta-analysis of vascular risk factors for ICH versus IS in Chapter 5 found hypertension and alcohol intake were significantly more frequent in ICH than IS in Chinese, but not in predominantly white populations. Nevertheless, these findings could be confounded by some factors such as age (mean age of onset was younger in Chinese for ICH versus IS, but similar in Whites), gender, other risk factors, and varying risk factor definitions.

To explore some of these issues further, I aimed to perform individual patient analyses of data from the National Taiwan University Hospital (NTUH) Stroke Registry in Chinese populations, comparing risk factor profiles between ICH and IS and adjusting for potential confounding factors. While Chinese make up the largest number of populations in the world, a better understanding of the reasons for a much higher proportion of ICH in Chinese could lead to a better realisation of the causes of ICH as well as efficient prevention strategies, and help to reduce the stroke burden in Chinese and around the world.

7.2 Methods

7.2.1 Subjects

The National Taiwan University Hospital (NTUH) Stroke Registry is a hospital-based registry in north Taiwan, prospectively recruiting consecutive acute stroke or transient ischaemic attack patients (TIA) arriving in the Emergency Department or being admitted to wards of Neurology, Neurosurgery, Internal Medicine, and Paediatrics. It was initiated in January 1995 and joined the national Taiwan Stroke Registry in 2006 to contribute to studies of risk factors, associations, clinical outcomes, and complications of stroke as well as its subtypes (Yip et al. 1997; Jeng et al. 1998; Hsieh et al. 2010; Lee et al. 2010; Chen et al. 2013; Hung et al. 2013). For inclusion, acute stroke or TIA patients were required to have onset within 10 days, with informed consent signed by the patients or family. In each consecutive patient, a neurologist assessed the patient and performed a neurological examination

soon after arrival, recorded demographic information and clinical symptoms and signs, reviewed medical records including previous medical history and vascular risk factors, arranged brain imaging [computed tomography (CT) immediately or further magnetic resonance imaging (MRI)] if necessary, and discussed the imaging findings with a neuroradiologist if needed. The Institutional Review Board of National Taiwan University Hospital approved the stroke registry. Since the causes and risk factors are quite different between childhood and adult stroke, in this study, I included first-ever or recurrent adult ICH and IS patients (aged 18 years or older) in NTUH stroke registry from 1 January 2006 to 31 December 2011.

7.2.2 Diagnosis of stroke and its types

The diagnosis of stroke was based on the clinical features - acute neurologic dysfunction of vascular origin with sudden (within seconds) or rapid (within hours) occurrence of symptoms and signs lasting for more than 24 hours, and brain CT or MRI findings (a corresponding lesion on brain imaging or no visible lesion) (Aho et al. 1980; Hatano et al. 1976). Strokes were classified as ischaemic stroke (IS), intracerebral haemorrhage (ICH), or subarachnoid haemorrhage (SAH) according to the standard definitions (Sudlow et al. 1997). Patients with old stroke and its complications, traumatic intracranial haemorrhage, subdural hematoma, no brain imaging or non-cerebrovascular causes for their clinical features were excluded.

7.2.3 Risk factor definitions

Vascular risk factors were collected through the included patients, family and medical records. Hence, hypertension as well diabetes was recorded based on history of hypertension or diabetes. Atrial fibrillation (AF) was defined as history of atrial fibrillation or evidence from electrocardiography. Ischaemic heart disease (IHD) was defined as history of angina or myocardial infarction. Hyperlipidaemia was recorded if patients had hypercholesterolaemia (>200 mg) or hypertriglyceridaemia (> 200 mg/dl). Smoking included current smoking for more than 10 cigarettes per day and previous smoking. Alcohol intake was defined as habitual drinking more than once per week. I also recorded previous stroke and history of TIA, defined as acute onset of transient focal neurological dysfunction lasting less than 24 hours.

7.2.4 Statistical analysis

For ICH versus IS, I used Student's t test to compare the mean age, and Pearson's chi-square test to compare the proportions of male gender, risk factors and 1 month case fatality between the groups. Since it was not assumed to contribute a linear change in odds of ICH versus IS, I divided age into five equal-sized categories. First, I calculated crude odds ratios (ORs) with 95% confidence intervals (CIs) for each risk factor. Then I fitted a logistic regression model for the relevant risk factor, adjusting for age categories and gender, obtaining adjusted ORs I. I developed a second logistic regression model to adjust simultaneously for all risk factors as well as age and gender. In the second model, I used stepwise selection and analysis of

variance to incorporate the strongly significant 2-way interactions among variables ($p<0.001$), and to choose the best fitting model. From the parameters of this model, I obtained adjusted ORs II.

In addition, I conducted subgroup analyses to examine risk factor associations with ICH versus IS in different subgroups if there was a strongly significant interaction among variables. All the statistical hypothesis tests were two-sided, and p values less than 0.05 were regarded as significant. Statistical analyses were performed with R statistical software (http://www.R-project.org/).

7.3 Results

7.3.1 Characteristics of ICH and IS patients

From 1 January 2006 to 31 December 2011, NTUH stroke registry consecutively recruited 6675 acute stroke and 300 TIA patients aged from 1 to 106 years. There were 4107 men and 2868 women. The response rate for the stroke registry in terms of the proportions of people providing informed consent was more than 90%. In the present study, I included first-ever or recurrent ICH or IS patients aged 18 years or older, including 1373 ICH patients and 4953 IS patients. For patients who had recurrent strokes during this period of time, I adopted the first stroke episodes. All these patients had brain CT imaging and 50% of them had further brain MRI and MR angiography.

Of these included ICH and IS patients in our study, ICH patients were younger than the IS group (mean age 61 years versus 68 years, $p<0.001$), while there was no significant difference in gender between the groups (males 62% in ICH and 59% in IS, $p=0.064$). ICH patients had a much higher 1 month case fatality than IS (19.3% versus 5.5%, $p<0.001$).

7.3.2 Risk factor comparisons for ICH versus IS

The clinical characteristics and risk factor distributions for ICH and IS are shown in Table 7.1. Generally, ICH patients had a lower prevalence of diabetes, AF, IHD, hyperlipidaemia, smoking, previous stroke and TIA than IS patients. Alcohol intake was slightly more common in ICH versus IS (crude OR 1.19, 95% CI 1.00 to 1.40), and so was hypertension though it did not differ significantly between two types of stroke (crude OR 1.01, 95% CI 0.87 to 1.17) (Figure 7.1). Nevertheless, the association with ICH versus IS became significantly higher in hypertension after adjusting for age and gender in the first logistic regression model (adjusted OR I 1.25, 95% CI 1.07 to 1.45), whereas the results of other risk factors remained in the same direction except that alcohol and previous stroke became statistically non-significant (alcohol adjusted OR I 0.98, 95% CI 0.82 to 1.17; previous stroke adjusted OR I 0.97, 95% CI 0.83-1.13).

In multiple logistic regression before incorporating interaction among variables, hypertension and alcohol intake were significantly associated with ICH in comparison to IS (hypertension adjusted OR II 1.60, 95% CI 1.42 to 1.95; alcohol

adjusted OR II 1.45, 95% CI 1.16 to 1.79), and the associations became stronger or stayed similar while incorporating strongly significant interactions in the second model (hypertension adjusted OR II 2.23, 95% CI 1.74 to 2.87; alcohol adjusted OR II 1.44, 95% CI 1.16 to 1.77; Figure 7.1). Fully adjusted analyses yielded similar results to unadjusted analyses in diabetes, AF, IHD, hyperlipidaemia, smoking and TIA, which were still negatively associated with ICH versus IS. Previous stroke remained of similar frequency in ICH and IS (adjusted OR II 1.04, 95% CI 0.89 to 1.22).

7.3.3 Subgroup analysis in patients of different ages

In the stepwise selection for the second logistic regression model, I found a strongly significant interaction between age and hypertension ($p<0.001$). There was a significant difference in the association across different age groups for hypertension, but not in other risk factors. Thus I carried out further subgroup analysis to examine the risk factor associations for ICH versus IS among five equal-sized age groups respectively (18-55 year, 56-64 year, 65-72 year, 73-80 year, and 81-106 year). Overall, the results were mostly qualitatively similar across the groups, but varied in size (Figure 7.2). Compared with older stroke patients, hypertension had a stronger association with ICH versus IS in younger stroke patients. The fully adjusted results showed that hypertension was significantly associated with ICH versus IS in patients of age 18-55 years (adjusted OR II 2.33, 95% CI 1.79-3.05), 56-64 years (adjusted OR II 2.33, 95% CI 1.58-3.48), and 65-72 years (adjusted OR II 1.84, 95% CI 1.22-

2.87). For patients aged 73 or beyond, the association with hypertension did not differ significantly between ICH and IS (age 73-80 adjusted OR II 0.81, 95% CI 0.56 to 1.18; age 81-106 adjusted OR II 0.96, 95% CI 0.63 to 1.50).

In terms of other risk factors, diabetes, AF, and hyperlipidaemia remained negatively associated with ICH versus IS in all age groups, whereas previous stroke stayed neutral between ICH and IS in every age group. IHD, smoking, alcohol and TIA had significant negative associations with ICH versus IS in some age groups but not in all (Figure 2). Statistically, there was no significant difference in association across different age groups in aforementioned risk factors.

7.4 Discussion

My results showed that ICH patients were relatively younger than IS patients, but there was no significant difference in gender between these two groups. Clinically, ICH patients had a higher 1 month case fatality than IS patients. In terms of risk factor comparisons between ICH and IS, unadjusted and adjusted analyses yielded qualitatively similar results, but varied in size of estimates and significance. Hypertension and alcohol intake both had positive associations with ICH than IS, whereas diabetes, AF, IHD, hyperlipidaemia, smoking and TIA were negatively associated with ICH versus IS. The positive association between hypertension and ICH versus IS became even more marked in younger stroke patients, and differed significantly across different age groups, with no clear association in older people (aged 73 years or beyond).

Although Chinese populations have higher age-adjusted ICH incidence and proportion than those in western countries (Chang et al. 1995; Jiang et al. 2006; Tsai et al. 2013), the data and analyses on risk factor comparisons to explore the possible reasons based on robust methods in relatively large numbers of patients are limited. Most information has been derived from studies on mainly white populations of European origins. My findings provide important information on the main risk factor differences for ICH compared with IS, which are consistent with the results from my previous meta-analyses in Chapter 5. After adjusting for possible confounders, hypertension and alcohol intake were independent risk factors for ICH as compared with IS in Chinese populations. Furthermore, they could be responsible – at least in part – for a higher proportion of ICH in Chinese as compared with predominantly white populations.

Few large scale studies in the literature and previous systematic reviews have directly compared risk factors between ICH and IS, in either Chinese or other populations in the world. An earlier systematic review from cohort and case-control studies in mainly white populations reported that risk factors for ICH were age, male sex, hypertension, and alcohol intake. In contrast, hypercholesterolaemia was associated with a lower risk or ICH (Ariesen et al. 2003). Recently, the INTERSTROKE study, a large international case-control study, conducted risk factor analyses for all stroke, IS and ICH among 3000 stroke cases and 3000 controls (O'Donnell et al. 2010). It enrolled stroke patients from 22 countries across low, middle and high income levels, and 38% from Southeast Asia (including Chinese). Of these included 3000 cases, 78% were IS and 22% were ICH. The study results

showed hypertension, smoking, waist-to-hip ratio, diet, and alcohol intake were significant risk factors for ICH. Hypertension was more strongly associated with ICH than IS, whereas the association with smoking appeared stronger with IS than ICH. However, risk factor associations for IS and ICH were not provided specifically for Chinese populations.

There is plenty of evidence showing that hypertension is one of the most important risk factors for ICH (O'Donnell et al. 2010; Ariesen et al. 2003; Takebayashi et al. 1983). In addition, existing evidence suggests that of ICH the association with hypertension probably differs among ethnic groups. Previous research and meta-analyses of data from Asia Pacific Cohort Studies among predominantly eastern Asians (including Chinese, Japanese, Korean and Thailand populations) and among predominantly white populations of European origin suggested a stronger association of increased blood pressure with haemorrhagic stroke among eastern Asians than white populations (Eastern Stroke and Coronary Heart Disease Collaborative Research Group. 1998; Woodward et al. Asia Pacific Cohort Studies Collaboration. 2005). Another meta-analysis comparing the effect of hypertension on stroke between Chinese and Caucasians from both cohort and case-control studies also reported a significantly stronger association with hypertension in Chinese than Caucasians, particularly on haemorrhagic stroke (Zhang et al. 2006). However, these studies were conducted for all haemorrhagic strokes, including both ICH and subarachnoid haemorrhage together though most of these events were likely due to ICH. No separate analysis for ICH was reported. My systematic reviews in Chapters 2 and 3 as well as my following meta-analysis in Chapter 5 showed that Chinese had

a higher incidence of total stroke, a higher proportion of ICH, and hypertension had a stronger association with ICH versus IS as compared with predominantly white populations. The individual patient data analysis presented here further confirms hypertension is a stronger, independent risk factor for ICH versus IS in Chinese after controlling for age, sex and other risk factors.

The reasons for a higher incidence of total stroke and ICH, and the greater association with hypertension for ICH in Chinese populations have not been fully understood. It is probably at least in part related to the preference of dietary intake with high salt, inadequate treatment of hypertension, and a higher proportion of deep ICH in Chinese populations (predominantly associated with hypertension) (Wang et al. 2012; Woo et al. 2002). Chinese people prefer to have high dietary intake of sodium. In the INTERMAP study among British, American, Japanese and Chinese populations, Chinese were found to have the highest daily sodium intake (as measured by 24-hour urinary collection), which was known to related to high blood pressure and to increase risk of stroke (Zhou et al. 2003, Zhao et al. 2004; He et al. 1999). Although the prevalence of hypertension in Chinese is similar to most white populations, the proportion of awareness, treatment and control rates are quite low (Gu et al. 2002; Su et al. 2008; Falaschetti et al. 2009; Wolf-Maier et al. 2003). From a recent study conducted in mainland China, only 45% were aware of high blood pressure, 28% took antihypertensive medication, and 8% achieved control target (<140/90mm Hg) (Gu et al. 2002). In Taiwan, despite improvements in awareness, treatment, and control rate after the implementation of the National Health Insurance system, the proportion of treatment and control are still relatively low, particularly in

younger stroke patients aged less than 65 years (Su et al. 2008). Thus, reduced dietary sodium intake and effective treatment of hypertension are supposed to have greater benefit of reducing incidence of ICH in Chinese populations.

In term of lipids, increased total cholesterol is associated with the risk of IS, but not haemorrhagic stroke in both Asian and white populations of European origin (Zhang et al. Asia Pacific Cohort Studies Collaboration. 2003). There seems to be a positive association of increasing cholesterol with IS and a negative association with haemorrhagic stroke. Furthermore, low total cholesterol and high blood pressure have been reported to have synergistic interaction on the risks of haemorrhagic stroke in Japanese (Suzuki et al. 2011). Apart from cholesterol, recent research has shown that low serum triglyceride is associated with increased risk of ICH though the exact mechanism to ICH is still unclear (Wieberdink et al. 2011). In my study, hyperlipidaemia was indeed significantly less frequent in ICH as compared with IS. No significant interaction was found between hyperlipidaemia and hypertension or other risk factors. Nevertheless, data on cholesterol and triglyceride were not available for me to do analyses of each of these separately. Further study of individual lipid components and the associations with ICH and IS may provide deeper insights in this field.

Despite the fact that effects of alcohol may be mediated through blood pressure due to its documented blood pressure elevating effect (Yoshita et al. 2005), in my study, alcohol intake was still a significant independent risk factor for ICH as compared with IS regardless of age, sex, hypertension, or other risk factors. The risk caused by alcohol appears to differ among types of stroke. Previous meta-analyses have shown

that alcohol has a dose-dependent relationship with haemorrhagic stroke, whereas it has a curvilinear relationship with IS - a protective effect for low to moderate intake and increased risk for high consumption (Renolds et al. 2003; Patra et al. 2010). Although the definitions of alcohol intake are different across the studies in meta-analyses and ICH and subarachnoid haemorrhage are not analysed separately in the latest review, there is still increasing evidence that risk of ICH increases with increasing alcohol intake, while for IS, modest alcohol intake (1-30 drinks per month) is protective, but heavier alcohol intake still increases risk (O'Donnell et al. 2010). The varying relationships of risk caused by alcohol are probably because of different mechanisms of different types of stroke. As alcohol intake becomes more common in Chinese populations due to westernisation of lifestyles, it may have further increasing impact on stroke since excessive alcohol intake is an established risk factor for both haemorrhagic and ischaemic strokes.

7.4.1 Strength and limitations

The current analyses provide important information on risk factor comparisons for ICH versus IS in Chinese populations, in whom there is a relatively higher stroke incidence, along with a much higher proportion of ICH and a lower proportion of IS among all strokes as compared with predominantly white populations. My study has several strengths. First, NTUH Stroke Registry is a well-established stroke registry, prospectively and systematically recruiting consecutive acute stroke patients since 1995 with comprehensive records of essential information including risk factors. My

analyses benefited from large numbers of patients and included recent data up to 2011. Second, the inclusion of acute stroke patients was based on a standard definition of stroke, having stroke onset within 10 days with timely brain imaging, early specialist assessment, and reliable classification of its pathological types (since the brain CT or MRI performance rate was 100% in this registry). Third, I used multiple logistic regression model to adjust for possible confounding factors including age, sex and other risk factors, and incorporated 2-way interactions among these variables. Furthermore, I carried out subgroup analyses to examine hypertension association with ICH versus IS in different age groups.

Nevertheless, I have to acknowledge several limitations. First, the registry is a hospital-based stroke registry, whereas an ideal study population is supposed to be community-based, including all stroke patients in a geographical area, irrespective of hospital admission rate (Sudlow et al. 1996; Feigin et al. 2004). Prevalence of risk factors and stroke subtypes may have some differences between hospitalized and non-hospitalized patients (Schulz et al. 2003). Second, risk factors in our study were collected through the patients, family and medical records prior to stroke occurrence. Though most included patients had available medical records before stroke, I could not totally exclude the possibility of recall bias from a few patients without records. In addition, the risk factor status was dichotomized, not continuously measured, making it impossible to assess the severity or the shape of association of risk factors with stroke types. Finally, although all included patients had brain CT imaging, only around 50% of them had brain MRI. The limited access to MRI precludes assessment of brain microbleeds.

7.4.2 Conclusion

In spite of a decreasing trend of ICH incidence in Chinese populations, there is still a relatively higher stroke incidence as well as a much higher proportion of ICH in all strokes as compared with white populations (Jiang et al. 2006; Tsai et al. 2013 in Chapter 3). Similar findings are also noted in other eastern Asians (Asch et al. 2010; Burke et al. 2006). ICH is a multifactorial disease caused by several risk factors and interactions. Here I report that hypertension and alcohol intake are independent risk factors for ICH versus IS regardless of age, sex, or other risk factors in a Chinese population in Taiwan, whereas diabetes, atrial fibrillation, IHD, hyperlipidaemia, smoking and TIA are negatively associated with ICH versus IS. Furthermore, the positive association with hypertension is stronger in younger stroke patients. The findings from my study and other research suggest that better treatment of hypertension as well as decreasing alcohol intake should have a great benefit to reducing ICH burden in Chinese populations.

Table

Table 7.1 Study characteristics and risk factor distributions in patients with ICH and IS in NTUH Stroke Registry, 2006-2011.

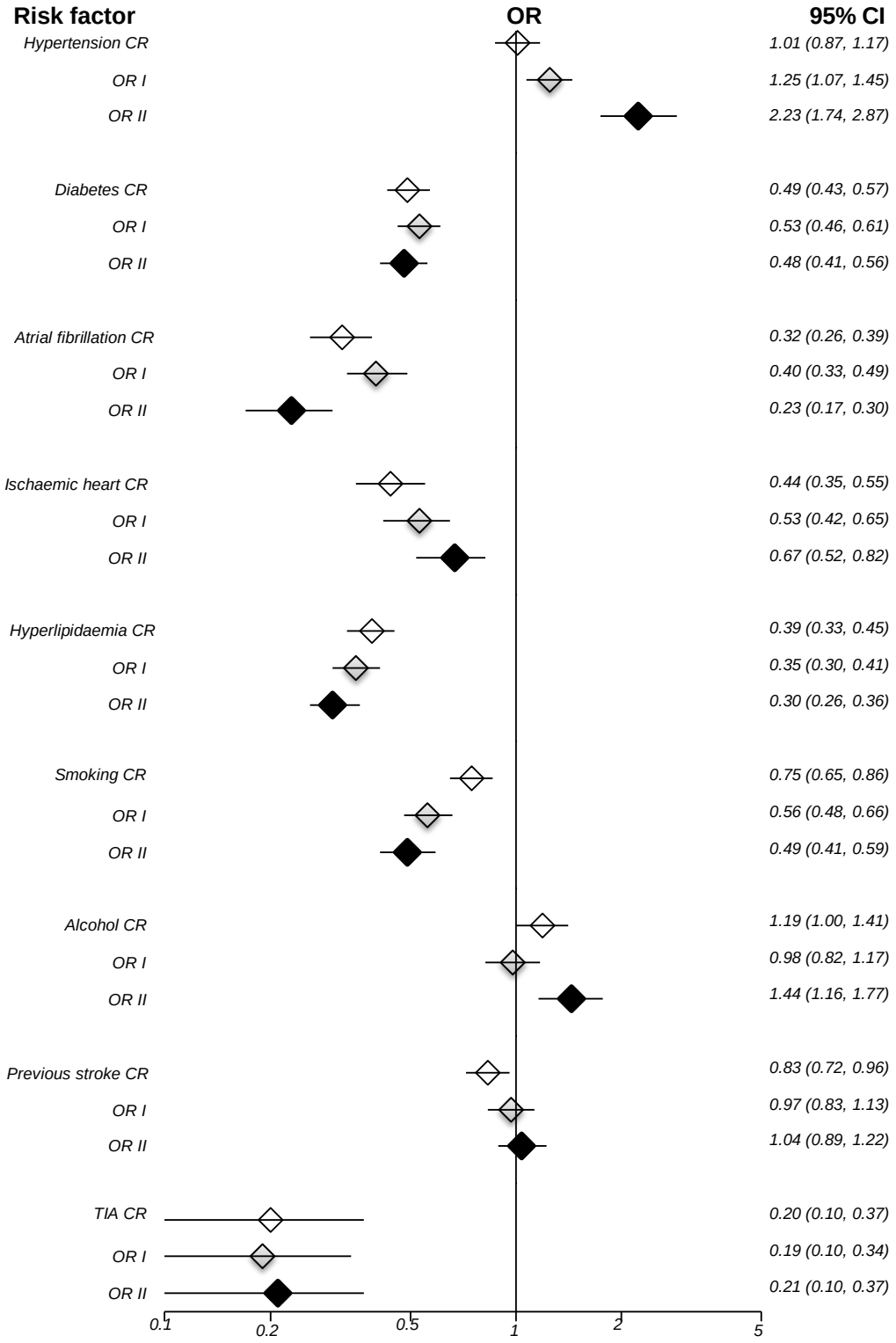
	ICH (N=1373)			**IS** (N=4953)			**ICH versus IS (P value)**
Mean Age in years (±SD)	61.4 (±15.7)			68.1 (±13.8)			P<0.001**
	N	(%)	(95% CI)	N	(%)	(95% CI)	
Gender (male)	850	61.9%	59.2-64.5%	2929	59.1%	57.8-60.5%	P=0.064*
Hypertension	1058	77.1%	74.7-79.2%	3809	76.9%	75.7-78.7%	P=0.904*
Diabetes	310	22.6%	20.4-24.9%	1838	37.1%	35.8-38.4%	P<0.001*
Atrial fibrillation	125	9.1%	7.6-10.8%	1180	23.8%	22.6-25.0%	P<0.001*
Ischaemic heart disease	102	7.4%	6.1-8.9%	759	15.3%	14.3-16.4%	P<0.001*
Hyperlipidemia	238	17.3%	15.3-19.4%	1744	35.2%	33.9-36.6%	P<0.001*
Smoking	327	23.8%	21.6-26.1%	1455	29.4%	28.1-30.7%	P<0.001*
Alcohol intake	221	16.1%	14.2-18.1%	689	13.9%	13.0-14.9%	P=0.041*
Previous stroke	282	20.5%	18.4-22.8%	1175	23.7%	22.5-24.9%	P=0.013*
TIA	11	0.8%	0.4-1.4%	193	3.9%	3.4-4.5%	P<0.001*
1 month case fatality	265	19.3%	17.2-21.5%	272	5.5%	4.9-6.2%	P<0.001*

ICH=intracerebral haemorrhage; IS=ischaemic stroke; NTUH=National Taiwan University Hospital; N=number; CI=confidence interval; SD=standard deviation; TIA=transient ischaemic attack.

** based on Student's t test; * based on Pearson's chi-square test.

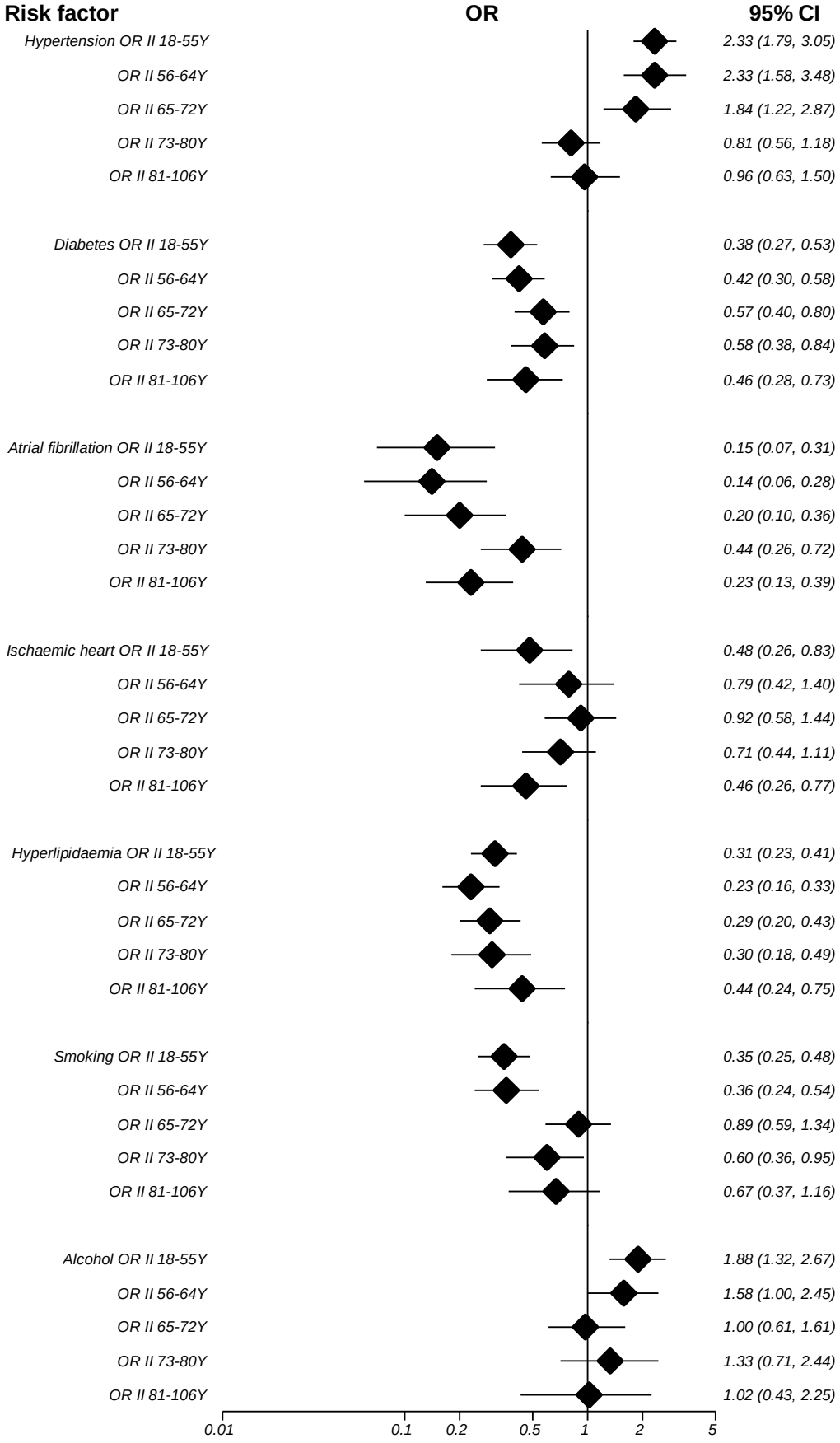
Figures

Figure 7.1 Risk factor analyses for ICH versus IS



OR=odds ratio; CR=crude odds ratio; OR I=adjusted odds ratio I (adjusting for age and gender); OR II=adjusted odds ratio II (adjusting for age, and gender and risk factors and incorporating the strong interaction); TIA=transient ischaemic attack; CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 7.2 Subgroup analyses of all risk factors for ICH versus IS in different age groups



OR II=adjusted odds ratio II (adjusting for gender and risk factors); Y=years; CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Chapter 8: Risk factors analyses for ischaemic stroke subtypes in NTUH patients

8.1 Introduction

Stroke is a heavy burden on Chinese populations (Liu et al. 2011). In Chapters 2 and 4, I reported that Chinese stroke patients have younger age of onset, a higher stroke incidence, and may also have different distributions of ischaemic stroke (IS) subtypes - a higher proportion of small vessel disease stroke (SVD) and a lower proportion of cardioembolism stroke (CE) compared with predominantly white populations (Tsai et al. 2013). Yet questions such as what might cause the differences remain unanswered. In Chapter 6, my risk factor meta-analyses in IS further showed that Chinese IS patients had a similar proportion of hypertension, diabetes, smoking and alcohol, and a lower prevalence of atrial fibrillation (AF), ischaemic heart disease (IHD) and hypercholesterolaemia compared with Whites. Associations of risk factors with individual IS subtypes were qualitatively similar (although different in size) in Chinese and predominantly white populations. Compared with other IS subtypes: large artery atherosclerosis (LAA) strokes were associated with diabetes; CE strokes were associated with AF and IHD; SVD (or lacunar) strokes were associated with hypertension and diabetes. However, these findings could be possibly confounded by some factors such as age, gender, other risk factors, incomplete information and variable definitions of some risk factors. In

addition, they may be driven by the risk factor dependent nature of the TOAST classification scheme.

To overcome the potential confounding effects, in the present study, I aimed to perform further analyses of individual patient data from the National Taiwan University Hospital (NTUH) Stroke Registry in Chinese populations. I evaluated the risk factor distributions in overall IS, compared the risk factor associations with each main IS subtype versus other subtypes using the Trial of Org 10172 in Acute Ischaemic Stroke (TOAST, a classification system incorporating risk factor in its definition) or the Oxfordshire Community Stroke Project (OCSP, a risk factor free classification system) classification, and adjusted for potential confounders (Adams et al. 1993; Bamford et al. 1991).

8.2 Methods

8.2.1 Subjects

In the present study, I obtained data from the National Taiwan University Hospital (NTUH) Stroke Registry, which was established in January 1995 and joined the national Taiwan Stroke Registry in 2006 to study the risk factors, associations, clinical outcomes, and complications of stroke and its subtypes (Yip et al. 1997; Jeng et al. 1998; Hsieh et al. 2010; Lee et al. 2010; Chen et al. 2013; Hung et al. 2013). It prospectively recruited consecutive acute stroke or transient ischaemic attack patients (TIA) patients arriving in the Emergency Department or being admitted to wards. For

inclusion, acute stroke or TIA patients were required to have onset within 10 days. Informed consents were signed by the patients or family. For each patient, a neurologist assessed the patient and performed neurological examinations upon arrival, recorded demographic information and clinical presentations, reviewed medical records including previous medical history and vascular risk factors, arranged brain imaging study [computed tomography (CT) or magnetic resonance imaging (MRI)] immediately, and discussed the imaging findings with a neuroradiologist if needed. The stroke registry was approved by the NTUH Institutional Review Board. Since the causes and risk factors are quite different between childhood and adult IS, in the present study, I included first-ever or recurrent adult IS patients aged 18 years or older from 1 January 2006 to 31 December 2011.

8.2.2 Diagnosis of ischaemic stroke and its subtypes

The diagnosis of IS was based on the clinical features - acute neurologic dysfunction of vascular origin lasting for more than 24 hours, and brain CT or MRI findings (a corresponding ischaemic lesion on brain imaging or no visible lesion) (Aho et al. 1980; Hatano et al. 1976). IS was classified into five aetiological subtypes (LAA, CE, SVD, other determined aetiology, and undetermined aetiology) according to the TOAST classification, or into the four anatomical subtypes of the OCSP classification scheme - lacunar infarct (LACI), total anterior circulation infarct (TACI), partial anterior circulation infarct (PACI), and posterior circulation infarct

(POCI) (Adams et al. 1993; Bamford et al. 1991). Patients with old stroke and its complications, intracranial haemorrhage, subarachnoid haemorrhage, subdural hematoma, no brain imaging or non-cerebrovascular causes for their clinical features were excluded.

8.2.3 Risk factor definitions

Vascular risk factors were collected through the included patients, family and medical records. Hence, hypertension as well diabetes was recorded based on history of hypertension or diabetes. Atrial fibrillation (AF) was defined as history of atrial fibrillation or evidence from an electrocardiography. Ischaemic heart disease (IHD) was defined as history of angina or myocardial infarction. Hyperlipidaemia was recorded if patients had hypercholesterolaemia (>200 mg) or hypertriglyceridaemia (> 200 mg/dl). Smoking included current smoking for more than 10 cigarettes per day and previous smoking. Alcohol intake was defined as habitual drinking more than once per week. I also recorded previous stroke and history of TIA, defined as acute onset of transient focal neurological dysfunction lasting less than 24 hours.

8.2.4 Statistical analysis

For IS subtypes, I used analysis of variance (ANOVA) to compare the mean age, and Pearson's chi-square test to compare the proportions of male gender and risk factors

among IS subtypes. Since it was not assumed to contribute a linear change in odds of each IS subtype versus other subtypes, I divided age into five equal-sized categories. First, I calculated proportions of risk factors in each IS subtype, and computed crude odds ratio (OR) with 95% confidence intervals (CIs) for LAA versus other subtypes, SVD versus other subtypes, and CE versus other subtypes for each risk factor in the TOAST classification. Then I fitted a logistic regression model for the relevant risk factor, adjusting for age categories and gender, obtaining adjusted ORs I. I developed a second logistic regression model to adjust simultaneously for all risk factors as well as age and gender. In the second model, I used stepwise selection and analysis of variance to incorporate the strongly significant 2-way interactions among variables ($p<0.001$), and to choose the best fitting model. From the parameters of this model, I obtained adjusted ORs II. IS subtypes using the OCSP classification were categorized into lacunar infarct (LACI) and non-lacunar infarct (NLAC) groups. I used the same method to obtain crude ORs, adjusted ORs I and II with 95% CIs for LACI versus NLAC.

In the IS subtypes using the TOAST classification, I did not include AF in the second logistic regression model since IS patients with the presence of AF were most likely assigned to CE subtype, irrespective of other risk factors and investigation results. If there was a strongly significant interaction among variables, I conducted further subgroup analysis to exam risk factor associations in different groups. All the statistical hypothesis tests are two-sided, and p values less than 0.05 were regarded as significant. Statistical analyses were performed with R statistical software (http://www.R-project.org/).

8.3 Results

8.3.1 Characteristics of overall IS patients

A total of 6675 acute stroke and 300 TIA patients were consecutively recruited into NTUH stroke registry from 1 January 2006 to 31 December 2011. The response rate for the stroke registry in terms of the proportions of people providing informed consent was more than 90%. Of these acute stroke patients, I included 4953 first-ever and recurrent IS patients aged 18 or older into current study. For patients who had recurrent strokes during this period of time, I adopted first stroke episodes. All registered patients had brain CT imaging and electrocardiography upon arrival. Around 80% of them had carotid duplex examination and 60% had further MR angiography to assess extracranial and intracranial vascular abnormality. The mean age of IS patients was 68.1 years (SD=13.8 years), and 59% of them were men. The clinical characteristics and risk factor distributions in overall IS patients are shown in Table 8.1. Generally, the prevalence of hypertension, diabetes, AF, and hyperlipidaemia in this study based in Taiwan was significantly higher, while the prevalence of smoking was significantly was lower than the pooled results in my risk factor meta-analysis for IS (Chapter 6) for all Chinese populations (nearly 90% from mainland China).

8.3.2 Risk factors for IS subtypes in the TOAST classifications

In the TOAST classifications, SVD was the most common IS subtype (27.5%), followed by CE (24.3%), undetermined (22.1%), LAA (21.0%), and other determined aetiology (5.0%) (Table 8.2). There were significant differences in age distributions among IS subtypes ($p<0.001$). CE subtype was the oldest stroke group (mean age 72.5 ± 13.2 years), while the subtype of other determined etiology had the youngest stroke patients (mean age 48.4 ± 14.4 years). LAA had the highest proportion of men (66.7%), whereas CE possessed the lowest proportion of men (51.9%). Distributions for the proportions of male gender and all vascular risk factors were significantly different among IS subtypes (Table 8.2).

Compared with other IS subtypes, LAA was associated with all risk factors studied, including hypertension, diabetes, IHD, hyperlipidaemia, smoking, alcohol intake, previous stroke and TIA (Figure 8.1). After controlling for age, gender and all risk factors, the results remained very similar except that IHD, smoking and alcohol did not differ significantly between groups. Among these significant risk factors, hypertension, diabetes, and TIA were the three leading risk factors with positive associations. The fully adjusted OR for hypertension was 1.94 (95% CI 1.59 to 2.38), for diabetes was 1.52 (95% CI 1.32 to 1.75), and for TIA was 1.72 (95% CI 1.24 to 2.36). There was no strongly significant interaction among variables.

CE subtype was positively associated with age and IHD in comparison with other IS subtypes in fully adjusted analyses (Figure 8.2). There was a strongly significant

interaction between IHD and age ($p<0.001$), and the association seemed to increase with younger age for CE versus others (Figure 8.3). While incorporating this interaction, the fully adjusted OR for IHD was 6.74 (95% CI 4.16 to 10.87). In contrast, CE was negatively associated with male gender, diabetes, hyperlipidaemia and smoking, whereas fully adjusted analyses did not show significant difference in alcohol, previous stroke and TIA between CE versus other subtypes.

In SVD versus other subtypes, unadjusted analyses showed positive associations with hypertension, diabetes, and hyperlipidaemia, and borderline associations with male gender and smoking (Figure 8.4). Strongly significant interactions were found between age and hypertension, and between hypertension and diabetes ($p<0.001$, Figures 8.5 to 8.7). While incorporating these interactions in the second multiple logistic regression model, the associations with hypertension and diabetes became much stronger. The fully adjusted OR for hypertension was 4.84 (95% CI 3.39 to 7.03), and for diabetes was 2.65 (95% CI 1.92 to 3.65). In contrast, SVD had a negative association with IHD (adjusted OR II 0.32, 95% CI 0.25 to 0.40), and a borderline negative association with previous stroke (adjusted OR II 0.83, 95% CI 0.71 to 0.97). There was no significant difference in smoking, alcohol, and TIA between SVD and others subtypes.

8.3.3 Risk factors for IS subtypes in the OCSP classifications

In IS subtype analyses using the OCSP classification, ANOVA showed significant differences of age distributions across subtypes ($p<0.001$) (Table 8.3). The mean age

of stroke onset was oldest in TACI subtype (69.6 ± 15.0 years), and youngest in POCI subtype (66.7 ± 13.9 years). POCI had the highest proportion of men (62.9%), whereas TACI possessed the lowest proportion of men (50.7%). There were significant differences in the distributions of proportions in male gender and all vascular risk factors except TIA.

In comparison to NLAC, LACI was positively associated with hypertension (adjusted OR II 4.58, 95% CI 3.16 to 6.75), diabetes (adjusted OR II 2.40, 95% CI 1.71 to 3.37) and hyperlipidaemia (adjusted OR II 1.55, 95% CI 1.34 to 1.79), while negatively associated with AF (adjusted OR II 0.10, 95% CI 0.07 to 0.13) and IHD (adjusted OR II 0.42, 95% CI 0.33 to 0.54) in fully adjusted analyses (Figure 8.8). Similar to the results for TOAST SVD versus other subtypes, there were significant and strong interactions between age and hypertension, and between hypertension and diabetes ($p<0.001$, Figures 8.9 to 8.11). As for other risk factors such as smoking, alcohol, previous stroke and TIA, they stayed neutral between LACI and NLAC. The unadjusted and adjusted analyses results for LAC versus NALC were close to those in SVD versus other subtypes using the TOAST classifications scheme.

8.4 Discussion

In this chapter, my results showed that the prevalence of hypertension, diabetes, AF, and hyperlipidaemia in overall IS patients based in Taiwan was higher, whereas the prevalence of smoking was lower than the results in my risk factor meta-analyses for IS (Chapter 6) based on all Chinese populations in different geographical areas

(nearly 90% from mainland China). In terms of risk factor associations, the findings after controlling for potential confounders were mostly close to my previous meta-analysis results in the TOAST classification. Compared with other IS subtypes: LAA strokes were associated with hypertension, diabetes, hyperlipidaemia and TIA; CE strokes were associated with IHD; SVD strokes were associated with hypertension, diabetes and hyperlipidaemia. In the OCSP classification for LAC versus NLAC, the unadjusted and adjusted analyses yielded similar results to SVD versus other subtypes in the TOAST classification scheme. There were positive associations with hypertension, diabetes and hyperlipidaemia, and negative associations with AF and IHD.

In my study, I found that the prevalence of several cerebrovascular risk factors of metabolic syndrome such as hypertension, diabetes, and hyperlipidaemia in overall IS patients based in Taiwan was higher than my previous risk factor meta-analyses for IS for all Chinese populations in Chapter 6 (nearly 90% from mainland China), and other studies from mainland China (Liu et al. 2006; Wang et al. 2006). Recently, the international REACH registry reported that there was a stepwise increase in the rates of hypertension, diabetes, hypercholesterolaemia and obesity in Chinese patients, from mainland China to Hong Kong/Singapore/Taiwan, and to North America/Western Europe (Chiu et al. 2010). These findings suggest that westernization of life style and dietary habits have a heavy impact on the prevalence of risk factors in these highly developed economic areas including Taiwan.

China and Taiwan may represent different stages of epidemiological transitions. Yusuf et al proposed several stages of epidemiological transitions of cardiovascular

diseases (Yusuf et al. 2001). The main circulatory diseases at the earliest stage are due to infections and nutritional deficiency such as rheumatic heart disease and nutritional cardiomyopathies, which are prevalent in sub-Saharan Africa and rural India. As infections reduce and nutrition improves, hypertension related disease such as haemorrhagic stroke and hypertensive heart disease become more common in the second stage, and China is a representative country of this stage. In the third stage, as the life expectancy and economics continue improving, people tend to have more high-fat diet, smoking and sedentary life styles. Atherosclerotic cardiovascular disease such as ischaemic heart disease, atherosclerotic stroke, and diabetes become more common, especially at younger age (e.g. Latin America and urban India). Taiwan is probably at this stage because of earlier economic development (Taiwan is one of the high-income countries based on the World Bank classification, while China is in the group of middle-come countries), democratic policies and more influence on diet, lifestyle and culture from the western countries. The epidemiological data in Taiwan could be useful to predict the future disease patterns in China. As mainland China is experiencing rapid economic and life style changes in recent decades, the prevalence of the aforementioned risk factors is likely to increase further in the years ahead. Prevention and better control of hypertension as well as diet and lifestyle modification through various education and intervention projects (e.g. heathy diet, smoking cessation, exercise program etc.) will improve the risk factors and reduce the associated cardiovascular diseases including ischaemic stroke in Chinese populations (Feigin et al. 2011; Yang et al. 1999; Kelly et al. 2008).

LAA strokes, which are pathophysiologically close to coronary heart disease, have been reported to be associated with age, male sex, and factors in metabolic syndrome as compared with other IS subtypes (Arboix et al. 2000; Grau et al. 2001; Silvestrelli et al. 2006). My findings are in line with previous studies, showing that hypertension, diabetes, and hyperlipidaemia are independent risk factors for LAA versus other subtypes after controlling for other confounders. Hypertension and diabetes are both well-established risk factor for ischaemic stroke, especially for large vessel and small vessel diseases (WHO Diabetes Drafting Group 1985). Compared with stroke related to extracranial atherosclerosis, diabetes was a more important factor for intracranial atherosclerosis related stroke (Rincon et al. 2009). Hyperlipidaemia is another well-known risk factor. Previous studies have shown that higher total cholesterol levels are associated with increased risk of ischaemic stroke, particularly large artery atherosclerosis and lacunar strokes (Tirschwell et al. 2004; Laloux et al. 2004).

In the present study, the proportion of CE subtype as well as the prevalence of AF in IS was higher than my systematic review in Chapter 4 and risk factor meta-analysis for IS in Chapter 6 for all Chinese populations. This may relate to the high performance rate of electrocardiography in NTUH. Every IS patient had electrocardiography examination upon arrival, and further continuous bedside electrographic monitoring was performed in around 25% IS patients admitted to the stroke intensive care unit, which was likely to detect AF. Although I did not include AF in the TOAST IS subtypes analyses because IS patients with the presence of AF were most likely assigned to CE subtype, irrespective of other risk factors or investigation results, my findings were similar to other studies (Arboix et al. 2000;

Schulz et al. 2003). Compared with other IS subtypes, CE had a totally different risk factor distribution. Apart from AF, CE was positively associated with IHD, while negatively associated with male gender, diabetes, hyperlipidaemia, and smoking. In literature, the most common causes contributed to cardioembolism are non-valvular AF, recent myocardial infarction, mechanical prosthetic valve, dilated myocardiopathy and mitral rheumatic stenosis (Arboix et al. 2012, Ferro et al 2003). Anticoagulation treatment is recommended for stroke prevention in patients with non-rheumatic AF and a history of stroke or TIA (Saxena R et al. 2004).

SVD was the most common IS subtype in this study, which was consistent with my systematic review in Chinese hospital-based studies using the TOAST classification (Chapter 4), and a recent community-based study using the Atherosclerosis Risk in Communities (ARIC) classification scheme in Chinese population (Tsai et al. 2013; Fang et al. 2012). SVD was positively associated with hypertension, diabetes, and hyperlipidaemia, while negatively associated with IHD. In fully adjusted analyses, the associations with hypertension and diabetes became even stronger for SVD versus others, and were significantly higher than those in LAA or CE versus others. Analyses for LACI versus NALC using the OCSP classification also showed very similar findings qualitatively and quantitatively. These findings suggest that hypertension and diabetes are independent and strong risk factors for lacunar strokes compared with other subtypes in our patients, regardless of age, gender and other risk factors. Recently, the Hisayama cohort study in Japan reported that the magnitude of the blood pressure impact on stroke differed among subtypes, being greatest for cerebral haemorrhage and lacunar infarction than other subtypes in IS (Arima et al.

2009). My findings are similar to this and other studies in eastern Asians (Fang et al. 2012; Arima et al. 2009; Lai et al. 2008), but slightly different from those in predominantly western populations, showing a marginal excess of hypertension and no difference of diabetes between lacunar and non-lacunar infarcts using TOAST or OCSP classification (Jackson et al. 2005; Schulz et al. 2003; Jackson et al. 2010). Differences in age and sex distributions and geographical areas, varying methods of case ascertainment, different risk factor definitions, as well as genuine differences in risk factor associations with lacunar infarcts among ethnic groups may account for these results.

8.4.1 Strengths and limitations

The current analyses provide important information on risk factor comparisons among IS subtypes in Chinese populations, in whom the distribution of IS subtypes are different from predominantly white populations, with a higher proportion of lacunar strokes and a lower proportion of cardioembolic stroke. My study has several strengths. First, NTUH Stroke Registry is a well-established registry, prospectively and systematically recruiting consecutive acute stroke patients since 1995 with relatively complete records of essential information including risk factors. My analyses benefited from inclusion of a large number of patients (nearly five thousands), and recent data from 2006 to 2011. Second, the inclusion of acute stroke patients was based on a standard definition of stroke, having stroke onset within 10 days with early specialist assessment, timely brain imaging, and detailed

investigations for aetiology. The brain CT or MRI as well as electrocardiography performance rate was 100%, around 80% had carotid duplex examination, and 60% had MR angiography to assess extracranial and intracranial vascular abnormality. Third, I used multiple logistic regression modelling to adjust for possible confounding factors including age, sex and other risk factors, and incorporated strongly significant interactions among risk factors to acquire the true independent risk factors for each IS subtype versus others.

Nevertheless, there are some limitations. First, the registry is a hospital-based stroke registry, whereas an ideal study population is supposed to be community-based, including all stroke patients in a geographical area, irrespective of hospital admission rate (Sudlow et al. 1996; Feigin et al. 2004). Prevalence of risk factors and stroke subtypes may possibly differ between hospitalized and non-hospitalized patients (Schulz et al. 2003). Second, risk factors in this study were collected from medical records prior to stroke occurrence, and from patients and family after the onset of stroke. Whilst most included patients had available medical records before stroke, I could not totally exclude the possibility of recall bias in case of a few patients without previous records. In addition, the risk factor status was dichotomized, not measured continuously. It is difficult to assess the severity or the shape of association of risk factors.

8.4.2 Conclusion

Accumulating evidence has suggested the distributions of ischaemic subtypes and risk factors vary among races and ethnicities, and there are different associations of risk factors among subtypes (Schulz et al. 2003; Jackson et al. 2005; Jackson et al. 2010; Fang et al. 2012; Lai et al. 2008; Ohira et al. 2006; Tsai et al. 2013). Here I report the independent risk factors for each IS subtype regardless of age, sex, or other risk factors in a Chinese population in Taiwan. While ischaemic stroke is the major part of the heavy stroke burden on Chinese, my findings could help shed light on the different contributions of risk factors among ischaemic stroke subtypes, providing insights into to effective strategies of stroke prevention and treatment.

Tables

Table 8.1 Study characteristics and risk factor distributions in overall IS patients, NTUH Stroke Registry 2006-2011, Taiwan.

	Overall IS (N=4953)		
Mean Age (Y)	68.1 (±13.8)		
	N	(%)	(95% CI)
Gender (male)	2929	59.1%	57.8-60.5%
Hypertension	3809	76.9%	75.7-78.7%
Diabetes	1838	37.1%	35.8-38.4%
Atrial fibrillation	1180	23.8%	22.6-25.0%
Ischaemic heart disease	759	15.3%	14.3-16.4%
Hyperlipidaemia	1744	35.2%	33.9-36.6%
Smoking	1455	29.4%	28.1-30.7%
Alcohol intake	689	13.9%	13.0-14.9%
Previous stroke	1175	23.7%	22.5-24.9%
Transient ischaemic attack	193	3.9%	3.4-4.5%

IS=ischaemic stroke; NTUH=National Taiwan University Hospital; N=number; CI=confidence interval.

Table 8.2 Study characteristics and risk factor distributions in IS patients using the TOAST classifications, NTUH Stroke Registry 2006-2011, Taiwan.

IS subtypes	TOAST classifications										P value
	SVD (N=1364)		LAA (N=1041)		CE (N=1203)		Other determined (N=248)		Undetermined (N=1097)		
	27.5%		21.0%		24.3%		5.0%		22.1%		P<0.001*
Mean age (Y)	67.8 (±11.8)		70.1(±11.4)		72.5 (±13.2)		48.4(±14.4)		66.2(±14.6)		P<0.001**
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Gender (male)	848	62.2%	694	66.7%	624	51.9%	163	65.7%	600	54.7%	P<0.001*
Hypertension	1124	82.4%	908	87.2%	928	77.1%	115	46.4%	734	66.9%	P<0.001*
Diabetes	556	40.8%	492	47.3%	379	31.5%	35	14.1%	376	34.3%	P<0.001*
Atrial fibrillation	41	3.0%	63	6.1%	1037	86.2%	10	4.0%	29	2.6%	P<0.001*
Ischaemic heart disease	96	7.0%	193	18.5%	337	28.0%	11	4.4%	122	11.1%	P<0.001*
Hyperlipidaemia	634	46.5%	437	42.0%	280	23.3%	68	27.4%	325	29.6%	P<0.001*
Smoking	434	31.8%	350	33.6%	270	22.4%	82	33.1%	319	29.1%	P<0.001*
Alcohol intake	197	14.4%	177	17.0%	134	11.1%	34	13.7%	147	13.4%	P=0.002*
Previous stroke	296	21.7%	301	28.9%	312	25.9%	34	13.7%	232	21.1%	P<0.001*
Transient ischaemic attack	43	3.2%	61	5.9%	53	4.4%	15	6.0%	21	1.9%	P<0.001*

IS=ischaemic stroke; NTUH=National Taiwan University Hospital; SVD=small vessel disease; LAA=large artery atherosclerosis; CE=cardioembolism; N=number; CI=confidence interval.

** based on analysis of variance (ANOVA); * based on Pearson's chi-square test.

Table 8.3 Study characteristics and risk factor distributions in IS patients using the OCSP classifications in NTUH Stroke Registry 2006-2011, Taiwan.

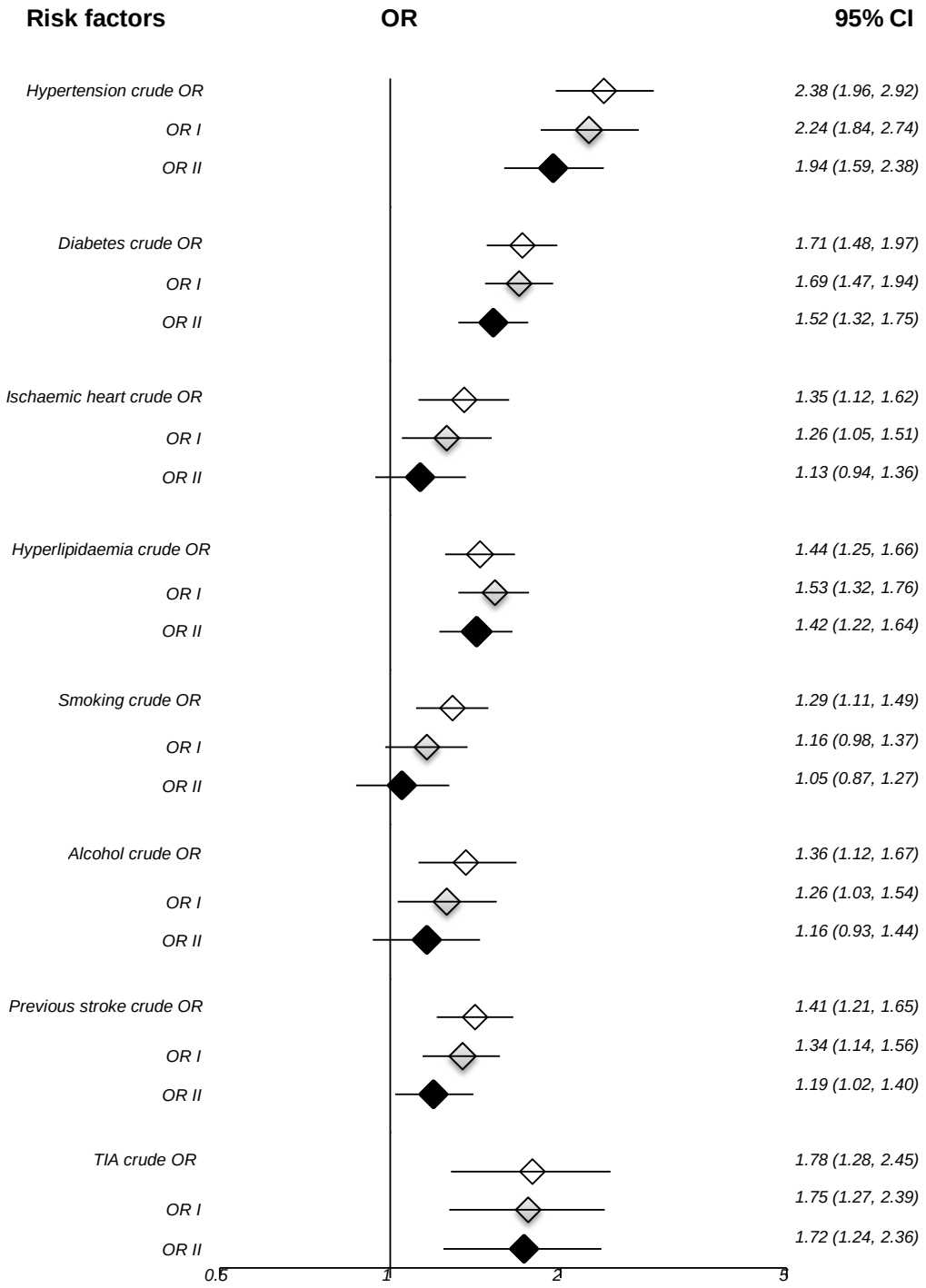
IS subtypes	OCSP classifications								
	LAC (N=1162)		**TACI (N=1033)**		**PACI (N=1586)**		**POCI (N=1172)**		P value
	23.5%		20.9%		32.0%		23.7%		P<0.001*
Mean age (Y)	67.8 (±11.8)		69.6 (±15.0)		68.3 (±14.3)		66.7 (±13.9)		P<0.001**
	N	(%)	N	(%)	N	(%)	N	(%)	
Gender (male)	726	62.5%	524	50.7%	942	59.4%	737	62.9%	P<0.001*
Hypertension	945	81.3%	755	73.1%	1173	74.0%	936	79.9%	P<0.001*
Diabetes	453	39.0%	308	29.8%	569	35.9%	508	43.3%	P<0.001*
Atrial fibrillation	38	3.3%	549	53.1%	375	23.6%	218	18.6%	P<0.001*
Ischaemic heart disease	85	7.3%	268	25.9%	251	15.8%	155	13.2%	P< 0.001*
Hyperlipidaemia	535	46.0%	238	23.0%	502	31.7%	469	40.0%	P<0.001*
Smoking	367	31.6%	256	24.8%	480	30.3%	352	30.0%	P=0.003*
Alcohol intake	166	14.3%	127	12.3%	207	13.1%	189	16.1%	P=0.043*
Previous stroke	251	21.6%	234	22.7%	413	26.0%	277	23.6%	P= 0.041*
Transient ischaemic attack	37	3.2%	42	4.1%	69	4.4%	45	3.8%	P= 0.469*

IS=ischaemic stroke; NTUH=National Taiwan University Hospital; LAC=lacunar infarct; TACI=total anterior circulation infarct; PACI=partial anterior circulation infarct; POCI=posterior circulation infarct; N=number; CI=confidence interval.

** based on analysis of variance (ANOVA); * based on Pearson's chi-square test.

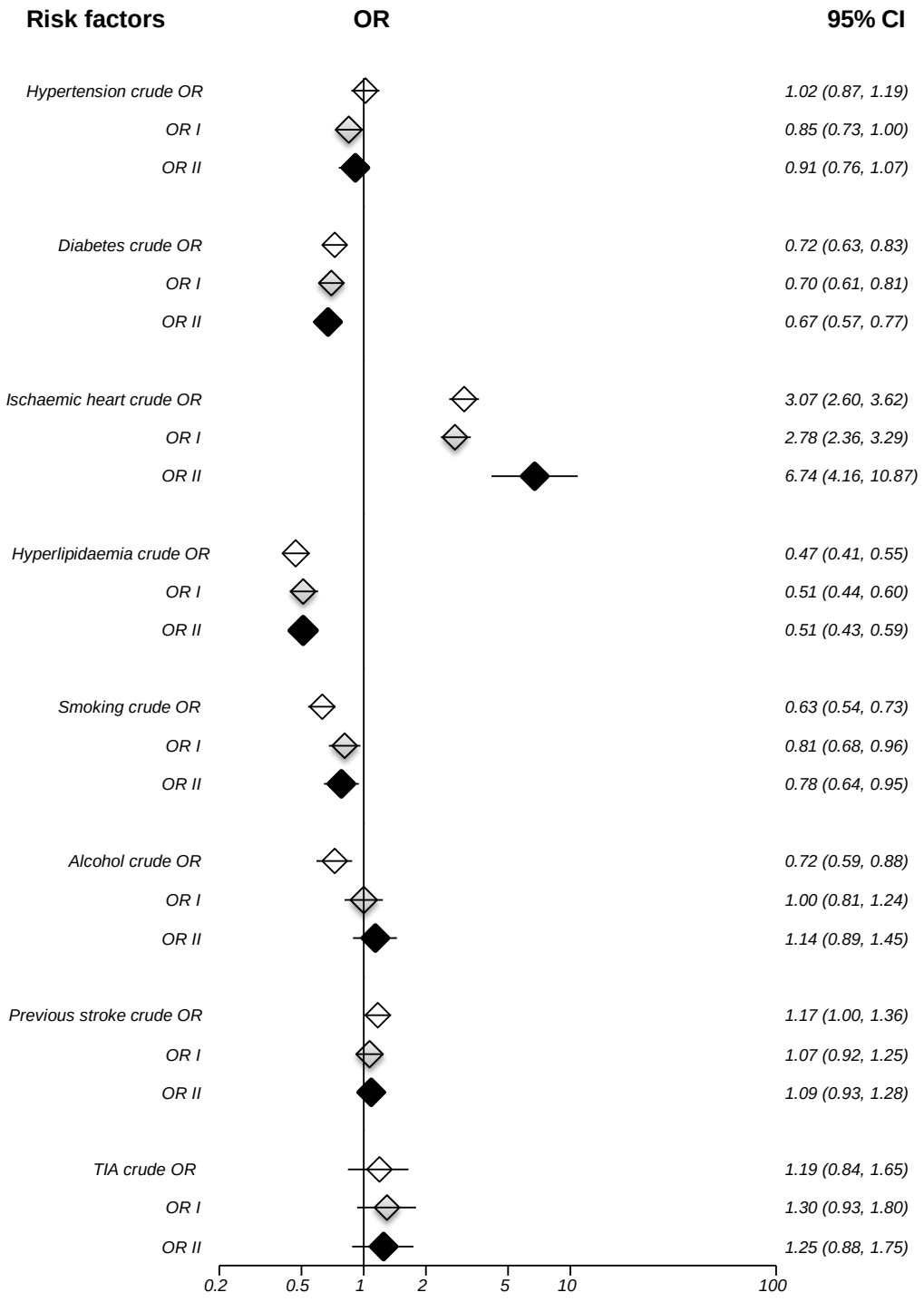
Figures

Figure 8.1 Risk factors for LAA versus other TOAST IS subtypes.



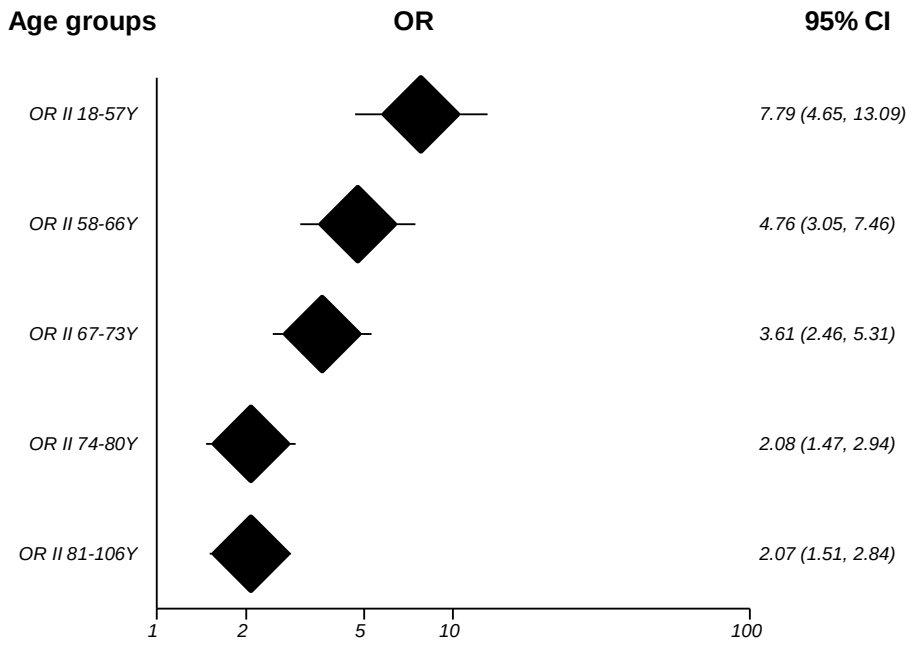
LAA=large artery atherosclerosis; IS=ischaemic stroke; OR=odds ratio; OR I=adjusted odds ratio I (adjusting for age and gender); OR II=adjusted odds ratio II (adjusting for age, gender and risk factors); TIA=transient ischaemic attack; CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.2 Risk factors for CE versus other TOAST IS subtypes.



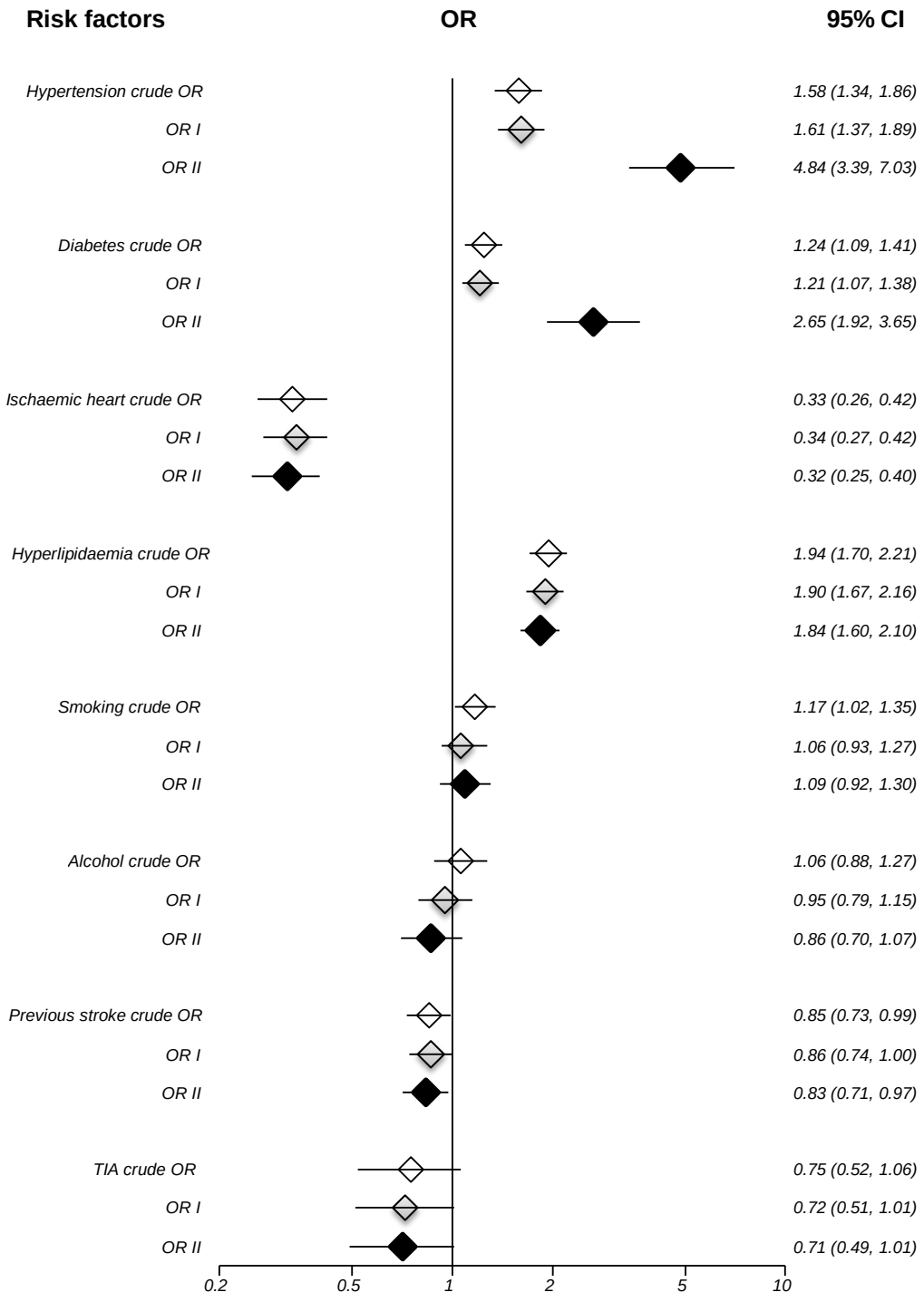
CE=cardioembolism; IS=ischaemic stroke; OR=odds ratio; OR I=adjusted odds ratio I (adjusting for age and gender); OR II=adjusted odds ratio II (adjusting for age, gender and risk factors, and incorporating a strongly significant interaction); TIA=transient ischaemic attack; CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.3 Subgroup analyses of ischaemic heart disease for CE versus other TOAST IS subtypes in different age groups.



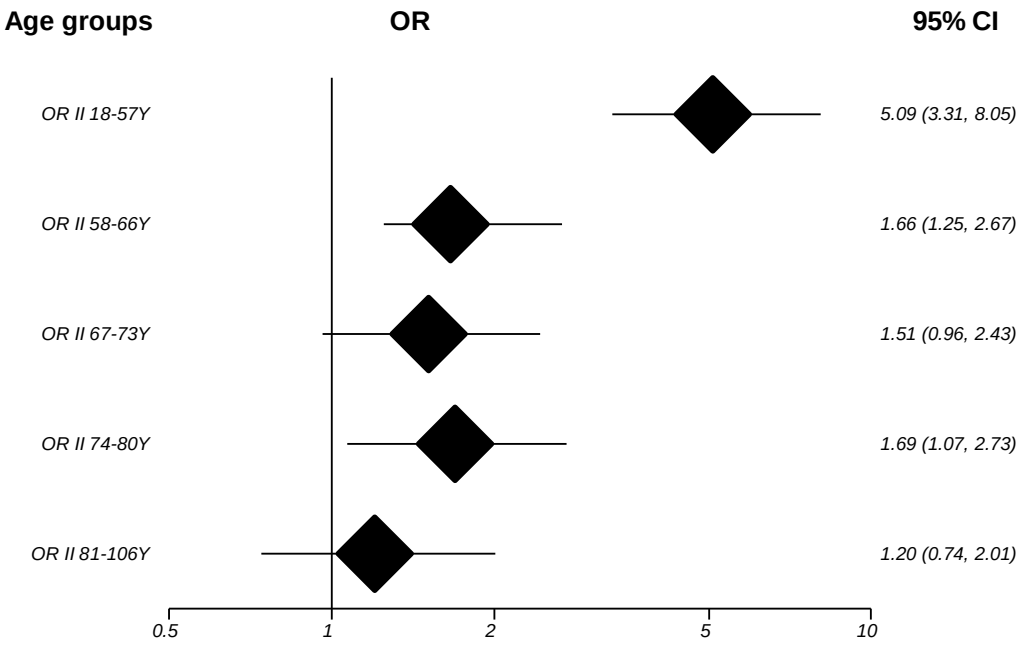
CE=cardioembolism; IS=ischaemic stroke; OR II=adjusted odds ratio II (adjusting for gender and other risk factors); CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.4 Risk factors for SVD versus other TOAST IS subtypes.



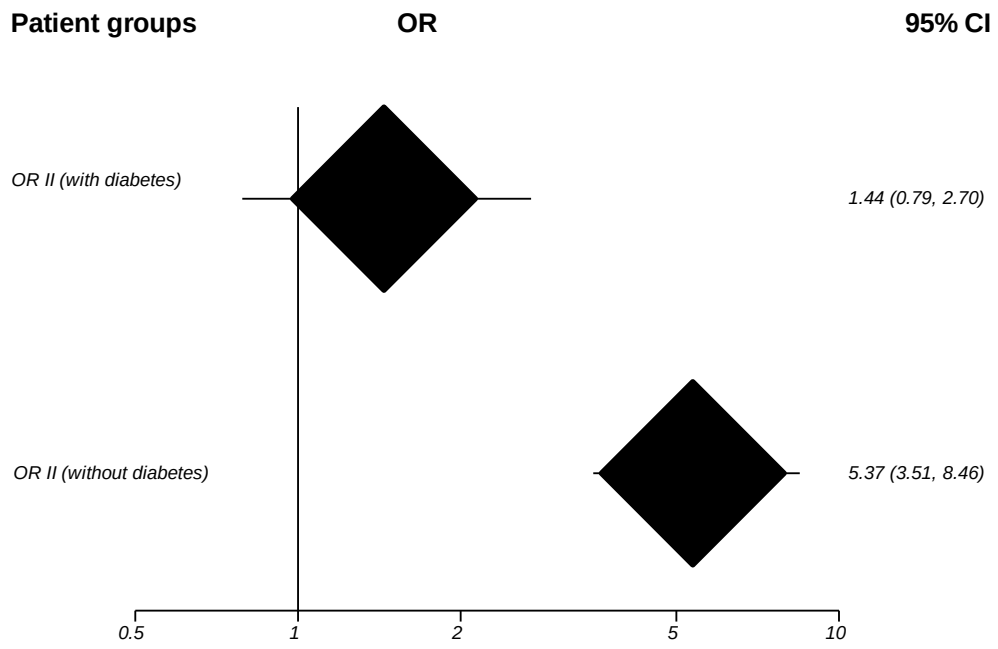
SVD=small vessel disease; IS=ischaemic stroke; OR=odds ratio; OR I=adjusted odds ratio I (adjusting for age and gender); OR II=adjusted odds ratio II (adjusting for age, gender, and risk factors, and incorporating strongly significant interactions); TIA=transient ischaemic attack; CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.5 Subgroup analyses of hypertension for SVD versus other TOAST IS subtypes in different age groups.



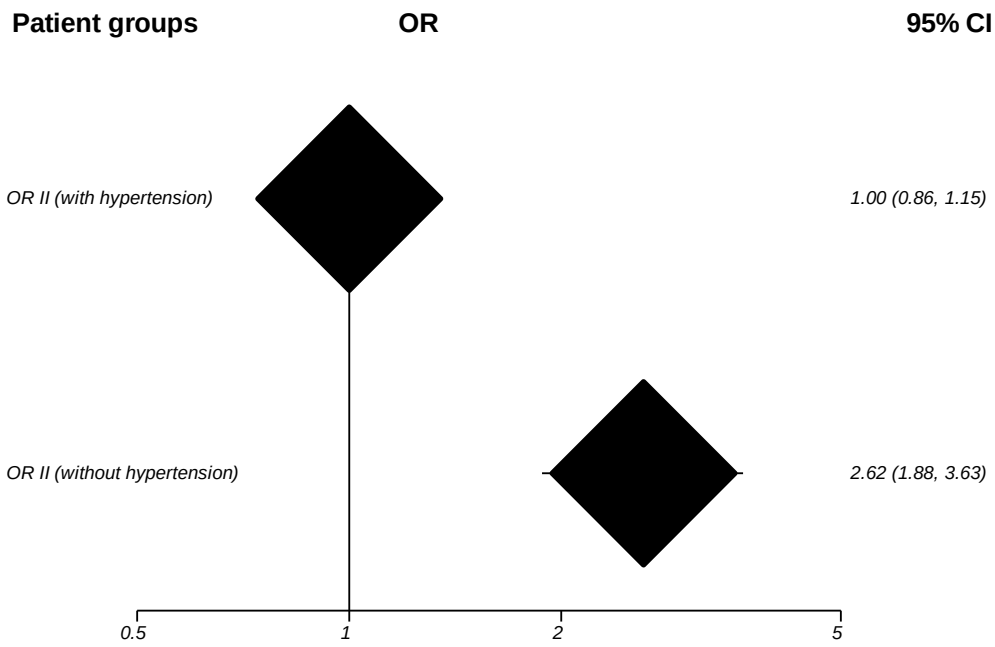
SVD=small vessel disease; IS=ischaemic stroke; OR II=adjusted odds ratio II (adjusting for gender and other risk factors); CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.6 Subgroup analyses of hypertension for SVD versus other TOAST IS subtypes in patients with or without diabetes.



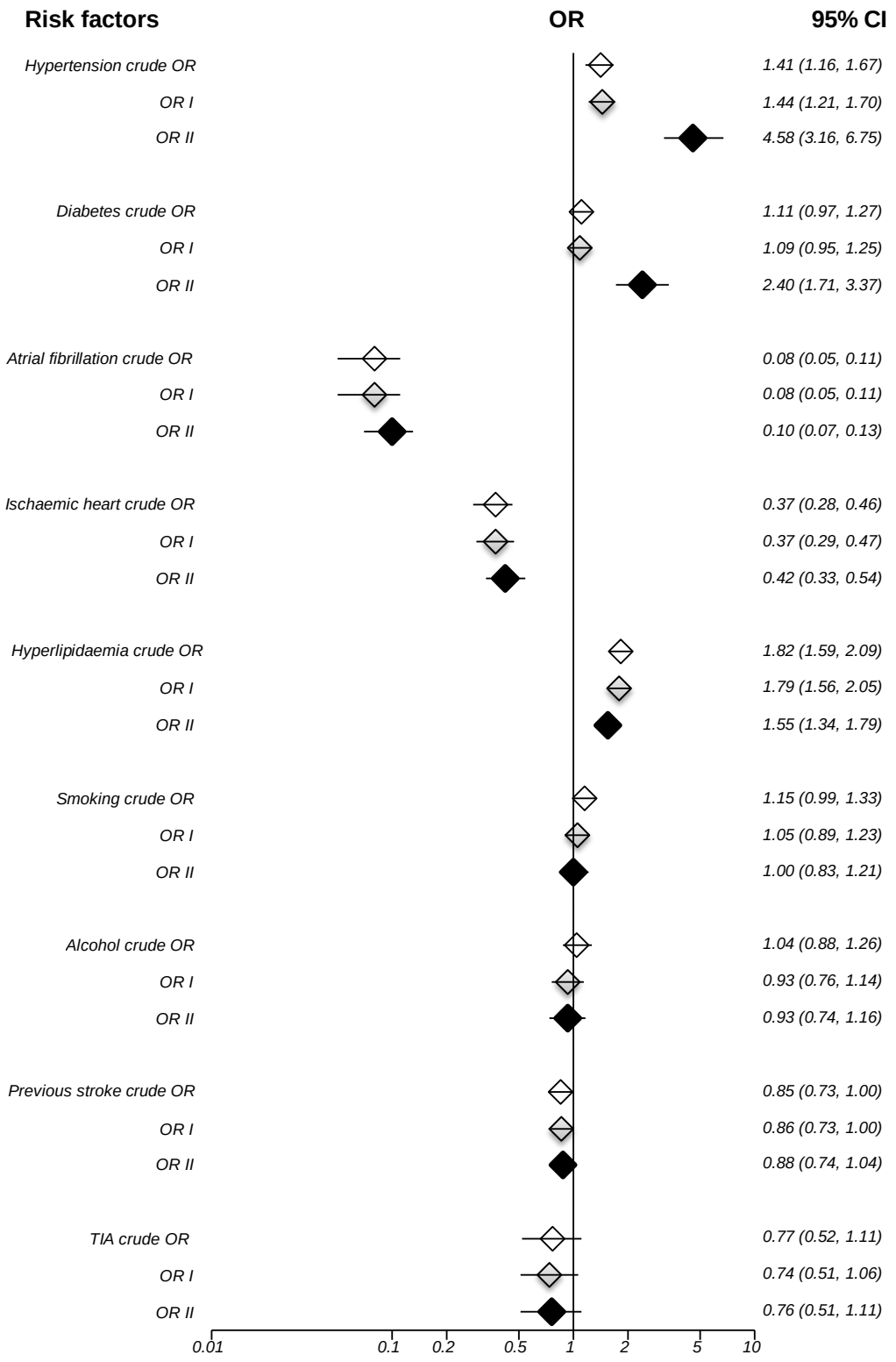
SVD=small vessel disease; IS=ischaemic stroke; OR II=adjusted odds ratio II (adjusting for age, gender and other risk factors); CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.7 Subgroup analyses of diabetes for SVD versus other TOAST IS subtypes in patients with or without hypertension.



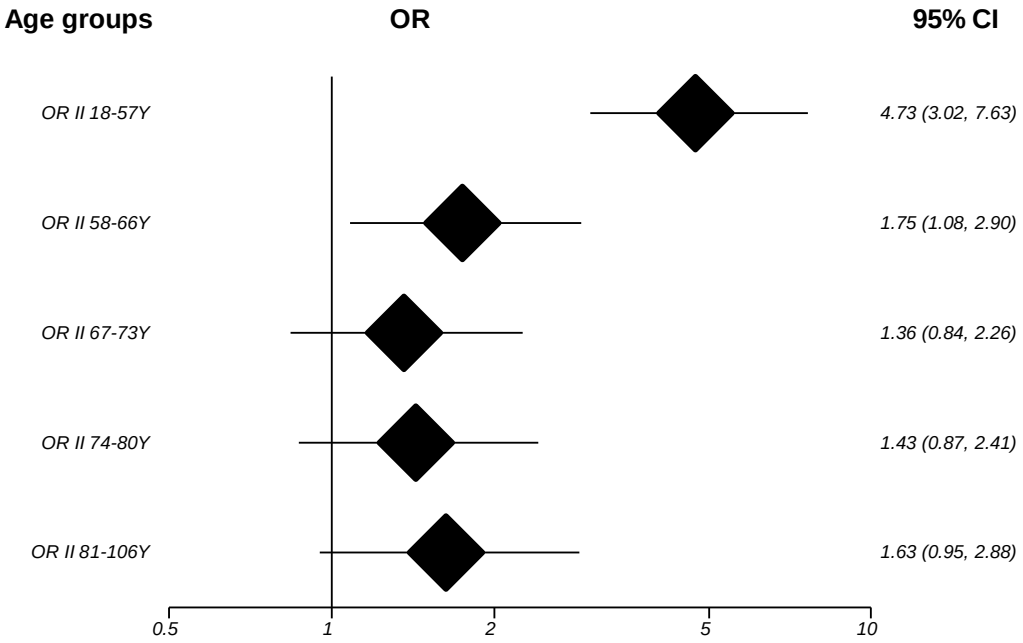
SVD=small vessel disease; IS=ischaemic stroke; OR II=adjusted odds ratio II (adjusting for age, gender and other risk factors); CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.8 Risk factors for LACI versus NLAC in the OCSP classification.



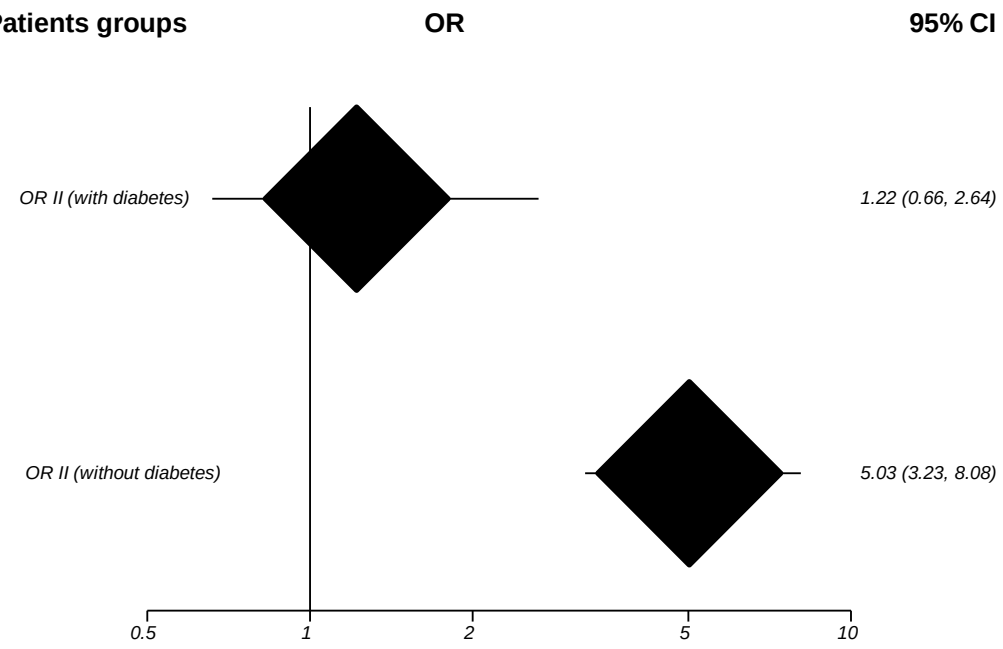
LACI=lacunar; NLAC=non-lacunar; IS=ischaemic stroke; OR=odds ratio; OR I=adjusted odds ratio I (adjusting for age and gender); OR II=adjusted odds ratio II (adjusting for age, gender, and risk factors, and incorporating strongly significant interactions); TIA=transient ischaemic attack; CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.9 Subgroup analyses of hypertension for LACI versus NLAC (OCSP classification) in different age groups.



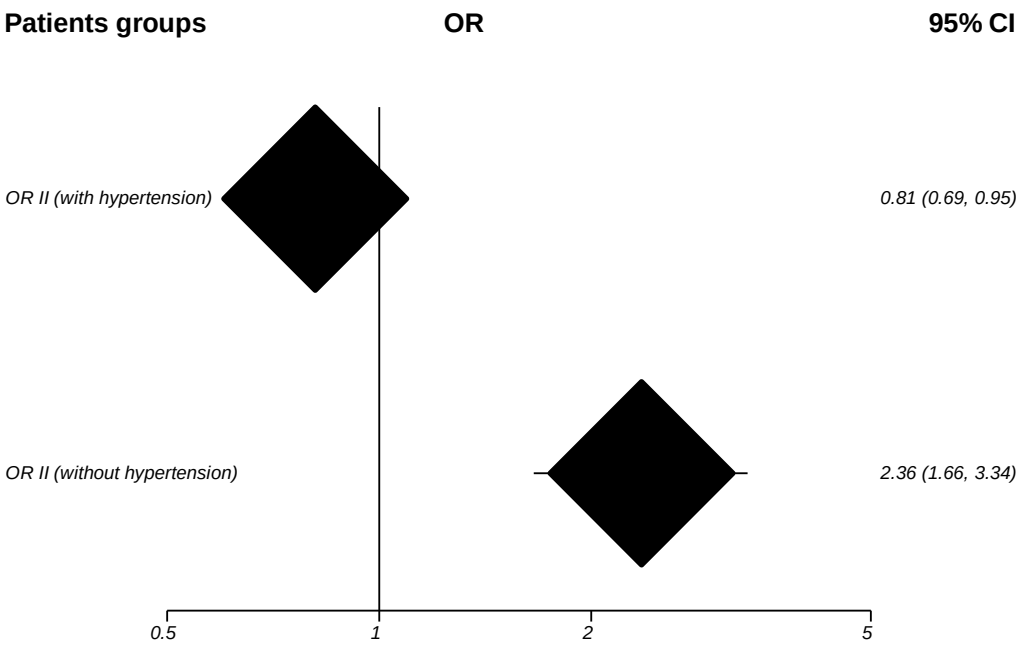
LACI=lacunar; NLAC=non-lacunar; IS=ischaemic stroke; OR II=adjusted odds ratio II (adjusting for gender and other risk factors); CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.10 Subgroup analyses of hypertension for LACI versus NLAC (OCSP classification) in patients with or without diabetes.



LACI=lacunar; NLAC=non-lacunar; IS=ischaemic stroke; OR II=adjusted odds ratio II (adjusting for age, gender and other risk factors); CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Figure 8.11 Subgroup analyses of diabetes for LACI versus NLAC (OCSP classification) in patients with or without hypertension.



LACI=lacunar; NLAC=non-lacunar; IS=ischaemic stroke; OR II=adjusted odds ratio II (adjusting for age, gender and other risk factors); CI=confidence interval. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs.

Section E: Summary and Conclusion

Chapter 9: Summary and implications for further research

9.1 Summary of stroke epidemiology and its subtypes in Chinese populations

9.1.1 Stroke incidence

Does stroke incidence in Chinese differ from that in white populations?

My systematic review in Chapter 2 showed that, compared with predominantly white populations, Chinese had a higher age-adjusted incidence of stroke, and a lower mean age of stroke onset. Additionally, I found that there was a striking variation among Chinese populations in different geographical areas (which varied around threefold in the age range 45-74 years). Earlier studies had suggested higher stroke incidence in Chinese versus white populations, and variable stroke incidence rates within China (with a north-south gradient), but did not include people aged older than 64 years and some comparisons included recurrent as well as first-ever strokes (Thorvaldsen et al, 1995; Wu et al. 2001). My results showed reliably that such differences existed after 1990 and extended previous findings to those aged 65 years and beyond, among whom most strokes occur. These differences were based on comparisons of methodologically robust community-based studies, including first-ever strokes in both admitted and not admitted to hospital, with appropriate age-standardization, and inclusion of an open-ended upper age band. They were therefore

unlikely to be an artefact of variable hospital admission rates or of incomplete adjustment for age.

In the literature, many factors have been suggested to explain the Chinese-Whites differences of stroke incidence as well as the variations among Chinese populations in overall stroke incidence, including differences in vascular risk factors, dietary habits (e.g. variable intake of salt), weather, socio-economic status, and genetic factors (Asch et al. 2010; Zhou et al. 2003; Wu et al. 2001; Yang et al. 2004; Zhao et al. 2004). These vary substantially within Chinese populations as well as between Chinese and white populations.

In terms of the trend of stroke incidence in Chinese populations, the Sino-MONICA-Beijing community-based stroke incidence study among people aged 25-74 years found, between 1984 and 2004 a 4% increase in age-standardized incidence of all types of stroke (Zhao et al. 2008). However, there are few comparable, large community-based data including older ages yet available after 2000. Since Chinese populations are experiencing rapid economic and lifestyle changes, there will be probably further changes in stroke incidence in the decades ahead.

9.1.2 Pathological types of stroke

Is the distribution of pathological types of stroke different between Chinese and white populations?

In Chapter 3, I showed that, compared with Whites, Chinese populations had an around twofold higher proportion of intracerebral haemorrhage (ICH), and a lower proportion of ischaemic stroke (IS). The proportion of ICH in Chinese was significantly higher either in all studies combined or in only community-based studies. In addition, there was a greater proportion of ICH in mainland China than Taiwan, and a striking variation of ICH within mainland China, with the highest proportion of ICH up to 52% in Changsha.

The Sino MONICA community-based stroke study (1987-1993) also reported a higher proportion of haemorrhagic stroke (ICH and subarachnoid haemorrhage) in Chinese among people aged 25-74 years, ranging from 25% to 64% (Wu et al. 2003). Subsequently, the Sino-MONICA-Beijing community-based stroke study among people aged 25-74 years further showed a 5% increase in IS and 1% decrease in haemorrhagic stroke between 1984 and 2004 (Zhao et al. 2008). My study found that the higher proportion of haemorrhagic stroke was due to ICH, not subarachnoid haemorrhage. Furthermore, despite of a decreasing trend of ICH, the significantly higher proportion of ICH had persisted in the most recent studies in Chinese populations, even those with highly developed economies, such as Taiwan. These changes occurred during a time of rapid economic development and increasing adoption of western lifestyles, increased dietary fat and cholesterol intake, increased mean cholesterol levels, increased prevalence of obesity and diabetes, and possibly better hypertension control.

9.1.3 Ischaemic stroke subtypes

Is the distribution of ischaemic stroke subtypes in Chinese different from those in white populations?

In Chapter 4, my systematic review showed that, compared with predominantly white populations, there was a significantly higher proportion of small vessel disease (SVD) strokes (lacunar infarction), a lower proportion of cardioembolism (CE) strokes and of other specific/undetermined IS subtypes in Chinese.

However, I could not find any community-based studies of IS subtypes based on the TOAST or OCSP classification. Since only hospital-based studies were available in Chinese populations, different hospital admission rates could contribute to the variations among Chinese studies as well as between the hospital-based Chinese studies and the community-based studies in Whites (Schulz et al. 2003). In addition, the proportion of strokes in the 'other or undetermined' ischaemic subtype using the TOAST classification scheme varied widely among the Chinese studies, and was generally lower than among studies in Whites. This could be due to differences in the investigations, interpretation, and application of aetiological classification systems for ischaemic stroke subtypes. The proportion of stroke cases with complete investigation would influence the assignment of IS subtypes, since the higher the proportion of complete investigations, the lower would be the proportion assigned an undetermined subtype (Jackson et al. 2005). The problem of variable investigation rates does not influence the anatomical OCSP classification system, which is based on clinical symptoms and signs, requiring no investigation results beyond a brain

scan to exclude haemorrhage (Bamford et al. 1991). This may explain the more consistent findings among the Chinese studies using the OCSP system, as well as making comparisons between studies based on this system more reliable. Although the OCSP-based Chinese-Whites comparisons still show a higher proportion of lacunar ischemic strokes in Chinese populations, community-based studies are needed to further support this finding.

9.1.4 Risk factors for ICH versus IS

Do the associations with risk factors differ between ICH and IS in Chinese as well as between Chinese and Whites?

To further explore the possible reasons for the observed differences in the proportions of the main pathological types of stroke - a twofold higher proportion of ICH and a lower proportion of IS in Chinese as compared to predominantly white populations, in Chapter 5, I performed meta-analyses to systematically assess the evidence for differences in the vascular risk factor profiles between ICH and IS in Chinese, and compared these results with data from predominantly white populations.

My results showed that the relative frequencies of risk factors in ICH versus IS were generally of similar direction in stroke patients from both Chinese and predominantly white populations, but the associations varied in size and significance. Both hypertension and alcohol intake were significantly more frequent in ICH versus IS in Chinese but not in white stroke patients, while both hypercholesterolaemia and

smoking were significantly less frequent in ICH versus IS in Whites but not Chinese stroke patients. As for diabetes, atrial fibrillation (AF) and ischaemic heart disease (IHD), they were significantly less common in ICH in both ethnic groups. However, the risk factor associations with ICH versus IS did not differ significantly between Chinese and Whites except for IHD, which had a stronger association with IS versus ICH in Chinese than predominantly white populations.

These meta-analyses results should be interpreted with caution since there was substantial statistical heterogeneity among the studies, which could arise from differences in age and sex distributions, methodological differences (e.g. case ascertainment methods), variable risk factor definitions, differences between geographical areas, as well as genuine differences in risk factor associations between ethnic groups. Because my meta-analyses were based on published data, I did not have individual patient data to allow adjustment for potential confounders such as age and gender.

Fortunately, I acquired an opportunity to have stroke research collaboration with National Taiwan University Hospital (NTUH), analysing data of nearly seven thousands Chinese acute stroke patients in NTUH stroke registry from 2006 to 2011. The NTUH Stroke Registry is a hospital-based registry based in north Taiwan, prospectively recruiting consecutive acute stroke or transient ischaemic attack patients (TIA) arriving in the Emergency Department or being admitted to wards. In Chapter 7, I was able to overcome the limitations of my meta-analyses of published studies, adjusting for age, gender and other risk factors. The findings were broadly consistent with the results from my meta-analysis, showing that hypertension and

alcohol intake were independent risk factors for ICH versus IS in Chinese populations regardless of age, sex, or other risk factors, whereas diabetes, atrial fibrillation, IHD, hyperlipidaemia, smoking and TIA were negatively associated with ICH versus IS. Furthermore, in subgroup analysis, the positive association with hypertension was found to be stronger in younger stroke patients.

9.1.5 Risk factors for IS subtypes

Are the prevalence of risk factors in IS and the associations of risk factors with IS subtypes in Chinese different from those in white populations?

In Chapter 6, I conducted subsequent risk factor meta-analyses for IS and its subtypes to explore the possible causes of the different distribution of IS subtypes in Chinese (a higher proportion of lacunar strokes and a lower proportion of CE strokes) as compared with predominantly white populations. My results showed that Chinese IS patients had a similar proportion of hypertension, diabetes, smoking and alcohol, and a lower prevalence of AF, IHD and hypercholesterolaemia compared with Whites. As for the associations of risk factors with individual IS subtypes, they were qualitatively similar (although different in size) in Chinese and predominantly white populations. Compared with other IS subtypes: large artery artherosclerosis (LAA) strokes were associated with diabetes; CE strokes were associated with AF and IHD; SVD (or lacunar) strokes were associated with hypertension and diabetes. However, these meta-analysis findings could be possibly confounded by some factors such as age, gender, other risk factors, incomplete information, variable investigations and

interpretations of IS classification system, and different definitions of some risk factors.

To overcome the potential confounding effects in the meta-analyses, in Chapter 8, I performed further analyses of individual patient data including nearly five thousand acute IS patients from the NTUH Stroke Registry of a Chinese population in Taiwan. Interestingly, I found that the prevalence of several risk factors of the metabolic syndrome, especially hypertension, diabetes, and hyperlipidaemia in overall IS patients based in Taiwan, was higher than my previous risk factor meta-analyses for IS for all Chinese populations in Chapter 6 and other reports from mainland China (Liu et al. 2006; Wang et al. 2006). My findings were consistent with the findings in the international REACH registry, which showed a stepwise increase in the rates of hypertension, diabetes, hypercholesterolaemia and obesity in Chinese patients, from mainland China to highly developed economic areas such as Hong Kong/Singapore/Taiwan, and to North America/Western Europe (Chiu et al. 2010). These findings suggest that westernization of life style and dietary habits have a heavy impact on the prevalence of risk factors in Chinese. Hong Kong and Taiwan are economically highly developed areas, and they probably represent the interim status of economic and epidemiological transition in Chinese populations.

In terms of risk factor associations, the findings after controlling for potential confounders were mostly close to my previous meta-analysis results except for lacunar strokes. Compared with other IS subtypes: LAA strokes were associated with hypertension, diabetes, hyperlipidaemia and TIA; CE strokes were associated with IHD. As for SVD (or lacunar) strokes, in fully adjusted analyses, hypertension and

diabetes were independent and strong risk factors regardless of age, sex and other risk factors in both TOAST and OCSP classifications. My findings are similar to other studies in eastern Asians (Fang et al. 2012; Arima et al. 2009; Lai et al. 2008), but slightly different from those in predominantly western populations, showing a marginal excess of hypertension and no difference of diabetes between lacunar and non-lacunar infarcts (Jackson et al. 2005; Schulz et al. 2003; Jackson et al. 2010). Differences in age and sex distributions and geographical areas, varying methods of case ascertainment, different risk factor definitions, as well as genuine differences in risk factors associations with lacunar infarcts among ethnic groups may account for these results.

9.2 Implications and plans for further research

9.2.1 Community-based studies

From my systematic reviews of stroke studies in Chinese populations, despite a comprehensive literature search, I found few community-based studies of incidence of stroke, pathological types of stroke or ischaemic stroke subtypes, and risk factors in Chinese populations without an upper age limit, especially after the year 2000. In addition, there were insufficient data for 1 month case fatality analysis. An ideal study population should be community-based with multiple overlapping sources, including all stroke patients in a geographical area, irrespective of the hospital admission rate (Sudlow et al. 1996; Feigin et al. 2004). Nevertheless, there were few studies based on ideal study populations in Chinese, and many stroke studies did not

include older patients. Stroke is a non-communicable disease mainly occurring in older people, and the incidence of stroke increases with each decade of life. Thus, studies with an upper age limit or including only hospital patients would exclude a considerable number of stroke patients, losing the full picture of stroke. Furthermore, distribution of stroke subtypes and prevalence of risk factors may possibly differ between hospitalized and non-hospitalized patients (Schulz et al. 2003).

Although Chinese populations have a relatively higher incidence of total stroke as compared with western countries, the data and analyses on stroke incidence, subtypes, and risk factors from large numbers of stroke patients in community-based studies using robust methods to explore the possible underlying reasons are quite limited. Most relevant information has been derived from studies on predominantly white populations. Well-designed community-based studies of stroke in Chinese would allow us to have accurate data on incidence of stroke and subtypes, to comprehensively assess risk factor profiles for stroke, to make reliable comparisons among countries or populations, to evaluate trends with time, to help planning more efficient strategies of stroke prevention, and ultimately to reduce the heavy stroke burden in Chinese populations as well as the total stroke burden around the world (Sudlow et al. 1996).

9.2.2 Intracerebral haemorrhage subtypes

ICH is the most catastrophic type of stroke, leading to high case-fatality, poor functional outcome, and heavy disability burden in the world (Feigin et al. 2009; Ash

et al. 2010; Qureshi et al. 2009). My systematic review in Chapter 3 showed that Chinese populations had around a twofold higher proportion of ICH as compared with predominantly white populations (28% versus 12%), and the differences became even greater when the comparisons were made solely based on community-based studies (34% versus 12%).

Recently, several studies have reported that risk factors for ICH vary according to the location of haemorrhage (Woo et al. 2002; Biffi at el. 2010; Martini et al. 2012). ICH is most commonly classified into lobar ICH and deep (non-lobar) ICH subtypes, and apoliprotein E (APOE) polymorphism is an established risk factor for ICH in white populations (Wermer et al. 2002; Woo et al. 2002; Martini et al. 2012). While hypertension appears to pose the greatest risk to deep ICH in the basal ganglia, thalamus, brainstem, cerebellum, or periventricular white matter, apolipoprotein genotypes APOE4 and APOE2 seem to have the highest attributable risk to lobar ICH (Woo et al. 2002). Additionally, a study based in Dijon suggested that ICH risk factor profiles were changing in recent decades (Bejot et al. 2013). They found an 80% increase in ICH incidence among people aged 75 years or older, whereas a 50% decrease was noted in individuals aged less than 60 years. A suggested explanation for the increasing ICH incidence in older people, who are prone to vasculopathies such as cerebral amyloid angiopathy, may be including use of antithrombotic drugs. In Chinese populations, hypertension is generally thought to account for the higher proportion of ICH in Chinese or other Asian populations, especially for deep ICH. Nevertheless, there have been few studies designed to assess the risk factors including medication use and genetic factors for ICH subtypes in Chinese

populations. Given that the ICH incidence and proportion are significantly higher in Chinese and other Asian populations, there is a pressing need for more studies to clarify the roles of risk factors for ICH and its subtypes in these populations.

9.2.3 Ischaemic stroke classification

In my study of IS subtypes in Chapter 4, I found the proportion of the "stroke of other determined or undetermined aetiology" IS subtype using the TOAST classification scheme varied widely among the Chinese studies. This could partly be due to differences in the interpretation, investigations, and application of the aetiological classification systems for IS subtypes. Currently, the TOAST classification is the most widely used classification scheme for IS subtyping. It is mainly based on clinical features of IS and other results from investigations for the possible aetiology of stroke such as neuroimaging, electrocardiography, echocardiography, neurosonography, cerebral angiography and various blood tests, with moderate inter-rater reliability (Gordon et al. 1993; Meschia et al. 2006). Although it is simple, logical, informative, and easy to use, the TOAST classification has several limitations. First of all, the accuracy and the proportions of IS subtypes may depend on the proportion of complete investigations. The higher the proportion of complete investigations, the lower the proportion which is assigned to the undetermined aetiology IS subtype. In addition, when patients have multiple aetiologies, they are assigned to the undetermined aetiology subtype, usually leading to a large group of undetermined subtype. Furthermore, TOAST classification is not

a risk factor-free classification scheme, and it could possibly lead to classification bias (Jackson et al. 2005).

As modern diagnostic technology and understanding of IS mechanisms have improved considerably in recent decades, there are several newly developed classification systems such as Causative Classification System (CCS), Atherosclerosis, Small-Vessel Disease, Cardiac Source, Other Cause (A-S-C-O) classification system, and Chinese Ischaemic Stroke Subclassification (CISS) system (Ay et al. 2005; Amarenco et al. 2009; Gao et al. 2011). A good classification system has to be valid, reliable, evidence-based and easy to use. Accurate classification is important to epidemiology studies including risk factors and prognosis, clinical trials of treatment for IS subtypes, and further genetic association research of stroke (Chen et al. 2012). More reliability and validity data in different ethnic groups are needed for these new classification systems.

9.2.4 Stroke genetics

At present, there is an increasing interest in the influence of genetic factors on stroke. Research in stroke genetics continues to make substantial advances (Meschia et al. 2013; Sharma et al. 2013). As technology improves, the genomic analysis of stroke has changed from candidate gene association studies to genome-wide association studies (Lanktree et al. 2010). Apart from monogenic stroke disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), recently, large-scale international research

collaborations have reported some new genetic risk factors to IS, which seem to be specific to IS subtypes. The International Stroke Genetics Consortium and the Wellcome Trust Case Control Consortium 2 performed a genome-wide association study of IS patients and controls of European origin (International Stroke Genetics Consortium; Wellcome Trust Case Control Consortium 2. 2012). They have replicated the associations of PITX2 and ZFHX3 with cardiogenic embolic stroke, and a locus 9p21 with large vessel stroke. In addition, they have identified a new association of HDAC9 with large vessel stroke on chromosome 7p21.1. Subsequent meta-analyses of genome-wide association studies in a large number of patients and controls of European ancestry by METASTROKE collaboration have confirmed the aforementioned findings (Traylor et al. International Stroke Genetics Consortium. 2012). These results suggest different genetic mechanisms have associations with different IS subtypes.

In ICH, there is increasing evidence of strong association of apolipoprotein E type (APOE4/APOE2) with lobar ICH, which is related to cerebral amyloid angiopathy (Woo et al. 2002; Biffi et al. 2010; Martini et al 2012; Rannikmae et al. 2013). Around one third of all lobar ICH patients are reported to be attributable to APOE2 or APOE4, whereas half of non-lobar ICH cases are attributable to hypertension (Woo et al. 2002). However, most of these studies have been conducted in white stroke patients of European descent, with few comparable data from other populations. Recently, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) study, which included 3457 Europeans and 2148 Asians (38%), found that patients carrying APOE 2 or APOE4 had an increased risk of both incident and

recurrent ICH, and both lobar and deep ICH. Moreover, most risk estimates in their study were higher in Asians than in Europeans (Tzourio et al. 2008). In Chinese populations, several genetic studies regarding APOE genotype as well as other genetic markers such as TNF-α gene and 1425G/A SNP in PRKCH have been reported recently to be associated with cerebral haemorrhage (Zhang et al. 2012; Chen et al. 2010; Wu et al. 2009). Clearly, further large-scale studies are necessary to replicate and confirm these findings, and to find the new genetic risk factors.

9.3 Conclusion

My systematic review in Chapters 2 to 4 has shown a younger onset of stroke, a relatively higher stroke incidence of total stroke, an around twofold higher proportion of ICH, a lower proportion of IS, and different distributions of ischaemic stroke subtypes, with a higher proportion of lacunar strokes and a lower proportion of cardioembolic strokes in Chinese compared with predominantly white populations since 1990, with substantial regional variations among Chinese populations. Also, from my risk factor meta-analyses for ICH versus IS in Chapter 5, I have showed differences between Chinese and predominantly white populations in the strength and significance of associations of several risk factors with ICH versus IS. Hypertension and alcohol intake are independent, modifiable risk factors for ICH versus IS in Chinese populations, regardless of age, sex, or other risk factors (Chapter 7). In terms of risk factor for IS (Chapters 6 and 8), Chinese IS patients have a similar prevalence of hypertension, diabetes, smoking and alcohol, and a

lower prevalence of AF, IHD and hypercholesterolaemia compared with Whites. The associations of risk factors with individual IS subtypes are mostly qualitatively similar (although differed in size) in Chinese and predominantly white populations. Compared with other IS subtypes: LAA strokes are associated with hypertension and diabetes; CE strokes are associated with AF and IHD; lacunar strokes are associated with hypertension and diabetes. The associations with hypertension and diabetes became stronger for lacunar strokes versus others after adjusting for potential confounders in Chinese populations.

Although non-modifiable risk factors such as age, gender, and genetics play certain roles in stroke, it is of vital importance to target modifiable risk factors since they are manageable through intervention of lifestyle and medication, and they may vary among populations. The findings in my studies have important clinical and public health implications, especially for Chinese populations. A better understanding of the underlying reasons for the higher incidence of total stroke and ICH as well as different distributions of IS subtypes could help shed light on different stroke mechanisms, guide further well-designed research in this area, better predict the potential impacts ahead due to the rapid growth in the economy and changing lifestyles, and contribute to making effective strategies of stroke prevention in Chinese populations.

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Appendices

Appendix 1. Search strategy for community-based stroke incidence studies

MEDLINE

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or intracranial hemorrhages/ or stroke/ or exp brain infarction/ or exp vertebral artery dissection/

2. Incidence/ or Cohort Studies/

3. 1 and 2

4. ((incident or incidence or new cases or trend$) and (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$ or SAH)).tw.

5. (((incident or incidence or new cases or trend$) and (brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia)) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$)).tw.

6. (((incident or incidence or new cases or trend$) and (brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa)) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

7. ((new or first$) adj5 stroke$).tw.

8. 3 or 4 or 5 or 6 or 7

9. china/ or hong kong/ or taiwan/

10. Asian Continental Ancestry Group/

11. (china or chinese or taiwan$ or hong kong).tw.

12. (china$ or hong kong or taiwan).cp.

13. chinese.lg.

14. 9 or 10 or 11 or 12 or 13

15. 8 and 14

EMBASE

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or occlusive cerebrovascular disease/ or stroke/

2. stroke unit/ or stroke patient/

3. 1 or 2

4. incidence/ or cohort analysis/

5. 3 and 4

6. ((incident or incidence or new cases or trend$) and (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$ or SAH)).tw.

7. (((incident or incidence or new cases or trend$) and (brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia)) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$)).tw.

8. (((incident or incidence or new cases or trend$) and (brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa)) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

9. ((new or first$) adj5 stroke$).tw.

10. 5 or 6 or 7 or 8 or 9

11. china/ or hong kong/ or taiwan/

12. chinese/

13. (china or chinese or taiwan$ or hong kong).tw.

14. (china or hong kong or "taiwan republic of china").cp.

15. chinese.sl.

16. chinese.lg.

17. 11 or 12 or 13 or 14 or 15 or 16

18. 10 and 17

Appendix 2. Search strategy for and stroke types/ischaemic subtypes and risk factors in Chinese

MEDLINE

1. china/ or hong kong/ or taiwan/

2. Asian Continental Ancestry Group/

3. (china or chinese or taiwan$ or hong kong).tw.

4. (china$ or hong kong or taiwan).cp.

5. chinese.lg.

6. 1 or 2 or 3 or 4 or 5

7. cerebrovascular disorders/cl or exp basal ganglia cerebrovascular disease/cl or exp brain ischemia/cl or exp carotid artery diseases/cl or exp intracranial arterial diseases/cl or exp "intracranial embolism and thrombosis"/cl or intracranial haemorrhages/cl or stroke/cl or exp brain infarction/cl or exp vertebral artery dissection/cl

8. 6 and 7

9. *cerebrovascular disorders/ep or exp *basal ganglia cerebrovascular disease/ep or exp *brain ischemia/ep or exp *carotid artery diseases/ep or exp *intracranial arterial diseases/ep or exp *"intracranial embolism and thrombosis"/ep or *intracranial haemorrhages/ep or *stroke/ep or exp *brain infarction/ep or exp *vertebral artery dissection/ep

10. 6 and 9

11. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or intracranial haemorrhages/ or stroke/ or exp brain infarction/ or exp vertebral artery dissection/

12. (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$ or SAH).tw.

13. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$)).tw.

14. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

15. 11 or 12 or 13 or 14

16. (type$ of stroke or stroke type$ or subtype$ or classification or TOAST or BAMFORD).tw.

17. (stroke adj5 categor$).tw.

18. risk factors/ or risk factor$.tw.

19. *cerebrovascular disorders/et or exp *basal ganglia cerebrovascular disease/et or exp *brain ischemia/et or exp *carotid artery diseases/et or exp *intracranial arterial diseases/et or exp *"intracranial embolism and thrombosis"/et or *intracranial haemorrhages/et or *stroke/et or exp *brain infarction/et or exp *vertebral artery dissection/et

20. 16 or 17 or 18 or 19

21. 6 and 15 and 20

22. 8 or 10 or 21

EMBASE

1. china/ or hong kong/ or taiwan/

2. chinese/

3. (china or chinese or taiwan$ or hong kong).tw.

4. (china or hong kong or "taiwan republic of china").cp.

5. chinese.sl.

6. chinese.lg.

7. 1 or 2 or 3 or 4 or 5 or 6

8. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or occlusive cerebrovascular disease/ or stroke/

9. stroke patient/ or stroke unit/

10. (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$ or SAH).tw.

11. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$)).tw.

12. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

13. 8 or 9 or 10 or 11 or 12

14. classification/ or exp clinical classification/ or exp disease classification/

15. (type$ of stroke or stroke type$ or subtype$ or classification or TOAST or BAMFORD).tw.

16. (stroke adj5 categor$).tw.

17. cardiovascular risk/ or risk factor/

18. risk factor$.tw.

19. 14 or 15 or 16 or 17 or 18

20. 7 and 13 and 19

21. *cerebrovascular disease/ep, et or *basal ganglion hemorrhage/ep, et or exp *brain hematoma/ep, et or exp *brain hemorrhage/ep, et or exp *brain infarction/ep, et or exp *brain ischemia/ep, et or exp *carotid artery disease/ep, et or *cerebral artery disease/ep, et or *cerebrovascular accident/ep, et or *occlusive cerebrovascular disease/ep, et or *stroke/ep, et

22. 7 and 21

23. 20 or 22

24. limit 23 to human

25. (199$ or 20$).em.

26. 24 and 25

Appendix 3. Search strategy for systematic review and meta-analysis of risk factors in stroke types/subtypes in white populations

MEDLINE

1. cerebrovascular disorders/cl or exp basal ganglia cerebrovascular disease/cl or exp brain ischemia/cl or exp carotid artery diseases/cl or exp intracranial arterial diseases/cl or exp "intracranial embolism and thrombosis"/cl or intracranial haemorrhages/cl or stroke/cl or exp brain infarction/cl or exp vertebral artery dissection/cl

2. *cerebrovascular disorders/ep or exp *basal ganglia cerebrovascular disease/ep or exp *brain ischemia/ep or exp *carotid artery diseases/ep or exp *intracranial arterial diseases/ep or exp *"intracranial embolism and thrombosis"/ep or *intracranial haemorrhages/ep or *stroke/ep or exp *brain infarction/ep or exp *vertebral artery dissection/ep

3. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or intracranial haemorrhages/ or stroke/ or exp brain infarction/ or exp vertebral artery dissection/

4. (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$ or SAH).tw.

5. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$)).tw.

6. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

7. 3 or 4 or 5 or 6

8. (type$ of stroke or stroke type$ or subtype$ or classification or TOAST or BAMFORD).tw.

9. (stroke adj5 categor$).tw.

10. risk factors/ or risk factor$.tw.

11. *cerebrovascular disorders/et or exp *basal ganglia cerebrovascular disease/et or exp *brain ischemia/et or exp *carotid artery diseases/et or exp *intracranial arterial diseases/et or exp *"intracranial embolism and thrombosis"/et or *intracranial haemorrhages/et or *stroke/et or exp *brain infarction/et or exp *vertebral artery dissection/et

12. 8 or 9 or 10 or 11

13. 7 and 12

14. 1 or 2 or 13

15. meta-analysis/

16. meta-analysis as topic/

17. (meta anal$ or meta-anal$ or metaanal$).tw.

18. "Review Literature as Topic"/

19. (systematic$ adj4 (review$ or overview$)).tw.

20. (selection criteria or (extract$ adj3 data)).ab.

21. review.pt. and (systematic.ab. or overview.ti.)

22. (handsearch$ or hand-search$ or manual search$).ab.

23. (search$ adj3 (MEDLINE or PUBMED or EMBASE or relevant journals or Science Citation Index or reference list$ or bibliograph$ or database$)).ab.

24. or/15-23

25. 14 and 24

26. (199$ or 20$).ed.

27. 25 and 26

EMBASE

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or occlusive cerebrovascular disease/ or stroke/

2. stroke patient/ or stroke unit/

3. (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$ or SAH).tw.

4. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$)).tw.

5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or parenchymal or intraventricular or infratentorial or supratentorial or basal gangli$ or subarachnoid or putaminal or putamen or posterior fossa) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

6. 1 or 2 or 3 or 4 or 5

7. classification/ or exp clinical classification/ or exp disease classification/

8. (type$ of stroke or stroke type$ or subtype$ or classification or TOAST or BAMFORD).tw.

9. (stroke adj5 categor$).tw.

10. cardiovascular risk/ or risk factor/

11. risk factor$.tw.

12. 7 or 8 or 9 or 10 or 11

13. 6 and 12

14. "systematic review"/ or "systematic review (topic)"/

15. meta analysis/ or "meta analysis (topic)"/

16. (systematic$ adj4 (review$ or overview$)).tw.

17. (meta anal$ or meta-anal$ or metaanal$).tw.

18. (selection criteria or (extract$ adj3 data)).ab.

19. overview.ti.

20. (search$ and (MEDLINE or PUBMED or EMBASE)).ab.

21. 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 13 and 21

23. limit 22 to human

24. (199$ or 20$).em.

25. 23 and 24

Appendix 4. A cover letter for research collaboration with National Taiwan University Hospital.

DIVISION *of* CLINICAL NEUROSCIENCES

The University of Edinburgh
Bramwell Dott Building
Western General Hospital
Crewe Road
Edinburgh EH4 2XU

Telephone 0131 537 2082
Fax 0131 332 5150
Email cathie.sudlow@ed.ac.uk
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Dr.Jiann-Shing, MD, PhD
Associate Professor
Stroke Center and Department of Neurology
National Taiwan University Hospital

4 July 2011

Dear Dr Jiann-Shing,

Potential research collaboration

I am pleased to introduce myself as Chung-Fen Tsai's supervisor for her PhD on epidemiology and genetics of stroke and its subtypes in Taiwan, China and Hong Kong. You will see from her summary report that she has made an excellent start on a systematic review of the relevant literature on studies of incidence of stroke, its pathological types and subtypes and risk factors.

She is keen to continue her research in this area with some analyses of relevant data. We wondered about the possibility of collaborating with you on analyses of the Taiwan Stroke Registry data, perhaps in particular from the National Taiwan University Hospital. Chung-Fen would be keen to discuss

some proposals with you. In particular, we considered that it might be of interest to assess:

(1) The distribution of pathological types and main aetiological subtypes in comparison with European origin populations

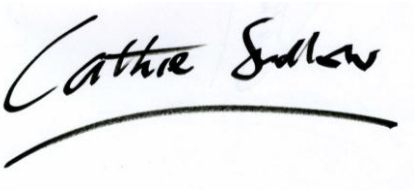
(2) The relative frequencies of vascular risk factors among different ischaemic stroke subtypes in comparison with European origin populations

(3) Family history of stroke and other vascular diseases among those with different stroke types and subtypes in comparison with European origin populations

(4) Genetic differences between aetiological subtypes of ischaemic stroke in comparison with European origin populations.

Chung-Fen will be in Taiwan from 6/7 July until early August and hopes to meet with you to discuss these ideas. If you are interested, I would be happy to discuss any of these further with you by email or telephone.

I look forward to hearing your thoughts in due course, and in the meantime, best wishes,



Yours sincerely,
Dr Cathie Sudlow
Senior Lecturer and Honorary Consultant Neurologist

Appendix 5. National Taiwan Stroke Registry – Patient information form

Stroke and Cerebral Atherosclerosis Study at NTUH (SCAN)

CI	Ath	Lacune	CEI	Specific	Unclassified	ICH	SAH	TIA

A. Basic Information:

Case No: ____ , Chart No : _____ , ID No. :
Name:_____ , Tel : _____ Ward :
Birth date: _____ , Age : ____ , Sex : ☐male , ☐female
Date of admission: _____ , Date of transferring to other ward :
Date of discharge: _____ , Duration of hospitalization : ____days
BW: ____kg, BL: ____cm

B. Past History:

1. Hypertension: ☐Yes, ☐No
2. Diabetes mellitus: ☐Yes, ☐No
3. Ischemic heart disease: ☐Yes, ☐No
4. Atrial fibrillation: ☐Yes, ☐No
5. Rheumatic heart disease: ☐Yes, ☐No； operation
6. Other heart disease:
7. Stroke: ☐Yes, ☐No； type: ☐CI, ☐ICH, ☐SAH
8. TIA: ☐Yes, ☐No
9. Smoking: ☐Yes（☐current, ☐ex-smoking, pack-year___）☐No
10. Drinking: ☐Yes, ☐No
11. Malignancy:
12. Other disease:

C. Family History:

1. HT: ☐grandparents, ☐parents, ☐brothers/sisters, ☐siblings
2. DM: ☐grandparents, ☐parents, ☐brothers/sisters, ☐siblings
3. Stroke: ☐grandparents, ☐parents, ☐brothers/sisters, ☐siblings
4. IHD: ☐grandparents, ☐parents, ☐brothers/sisters, ☐siblings

D. Preset Illness:

1. Stroke/TIA onset date/time:
2. Symptoms/signs: ☐headache, ☐dizziness/vertigo, ☐vomiting, ☐fever, ☐neck stiffness, ☐conscious disturbance (☐drowsiness, ☐stupor, ☐coma), ☐weakness (☐R, ☐L, ☐face, ☐UL, ☐LL), ☐paresthesia (☐R, ☐L, ☐face,

☐UL, ☐LL), ☐diplopia, ☐ataxia, ☐aphasia, ☐dysarthria, ☐dysphagia, ☐sphincter incontinence, ☐mental confusion, ☐ visual field defect, ☐seizure, Others:

3. Duration of onset to door: ☐<3h, ☐3-6h, ☐6-12h, ☐12-24h, ☐2-3D, ☐4-7D, ☐>7D
4. Date/time of ER arrival:
5. Onset-to-peak: ☐sudden, ☐<1h, ☐1-3h, ☐3-6h, ☐6-12h, ☐12-24h, ☐2-3D, ☐>3D
6. Initial GCS:_____ Initial NIHSS:
7. Initial blood pressure: ___/___mmHg

E. Complications: ☐death (Time___), due to ☐chest infection, ☐UTI, ☐UGI bleeding, ☐LGI bleeding, ☐GU bleeding, ☐acute coronary syndrome, ☐AMI, ☐pressure sore, ☐falls, ☐fracture, ☐depression, ☐DVT, ☐pulmonary embolism, ☐painful shoulders, ☐respiratory failure, ☐epileptic seizure (the ___day), others :

F. Images of Brain: ☐CI, ☐ICH, ☐SAH By ☐CT (Time), ☐MRI (Time)

CI site: ☐cortical, ☐small subcortical (lacune), ☐large subcortical, ☐small brainstem, ☐large brainstem/cerebellum, ☐ negative

CH site: ☐lobe/cortical, ☐putamen, ☐thalamus, ☐putamen-thalamus, ☐cerebellum, ☐pons, ☐caudate, ☐IVH, ☐multiple, Others : Sites:

MRA:
CTA:
Angiography:

G. Biochemistry:

1. CBC: Hb___ , Hct___ , WBC___ , PLT
2. Glucose AC____ , HbA1C____ UA
   CHOL____ , TG____ , HDL____ , LDL
3. PT: ____/____ INR____ PTT : ____/
4. BUN/CR: ____/
5. AST/ALT: ____/

H. EEG, ECG and CXR:

1. EEG: ☐normal, ☐focal SW, ☐diffuse SW(☐with, ☐without focal predominance), ☐focal spikes
2. ECG: ☐ Af, ☐LVH, ☐Q waves, others :

3. CXR : ☐Cardiomegaly, ☐Aortic wall calcification

I. Ultrasonography:

1. Duplex of neck vessels (No._____) :
ECCA atherosclerosis: ☐present, ☐absent CCA IMT: R__mm, L__mm
ECCA stenosis ≥ 50%: ☐present, ☐absent

Plaque scoring:

	CCA1	CCA2	Bulb	ICA	ECA
Right					
Left					

Total score:

2. TCDI (No._____)

3. TTE:

4. TEE: