Blood pressure and stroke pathological types in China: an analysis of 500,000 men and women in the China Kadoorie Biobank study

Benjamin W. H. Lacey

MBChB(Edin) MSc(Oxon) FFPH(UK)

St Cross College, University of Oxford

A thesis submitted for the degree

of Doctor of Philosophy

Clinical Trial Service Unit and

Epidemiological Studies Unit (CTSU),

Trinity Term 2013

Abstract

Blood pressure and stroke pathological types in China: an analysis of 500,000 men and women in the China Kadoorie Biobank study

Benjamin W. H. Lacey, St Cross College, University of Oxford.

A thesis submitted for the degree of Doctor of Philosophy, Trinity Term 2013.

Background: Stroke is a leading cause of disability and premature death in China and blood pressure is widely considered to be a major cause. Despite this, substantial uncertainty remains about the shape and strength of the association between blood pressure and stroke pathological types in China.

Methods: Information from the China Kadoorie Biobank study (a prospective cohort study of 0.5 million men and women in China recruited during 2004-8) was used to relate usual blood pressure to risk of stroke, by stroke pathological type (cerebral infarction [ischaemic stroke], intracerebral haemorrhage and subarachnoid haemorrhage). Prospective analyses excluded participants with a history of vascular disease recorded at baseline; involved correction for regression dilution bias; used incident stroke events for which the diagnosis involved a head CT or MRI scan; and, assessed for confounding and effect modification by major vascular risk factors. These prospective analyses were informed by a set of prior analyses, including: a description of baseline associations between blood pressure and other vascular risk factors, to identify potential confounders; analyses of resurvey blood pressure data from ~20 000 participants, to assess regression dilution bias; and analyses of stroke follow-up data, involving an adjudication 'sub-study' performed specifically as part of this thesis, to evaluate the diagnostic accuracy of incident stroke events (~1000 events were adjudicated).

Results: During 2.1 million person-years at risk, there were 5783 incident stroke events. At ages 40-79 years, the proportional difference in risk of both cerebral infarction and intracerebral haemorrhage associated with a given absolute difference in usual blood pressure was constant throughout the range of blood pressures examined (SBP 120-170 mm Hg, DBP 70-100 mm Hg). Overall, the strength of association was approximately 1.5-times greater for intracerebral haemorrhage than for the other stroke pathological types: 10 mm Hg higher usual SBP was associated with 82% (95% CI: 76%-89%) higher risk of intracerebral haemorrhage, 47% (44%-50%) higher risk of cerebral infarction and 52% (35%-71%) higher risk of subarachnoid haemorrhage (the overall mean age at event for each stroke pathological type was ~60 years). For both cerebral infarction and intracerebral haemorrhage, there was strong evidence of major effect modification by age and to a lesser extent by a number of other vascular risk factors. The associations by age were around a third as extreme at age 70-79 years than at 40-49 years. The annual absolute differences in risk associated with a given absolute increase in usual blood pressure, however, were greater at older age.

Conclusions: In Chinese adults, usual blood pressure was strongly and positively related to risk of all stroke pathological types. The strength of association was greater for intracerebral haemorrhage than other stroke pathological types. For both cerebral infarction and intracerebral haemorrhage, there was evidence of major effect modification by age. The overall effect of blood pressure on stroke risk was much greater than estimated by previous prospective studies in China, particularly for intracerebral haemorrhage.

Acknowledgements

Firstly, I would like to express my gratitude to the participants of China Kadoorie Biobank.

I would like to thank my supervisors, Dr Gary Whitlock and Prof Zhengming Chen; their time and guidance have been essential to this thesis and, no doubt, invaluable to my career. I am also indebted to Dr Sarah Lewington for her extensive statistical and epidemiological advice, and for reviewing an earlier version of the full manuscript. Sarah helped supervise the thesis during the final six months, owing to a serious illness affecting Gary.

I have also been supported by the wider China Kadoorie Biobank team, both in Oxford and China. In particular, I would like to acknowledge statistical support from Dr Margaret Smith, support with technical database issues from Mr Alex Williams, graphics support from Mr Paul Sherliker and clinical support from Dr Yiping Chen.

I would like to thank Dr Cathie Sudlow and Dr William Whiteley, from the Stroke Research Group at the University of Edinburgh, for their advice on several clinical aspects of the study and their help in conducting the UK pilot of the adjudication sub-study.

I am extremely grateful to Dr Premila Webster, Head of the School of Public Health at NHS Oxford Deanery, for her pastoral care and for arranging my DPhil placement. I am also grateful to Prof Sir Rory Collins and Prof Sir Richard Peto, co-directors of the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), for the opportunity of working at CTSU and the financial contribution of the Unit towards my DPhil studies.

Lastly, I would like to thank my family: my parents, Hubert and Sue; my grandparents, Percy, Margaret, Richard and Constance; my siblings, Emma and Joff; and my wife, Kate, to whom this thesis is dedicated. I am extremely lucky to have such a wonderful, supportive family.

Contents

Abstract ii

Acknowledgements iv

Contents vi

List of Tables viii

List of Figures xiv

List of Abbreviations xx

Chapter 1: Introduction 1

1.1 Definition of stroke and the main pathological types of stroke 1

1.2 Stroke occurrence in China 3

1.3 Blood pressure and stroke 7

1.4 Other main known determinants of stroke 11

Chapter 2: Literature Review 23

2.1 Selected articles 24

2.2 Integration and appraisal of evidence 31

2.3 Aims of thesis 35

Chapter 3: Methods 40

3.1 Baseline survey 41

3.2 Resurveys 44

3.3 Follow-up 45

3.4 Adjudication sub-study 47

3.5 Selection of variables and data analyses 51

Chapter 4: Results 68

4.1 Participant characteristics 68

4.2 Baseline associations of blood pressure with major potential confounders..70
4.3 Regression dilution ratios for blood pressure 77
4.4 Completeness and accuracy of incident stroke events.................................79
4.5 Stroke incidence rates 85
4.6 Associations of usual blood pressure with stroke incidence..........................87
Chapter 5: Discussion 150
5.1 Summary of main findings 150
5.2 Strengths and limitations of the study...151
5.3 Consistency with published literature 160
5.4 Causality...170
5.5 Future research 172
5.6 Public health implications 175
5.7 Conclusion...176
Appendix A: China Ecological Study results 180
Appendix B: CKB additional results: baseline analyses 189
Appendix C: CKB additional results: incident stroke events..............................203
Appendix D: CKB additional results: prospective analyses (I) 214
Appendix E: CKB additional results: prospective analyses (II)...........................229
Appendix F: CKB adjudication sub-study stroke adjudication form......................251
References..257

List of Tables

Table 1.1: Stroke mortality rates at age 35-69 years in 2008, by sex....................19

Table 2.1: Characteristics of studies included in Literature Review.......................38

Table 2.2: Key results of studies included in Literature Review.............................39

Table 4.1: Baseline demographic characteristics, by area (among 488 789 participants)..100

Table 4.2: Other selected baseline characteristics, by sex (among 488 789 participants)..101

Table 4.3: Baseline associations of blood pressure with sex, education and area (among 488 789 participants)..106

Table 4.4: Baseline associations of blood pressure with dietary variables (among 488 789 participants)..108

Table 4.5: Baseline associations of blood pressure with other variables (among 488 789 participants)..111

Table 4.6: Baseline demographic characteristics of resurveyed participants, by area (among 18 791 participants resurveyed)..113

Table 4.7: Regression dilution ratios for blood pressure using Rosner's regression method, by age and sex specific baseline groups (among 18 791 participants resurveyed) 117

Table 4.8: Regression dilution ratios calculated using the group method and intraclass correlation coefficient method, by age- and sex-specific baseline groups (among 18 791 participants resurveyed)..118

Table 4.9: Number of incident stroke events, by area and pathological type of stroke (among 488 789 participants)..120

Table 4.10: Number of incident stroke events reported by the disease surveillance system, by area and pathological type of stroke (among 488 789 participants) ..121
Table 4.11: Number of incident stroke events known to have been imaged by CT/MRI scan, by area and pathological type of stroke (among 488 789 participants)..122
Table 4.12: Adjudication sub-study: stroke events selected, by surveillance system, hospital tier, area and stroke pathological type 124
Table 4.13: Adjudication sub-study: comparison of CKB reported diagnoses and adjudicated diagnoses (among 1022 stroke events) 125
Table 4.14: Adjudication sub-study: positive predictive value (PPV) of ischaemic stroke, by surveillance system, hospital tier, area, age and sex (among 807 ischaemic stroke events)..126
Table 4.15: Number and crude incidence rate of incident stroke events, by age, sex and pathological type (among 455 438 participants) 128
Table 4.16: Number and crude incidence rate of incident stroke events, by area and pathological type of stroke (among 455 438 participants) 129
Table 4.17: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher usual SBP and 5 mm Hg higher usual DBP, progressively adjusted for major potential confounders (among 455 438 participants)................................132
Table 4.18: Intracerebral haemorrhage incidence (1071 events): hazard ratios per 10 mm Hg higher usual SBP and 5 mm Hg usual DBP, progressively adjusted for major potential confounders (among 455 438 participants)................................140
Table 4.19: Comparison between blood pressure indices as predictors of incidence of cerebral infarction and intracerebral haemorrhage, by age and by sex (among 455 438 participants)...149

Table A.1: Pearson's correlation coefficients of county stroke mortality at age 35-69 in 1986-88 with county level values of vascular risk factors in 1989, in 67 counties in China, by sex 181
Table A.2: Literature Review database searches: textwords and MeSH terms...187
Table A.3: Diagnostic criteria for stroke pathological types 188
Table B.1: Number of participants recruited at baseline and number excluded from analyses, by area 190
Table B.2: Criteria for excluding participants with outlying values in key variables 191
Table B.3: Baseline correlations between blood pressure, adiposity variables, and physical activity in MET hours/day (among 199 825 males and 288 964 females participants)....192
Table B.4: Baseline associations of blood pressure with age, for males and females, minimally adjusted (among 488 789 participants)....193
Table B.5: Baseline associations of blood pressure with measures of adiposity, with adjustment for other adiposity measures (among 488 789 participants)......194
Table B.6: Baseline associations of blood pressure with alcohol intake, with adjustment for smoking (among 488 789 participants)....195
Table B.7: Baseline associations of blood pressure with measures of adiposity, minimally adjusted (among 488 789 participants) 196
Table B.8: Baseline associations of blood pressure with alcohol intake and month of baseline survey, minimally adjusted (among 488 789 participants)....197
Table B.9: Baseline associations of blood pressure with other selected variables, minimally adjusted (among 488 789 participants) 198

Table B.10: Baseline associations of blood pressure with measures of adiposity, extensively adjusted (among 488 789 participants)..199

Table B.11: Baseline associations of blood pressure with dietary variables, extensively adjusted (among 488 789 participants)..200

Table B.12: Baseline associations of blood pressure with alcohol intake and month of baseline survey, extensively adjusted (among 488 789 participants)..............201

Table B.13: Baseline associations of blood pressure with other variables, extensively adjusted (among 488 789 participants)..202

Table C.1: Number of incident stroke events, by age, by sex and by area (among 488 789 participants)...204

Table C.2: Number of incident stroke events reported by the disease surveillance system, by age, by sex and by area (among 488 789 participants)....................205

Table C.3: Number of stroke deaths reported by the mortality surveillance system, by age, by sex and by area (among 488 789 participants).................................206

Table C.4: Number of incident events of each stroke pathological type, by age and sex (among 488 789 participants) 208

Table C.5: Number of incident stroke events of each pathological type known to have been imaged by CT/MRI scan, by age and sex (among 488 789 participants) 209

Table C.6: Adjudication sub-study: comparison of CKB data diagnoses and the adjudicated diagnoses in 902 'matched' stroke events 210

Table C.7: Adjudication sub-study: comparison of CKB data diagnoses and adjudicated diagnoses, restricted to events used in subsequent prospective analyses (among 416 ischaemic stroke events)..211

Table C.8: Adjudication sub-study: positive predictive value (PPV) of ischaemic stroke, by surveillance system, hospital tier, area, age and sex; restricted to events used in subsequent prospective analyses (among 416 ischaemic stroke events) 212

Table C.9: Adjudication sub-study: comparison of CKB data diagnoses and the adjudicated diagnoses in 362 stroke events known to have been imaged by CT/MRI scan 213

Table D.1: Associations of stroke incidence with age, sex, education and area, by main stroke pathological types (among 455 438 participants)....................215

Table D.2: Associations of stroke incidence with measures of adiposity at baseline, by main stroke pathological types (among 455 438 participants)....................218

Table D.3: Associations of stroke incidence with measures of adiposity at baseline, additionally adjusted for other measures of adiposity (among 455 438 participants)....................219

Table D.4: Associations of stroke incidence with dietary variables at baseline, by main stroke pathological types (among 455 438 participants)....................220

Table D.5: Associations of stroke incidence with alcohol intake at baseline and month of baseline survey, by stroke pathological type (among 455 438 participants)....................223

Table D.6: Associations of stroke incidence with other variables at baseline, by main stroke pathological types (among 455 438 participants)....................224

Table D.7: Associations of stroke incidence with measures of adiposity at baseline, extensively adjusted (among 455 438 participants)....................225

Table D.8: Associations of stroke incidence with dietary variables at baseline, extensively adjusted (among 455 438 participants)....................226

Table D.9: Associations of stroke incidence with alcohol intake at baseline and month of baseline survey, extensively adjusted (among 455 438 participants)...227

Table D.10: Associations of stroke incidence with other variables at baseline, extensively adjusted (among 455 438 participants)..228

Table E.1: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher baseline SBP and 5 mm Hg higher baseline DBP, progressively adjusted for major potential confounders (among 455 438 participants)............................230

Table E.2: Intracerebral haemorrhage incidence (1071 events): hazard ratios for 10 mm Hg higher baseline SBP and 5 mm Hg higher baseline DBP, progressively adjusted for major potential confounders (among 455 438 participants) 231

Table E.3: Comparison between blood pressure indices as predictors of incidence of cerebral infarction and intracerebral haemorrhage, by age and by sex (among 455 438 participants)...250

List of Figures

Figure 1.1: Stroke pathological types and subtypes 20

Figure 1.2: Stroke mortality at age 35-69 in 1986-88, by sex, in 67 counties in China 21

Figure 1.3: A model of the main causal relationships between common vascular risk factors and stroke pathological types 22

Figure 2.1: Flow chart of selection process for articles included in Literature Review 37

Figure 3.1: Map of China with locations of the China Kadoorie Biobank survey areas 67

Figure 4.1: Frequency distribution of baseline SBP values, by sex (among 488 789 participants)...102

Figure 4.2: Frequency distribution of baseline DBP values, by sex (among 488 789 participants)...103

Figure 4.3: Baseline associations of blood pressure with age, by sex (among 488 789 participants)...105

Figure 4.4: Baseline associations of SBP with measures of adiposity (among 488 789 participants)...107

Figure 4.5: Baseline associations of blood pressure with alcohol intake (among 488 789 participants)...109

Figure 4.6: Baseline associations of blood pressure with month of baseline survey (among 488 789 participants)..110

Figure 4.7: Serial changes in mean blood pressure within groups defined by baseline blood pressure quintiles (among 18 791 participants resurveyed) 114

Figure 4.8: Scatter plot of resurvey blood pressure vs baseline blood pressure (among 18 791 participants resurveyed) 115
Figure 4.9: Resurvey blood pressure vs baseline blood pressure (among 18 791 resurveyed participants) 116
Figure 4.10: Number and proportion of incident stroke events known to have been imaged by CT/MRI scan, by pathological type of stroke (among 488 789 participants)..123
Figure 4.11: Cerebral infarction incidence (4513 events) versus usual SBP and usual DBP (among 455 438 participants)..131
Figure 4.12: Cerebral infarction incidence (4513 events) in each decade of age at risk versus usual SBP (among 455 438 participants) 133
Figure 4.13: Cerebral infarction incidence (4513 events) in each decade of age at risk versus usual DBP (among 455 438 participants)..134
Figure 4.14: Cerebral infarction incidence (4513 events): age-specific hazard ratios for 10 mm Hg higher usual SBP, by sex (among 455 438 participants) 135
Figure 4.15: Cerebral infarction incidence (4513 events): age-specific hazard ratios for 5 mm Hg higher usual DBP, by sex (among 455 438 participants) 136
Figure 4.16: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher usual SBP, by set (I) of potential effect modifiers (among 455 438 participants)..137
Figure 4.17: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher usual SBP, by set (II) of potential effect modifiers (among 455 438 participants)..138
Figure 4.18: Intracerebral haemorrhage incidence (1071 events) versus usual SBP and usual DBP (among 455 438 participants)..139

Figure 4.19: Intracerebral haemorrhage incidence (1071 events) in each decade of age at risk versus usual SBP (among 455 438 participants) 141

Figure 4.20: Intracerebral haemorrhage incidence (1071 events) in each decade of age at risk versus usual DBP (among 455 438 participants)..............................142

Figure 4.21: Intracerebral haemorrhage incidence (1071 events): age-specific hazard ratios for 10 mm Hg higher usual SBP, by sex (among 455 438 participants)...143

Figure 4.22: Intracerebral haemorrhage incidence (1071 events): age-specific hazard ratios for 5 mm Hg higher usual DBP, by sex (among 455 438 participants)...144

Figure 4.23: Intracerebral haemorrhage incidence (1071 events): hazard ratios for 10 mm Hg higher usual SBP, by set (I) of potential effect modifiers (among 455 438 participants)..145

Figure 4.24: Intracerebral haemorrhage incidence (1071 events): hazard ratios for 10 mm Hg higher usual SBP, by set (II) of potential effect modifiers (among 455 438 participants)..146

Figure 4.25: Stroke incidence: hazard ratios per 10 mm Hg higher usual SBP for each stroke pathological type, by diagnostic certainty of stroke events (among 455 438 participants)..147

Figure 4.26: Stroke incidence: hazard ratios per 5 mm Hg higher usual DBP for each stroke pathological type, by diagnostic certainty of stroke events (among 455 438 participants)..148

Figure 5.1: Cerebral infarction incidence: age-specific hazard ratios for 10 mm Hg higher usual SBP in the CKB study and other studies..178

Figure 5.2: Intracerebral haemorrhage incidence: age-specific hazard ratios for 10 mm Hg higher usual SBP in the CKB study and other studies 179

Figure A.1: Scatter plots of county stroke mortality at age 35-69 in 1986-88 with county level values of vascular risk factors in 1989, in 67 counties in China, by sex 182

Figure E.1: Male: cerebral infarction incidence (2246 events): hazard ratios for 10 mm Hg higher usual SBP, by potential effect modifiers (among 184 949 male participants)..232

Figure E.2: Female: cerebral infarction incidence (2267 events): hazard ratios for 10 mm Hg higher usual SBP, by potential effect modifiers (among 270 489 female participants)..233

Figure E.3: Overall: cerebral infarction incidence (4513 events): hazard ratios for 5 mm Hg higher usual DBP, by set (I) of potential effect modifiers (among 455 438 participants)..234

Figure E.4: Overall: cerebral infarction incidence (4513 events): hazard ratios for 5 mm Hg higher usual DBP, by set (II) of potential effect modifiers (among 455 438 participants)..235

Figure E.5: Male: cerebral infarction incidence (2246 events): hazard ratios for 5 mm Hg usual DBP, by potential effect modifiers (among 184 949 male participants)..236

Figure E.6: Female: cerebral infarction incidence (2267 events): hazard ratios for 5 mm Hg usual DBP, by potential effect modifiers (among 270 489 female participants)..237

Figure E.7: Male: intracerebral haemorrhage incidence (608 events): hazard ratios for 10 mm Hg usual SBP, by potential effect modifiers (among 184 949 male participants)....238
Figure E.8: Female: intracerebral haemorrhage incidence (463 events): hazard ratios for 10 mm Hg usual SBP, by potential effect modifiers (among 270 489 female participants)....239
Figure E.9: Overall: intracerebral haemorrhage incidence (1071 events): hazard ratios for 5 mm Hg usual DBP, by set (I) of potential effect modifiers (among 455 438 participants)....240
Figure E.10: Overall: intracerebral haemorrhage incidence (1071 events): hazard ratios for 5 mm Hg usual DBP, by set (II) of potential effect modifiers (among 455 438 participants)....241
Figure E.11: Male: intracerebral haemorrhage incidence (608 events): hazard ratios for 5 mm Hg higher usual DBP, by potential effect modifiers (among 184 949 male participants)....242
Figure E.12: Female: intracerebral haemorrhage incidence (463 events): hazard ratios for 5 mm Hg higher usual DBP, by potential effect modifiers (among 270 489 female participants)....243
Figure E.13: Stroke incidence: age-specific hazard ratios for 10 mm Hg higher usual SBP, by main stroke pathological types (among 455 438 participants)....244
Figure E.14: Stroke incidence: age-specific hazard ratios for 5 mm Hg higher usual DBP, by main stroke pathological types (among 455 438 participants)....245
Figure E.15: Excluding participants taking blood pressure medication: cerebral infarction incidence (4054 events): age-specific and sex-specific hazard ratios for

10 mm Hg higher usual SBP and 5 mm Hg higher usual DBP (among 438 837 participants)..246

Figure E.16: Excluding participants taking blood pressure medication: intracerebral haemorrhage incidence (959 events): age-specific and sex-specific hazard ratios for 10 mm Hg higher usual SBP and 5 mm Hg higher usual DBP (among 438 837 participants)..247

Figure E.17: Restricted to stroke events not known to involve imaging with CT/MRI scan: stroke incidence: age-specific and sex-specific hazard ratios for 10 mm Hg higher usual SBP, by main stroke pathological types (among 455 438 participants) 248

Figure E.18: Restricted to stroke events not known to involve imaging with CT/MRI scan: stroke incidence: age-specific and sex-specific hazard ratios for 5 mm Hg higher usual DBP, by main stroke pathological types (among 455 438 participants) 249

Figure F.1: CKB event adjudication form for stroke...252

List of Abbreviations

SBP	Systolic blood pressure
DBP	Diastolic blood pressure
CKB	China Kadoorie Biobank
CTSU	Clinical Trial Service Unit and Epidemiological Studies Unit
CT	Computed tomography scan
MRI	Magnetic resonance imaging
BMI	Body mass index
MET	Metabolic equivalent of task
SD	Standard deviation
RR	Relative risk
HR	Hazard ratio

Chapter 1: Introduction

Stroke is a leading cause of disability and premature death in China, accounting for ~2 million deaths in 2008.[1] Raised blood pressure is widely considered to be a major cause,[2] but many important details about the relationship between blood pressure and stroke in China remain unclear. This thesis addresses the uncertainties about the shape and strength of the associations between usual blood pressure and risk of the main pathological types of stroke, using cross-sectional, resurvey and prospective data from the largest ever prospective observational study in China, the China Kadoorie Biobank.[3]

This chapter first defines stroke and the main pathological types of stroke; it then describes the occurrence of stroke in China; this is followed by an introduction to the main known determinants of stroke worldwide, focusing on the relationship between blood pressure and stroke. The current evidence describing the relationship between blood pressure and stroke specifically in China is not covered in this chapter, however, but is reviewed systematically in chapter 2, the Literature Review.

1.1 Definition of stroke and the main pathological types of stroke

Stroke has been defined by the World Health Organization as ‘a clinical syndrome consisting of rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than that of vascular origin'.[4] This definition has remained virtually unchanged since it was originally proposed in the 1960s and is a standard definition used throughout the world in epidemiological research and clinical practice.[5] It is a clinical diagnosis and does not require radiological imaging findings. The 24 hour threshold was set arbitrarily as a means of increasing the specificity of clinically diagnosing conditions of primary vascular origin likely to have resulted in permanent neurological injury.[6]

Stroke is not a single disease: it is a heterogeneous group of cerebrovascular disorders. There are three major pathological types: ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage.[7] Ischaemic stroke occurs as a result of an occlusion or significant stenosis of an artery supplying the brain, intracerebral haemorrhage occurs as a result of an arterial bleed directly into an intraparenchymal region of the brain, and subarachnoid haemorrhage occurs as a result of an arterial bleed directly into the subarachnoid space. Each type can be further divided into subtypes according to the pathological nature, or site within the brain, of the causative lesion (figure 1.1). Diagnosing the pathological type of stroke requires clinical criteria of stroke to be fulfilled together with the appropriate findings from an autopsy or radiological imaging of the head using a computed tomography (CT) scan or magnetic resonance imaging (MRI); subarachnoid haemorrhage can also be diagnosed from the appropriate findings of a lumbar puncture.[8]

1.2 Stroke occurrence in China

A few well-designed studies have attempted to measure the incidence of stroke in various parts of China since the 1980s.[9,10,11] The most internationally comparable results are from the World Health Organisation MONICA project. This is an international collaborative study, initiated in 1981, with the objective of measuring trends and determinants of cardiovascular disease in a selection of populations around the world, including China. The Sino-MONICA project measured stroke incidence in Beijing between 1985 and 1987 as part of this study.[10] Annual stroke incidence rates in Beijing at age 35 to 64 years, age-standardised to the Segi World Population, were 275 per 100 000 for males and 125 per 100 000 for females. The incidence of stroke in the other MONICA sites that measured stroke incidence at this time (those in western or eastern Europe, including Russia) ranged from 100 to 290 per 100 000 for males and 50 to 220 per 100 000 for females. The incidence of stroke in Beijing was higher than other MONICA sites in central and southern Europe and lower than sites in Russia, Finland and Lithuania.[10] These comparatively high stroke incidence rates in Beijing are consistent with high stroke mortality rates reported through China's mortality surveillance system at a national level. National stroke mortality rates in 2008 at age 35-69 years were considerably higher in China for both sexes than in Japan, USA and UK, and somewhat higher than in Poland (table 1.1).

The Sino-MONICA project was expanded in 1987 to include 17 regions, distributed throughout China; the study measured stroke incidence between 1987 and 1993.[11] It found considerable variation in incidence, with a ten-fold difference between sites: the annual incidence rates at age 35-64 years, again, age-standardised to the Segi World Population, ranged from 74 to 751 per 100 000 for males and 41 to 406 per 100 000 for females. In both sexes, the incidence tended to be higher in northern than southern regions. Similar studies of stroke mortality in China have also described a marked geographic variation, with higher rates in the north of the country.[12,13,14] Figure 1.2 illustrates the geographic variation in stroke mortality in 67 rural counties in China from a study[14] conducted in the late 1980s, but independently analysed and mapped here, for the purpose of this thesis. The study shows that county stroke mortality rates were uniformly high compared to the West; the equivalently calculated annual stroke mortality rates at age 35-69 years for 1990 in the UK was 41 deaths per 100 000 for males and 32 deaths per 100 000 for females.[14] The reason for the enormous variation in stroke incidence and mortality in China remains largely unexplained.[3] Further analyses from the same study, found that the geographic variation in rates in China was poorly explained by variation in the prevalence of established vascular risk factors, such as blood pressure and blood cholesterol level, at a county level (table A.1 and figure A.1 in appendix A).

The Sino-MONICA project in Beijing continued until 2004.[15] Overall, the incidence of stroke at age 25-74 years increased in both males and females over the 20-year study period. Age-standardised to population distribution of the China national census in 2000, the annual incidence of stroke in males, increased from 208 to 291 per 100 000 and in females from 171 to 205 per 100 000. Clinical criteria rather than CT or MRI were used to diagnose the pathological type of stroke in the first few years of the study and, as such, reliable incidence rates by stroke pathological type are only available for the last decade of the study, from 1994 to 2004: the CT scan rate increased from <5% of all reported strokes in 1985 to 84% in 1994, and 97% in 2004. In males, the annual incidence of ischaemic stroke at age 25-74 years slightly increased over this last decade, from 236 to 242 per 100 000, whereas the incidence of intracerebral haemorrhage fell from 70 to 49 per 100 000. Likewise, in females, the annual incidence of ischaemic stroke at age 25-74 years increased over the same period from 159 to 183 per 100 000, whilst that of intracerebral haemorrhage fell from 63 to 22 per 100 000.

The incidence rates for each pathological type of stroke in the Sino-MONICA project in Beijing are higher than those reported in high quality studies conducted in the West at around the same time. [16,18,19] For comparison, the annual incidence rates at age 25-74 years in the North East Melbourne Stroke Incidence Study[17] for 1996 to 1997, age-standardised to the Chinese population in 2000[18] (age-specific comparisons were not possible as these were not reported for the Sino-MONICA project in Beijing), were 117 per 100 000 and 27 per 100 000, for ischaemic stroke and intracerebral haemorrhage, respectively, in males, and 86 per 100 000 and 18 per 100 000, for ischaemic stroke and intracerebral haemorrhage, respectively, in females. These rates for ischaemic stroke are around half those reported in the Sino-MONICA project in Beijing in 1994, and for intracerebral haemorrhage somewhat less than half. The rates in North East Melbourne were broadly similar to other community-based studies conducted in the UK,[16] USA[18] and other parts of Australasia[19] around this time.

The reason for the particularly high rates of intracerebral haemorrhage in the Sino-MONICA project in Beijing in the mid-1990s, and the major reduction since, is not clear. Other stroke incidence studies in China have also described particularly high rates of intracerebral haemorrhage,[9,19,20] as have other studies in parts of East Asia.[21] None of the incidence studies identified, however, including the Sino-MONICA project in Beijing (the highest quality stroke incidence study in China identified), fulfilled suggested 'ideal criteria'[21] for stroke incidence studies; the main methodological weakness were low rates of CT/MRI scanning, poor case ascertainment methods and a lack of standard diagnostic criteria for stroke pathological types. As such, methodological weakness cannot be excluded as a possible explanation for the high rates of intracerebral haemorrhage. Despite this, the rates of stroke (of all pathological types combined) in some parts of China are undoubtedly much higher than the West, the reason for which has not been fully explained.

The Sino-MONICA project in Beijing also measured the incidence of subarachnoid haemorrhage from 1985 to 1993. Age-standardised to the Segi World Population, the annual incidence at age 25-64 years was 1.9 per 100 000 for males and 2.0 per 100 000 for females.[22] This was lower than other MONICA sites in Europe and Russia, which had annual incidence rates ranging from 4.8 to 26.0 per 100 000. Case-ascertainment of subarachnoid haemorrhage in Beijing was considered to be poor and as such the reported incidence is likely to be an underestimate of the true incidence.[22]

1.3 Blood pressure and stroke

There is substantial evidence from clinical trials and observational studies that blood pressure is a cause, and an important cause, of stroke. Meta-analyses of randomised controlled trials[23,24,25] have shown conclusively that blood pressure-lowering medication reduces the risk of stroke: lowering usual blood pressure by 10 mm Hg SBP has been shown to reduced stroke risk by ~40%.[25] The consistency in the relationship between blood pressure lowering and the risk of stroke across the classes of blood pressure medications, despite their different modes of action, suggests that blood pressure reduction itself explains the preventive effect of these drugs. To date, the most reliable estimates for the age-specific associations between blood pressure and stroke have been produced by two meta-analyses of prospective studies: the Prospective Studies Collaboration study[26] and the Asia Pacific Cohort Studies Collaboration study.[27]

The Prospective Studies Collaboration published a meta-analysis in 2002 using individual records from 958 074 participants in 61 studies conducted mainly in the West: ~70% of participants were from Europe, ~20% from North America or Australia and the remainder from Japan or China. During 12.7 million person-years of follow-up, there were 11 960 deaths attributed to stroke: 2083 ischaemic strokes, 2541 intracerebral haemorrhages, 712 subarachnoid haemorrhages and 6624 unclassified.

The Asia Pacific Cohort Studies Collaboration published a meta-analysis in 2003 using individual records from 425 325 participants in 37 cohort studies. Unlike the

Prospective Studies Collaboration, most of the studies involved in this meta-analysis were conducted in East Asia: 43% of participants were from South Korea, 28% from mainland China, 8% from Japan, 4% from elsewhere in Asia and 17% from Australia or New Zealand. During 3.0 million person-years of follow-up, there were 5178 stroke events (fatal and non-fatal stroke events): 1802 ischaemic strokes, 1531 intracerebral haemorrhages, and 1845 other or unclassified strokes.

Both meta-analyses found that the associations between usual blood pressure and stroke were approximately log-linear at all levels of blood pressure down to at least 115 mm Hg SBP and around 75 mm Hg DBP. Both studies also found effect modification by age, with progressively shallower associations with increasing age. At ages 60-69 years, 10 mm Hg higher usual SBP was associated with a similar increase in stroke risk in both studies: 52% (95% CI: 49-56) in the Prospective Studies Collaboration study and 56% (52-61) in the Asia Pacific Cohort Studies Collaboration study. The Prospective Studies Collaboration found weak evidence of slightly stronger age-specific associations in males than females, whereas the Asia Pacific Cohort Studies Collaboration found the strength of association did not differ by sex. The Asia Pacific Cohort Studies Collaboration study presented main results for SBP rather than DBP; the Prospective Studies Collaboration study presented main results for both indices but found SBP to be a slightly better predictor of stroke risk than DBP.

The Prospective Studies Collaboration study did not find major differences in the strength of the age-specific associations between ischaemic stroke and intracerebral haemorrhage: at age 60-69 years, 10 mm Hg higher usual SBP was associated with 49% (95% CI: 4-56) increased risk of ischaemic stroke and 52% (46-60) increased risk of intracerebral haemorrhage. By contrast, the Asia Pacific Cohort Studies Collaboration study found evidence of stronger associations for intracerebral haemorrhagic than ischaemic stroke at age 50-69 years but not at older ages: at age 60-69 years, 10 mm Hg increase in usual SBP was associated with 54% (95% CI: 45-64) increased risk of ischaemic stroke and 67% (95% CI: 59-79) increased risk of intracerebral haemorrhage; at age 50-59 years, the difference in strength of association was more marked: 10 mm Hg increase in usual SBP was associated with 75% (95% CI: 64-89) increased risk of ischaemic stroke and 113% (100-127) increased risk of intracerebral haemorrhage.

The Asia Pacific Cohort Studies Collaboration study reported the age-adjusted rather than age-specific associations between usual blood pressure and risk of subarachnoid haemorrhage. Overall, 10 mm Hg higher usual SBP was associated with 52% (95% CI: 33-72) higher risk of subarachnoid haemorrhage (mean age at death from subarachnoid haemorrhage was 65 years). At 60-69 years in the Prospective Studies Collaboration study, 10 mm Hg higher usual SBP was associated with 46% (95% CI: 35-58) higher risk of subarachnoid haemorrhage; the associations for subarachnoid haemorrhage in other age groups were slightly weaker than for the other pathological types.

The statistical methods employed in the two meta-analyses were similar. In particular, both excluded participants with a history of vascular disease at baseline, to limit the effect of reverse causality. They also both used re-survey data on blood pressure to correct for regression dilution bias; this is the bias that results from the inaccuracy with which a single blood pressure measurement characterises an individual's long-term average (or 'usual') blood pressure due to technical measurement error and real temporal variation.[28]

A major limitation of both meta-analyses, however, was the small proportion of stroke pathological type events for which there was evidence that a CT or MRI had been performed. Information on whether a CT or MRI had been performed was only available for around half the studies in the Asia Pacific Cohort Studies Collaboration study, and only half the strokes in these studies are reported as having had a CT or MRI. The proportion of pathological types of stroke diagnosed with CT or MRI in the Prospective Studies Collaboration study was not reported, but for many of the older studies included in the analysis, the technology was simply not available. Without evidence from CT or MRI, misclassification between pathological types of stroke is likely, and high rates of misclassification would tend to attenuate any differences in the strength of associations between pathological types of stroke. Misclassification of pathological type may have been greater in the Prospective Studies Collaboration study, which could account for the lack the differences in the strength of the associations between pathological types reported by the study; or, it may be that there are different pathological mechanisms underlying the pathological types of stroke in the different populations (one being mainly Western, the other mainly East Asian). Another limitation of both meta-analyses was the extent to which they could examine the associations for confounding and effect modification; neither meta-analysis was able to conduct the detailed examination of these associations which a large single study would allow, especially by pathological types of stroke.

1.4 Other main known determinants of stroke

The topic of this thesis is stroke and blood pressure in China, the other main known determinants of stroke risk will be introduced here because of their direct relevance to understanding the relationship between blood pressure and stroke risk. The evidence is described for each stroke pathological type, where available, although this is somewhat more limited for subarachnoid haemorrhage than for the other pathological types. A model of the causal relationships between common vascular risk factors, including blood pressure, and stroke is illustrated in figure 1.3.

1.4.1 Age and sex

Age is a major determinant of stroke. In recent studies conducted in the West, the risk of ischemic stroke and intracerebral haemorrhage approximately doubled for each successive decade after age 55; the risk of subarachnoid haemorrhage also increased with age but to lesser degree.[29,30] The extent to which the increase in risk of stroke with age is due to the greater cumulative effects of prolonged exposure to, and higher levels of, vascular risk factors at older ages, and the extent to which it is due to general degenerative effects of aging itself on the cardiovascular system, is unknown.[31] In these same populations, males have higher age-specific incidence rates than females for ischemic stroke and intracerebral haemorrhage, whereas women have a higher age-specific incidence than men for subarachnoid haemorrhage. [31,32]

1.4.2 Smoking

A positive association between smoking and risk of stroke has been demonstrated in numerous prospective studies,[33,34,35,36] and the totality of evidence has established this relationship as causal. The British Doctors' Study[33] provides the most reliable estimates to date for the risks of lifelong smoking. The results of 50 years of follow-up in this male cohort found that stroke mortality, indirectly standardised for age and study year, was 2.8 per 1000 men per year for lifelong non-smokers compared to 4.3 per 1000 men per year in current smokers. In addition, higher current cigarette intake among current smokers was associated with higher stroke mortality. Results were not given by stroke pathological type as CT and MRI were not available until late in the study.

The association of smoking with risk of stroke by pathological type was assessed in a meta-analysis of thirty-two observational studies[34] published in 1989. Smoking was found to be associated with increased risk of ischaemic stroke and subarachnoid haemorrhage, but not of intracerebral haemorrhage: the risk of stroke in current smokers relative to never smokers was 1.92 (95% CI: 1.71-2.16) for ischaemic stroke, 1.01 (0.81-1.26) for intracerebral haemorrhage and 2.93 (2.48-3.46) for subarachnoid haemorrhage. Meta-analyses conducted by the Asia Pacific Cohort Studies Collaboration and published in 2005,[35,36] found that smoking was positively associated with all pathological types of stroke: the risk of stroke in current smokers relative to never smokers was 1.50 (95% CI: 1.19-1.91) for ischaemic stroke, 1.23 (1.01-1.49) for intracerebral haemorrhage and 2.4 (1.8-3.4) for subarachnoid haemorrhage.

1.4.3 Lipids

Commonly measured blood lipid concentrations include low-density lipoprotein (LDL) cholesterol particles, high-density lipoprotein (HDL) cholesterol particles and triglycerides; total cholesterol is mainly comprised of LDL and HDL cholesterol. Randomised trials of statin therapy have shown that lowering LDL cholesterol reduces the risk of ischaemic stroke, but may slightly increase the risk of intracerebral haemorrhage. A meta-analysis of randomised controlled trials by the Cholesterol Treatment Trialists' Collaborators[37] found a relative risk per mmol/L LDL cholesterol reduction of 0.79 (95% CI: 0.74-0.85) for ischaemic stroke and 1.12 (95% CI: 0.93-1.35) for intracerebral haemorrhage. By contrast, prospective cohort studies[38,39] have found little or no evidence of associations between LDL cholesterol and stroke risk; this inconsistency with the trial results remains unexplained.

The relationship between HDL cholesterol and stroke is less clear. Meta-analyses of prospective cohort studies[38,39] have not found convincing evidence of an association with either ischaemic stroke or intracerebral haemorrhage. The relationship between triglycerides and risk of stroke is also unestablished. Prospective cohort studies[39,40] have described positive associations with stroke before adjustment for other cholesterol fractions and no association after, although it is not clear whether adjustment is appropriate, since these cholesterol fractions may lie on the causal pathway between triglycerides and stroke.[40]

1.4.4 Diabetes

Meta-analyses of prospective cohort studies have found strong positive associations between diabetes and risk of ischaemic stroke, and weak evidence of a positive association with risk of intracerebral haemorrhage. A meta-analysis of prospective studies by the Emerging Risk Factors Collaboration,[39] found the risk of stroke in diabetics relative to those without diabetes was 2.19 (95% CI: 1.98-2.41) for ischemic stroke and 1.14 (95% CI: 0.90-1.43) for intracerebral haemorrhage. A meta-analysis of prospective cohort studies by the Asia Pacific Cohort Studies Collaboration[35] found similar relative risks: 2.16 (95% CI: 1.44-3.24) for ischaemic stroke and 1.41 (95% CI: 0.99-2.01) for intracerebral haemorrhage. This study found no evidence of difference in relative risks between studies conducted in Asia and Australasia. Both meta-analyses adjusted for age, smoking, BMI, and SBP, and the Asia Pacific Cohort Studies Collaboration additionally adjusted for total cholesterol. As there is evidence that diabetes may cause both dyslipidaemia[41] and raised blood pressure,[42] these associations should be interpreted as partly controlled for these possible intermediate factors.

1.4.5 BMI

Meta-analyses conducted by the Prospective Studies Collaboration[43] and the Asia Pacific Cohort Studies Collaboration[44] have found no evidence of an association between BMI and ischaemic stroke risk at lower BMI (15 to ~25 kg/m^2) and positive log-linear associations at higher BMI (>25 kg/m^2). The positive association between BMI and ischaemic stroke is probably causal[43] and may be accounted for by the effects of BMI on blood pressure, cholesterol and risk of diabetes.[45] The shape and strength of the association between BMI and intracerebral haemorrhage is less clear. The meta-analysis by the Prospective Studies Collaboration, found no material difference in the associations for ischaemic stroke and intracerebral haemorrhage.[43] The meta-analysis by the Asia Pacific Cohort Studies Collaboration, found no evidence of an association with risk of intracerebral haemorrhage at BMI <30 kg/m² and weak evidence of a positive association at BMI ≥30 kg/m².[44] There was no evidence in this meta-analysis that the association differed majorly between Asia and Australasia for either pathological type of stroke.

1.4.6 Alcohol

Many studies have shown a U- or J-shaped association between stroke mortality and alcohol consumption, in which people who drink light or moderate amounts have a lower risk than non-drinkers, while those who drink large amounts have a higher risk.[46] A meta-analysis conducted in 2003,[47] found that people who drank on average <12g of alcohol per day had a 20% (95% CI: 9-25) lower risk of ischemic stroke than non-drinkers, while those who drank ≥60g per day had a 69% (34-115) increased risk of ischaemic stroke. In the same meta-analysis, any alcohol intake was associated with an increased risk of intracerebral haemorrhage, and individuals who drank ≥60g of alcohol per day had over twice the risk of non-drinkers (RR 2.18 [1.48-3.20]). The totality of evidence suggests that the relationship between long-term drinking of large amounts of alcohol and both ischaemic and intracerebral haemorrhage is causal,[46] and likely to be mediated primarily by the adverse effects of alcohol on blood pressure,[48] despite an apparent beneficial effect on blood lipids.[49] The benefit of light drinking on the risk of ischaemic stroke, however, is still uncertain: it could also be due to residual confounding, contamination of the non-drinking group with ex-drinkers or failure to account for the within-person variation in alcohol intake.[46]

1.4.7 Physical activity

Meta-analyses of observational studies[50,51] have found a negative association between physical activity and risk of stroke. For example, a meta-analysis of observational studies[50] in 2003, showed that highly active individuals had a relative risk of ischaemic stroke and intracerebral haemorrhage of 0.79 (95% CI: 0.69-0.91) and 0.66 (0.48-0.91), respectively, compared to low activity individuals. The lack of consistency in the measures of physical activity does not allow meta-analyses to reliably determine the relative risk of stroke for a given absolute difference in physical activity; and single studies investigating the relationship between physical activity and stroke have been relatively small. Despite this, the negative association between physical activity and stroke risk is likely to be causal, and may be mediated by the effects of physical activity on blood pressure, blood lipids and adiposity.[52]

1.4.8 Diet

The associations between several aspects of diet and stroke have been investigated, in particular for intake of fats, salt, and fruit and vegetables. The evidence examining an association between dietary fats intake and risk of stroke is limited. The best trial and epidemiological studies to date have not found evidence to support a direct causal effect.[53,54] However, there is good evidence of an association between lower intake of saturated fat and reduced LDL cholesterol blood concentration,[55] which in turn is known to reduce the risk of ischaemic stroke.[37]

A number of ecological and observational studies have found a positive association between salt intake and higher risk of stroke.[56] This association is likely to be causal and mediated, wholly or in part, through the effect of sodium on blood pressure, established in randomised controlled trials.[57,58]

A meta-analysis conducted in 2006 attempted to pool all available data on the association between consumption of fruit and vegetables and risk of stroke.[59] Greater consumption was associated with lower risk of both ischaemic stroke and intracerebral haemorrhage, although the extent to which confounding by known vascular risk factors may account for these associations is uncertain. Blood pressure has been proposed as one of the mechanisms by which fruit and vegetable consumption may reduce stroke risk: high fruit and vegetable intake has been negatively associated with blood pressure in both prospective studies[60] and in sub-group analyses of dietary trials.[61,62]

1.4.9 Other causes

There are a host of rare or less well established causes of stroke. A number of drugs have been found to increase the risk of ischaemic stroke, including the oral contraceptive pill, amphetamines and cocaine. Statins and antithrombotic medication have been found to reduce the risk of ischaemic stroke whilst slightly increasing the risk of intracerebral haemorrhage.[31] Blood pressure-lowering medication use has been found to reduce the risk of stroke, and there is some evidence that their effect on reducing blood pressure variability may reduce the risk of stroke independently of their effect on long-term average blood pressure.[63] Cardiac conditions (such as atrial fibrillation) and carotid artery atheroma, which may give rise to emboli, increase the risk of ischaemic stroke.[31] There are also likely to be genetic causes of stroke: a large stroke genetics consortium[64] has been established and several genetic variants have been found to be associated with ischaemic stroke[65] and intracerebral haemorrhage.[66] In addition, many of the physiological causes of stroke, such as high blood pressure, diabetes, and dyslipidaemia have been found to have genetic determinants.[67]

1.4.10 Overall assessment

Internationally, the relevance of certain common risk factors (such as blood pressure, smoking, alcohol drinking and BMI) to stroke is well established. There is still substantial uncertainty, however, about the strength of their relationships with the each of the stroke pathological types and whether these vary in different populations. For a number of other factors, there is still substantial uncertainty about their relevance to stroke in general or to specific pathological types (e.g. blood lipids and haemorrhagic stroke). A comprehensive assessment of the relationship between blood pressure and stroke pathological types requires large studies, with accurately diagnosed stroke pathological types, in different parts of the world. Studies capable of investigating such relationships in China have only become feasible over the last 5-10 years after the use of CT and MRI became widespread.

Table 1.1: Stroke mortality rates at age 35-69 years in 2008, by sex

Rates for China are from the Ministry of Health of the People's Republic of China,[68] and rates for other countries are from the World Health Organisation.[69] Rates were age-standardised by taking the unweighted average of the component five-year mortality rates (e.g. 35-39, 40-44,…65-69 for the age range 35-69 years).

	Stroke deaths/100,000/year					
	China, rural	China, urban	Poland	Japan	USA	UK
Male	150	103	93	49	27	27
Female	89	56	42	21	21	20

Figure 1.1: **Stroke pathological types and subtypes**[70,71,72]

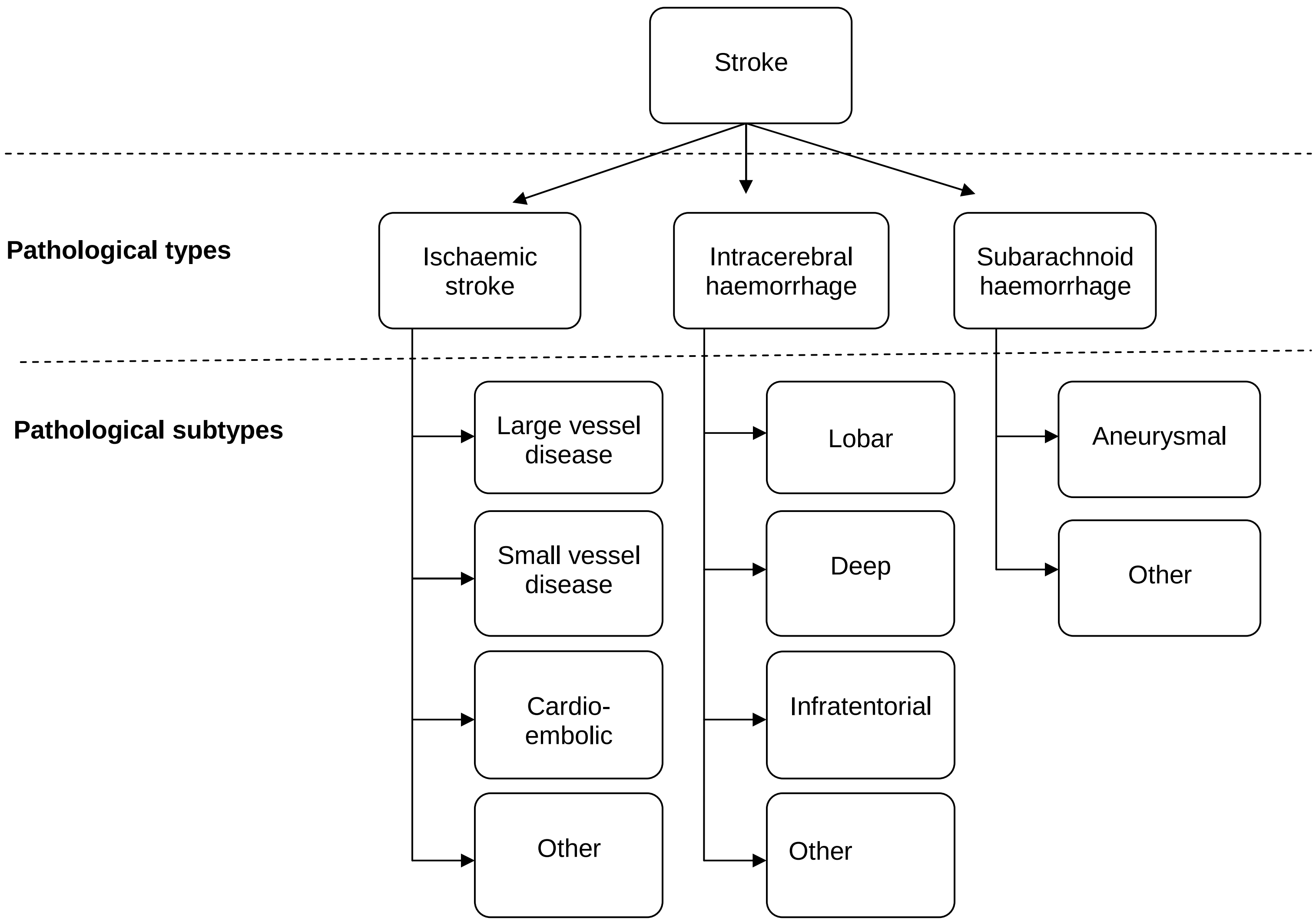


Figure 1.2: Stroke mortality at age 35-69 in 1986-88, by sex, in 67 counties in China

Original analyses of the China Ecological Study of 69 rural counties (two counties did not report stroke mortality rates): maps of mainland China with study counties designated by bullets, coloured by age-standardised stroke mortality rate for those aged 35-69 years (deaths/100,000/year) in 1986-88, by sex. Mortality rates were age-standardised by taking the unweighted average of the component five-year mortality rates.

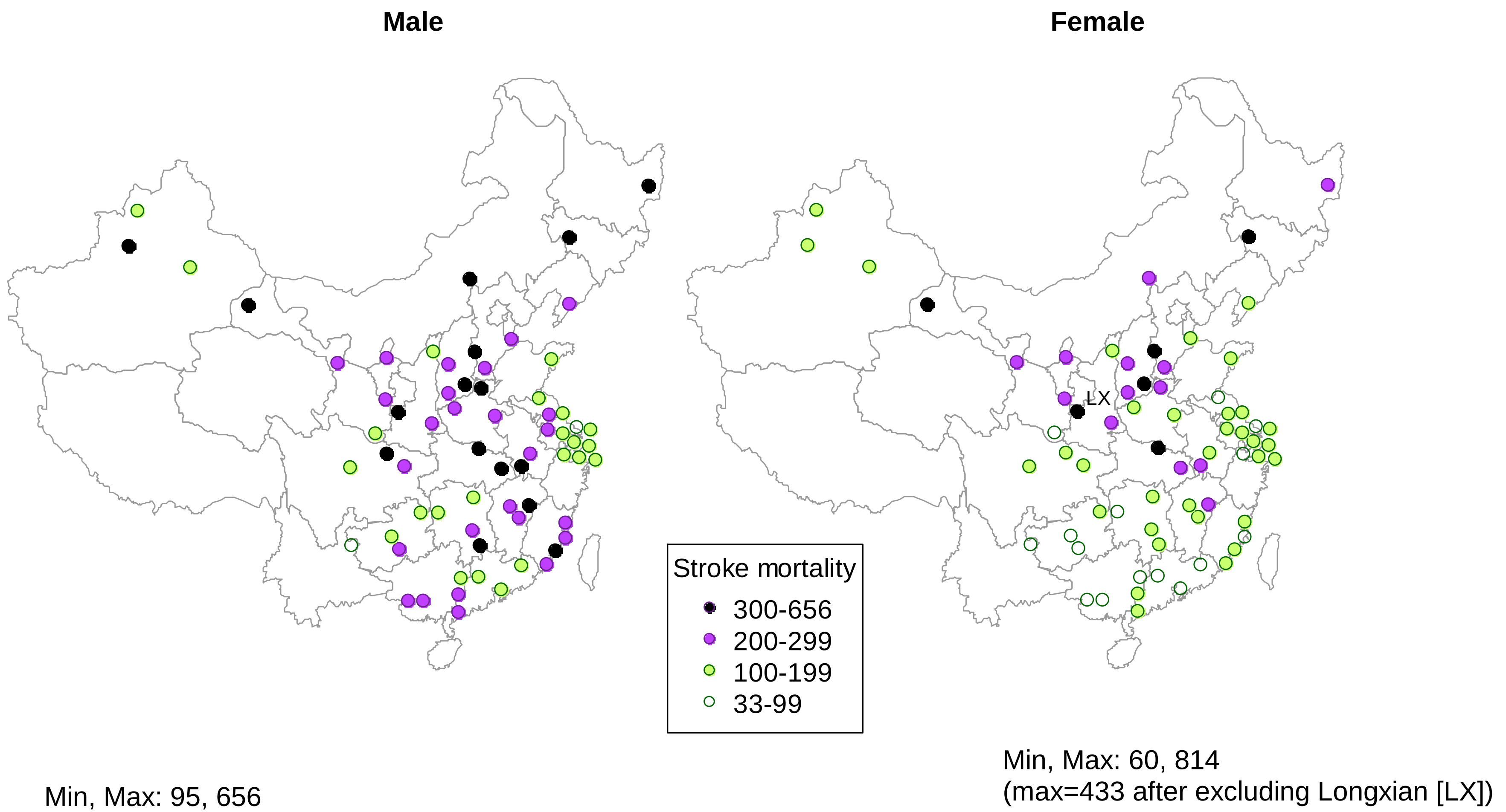
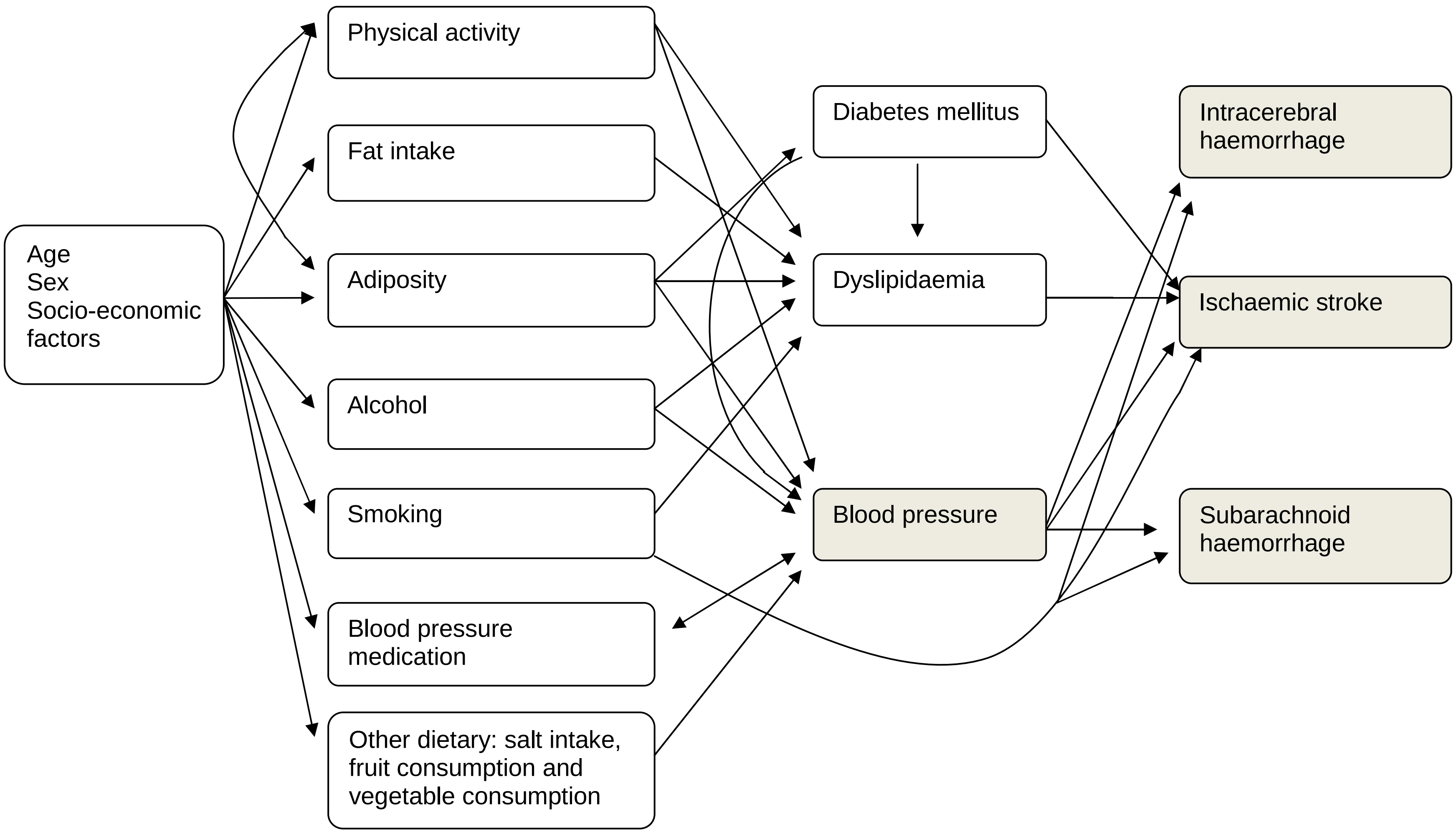


Figure 1.3: A model of the main causal relationships between common vascular risk factors and stroke pathological types[2]

Arrows indicate the direction of causality with double arrows indicating the potential for causality in both directions at different times.



Chapter 2: Literature Review

As the topic of this thesis is blood pressure in relation to stroke in China, this Literature Review summarises and appraises all available evidence in the English language from prospective studies on this topic. The results from the Asia Pacific Cohort Studies Collaboration (with 28% of participants from mainland China) was discussed in the Introduction rather than here, as results specific to China have not been reported.

A literature search was conducted to identify articles from prospective cohort studies conducted in China that reported an association between blood pressure and stroke incidence or stroke mortality. I searched MEDLINE (from 1950), Global Health (from 1973) and EMBASE (from 1980) in June 2010, using the keywords or MeSH terms associated with ‘stroke’, ‘blood pressure’, ‘cohort studies’, and ‘China’ (the full list of keywords and MeSH terms used can be found in table A.2 in appendix A).

There were 281 articles identified by the search which were then processed according to the flowchart shown in figure 2.1. Of these articles, 92 were duplicates and so were excluded. The abstracts of the remaining 189 articles were reviewed and assessed against pre-specified selection criteria: articles were required to report results from prospective cohort studies conducted in mainland China; the outcome needed to be stroke incidence or stroke mortality rather than, for example, stroke recurrence; for practical reasons, the study had to be published in English; and, lastly, articles were excluded where the total number of stroke events was too small to produce reliable results, for which purpose, an arbitrary threshold of 50 stroke events was set.

Five articles met all the selection criteria and these are discussed in turn, below, in ascending year of their baseline survey, and then collectively at the end of the section. The relative risk estimates for the linear associations between blood pressure and stroke reported in these articles have been re-calculated for 10 mm Hg higher SBP and 5 mm Hg higher DBP to facilitate comparisons between studies. The key study characteristics and results of each study are presented in tables 2.1 and 2.2.

2.1 Selected articles

2.1.1 Chinese Steelworkers Cohort Study (1974-1993)

The Chinese Steelworkers Cohort Study[73] recruited 5092 male steelworkers without a prior history of vascular disease from the workforce of the Beijing Iron and Steel Complex between 1974 and 1984. Participants were aged 18-74 years at recruitment and the mean age was 45 years. They were followed up until 1993 by way of in-person interview or telephone call; if the participant had died, a relative was interviewed. Self-reported outcomes were confirmed by a review of hospital medical records. At the conclusion of the study, there were 152 incident stroke events of which 87 were ischaemic strokes, 58 were intracerebral haemorrhages and 7 were unclassified. The proportion of stroke pathological types for which the diagnosis was known to have involved a CT or MRI scan was not given, but it is likely to have been low as CT and MRI scanners were rare in

China at this time. There were 144 participants noted to have been lost to follow-up at the end of the study.

Adjusted for age, total cholesterol, BMI, and smoking, 10 mm Hg higher baseline SBP was associated with 38% (95% CI: 29-49) higher stroke risk and 5 mm Hg higher baseline DBP was associated with 34% (26-42) higher stroke risk. No resurvey of blood pressure was undertaken and, as such, no corrections were made for regression dilution bias.[28] The strength of the associations between blood pressure and stroke risk by pathological type were not reported for a given increase in blood pressure. For each pathological type of stroke, the SBP at baseline was categorised into four groups (<120, 120-140, 140-160 and ≥160 mm Hg) and risk of stroke in each group was given relative to the lowest blood pressure group. Results were also given for DBP, divided into four categories (<80, 80-90, 90-95, ≥95 mm Hg). The mean blood pressure in each blood pressure group was not given. The risk of ischaemic stroke for those in the highest blood pressure group relative to the lowest was 9.8 (95% CI: 4.3-22.3) for SBP and 4.9 (2.5-10.0) for DBP. There was weak evidence of stronger associations for intracerebral haemorrhage: the equivalent relative risks were 21.2 (95% CI: 6.7-26.4) for SBP and 10.6 (4.2-12.6) for DBP.

2.1.2 Prospective Study of 212 000 Chinese Men (1990-2002)

This much larger study started recruitment around 15 years later than the Chinese Steelworkers Cohort Study. It recruited a nationally representative cohort of 212 000 Chinese men from 1990 to 1991.[74] Participants were recruited from 45 areas across China, which were selected at random from the 145 Disease

Surveillance Points (these were areas established in the 1980s to provide a nationally representative sample of mortality statistics for the entire country and are co-ordinated by the Chinese Center for Disease Control). After the baseline survey, the vital status of each study participant was monitored passively through these death registries with active confirmation of vital status assessed annually by local residential committees. Causes of death were sought from official death certificates, supplemented as necessary by a review of medical records.

The results presented in the article were based on follow-up to January 2002 among men aged 40-79 years at baseline (mean 54 years) with no reported history of vascular disease. The authors restricted analyses to deaths occurring at age 40-79 years because of the difficulty in reliably assigning an underlying cause of death at older ages. There were 27 758 deaths in this age group, of which 5766 (21%) were attributed to stroke. Of these stroke deaths, 1231 were attributed to ischemic stroke, 3609 to intracerebral haemorrhage, 356 to subarachnoid haemorrhage and 570 were of unspecified pathological type. As in the previous study of Chinese Steelworkers, the proportion of stroke pathological types for which the diagnosis was known to have involved a CT or MRI scan was not given, but is likely to have been low.

The study found a positive, approximately log-linear association between SBP and stroke mortality, with no evidence of a threshold within the range of SBP measured in the study (100 to 180 mm Hg); the association was noted to be slightly steeper for SBP over 130 mm Hg than below it. On average, 10 mm Hg higher baseline SBP was associated with 20% (95% CI: 19-21) higher risk of stroke mortality. This estimate appears to be only half as strong as that in the Chinese Steelworkers Cohort Study (but based on nearly 40 times as many stroke events), and unlike that study, the strength of the association was much the same for both ischaemic stroke (19% [95% CI: 16-22]) and intracerebral haemorrhage (21% [95% CI: 20-26]). Smoking was reported as having a slight modifying effect on the relation, with weak evidence of a steeper association in non-smokers (24% [95% CI: 21-28] per 10 mm Hg higher baseline SBP) than smokers (20% [95% CI: 18-22]); the associations by smoking were not given separately for ischaemic stroke and intracerebral haemorrhage. A positive association between DBP and stroke mortality was also noted, although the data was not shown. Hazard ratios were adjusted for age, area, smoking and alcohol intake, and not corrected for regression dilution bias.

2.1.3 China National Hypertension Survey Epidemiology Follow-up Study (1991-2000)

The baseline survey of the China National Hypertension Survey was conducted in 1991.[75] As with the Prospective Study of 212 000 Chinese Men, the study aimed to select a nationally representative sample. A multistage random cluster sampling design was used to sample those aged over 15 years from all 30 provinces of mainland China. A follow-up survey was conducted in 17 of the 30 provinces from 1999 to 2000 to assess the vital status and disease outcomes of participants aged ≥40 years. There were 169 871 participants of the 1991 survey from the 17 provinces who were ≥40 years of age and as such eligible to participate in the re-survey. The mean age of participants at baseline was 56 years and 51% were female. The re-survey involved an in-depth interview with the participant, or relative if the participant had died, but not (apparently) any measurement of blood pressure. Hospital records were obtained if the participant reported an admission. The death certificate and medical history prior to death was obtained if the participant had died. An assessment committee in each province reviewed all the information on each case to confirm or reject the occurrence of study outcomes using pre-established criteria. Participants with a history of vascular disease at baseline were excluded from the analyses. In total, 2303 cases of incident stroke identified in the resurvey. 6.6% of the population was lost to follow-up.

Overall, 10 mm Hg higher baseline SBP was associated with 25% (95% CI: 24-26) higher risk of stroke, and 5 mm Hg higher baseline DBP was associated with 22% (20-23) higher risk of stroke. These hazard ratio were adjusted for age, sex, smoking, alcohol intake, physical activity, body mass index, blood pressure-lowering medication use, education level, geographic region (south/north), and urbanisation (urban/rural). These results were quantitatively similar to the Prospective Study of 212 000 Chinese Men, and were also not corrected for regression dilution bias.

Some effect modification was reported by age, smoking and BMI, with stronger associations at <60 years of age compared to ≥60 years; in 'ever smokers' compared to 'never smokers' (the opposite of the Chinese Prospective Study of 212 000 Chinese Men); and at BMI <25kg/m^2 compared to BMI ≥25kg/m^2. The associations within each of these subgroups were displayed graphically and not numerically (neither were p-values for interaction given). Visually, the effect modification by age appeared marked and that for smoking and BMI slight. The results were not reported by stroke pathological type.

2.1.4 Jiangxi Province Rural Cohort Study (1994-2000)

The Jiangxi Province Rural Cohort Study[76] recruited 50 252 participants from eight rural areas in Jiangxi Province between 1994 and 1996. All participants were required to be 40 years or over at baseline. The mean age of participants was 55 years and 49% were female. Follow-up continued until 2000. Causes of death were determined from death certificates, supplemented if necessary by medical records and by asking the village physicians or family members (it is not reported whether further efforts were made to verify diagnoses reported solely by family members). Participants with a history of vascular disease at baseline were excluded from analyses. There were 3358 deaths during follow-up of which 632 were from stroke: 76 from ischaemic stroke, 432 from intracerebral haemorrhage, 34 from subarachnoid haemorrhage and 90 of uncertain pathological types. The proportion of strokes for which the diagnosis was known to have involved a CT or MRI scan was not reported. There were 225 participants lost to follow-up.

Blood pressure at baseline was classified as 'normal' (defined in this study as SBP <130 mm Hg and DBP <85 mm Hg), 'high-normal' ($130 \le SBP \le 139$ and/or $85 \le DBP \le 89$) or 'hypertensive' ($SBP \ge 140$ and/or $DBP \ge 90$ and/or those who had a history of hypertension). The hazard ratio of those with hypertension and high-normal blood pressure, compared to those of normal blood pressure, as defined, was 1.40 (95% CI: 1.11-1.77) and 2.12 (1.78-2.54), respectively. The mean blood pressure in these blood pressure groups was not given, so it is not possible to accurately quantify the relative risk of stroke associated with a given absolute difference in baseline blood pressure. Hazard ratios were adjusted for sex and age. Further adjustment for study area, smoking, alcohol intake, BMI and salty food intake, reportedly had little material effect on the hazard ratios. The results were not given by stroke pathological type.

2.1.5 Shanghai Women's Health Study (2000-2007)

The Shanghai Women's Health Study[77] is an on-going prospective cohort study of 74 942 women, recruited between 1997 and 2000. All women aged 40-70 years and resident in seven urban districts of Shanghai were eligible for recruitment. Blood pressure was initially measured at the first follow-up survey (2000-2002) rather than the baseline survey. Cohort members were followed through biennial in-person follow-up surveys. The third follow-up survey (the last prior to the publication of the article) occurred from 2004-2007. The Shanghai Vital Statistics Registry database was reviewed annually to check for deaths not identified by the surveys. The response rate for the first and third follow-up surveys were 99% and 97% of the baseline survey participants, respectively. The article reported results on 68 438 women (with a mean age at baseline of 55 years) who had blood pressure measurements taken at the first follow-up survey. There had been 1574 deaths between the first and third follow-up surveys of which 338 were from stroke; the numbers of stroke of each pathological type were not reported. Participants with a history of vascular disease when blood pressure was measured were not excluded from the analyses in this study, and as such the results may be biased by reverse causation.

The authors categorised SBP at baseline into five groups (<120, 120-129, 130-139, 140-159 and ≥160 mm Hg) and risk of stroke in each group was given relative to that of the lowest blood pressure group. Results were also given for DBP, divided into five categories (<80, 80-84, 85-89, 90-99, ≥100 mm Hg). The risk of stroke for those in the highest blood pressure category relative to the lowest was 5.6 (95% CI: 3.4-9.0) for SBP and 7.2 (4.7-11.2) for DBP; the p-value for trend was reported as <0.01 for both SBP and DBP. The relative risk of stroke associated with a given absolute difference in baseline blood pressure was reported for women classified as pre-hypertensive only (defined in this study as those with baseline SBP measurements of 120-139 mm Hg). There were 71 stroke deaths in this group and the mean age at baseline or death was not given. Adjusted for age, education, waist-hip ratio, smoking, diabetes and a history cardiovascular disease, 10 mm Hg higher baseline SBP was associated with 56% (95% CI: 6-128) higher risk of stroke mortality. This was a much higher point estimate than in any of the other studies, but with a much broader confidence interval. A resurvey of blood pressure was not conducted, and as such, no correction was made for regression dilution bias.

2.2 Integration and appraisal of evidence

There appear to have been five prospective studies of blood pressure and stroke in China that published analyses, with at least 50 stroke events, in an English language journal. The Chinese Steelworkers Cohort Study was slightly older than the other studies: recruitment for this study started in 1974 and follow-up continued for 14 years, whereas the other studies conducted their baseline survey in the 1990s and the period of follow-up varied between five and ten years. All the studies recruited young or middle aged adults: the mean age at baseline ranged from 45 to 56 years. Three studies[73,74,77] restricted participation by sex whereas two studies[75,76] recruited ~50% from each sex. The Chinese Steelworkers Cohort Study recruited participants who worked for a single employer whereas the other studies were population-based.

The studies varied greatly in the number of participants recruited and the number of stroke events recorded. The two largest studies were the Prospective Study of 212 000 Chinese Men which recorded 5766 stroke deaths, and the China National Hypertension Survey Epidemiology Follow-up Study which recruited 169 871 participants of both sex and recorded 7151 stroke events; both studies attempted to select nationally representative samples. The other three studies[73,76,77] recruited participants from particular regions in China and were much smaller by comparison, reporting around a thousand stroke events between them. With the exception of the Shanghai Women's Health Study, participants with a history of vascular disease were excluded from the analyses reported in the studies. As vascular disease may affect blood pressure, including participants with a history of vascular disease may cause bias a result of reverse causation.

All of the studies reported a positive association between blood pressure at baseline and risk of stroke. Four of the five studies reported the relative risk of stroke associated with a given absolute difference in baseline blood pressure;[73,74,75,77] the Jiangxi Province Rural Cohort Study[76] did not report the strength of this association (or provide enough information for it to be calculated).

The two largest studies reported results that were somewhat similar: 10 mm Hg higher baseline SBP was associated with 20% (95% CI: 19-21) higher total stroke risk in the China Prospective Study of 212 000 Men and 25% (24-26) higher risk in the China National Hypertension Survey Epidemiology Follow-up Study. The other studies for which such estimates could be calculated had much higher point estimates: 38% (95% CI: 29-49) in the Chinese Steelworkers Cohort Study and 56% (6-128) in the Shanghai Women's Health Study (although the confidence intervals were so wide in the Shanghai study that they encompass a very wide range of possibilities). The risk of stroke for 5 mm Hg higher DBP was similar to 10 mm Hg higher SBP in the two studies[73,75] which reported these results. Comparisons in the strength of association between studies is made more difficult here because none reported age-specific results (or mean age at death from stroke), and in many populations,[26,27] relative risks for stroke in relation to blood pressure are more extreme at younger ages.

A resurvey of blood pressure was not undertaken in any of the studies identified, and no corrections were made for regression dilution bias. The Asia Pacific Cohort Studies Collaboration[27] (which had 83% of participants from East Asia, including 28% from China) had a regression dilution bias correction factor of 0.56 for SBP (for age groups less than 70 years of age). Applying this correction factor to the results of the two largest studies (i.e. dividing the log of the relative risk by 0.56) would mean 10 mm Hg higher usual SBP was associated with about 40% higher risk of stroke in the China Prospective Study of 212 000 Men and 50% higher risk of stroke in the China National Hypertension Survey Epidemiology Follow-up Study.

Effect modification of the association between blood pressure and stroke was investigated by only a few of the studies identified. The China National Hypertension Survey Epidemiology Follow-up Study was the only study to describe effect modification by age, with a stronger association at <60 years of age compared to ≥60 years, although the actual relative risks in these age groups was not reported. The study also reported stronger associations at BMI <25 kg/m^2 compared to at BMI ≥25 kg/m^2. Both the China National Hypertension Survey study and the China Prospective Cohort study of 212 000 Men described effect modification by smoking, with the former describing a stronger association in smokers than non-smokers and the latter reporting the opposite.

Only two of the studies reported results by pathological type.[73,74] The Chinese Steelworkers Cohort study found weak evidence of stronger associations for intracerebral haemorrhage than ischaemic stroke for both SBP and DBP. In contrast, the much larger China Prospective study of 212 000 men found no evidence of such differences. The proportion of strokes in these studies for which the diagnosis of the pathological type was known to have involved imaging by CT or MRI scan was not given, but may have been low.

Blood pressure is known to be a major cause of stroke yet reliable estimates of the associations between blood pressure and stroke pathological types in China have not been produced. This information needs to be known if the true burden of excess stroke due to blood pressure is to be quantified reliably: an important prerequisite to the appropriate selection of public health and clinical measures to prevent stroke in China.

2.3 Aims of thesis

This review has established that little can be known with any certainty from the English-language literature about the relationship between stroke and blood pressure in China, except that there is a qualitatively positive association. The quantitative strength of the association varied considerably between studies and was often based on small numbers of events. None of the studies corrected their results for regression dilution bias, and one study may have had substantial bias from reverse causation by not excluding participants with a history of vascular disease at baseline. These points apply to overall stroke, and with even greater force to stroke pathological types.

Against this background, the primary aim of this thesis is to describe the prospective associations in the China Kadoorie Biobank of usual blood pressure with (a) ischaemic stroke incidence and (b) intracerebral haemorrhage incidence, after taking account of prior disease, potential confounders, regression dilution bias and diagnostic accuracy of stroke pathological types (to avoid extensive misclassification).

Furthermore, the secondary aims are:

- To describe the main cross-sectional determinants of blood pressure in the China Kadoorie Biobank, to identify potential confounders

- To assess the level of within-person variability of blood pressure measurements in the China Kadoorie Biobank, so that associations can be corrected for regression dilution bias
- To assess the completeness of identification of stroke events during the first ~5 years of follow-up in the China Kadoorie Biobank, and the accuracy of diagnosis of stroke pathological type
- To assess whether the associations in the primary objective differ importantly by age, sex, area or other common characteristics or lifestyle risk factors
- To describe the associations in the China Kadoorie Biobank of usual blood pressure with: (a) subarachnoid haemorrhage; (b) stroke of unconfirmed pathological subtype; and (c) total stroke.

Figure 2.1: Flow chart of selection process for articles included in Literature Review

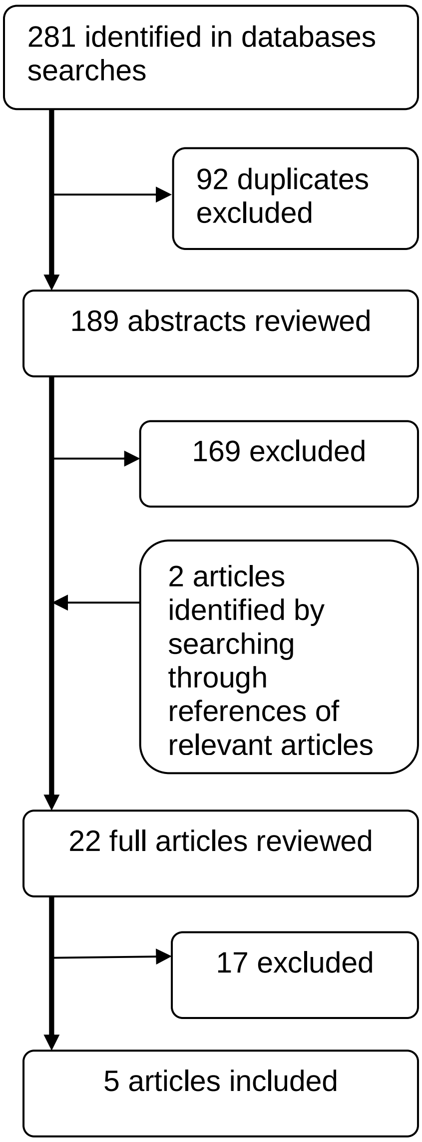


Table 2.1: Characteristics of studies included in Literature Review

Study name, date of publication	Year of baseline survey	Region	Participants, n	Female, %	Mean age at baseline,* years	Mean duration of follow-up, years	Number of stroke events†
Chinese Steelworkers Cohort Study, 2004 [73]	1974	Beijing	5 092	0	45	14	152‡
China Prospective Study of 212 000 Men, 2007 [74]	1990	45 areas	211 946	0	54	10	5 766
China National Hypertension Survey Epidemiology Follow-up Study, 2008 [75]	1991	17 provinces	169 871	51	56	7	7 151‡
Jiangxi Province Cohort Study, 2003 [76]	1994	Jiangxi Province	50 252	50	55	5	542
Shanghai Women's Health Study, 2009 [77]	1997	Shanghai	68 438	100	55	5	338

* None of the studies reported mean age at event.
† None of the studies reported the proportion of stroke events for which the diagnosis was known to have involved a CT or MRI scan.
‡ Studies measured fatal and non-fatal stroke event (other studies measured stroke mortality only).

Table 2.2: Key results of studies included in Literature Review

Study name, date of publication	Stroke pathological type	Hazard ratio (95% CI) per 10 mm Hg higher baseline SBP*	Variables adjusted for:	Corrected for regression dilution? (Yes/No)	Variable for which presence or absence of effect modification was reported
Chinese Steelworkers Cohort Study, 2004[73]	All	1.38 (1.29-1.49)	Age, total cholesterol, BMI and smoking	No	None reported
China Prospective Study of 212 000 Men, 2007[74]	All Ischaemic stroke Intracerebral haemorrhage	1.20 (1.19-1.21) 1.19 (1.16-1.22) 1.21 (1.20-1.26)	Age, study area, smoking, alcohol intake	No	Smoking
China National Hypertension Survey Epidemiology Follow-up Study, 2008[75]	All	1.25 (1.24-1.26)	Age, sex, BP-lowering medication use, smoking, alcohol intake, physical activity, BMI, education, geographic region (north/south), urban/rural area	No	Age, smoking and BMI
Jiangxi Province Cohort Study, 2003[76]	All	-†	-	No	None reported
Shanghai Women's Health Study, 2009[77]	All	1.56 (1.06-2.28)‡	Smoking, waist-hip ratio, education, diabetes, history of vascular disease	No	None reported

* Results from studies were re-calculated for 10 mm Hg higher SBP to facilitate comparisons between studies.
† Not calculable from results given in this study.
‡ Sub-group of participants with baseline SBP of 120-139 mm Hg (71 stroke deaths in this group).

Chapter 3: Methods

The China Kadoorie Biobank (CKB) is a large blood-based prospective cohort study in China. It was jointly established by the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) of the University of Oxford, and the China National Center for Disease Control. It has the broad research aim of providing reliable estimates of the strength of the relationships between risk factors and cause-specific mortality and morbidity, and focuses chiefly on the major common chronic diseases (stroke, ischaemic heart disease, diabetes, chronic obstructive pulmonary disease and cancers).[78]

Baseline information for the study was collected between 2004 and 2008 on 0.5 million adults, aged 35 to 74, from the general population in ten geographically defined areas in China. A resurvey of a random selection of about five percent of the participants was conducted in 2008 to allow refinement of the estimated levels of risk factors assessed at baseline. Follow-up of cause-specific mortality and morbidity is through established disease registries in each of the study areas. An adjudication 'sub-study' was conducted in 2011-12, as part of this thesis, to assess the diagnostic accuracy of stroke events identified by the registries.

This section describes the data collection methods of the CKB and the adjudication sub-study, followed by description of the statistical methods employed in this thesis. Ethics approval for the CKB was received from the University of Oxford, the China National Center for Disease Control and the research boards at the local branches of the China National Center for Disease Control in each of the areas which participated in the study.

3.1 Baseline survey

3.1.1 Study areas

Ten areas were selected to participate in the CKB study: five urban and five rural (figure 3.1). They were chosen to maximise the potential to investigate the relationships between a broad range of exposures and common diseases, and were not selected to be representative of China as a whole. Selection criteria for the set of ten areas included: a wide geographic distribution; variation in disease patterns and exposures; relatively settled populations where it was reasonable to expect movement out of the area would be low; established systems for mortality follow-up; and a clear commitment and capacity from local staff.

3.1.2 Study participants

Residents of the selected areas were invited to attend a temporary assessment centre in the local community. A team of 15 full-time staff were recruited in each of the areas to conduct the survey. The teams were required to include those with medical training and those with practical experience of surveys. In each area, the teams began with a publicity campaign to raise awareness of the study with the local residents. Residents between the ages of 35 and 74 were identified through the public registry records held by the local Public Security Bureau. These residents were sent a letter together with a study information leaflet, delivered door-to-door by local community leaders and health workers, inviting them to attend a temporary assessment centre.

On arrival at the assessment centre, residents were required to show their national identification card, otherwise they were ineligible to participate. To encourage participation, if a resident attending the centre was slightly outside of the age limits, they were still allowed to participate. Those eligible were then informed about the nature of the study and asked to sign the consent form. The consent included permission for study staff to monitor the person's health through local clinics, hospitals and official disease registration systems. It was made clear to participants that the results of the study would be analysed anonymously. Participants received feedback on the physical measurements and blood spot tests taken at the assessment centre from a medically qualified member of the study staff.

3.1.3 Data collection

Participants visited several stations in the assessment centre and, on average, a visit lasted 60-75 minutes. The physical measurements station included height, weight, waist circumference, hip circumference, lung function tests, a carbon monoxide breath test, blood pressure and pulse rate. All measurements used standard instruments and protocols. A 10 ml non-fasting venous blood sample was taken and stored in portable, insulated cool boxes with ice packs. The packs were transferred within a few hours to a local study laboratory for processing and short-term storage (~3-4 months), before shipment to Beijing and Oxford for long term storage in liquid nitrogen tanks. The blood samples had not undergone any analyses at the time of writing and thus are not considered any further in this thesis.

Blood pressure was measured using a LifeSource UA-779 digital sphygmomanometer, taken after participants had been allowed to rest in a seated position for at least five minutes. Initially, two measurements were taken by placing the sphygmomanometer cuff around the participant's upper arm. If the difference between the two measurements was >10 mm Hg for SBP, a third measurement was made and the last two measurements recorded. Procedures were standardised across the ten study sites and all measurements were made by specifically trained study personnel. All devices were constantly maintained and frequently calibrated. All the physical measurements and blood spot result values for each participant were recorded on the back of their consent form. These were then entered twice onto a study laptop at the questionnaire station.

The questionnaire station involved a one-to-one interview with a member of the CKB regional co-ordinating team. Answers were entered directly onto a study laptop using software developed specifically for the project by the CKB information technology team. The software brought missing items, extreme values or logic errors to the attention of the interviewer. The questionnaire had sections on: general demographic characteristics; socioeconomic status; health behaviours such as smoking, alcohol intake, diet and physical activities; family and personal medical history; questions on sleeping habits, mood and mental state; and, for women, reproductive history.

3.1.4 Quality control procedures

Efforts were made to ensure high quality data collection procedures were followed in each of the ten areas. All materials and equipment required for the baseline survey were supplied centrally. The standard operating procedures were tested in a pilot study. Training was given to the staff at the regional coordinating centres conducting the baseline survey, including sessions on communication skills, the scientific rationale for the study and the practical procedures for conducting the survey, including the operation and maintenance of instruments. The teams started their survey work immediately after the training, under the direct supervision of CKB staff from Oxford and Beijing for about a week, to ensure that all procedures were followed appropriately. Each staff member was given a unique study identification number that was entered on the study laptops prior to data entry. This allowed the entries made by particular staff member to be identified and monitored throughout the survey period. In total, there was 354 staff involved in conducting the survey, with 201 staff completing 95% of the total number of data entries.

3.2 Resurveys

A quality control survey was conducted concurrently to the baseline survey to assess consistency in data collection. Around three percent of participants in each of the ten areas were randomly selected for reassessment two to six weeks after their baseline assessment. A simplified version of the baseline survey form was used, but the procedures for blood pressure measurement were the same as the baseline survey. In total, there were 15 728 participants of the quality control survey.

A formal resurvey of participants was conducted from August to October 2008, soon after the baseline survey was completed. In each of the ten areas, a participant list was generated using cluster random sampling, with the administrative unit (rural village or urban residential committee) as the sampling unit. The procedures for data collection were the same as in the baseline survey, with a number of additional assessments. Blood pressure measurements were taken in exactly the same way as the baseline survey. Around five percent of the baseline sample was invited for resurvey, and there was an 80% response rate. In total, there were 19 788 participants in the formal resurvey.

3.3 Follow-up

Participants were followed-up using established mortality and morbidity surveillance systems. All ten areas were part of the mortality surveillance system established by the Chinese Ministry of Health in the 1980s to provide nationally representative mortality statistics (the Disease Surveillance Point system[79]). Within each area, death certificates were sent to the local branch of the China National Center for Disease Control, where regional offices of the CKB study were also based. Information from these death certificates was entered by staff at the regional China National Center for Disease Control into a database, which was then cross-checked regularly by local CKB staff to identify deaths in study participants. Deaths were coded using the 10th edition of the International

Classification of Diseases (ICD-10).[80] These CKB staff did not have access to patient information from the baseline or repeat surveys.

In nine of the ten study areas, there were also established registries for incident cases of chronic disease (stroke, ischaemic heart disease, diabetes and cancer); Qingdao had a registry for cancer but not other chronic diseases. As with the mortality surveillance system, this disease incidence surveillance system was a government initiative to monitor national disease rates.[81] The system relied on clinicians working in local or regional hospitals, out-patient departments or rural clinics to complete a short disease surveillance form, after diagnosing a new case, which was then forwarded to the local branch of the China National Center for Disease Control. As with mortality events, disease event registries were cross-checked by CKB staff working at these local branches to identify events in study participants. Incidence disease surveillance will be supplemented in the future by linkage to health insurance claim databases which are kept by local government in each of the areas; such data were not available at the time the analyses in this thesis were undertaken. CKB staff in each of the ten areas were required to periodically check the official residential records of the Public Security Bureau to identify those who had moved out of the area and were, therefore, lost to follow-up.

In the prospective analyses conducted in this thesis, incident stroke events were defined as first-ever-in-a-lifetime strokes reported by either the disease or mortality surveillance systems. Each first-ever-in-a-lifetime stroke event was assigned the same pathological type as that reported by the surveillance system. The occurrence of a first stroke event increases the risk that the participant will experience further stroke events, of any pathological type.[82,83] As such, it was decided to censor at the first stroke event, even when investigating associations by stroke pathological type, so as not to conflate risk from the exposure of interest with risk from the sequelae or treatment of the first stroke event (there were 242 subsequent stroke events excluded which were of a different pathological type to the first-ever-in-a-lifetime stroke). Where strokes of different pathological types were reported to have occurred on the same day, the pathological type of stroke was re-classified as 'unspecified stroke' (there were 94 strokes reclassified in this way). As the accurate diagnosis of ischaemic stroke or intracerebral haemorrhage requires a CT or MRI scan (or autopsy, although these are extremely rare in China), stroke events in the main prospective analyses were restricted to those for which the diagnosis was known to have involved a CT or MRI scan. Participants with a self-reported history of vascular disease at baseline were excluded from analyses to limit the effects of reverse causality (n = 23 129).

3.4 Adjudication sub-study

The stroke adjudication sub-study aimed to assess the diagnostic accuracy of incident stroke events reported to the CKB study. It was led by me and conducted during 2011-12. In brief, it involved locating and retrieving the relevant medical notes on a selection of stroke events reported to the study from each of ten areas. Copies of the relevant parts of the medical notes were taken, and reviewed by a clinician in Oxford using objective diagnostic criteria to assess the diagnostic accuracy of each stroke event.

Initially, I produced a set of definitions and diagnostic criteria for stroke and pathological types of stroke, in collaboration with neurologists from the Western General Hospital, University of Edinburgh (table A.3 in appendix A). These diagnostic criteria formed the basis of a survey form that was used to guide the adjudication of stroke events from patients' notes. I then piloted this survey form in the Western General Hospital, Edinburgh, and it was refined as a result.

A second pilot was conducted in Suzhou (one of the CKB study sites in China, see figure 3.1). Several hospitals in both the centre and outskirts of Suzhou were visited by me and a number of Chinese colleagues involved in the CKB study. Access to CT and MRI scanners varied markedly by hospital tier: almost all higher tier hospitals visited had access to scanners whereas these were rare in lower tier hospitals. The survey form was refined again following this pilot. Parts of the form were then standardised with other survey forms being developed for adjudication sub-studies for other chronic disease events in the CKB study (ischaemic heart disease, diabetes and six types of cancer): see appendix F for the final survey form. The pilot study in China also allowed the standard operating procedures for the collection of medical records to be finalised. In particular, the set of key documents from the medical notes required to adjudicate events was established. These included the admission record (with history and examination on presentation), results of investigations (CT and MRI scans, lumbar puncture analysis, ECG, echocardiogram and Doppler ultrasound of the neck or intracranial arteries) and the discharge summary.

It was clear from the pilot study in China that the tier of reporting hospital might be a major determinant of the accuracy of stroke diagnoses (given the variation in access to CT or MRI scanners by tier). As such, it was important that there would be adequate sampling of stroke events from each tier. Some areas, however, had several dozen hospitals which reported disease events, and it would not be feasible for CKB staff to collect information from all of these. It was decided, therefore, to stratify the sampling of events by hospital tier and select the three or four hospitals within each tier with the highest number of events. The study aimed to collect information on 100 stroke events in each area, divided equally, where possible, by hospital tier. This would allow a good assessment of the general diagnostic accuracy of stroke events within each hospital tier and was the limit of what the financial and human resources available would allow.

Events were selected mostly from the incidence disease surveillance system, with other events selected from the health insurance surveillance system. The health insurance surveillance system was a database of hospitalised events in each area that was being assessed at the time of writing as a possible enhancement to the disease incidence surveillance system. Health insurance events were selected for the adjudication sub-study, despite not being included in the prospective analyses in this thesis, as this system was likely to be a major source of stroke events for the CKB study in the future. It was not possible to trace efficiently any hospital admission prior to death from death certificates: preliminary analyses of stroke mortality data indicated that a large proportion of stroke deaths occurred at home and information on the name of any hospitals involved in the diagnosis, and the associated admission date, was not routinely collected. The most recent events from each hospital were selected to increase the likelihood that the medical notes had not been destroyed or put into long term storage off-site.

CKB staff in each of the ten areas were given a list of selected hospital names and stroke events, selected by the CKB team in Oxford. Permission was obtained from the government health bureau in each area to visit the listed hospitals and take copies of hospital records. The medical notes for the admission relating to the specific stroke event were identified by cross-checking the hospital admission records for the patient's name, date of birth and admission date. In most cases, the records were electronic but in a small number of hospitals it was a paper-based system. If the admission could not be found, the CKB study team selected another stroke event from a 'back-up' list of stroke events diagnosed in the same hospital, provided by the CKB team in Oxford. Events from the back-up list were selected until a set of medical notes were identified. Copies of the key documents were made by photocopier or by taking a digital photo. Paper copies were then scanned into computers at the local branch of the China National Center for Disease Control and transferred together with any photos by secure intranet connection to CTSU in Oxford. All stroke events were adjudicated at CTSU by a senior Chinese-speaking clinical fellow (Dr Yiping Chen). I observed the adjudication of the first 250 stroke cases and addressed any procedural questions. A paper copy of the stroke survey from was competed for each stroke event and entered twice into a database by administrative staff at CTSU.

3.5 Selection of variables and data analyses

3.5.1 Selection of baseline variables

SBP and DBP variables from the baseline survey were selected, together with other variables which might potentially confound of the association between blood pressure and stroke incidence. The causal model (figure 1.3) was used to identify potential confounders; measures of most risk factors in the model were included in the baseline survey. The following variables were selected: first SBP measurement, second SBP measurement, first DBP measurement, second DBP measurement, age, sex, area, education, BMI, waist circumference, hip circumference, waist-hip ratio, frequency of fresh fruit consumption, frequency of fresh vegetable consumption, frequency of tea intake, alcohol intake, smoking, physical activity (MET hours/day), diabetes, blood pressure-lowering medication use and month of baseline survey. The participants' month of baseline survey was selected, despite not being in the causal model, to explore the seasonal variation in blood pressure.[84]

3.5.2 Definitions and categorisation of baseline variables

Each participant's baseline SBP and DBP was calculated as the mean of their two recorded measurements at baseline. Age at baseline was divided into eight groups: 30-<40, 40-<45, 45-<50, 50-<55, 55-<60, 60-<65, 65-<70, 70-<80 years. Education was categorised according to the highest level of education received: no formal education, primary school, middle school, high school or further education (technical college or university).

BMI was calculated by dividing weight in kilograms by the square of their height in metres. Waist-hip ratio was calculated by dividing waist circumference in centimetres by hip circumference in centimetres. All measures of adiposity (BMI, waist circumference, hip circumference and waist-hip ratio) were categorised into quintiles.

For dietary variables, the baseline questionnaire asked participants the frequency of their usual consumption over the last year. Consumption of fresh fruit and fresh vegetables were categorised as never/rarely, monthly, 1-3 days per week, 4-6 days per week or daily; however, as 95% of participants reported consuming fresh vegetables daily, this was re-coded as a binary variable (daily or not daily). Tea intake was categorised as never/rarely, occasional, monthly or weekly.

For alcohol intake, participants were categorised according to their frequency of their usual consumption over the last year (never/rarely, occasional, monthly or at least weekly), and those who drank alcohol at least weekly were categorised further according to the quantity of alcohol they reported consuming in a ‘typical’ week. Participants were also asked about their alcohol consumption before the last year: those who had drank alcohol ‘at least weekly’ in the past but not over the last year were categorised as ‘ex-weekly’ drinkers; those who drank at least weekly over the last year who reported that their alcohol consumption had ‘decreased at lot’ compared with some years ago were classified as ‘reduced-intake’ drinkers.

The number of participants who had their baseline survey in January or February was lower than in other months; the annual holiday for Chinese New Year interrupted the recruitment of participants (the date of Chinese New Year varies because it is set by a lunar calendar). As such, participants recruited in these months were combined into a single category.

Physical activity was expressed in metabolic equivalent of task (MET) hours performed per day, on average, over the last year. This is a means of expressing a person's average level of physical activity over a period of time by combining the intensity and duration of different physical activities into a single measure.[85] MET values are estimates of energy expenditure relative to an individual's rate of energy expenditure at rest (their resting metabolic rate), and as such the value is independent of a participant's weight. Participants answered questions on the type and duration of physical activities at work and leisure over the year prior to the survey. Each activity was assigned a MET value previously devised from physical activity research[85] and this was multiplied by the hours per day on average that the activity was performed. For example, walking at a moderate pace was assigned a MET value of four (energy expenditure whilst walking is approximately four times that at rest) so that two hours of walking per day on average would give a value of 8 MET hours per day for this activity. A participant's total MET hours per day was the sum of the MET hours per day for each activity they performed.

Participants were classified as diabetic at baseline if they reported a history of diabetes in the baseline survey questionnaire, or their random blood glucose test during the baseline survey was ≥11.1 mmol/l, or their fasting blood glucose (taken the following day in those with a raised random blood glucose test [set at ≥7.8 mmol/l in this study]) was ≥7.0 mmol/l. These blood glucose values are consistent with the diagnostic criteria for diabetes recommended by the World Health Organisation.[86]

For smoking, participants were categorised as current smokers, never smokers, occasional smokers or ex-regular smokers. Lastly, blood pressure-lowering medication use was defined in this study as use of any allopathic blood pressure-lowering medication (rather than Chinese traditional blood pressure-lowering medicine), including: angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers, calcium-channel blockers and diuretics.

3.5.3 Preliminary descriptive analyses

A set of preliminary analyses were conducted to describe the distribution of selected variables and identify missing, erroneous or outlying values. Bar charts were produced to describe the distribution of categorical variables, whereas histograms and descriptive statistics (mean, standard deviation, median, minimum and maximum values) were used to describe the distribution of numerical variables. Scatter plots were produced to identify outlying values and the inter-relationship between numerical values. Consistency between first and second blood pressure readings for both SBP and DBP was checked; and logical consistency between SBP and DBP values was also checked to ensure SBP values were always greater than DBP values.

3.5.4 Participant exclusions

An initial set of exclusions to the baseline data were made to address data entry issues. There were 515 681 participant entries made during the baseline survey. Some participants, however, were found to have been inadvertently assessed twice (n = 2208); a number of other participants withdrew before the assessment was complete (n = 261); and one participant was excluded because of major data errors identified soon after entry. These entries (or second entries in the case of those assessed twice) were excluded. An additional 320 participants were excluded because their age at baseline was outside of pre-specified age range of interest for the study (30 to 79 years). There were 512 891 participants remaining following these exclusions.

Participants were further excluded from the cross-sectional, resurvey and prospective analyses if they had a self-reported history at baseline of stroke/TIA or heart disease (n = 23 129, for all vascular disease) or missing values (n = 2, both for weight, used in the calculation of BMI): table B.1 in appendix B. Participants with outlying values in key variables, found during preliminary descriptive analyses, were also excluded, given that these may have a considerable impact on the results of some analyses (n = 1059): tables B.1 and B.2 in appendix B. These combined exclusions left 488 789 participants (male n = 199 825, female n = 288 964) for the cross-sectional analyses.

3.5.5 Selection of confounders

Throughout the thesis, potential confounders of associations were identified using a combination of *a priori* knowledge and empirical findings. For each association, an initial set of important confounders were selected from *a priori* knowledge. These were included in regression models, irrespective of whether they were found to materially change the estimates of the strength of association. Other potential confounders were only controlled for where they were found by exploratory analyses to materially change the estimates of the strength of association. The causal model in figure 1.3 was useful in selecting potential confounders: to check that major potential confounders had not been overlooked or selected inappropriately (in particular, that they were not on the causal pathway between the exposure and outcome of interest, or a common effect of both exposure and outcome).[87,88] The effect of confounding was explored further by sensitivity analyses (reported in appendices): associations were firstly adjusted for age, sex, education and area only; and then more extensively adjusted for all other measured risk factors, where appropriate.

3.5.6 Analyses of baseline data

The cross-sectional associations of baseline SBP and DBP with the other measured vascular risk factors were estimated using general linear models, adjusted for potential confounders (included as covariates in the regression models). The associations of blood pressure with age, sex, education and area were adjusted for each other. The associations of blood pressure with other risk factor were adjusted for age, sex, education, area plus other potential confounders, where appropriate: the associations with diabetes were further adjusted for adiposity (BMI, waist circumference and hip circumference); the associations with alcohol and smoking were further adjusted for each other; the associations with blood pressure-lowering medication use were further adjusted for other causes of blood pressure (physical activity, adiposity, diabetes, alcohol intake, fresh fruit consumption and fresh vegetable consumption); and the associations with measures of adiposity were mutually adjusted, to determine the shape and strength of their associations with blood pressure independent of each other. Least-square means (and 95% confidence intervals) of SBP and DBP within each category of the selected variables were calculated.

3.5.7 Analysis of resurvey data

The regression dilution ratio is the proportional reduction in strength of association between a risk factor and disease that occurs when risk is plotted against baseline levels of a risk factor instead of long-term average levels. Dividing the log of the relative risks (and their standard errors), calculated using baseline levels of a risk factor, by the regression dilution ratio will correct the relative risks for regression dilution bias.

Regression dilution ratios for blood pressure were calculated using blood pressure values from the baseline and resurvey. In total, there were 19 788 participants resurveyed. A set of preliminary descriptive analyses of SBP and DBP in the resurvey data were conducted, including descriptive statistics, histograms and scatter plots. Participants excluded from cross-sectional analyses were also excluded from regression dilution analyses (n = 988), together with participants with outlying blood pressure values at resurvey (n = 50). There were 18 791 participants included in the analyses of resurvey data following these exclusions.

The mean blood pressures at baseline and resurvey were calculated within groups defined by baseline blood pressure quintiles. These values were plotted against the time interval between the surveys to demonstrate the serial changes in blood pressure within these groups. This set of analyses were replicated on data from the quality control survey, and added to the same plot; the same exclusion criteria as for the resurvey were applied (n = 811 excluded), leaving 14 911 participants.

The shape and strength of the association between baseline and resurvey blood pressures was assessed by plotting the mean blood pressure at resurvey against mean blood pressure at baseline within groups defined by baseline blood pressure quintiles. Rosner's regression method[89,90] was used to calculate regression dilution ratios; the regression dilution ratio being estimated as the slope of the regression line between baseline and resurvey blood pressures. Rosner's regression method was used to produce regression dilution ratios by age at baseline and sex: firstly, by separate simple linear regression analyses on each age and sex group, and then, by a single multiple linear regression analysis with interaction terms for all permutations of baseline blood pressure (SBP or DBP), age and sex. For comparison, regression dilution ratios were also calculated using the group method (in quintiles)[91] and the intraclass correlation coefficient;[92] unlike Rosner's regression method these other methods required participants to be divided into groups by age and sex, with significant loss of power as a result.

3.5.8 Completeness and accuracy of incident stroke events

The completeness of follow-up of stroke events reported by the surveillance systems by November 2011 was assessed. For each stroke pathological type in each area, following was described: the number (and crude rate) of all incident stroke events reported by either the disease or mortality surveillance systems; the number of incident stroke events reported by just the disease surveillance system; and the incident stroke events for which the diagnosis was known to have involved a CT or MRI scan. This latter group, which was used in prospective analyses, was a subset of those reported by the disease surveillance system; the use of CT or MRI scan to diagnose the pathological type of stroke event was not recorded by the mortality surveillance system.

The number of stroke events selected for the adjudication sub-study were described by surveillance system, hospital tier, area and stroke pathological type. Analyses were restricted to stroke events for which the participant information in the medical notes matched participant information in the CKB study (name, sex, year of birth and admission dates within one month); this ensured that the medical notes for the correct stroke event in the CKB study were analysed. The pathological type of stroke event reported to the CKB study was then compared to the diagnosis assigned during adjudication; the proportion of events of each stroke pathological type for which the diagnosis was confirmed during adjudication process was calculated (positive predictive value). Variation in the positive predictive value of ischaemic stroke was further analysed by surveillance system, hospital tier, area and age at event. Sensitivity analyses were conducted by calculating positive predictive values for each stroke pathological type after restricting the analyses to adjudicated stroke events used in prospective analyses.

The results of this sub-study indicated that ischaemic stroke in the CKB study would more appropriately be described, at present, as cerebral infarction (used in this thesis to mean events for which there was evidence of cerebral infarction from a CT or MRI scan, with or without sufficient clinical evidence of the signs/symptoms of stroke). As such, ischaemic stroke in subsequent sections is referred to as cerebral infarction.

3.5.9 Stroke incidence and exclusions for prospective analyses

The incidence of stroke events, reported between the baseline survey and November 2011, included in the subsequent prospective analyses were described for each pathological type by age and sex and by area. Participants excluded from cross-sectional analyses were also excluded from this and further prospective analyses. Events and person-years of follow-up from Qingdao (participants = 33 351) were also excluded because there were no stroke events reported in this area that were known to have involved a CT or MRI scan (the disease surveillance system had not yet been initiated in Qingdao). Events and person-years outside of the age range 40 to 79 years were excluded (events = 61) as the few events for each pathological type outside of this age range would not produce reliable results in the prospective analyses at age <40 or ≥80 years. Following these exclusions, there were 455 438 participants with a total of 2.1 million person-years of follow-up and 5783 incident stroke events: 4513 cerebral infarction events, 1071 intracerebral haemorrhage events, 85 subarachnoid haemorrhage events and 114 other or unspecified stroke events.

3.5.10 Associations of usual blood pressure and stroke incidence

Prospective analyses were conducted on 455 438 participants (184 949 males and 270 489 females), following the exclusions described in the previous section. The associations between usual blood pressure and each stroke pathological type were analysed and described separately. The associations for cerebral infarction and intracerebral haemorrhage were described in greater detail than for subarachnoid haemorrhage or unspecified stroke because of the few events for these latter pathological types.

Cox proportional hazards regression models were used to investigate the associations. A statistical program developed within CTSU was employed to run the models. Participants were censored after their first stroke event, at the date of loss to follow-up or at death. Models were stratified by area and five-year age at risk group. This meant the proportional hazards assumption did not have to be assumed between age groups in or between each area, although it was still assumed within each 5 year age group in each area. 95% confidence intervals about the hazard ratios were calculated using the floating absolute risk method;[93] this appropriately attributes variance to the reference group and other groups, to allow confidence intervals to be used to compare risks in any two groups, rather than solely between the reference group and another group.

The shapes of the associations between usual blood pressure and risk of cerebral infarction and intracerebral haemorrhage were assessed by plotting usual blood pressure against risk of the stroke pathological type. Participants were divided into five groups according to baseline blood pressure. The following blood pressure groups were chosen to give a broad range of blood pressure groups whilst maintaining reasonable numbers of strokes in each group: <125, 125-<145, 145-<165, 165-<185, ≥185 mm Hg for SBP and <75, 75-<85, 85-<95, 95-<105, ≥105 mm Hg for DBP. The hazard ratios were adjusted for age, sex, education and area, and calculated relative to the lowest blood pressure group. A graphics program developed by CTSU, specifically to graph the results from the Cox proportional hazards statistical program, was used to produce the basic plots to which refinements were made. The mean blood pressure in each of the blood pressure groups was recalculated to take account of regression dilution bias: the differences between the overall mean blood pressure and the mean blood pressure in each blood pressure group were multiplied by the overall regression dilution ratio (calculated as described below); these new differences were added to the overall mean blood pressure to give the corrected mean blood pressures in each blood pressure group. The effect was to increase the slope of the log-linear association by a factor equal to the inverse of the regression dilution ratio.

Age, sex, education and area were considered important *a priori* confounders that would be controlled for in analyses of the relationship between blood pressure and stroke pathological type, irrespective of whether they were found to materially change the estimates of the strength of association. The effect of other major potential confounders was assessed by progressive adjustment of the associations between blood pressure and risk of cerebral infarction and intracerebral haemorrhage; potential confounders were progressively added as covariates in the Cox proportional hazards regression models. As the relationship between usual blood pressure and risk of both cerebral infarction and intracerebral haemorrhage was log-linear, the associations were reported as hazard ratios per 10 mm Hg higher usual SBP and per 5 mm Hg higher usual DBP. Correction for regression dilution bias was made by dividing the log of the hazard ratios by the overall regression dilution ratio, and taking the exponential.

The shapes of the associations by age were examined further in a set of plots produced in much the same way to the overall plots. Participants were divided into the same five blood pressure groups but then stratified by ten-year age at risk groups, yielding at total of twenty groups. The hazard ratios were estimated relative to the lowest blood pressure group at the youngest age (40-49 years). The mean of the sex-specific regression dilution ratios within each age group were used to correct for regression dilution bias within each age group. The mean blood pressure in each of the blood pressure groups were recalculated to take account of regression dilution bias in the same way as previously described for the overall plots, except age-specific regression dilution ratios and age-specific overall means were used.

The strength of the age- and sex-specific associations between usual blood pressure, and risk of cerebral infarction and intracerebral haemorrhage were reported as hazard ratios per 10 mm Hg higher usual SBP and per 5 mm Hg higher usual DBP. Correction for regression dilution was made to each age- and sex-specific hazard ratio (and its standard errors) by dividing the log of the age- and sex-specific hazard ratios (and their standard errors) by the equivalent age- and sex-specific regression dilution ratio (calculated using Rosner's regression method,[89] as described earlier), and taking the exponential. The corrected overall hazard ratio was the weighted average of the corrected age- and sex-specific hazard ratios (weighted by the inverse variance of the log hazard ratios). The corrected age-specific hazard ratios and corrected sex-specific hazard ratios were the weighted average of their component corrected age- and sex-specific hazard ratios. The overall regression dilution ratio was calculated by dividing the log of the corrected overall hazard ratio by the log of the overall hazard ratio uncorrected regression dilution bias.

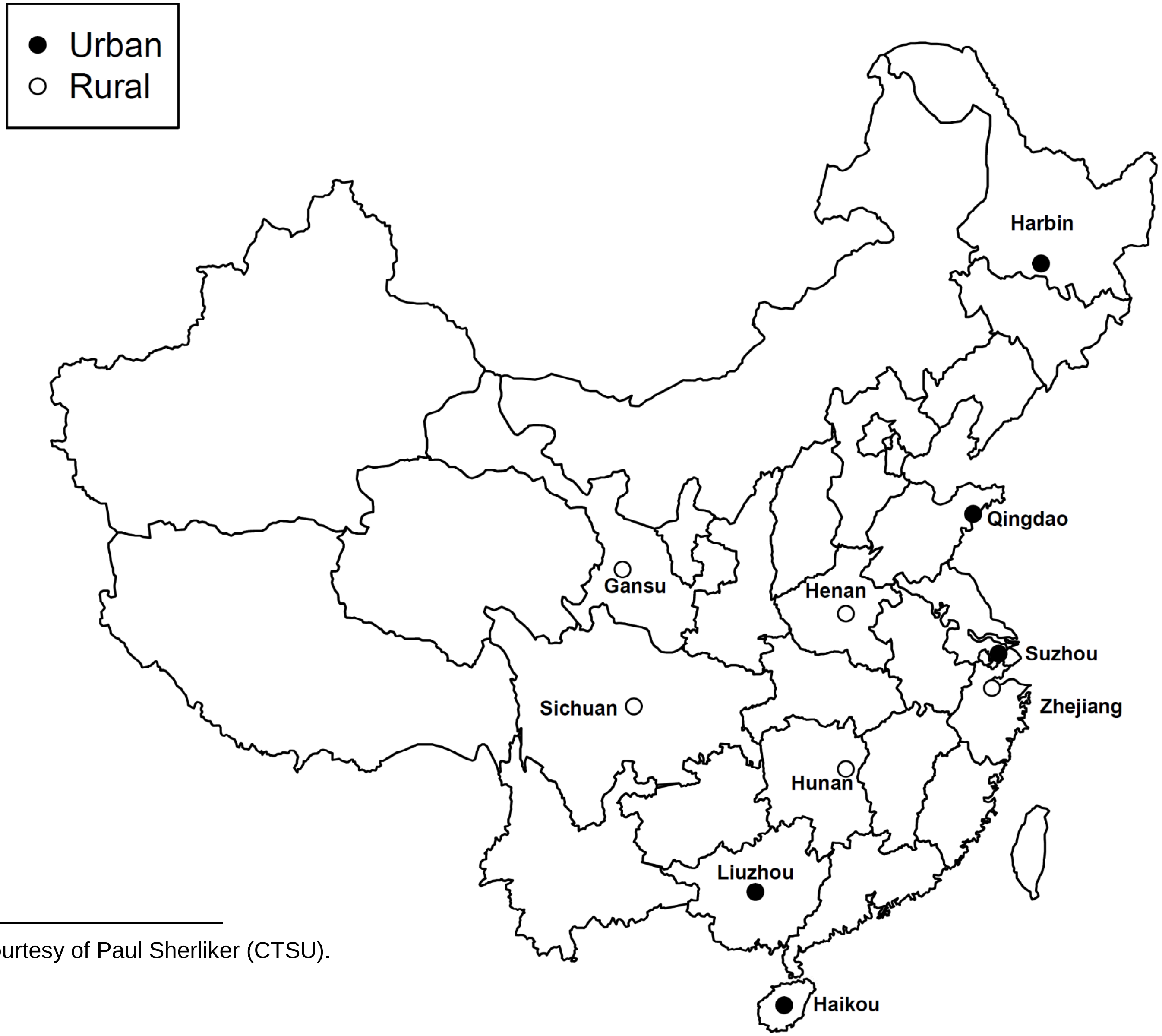
Effect modification of the main associations for cerebral infarction and intracerebral haemorrhage were investigated by stratifying by levels of the potential effect modifier and applying the same methods as described above to calculate the overall hazard ratio corrected for strata-specific regression dilution bias. A chi-squared test of heterogeneity was used to assess whether there was sufficient evidence to reject the null hypothesis that there were no differences in the strength of association between levels of the effect modifier. Effect modification of the associations were assessed by area (urban/rural), alcohol intake, smoking, BMI, physical activity (MET hours/day), diabetes and blood pressure-lowering medication use. Effect modification by area (urban/rural), alcohol intake, smoking, BMI and physical activity was further assessed for males and females separately. Effect modification by diabetes and blood pressure-lowering medication use was assessed for both sexes combined only, as there were too few participants in some categories to allow the sex-specific regression dilution ratios to be reliably estimated for either sex. Variation in the strength of association using fatal stroke events (defined as events followed by death within 30 days) and non-fatal events (defined as events not followed by death within 30 days) was also examined for both sexes combined. A forest plot graphics program developed by CTSU was used to illustrate the strength of associations by potential effect modifiers.

The strength of the overall associations between usual blood pressure and risk of subarachnoid haemorrhage and unspecified stroke were reported as hazard ratios per 10 mm Hg higher usual SBP and per 5 mm Hg higher usual DBP. There were insufficient events of either of these stroke pathological types to assess the shape of the associations or to assess for effect modification. The strength of the overall associations between usual blood pressure and all stroke pathological types were compared in a set of figures, which also reported the strength of the overall associations using stroke events not known to have involved imaging with CT or MRI scan. These latter associations were calculated for each pathological type in the same way as stroke events known to have involved imaging. The overall associations between usual blood pressure and all stroke events combined was calculated as the weighted average of the hazard ratios for each stroke pathological type (using stroke events known and not known to have involved imaging).

Lastly, the informativeness of a single blood pressure measurement at baseline for predicting risk of cerebral infarction and intracerebral haemorrhage was compared between SBP, DBP and other blood pressure indices derived from these measures (mid blood pressure = 1/2SBP +1/2DBP, mean arterial pressure = 2/3SBP + 1/3DBP, and pulse pressure = SBP-DBP). Informativeness was defined as the chi-squared (X^2_1) value relating the blood pressure index to the incidence of cerebral infarction and intracerebral haemorrhage, using stroke events known to have involved imaging. The overall X^2_1 value for each blood pressure index was the sum of the age and sex-specific X^2_1 values. These values were expressed as a proportion of the X^2_1 value for the overall most predictive blood pressure index.

SAS version 9.2 was used for all statistical analyses and all figures were produced using the R statistical software.

Figure 3.1: Map of China with locations of the China Kadoorie Biobank survey areas[a]



[a] Figure courtesy of Paul Sherliker (CTSU).

Chapter 4: Results

The main results reported in this chapter are the associations between usual blood pressure and incidence of stroke pathological types, overall and by potential effect modifiers. Before these results are presented, however, the baseline characteristics of the analysed population are described; associations of blood pressure with potential confounders of the main associations are considered; regression dilution ratios for blood pressure are presented; and the completeness and accuracy of incidence stroke events in the CKB study is assessed, with a particular emphasis on results from the adjudication sub-study.

4.1 Participant characteristics

Descriptive analyses were conducted on 488 789 participants, after excluding 24 102 participants with a history of vascular disease or outlying values of key variables, as described in Methods. In this sample, the number recruited from each of the ten areas varied from 28 955 in Haikou to 60 300 in Henan (table 4.1). 59% of participants were female and the mean age for males and females was 52 years and 51 years, respectively. In total, 49% of the participants were educated to middle school or higher (males 58% and females 43%; urban 68% and rural 35%).

The overall mean BMI was 23.6 kg/m^2, and was slightly lower in males (23.4 kg/m^2) than females (23.7 kg/m^2): table 4.2. On average, waist circumference was slightly larger in males (81.8 cm) than females (78.8 cm), but hip circumference was much the same in both sexes (males 90.5 cm, females 91.0 cm), such that the average waist-hip ratio was slightly higher in males (90.2%) than females (86.5%). Participants had, on average, 26.0 MET hours/day of exercise (males 27.2 MET hours/day, females 25.2 MET hours/day).

A higher proportion of males than females were smokers and regular alcohol drinkers: 62% of males were smokers compared to 2% of females; 34% of males drank alcohol at least once per week on average compared to 2% of females. Males also drank tea more frequently than females: 51% of males drank tea at least once per week on average compared to 21% of females. Almost all participants consumed fresh vegetables daily (95%), whereas only 21% of males and 14% of females consumed fresh fruit daily. 5% of participants were diabetic: 3% had a self-reported history of diabetes and a further 2% were diagnosed from the blood glucose tests performed during the baseline survey. 4% of participants at baseline reported currently using allopathic blood pressure-lowering medication (ACE inhibitor, beta-blocker, calcium channel blocker or diuretic).

Mean SBP and DBP at baseline were slightly higher in males than females (figures 4.1 and 4.2). Mean (SD) SBP was 132.3 (19.7) mm Hg in males and 129.4 (21.7) mm Hg in females (figure 4.1); the median SBP values were slightly lower (males 129.5 mm Hg, females 126.0 mm Hg). The mean DBP in males was 79.1 mm Hg (SD 11.3) and 76.7 mm Hg (10.8) in females (figure 4.2). The median DBP was 78.5 mm Hg in males and 76.7 mm Hg in females. For both sexes, SBP and DBP were approximately normally distributed, though slightly skewed to the right, and there was minor digit preference for even integers. SBP and DBP were strongly correlated (table B.3 in appendix B): the Pearson partial correlation coefficients (r), adjusted for area and age, was 0.77 for males and 0.74 for females.

4.2 Baseline associations of blood pressure with major potential confounders

This section describes the associations between blood pressure and a range of risk factors for stroke which might confound the main associations in this thesis between usual blood pressure and incidence of stroke pathological types. The strength of the associations with age, sex, education and area are described, adjusted for each other. The associations with other variables are adjusted only for age, sex, education and area, unless otherwise stated. Sensitivity analyses were conducted as described in Section 3.5.5: associations adjusted only for age, sex, education and area are given in tables B.7-B.9 in appendix B, and associations further adjusted for a more extensive set of other potential confounders are given in tables B.10-B.13 in appendix B. These sensitivity analyses are discussed below only where the strengths of the associations were materially different from those reported in the main results.

4.2.1 Age, sex, education and area

There was a strong positive association between age and SBP in each sex: figure 4.3 (table B.4 in appendix B). The association was approximately linear for both sexes and, on average, more than twice as steep in females as in males: 10 years extra of baseline age was associated with 7.7 mm Hg (95% CI: 7.2-8.2) higher SBP in females and 3.6 mm Hg (3.1-4.2) higher SBP in males ($p_{heterogeneity}$ = <0.001). The association between DBP and age was non-monotonic, with a positive association in age groups less than 50 years and a negative association thereafter. The shape of the association was similar in males and females (figure 4.3). Analyses by area found that the shape and strength of the associations between age and both SBP and DBP were much the same in all ten areas.

Overall mean blood pressure was higher in males than females by 2.5 mm Hg (95% CI: 2.3-2.6) SBP and 2.5 mm Hg (2.4-2.5) DBP: table 4.3. The difference in mean blood pressure between the sexes varied, however, by age (figure 4.3). Mean SBP was somewhat higher in males than females in age groups less than 50 years and slightly higher in females than males in older age groups. Mean DBP was higher in males than females at all ages, although the difference narrowed with increasing age.

There was a negative association between level of education and both SBP and DBP: table 4.3. Participants with a technical college or university education had on average 5.3 mm Hg (95% CI: 5.0-5.6) lower SBP and 1.4 mm Hg (1.2-1.5) lower DBP than those who had not received any formal education.

There was considerable variation in both SBP and DBP by area: table 4.3. The lowest mean SBP was in Haikou (123.8 mm Hg [95% CI: 123.6-124.1]) and the highest was in Henan (134.3 mm Hg [134.1-134.4]). The lowest mean DBP was also in Haikou (74.4 mm Hg [95% CI: 74.3-74.6]) with the highest in Zhejiang (80.0

mm Hg [79.9-80.1]). Overall, the five rural areas had slightly higher mean blood pressure levels than the five urban areas, by 2.8 mm Hg (95% CI: 2.6-2.9) for SBP and by 0.4 mm Hg (0.4-0.5) for DBP (adjusted for age, sex, education and area).

4.2.2 Adiposity

There were strong positive linear associations between each of the four simple adiposity measures and both SBP and DBP (figure 4.4 illustrates these relationships for SBP): 5 kg/m^2 higher BMI was associated with 8.2 mm Hg (95% CI: 8.2-8.3) higher SBP and 4.3 mm Hg (4.3-4.4) higher DBP; 10 cm higher waist circumference with 5.3 mm Hg (95% CI: 5.2-5.3) higher SBP and 2.8 mm Hg (2.8-2.8) higher DBP; 10 cm higher hip circumference with 6.9 mm Hg (6.9-7.0) higher SBP and 3.7 mm Hg (3.7-3.8) higher DBP; and 10 percentage points higher waist-hip ratio with 5.8 mm Hg (5.8-5.9) higher SBP and 3.1 mm Hg (3.0-3.1) higher DBP.

The strengths of these associations were reduced by further adjustment for the other adiposity variables: figure 4.4. The associations for BMI were reduced only slightly, those for waist and waist-hip ratio by about a half, and that for hip circumference so entirely that it became slightly negative: 5 kg/m^2 higher BMI was associated with 7.2 mm Hg (95% CI: 7.0-7.3) higher SBP and 3.5 mm Hg (3.4-3.6) higher DBP; 10 cm higher waist circumference with 2.6 mm Hg (2.5-2.7) higher SBP and 1.3 mm Hg (1.2-1.3) higher DBP; 10 cm higher hip circumference with 0.5 mm Hg (0.4-0.7) lower SBP and 0.2 mm Hg (0.2-0.3) lower DBP; and 10 percentage points higher waist-hip ratio with 2.0 mm Hg (1.9-2.1) higher SBP and 1.0 mm Hg (0.9-1.0) higher DBP (table B.5 in appendix B).

Blood pressure was more strongly associated with BMI than the other adiposity measures, as illustrated in figure 4.4 of the associations between quintiles of adiposity measures and SBP, both with and without adjustment for other adiposity variables. Further adjustment for a more extensive set of other potential confounders (table B.10 in appendix B), did not materially change the strength of the associations for BMI; the associations with waist circumference and waist-hip ratio became slightly more positive; and those with hip circumference slightly more negative.

4.2.3 Dietary variables

There was a moderately negative association between frequency of fresh fruit consumption and both SBP and DBP (both $p_{trend} = <0.0001$): table 4.4. Daily consumers of fresh fruit had, on average, 3.2 mm Hg (95% CI: 2.9-3.4) lower SBP and 1.1 mm Hg (0.9-1.2) lower DBP than those who never or rarely consumed fresh fruit. There was no evidence, however, that SBP or DBP were strongly related to the frequency of fresh vegetable consumption (both $p_{heterogeneity} = \geq 0.2$): table 4.4.

There was a slight positive association between frequency of tea intake and both SBP and DBP (both $p_{trend} = <0.0001$): table 4.4. Weekly tea drinkers had on average a 1.4 mm Hg (95% CI: 1.3-1.6) higher SBP and 1.0 mm Hg (0.9-1.1) higher DBP than those who never or rarely drank tea. Further adjustment for a more extensive set of potential confounders (table B.11 in appendix B) reduced the average difference in SBP and DBP by just under a half: weekly tea drinkers had on average a 0.7 mm Hg (95% CI: 0.6-0.9) higher SBP and 0.6 mm Hg (0.5-0.7) higher DBP than those who never or rarely drank tea. This reduction was almost wholly the result of adjustment for adiposity (BMI, waist circumference and hip circumference): adjusted for age, sex, education, area and adiposity, weekly tea drinkers had on average a 0.6 mm Hg (95% CI: 0.4-0.7) higher SBP and 0.6 mm Hg (0.5-0.6) higher DBP than those who never or rarely drank tea.

4.2.4 Other variables

There was a J-shaped association between alcohol intake and both SBP and DBP, adjusted for age, sex, education, area and smoking: figure 4.5, and table B.6 in appendix B. Occasional alcohol drinkers had the lowest average blood pressure; never drinkers had on average 2.0 mm Hg (95% CI: 1.9-2.1) higher SBP and 0.9 mm Hg (0.8-0.9) higher DBP, than occasional alcohol drinkers; and those with an average intake of >210 g per week had 6.4 mm Hg (95% CI: 6.1-6.6) higher SBP and 4.1 mm Hg (4.0-4.2) higher DBP. Ex-weekly and reduced-intake drinkers had blood pressures consistent with participants who had an average intake of 70-<140 g per week.

Mean blood pressure varied by month of baseline survey: figure 4.6, and table B.8 in appendix B. Both mean SBP and mean DBP were lowest in July and August, and increased every month to January/February. Participants recruited in August had on average 10.9 mm Hg (95% CI: 10.7-11.2) lower SBP and 3.8 mm Hg (3.7-3.9) lower DBP than participants recruited in January/February.

There was a slight negative association between physical activity, as measured by MET hours/day, and both SBP and DBP: table 4.5. 10 MET hours/day higher level of physical activity was associated with 0.25 mm Hg (95% CI: 0.21-0.30) lower SBP and 0.29 mm Hg (0.27-0.32) lower DBP. Further adjustment of other potential confounders did not materially affect the strength of these associations (table B.13 in appendix B); further adjustment did not include adiposity (BMI, waist circumference and hip circumference), however, as it may lie on the causal pathway between physical activity and blood pressure (figure 1.3). Adjusting for age, sex, education, area and adiposity, there was no association with SBP and the association with DBP was reduced in strength by just under a half: 10 MET hours/day higher level of physical activity was associated with 0.04 mm Hg (95% CI: 0.08- -0.02) lower SBP and 0.17 mm Hg (0.15-0.20) lower DBP. This indicated that much of the effect of physical activity on blood pressure was mediated through adiposity.

There was a negative association between smoking and both SBP and DBP (adjusted for age, sex, education, area and alcohol intake): table 4.5. Current smokers had, on average, 2.9 mm Hg (95% CI: 2.7-3.2) lower SBP and 1.7 mm Hg (1.6-1.9) lower DBP than those who had never smoked. Adjusted only for age, sex, education and area (but not alcohol), the average difference in blood pressure between current and never smokers was somewhat less than when alcohol was included in the model (table B.9 in appendix B). Adjusting for a more extensive set of potential confounders (table B.13 in appendix B), slightly reduced the strength of association: current smokers had 2.2 mm Hg (95% CI: 2.0-2.4) lower SBP and 1.3 mm Hg (1.2-1.4) lower DBP, on average, than those who had never smoked. This change was found to be accounted for by adjustment for four risk factors: fresh fruit consumption, tea intake and month of baseline survey, all slightly increased the strength of the association when added separately to the model (together with age, sex, education, area and alcohol intake); whereas adding adiposity (BMI, waist circumference and hip circumference) to the model reduced the strength of the association.

There was a moderate positive association between history of diabetes and SBP (adjusted for age, sex, education, area and adiposity), and a slight positive association for DBP (table 4.5). Participants with a history of diabetes had 5.6 mm Hg (95% CI: 5.3-5.8) higher SBP and 0.5 mm Hg (0.3-0.6) higher DBP, on average, than those without diabetes. Adjusted only for age, sex, education and area, the differences in average blood pressure between those with and without diabetes was somewhat greater than when adiposity was included in the model (table B.9 in appendix B).

There was a strong positive association between use of blood pressure-lowering medication and both SBP and DBP (adjusted for age, sex, education, area, adiposity, fresh fruit consumption, fresh vegetable consumption, tea intake, alcohol intake, month of baseline survey, MET hours/day, smoking and diabetes): table 4.5. Participants using blood pressure-lowering medication at baseline had 15.1 mm Hg (95% CI: 14.8-15.3) higher SBP and 6.7 mm Hg (6.5-6.8) higher DBP, on average, than those who did not report such use. Adjusted only for age, sex, education and area, the differences in average blood pressure between participants using and not using blood pressure-lowering medication was somewhat greater than when other variables were included in the model (table B.9 in appendix B).

4.3 Regression dilution ratios for blood pressure

Following exclusions (described in Methods), analyses were conducted on 18 791 participants with both baseline and resurvey blood pressure values. The demographic characteristics of the participants resurveyed (performed on average 2.6 years after the baseline survey) were similar to the overall baseline survey: 61% were female compared with 59% at baseline, and the mean age at baseline was 52 years, both overall and for those resurveyed (table 4.6).

Participants of the resurvey were divided into quintiles defined by their blood pressure at baseline (figure 4.7). The range of the quintile means reduced markedly between baseline and resurvey. The SBP range at baseline was 59 mm Hg, reducing to 39 mm Hg at resurvey: a regression dilution ratio of 0.66. For DBP, the baseline range was 31 mm Hg reducing to 20 mm Hg at resurvey: a regression dilution ratio of 0.65.

The reduction in quintile means between baseline and quality control survey (figure 4.8) indicates that most regression to the mean occurred by the time of the quality control survey (SBP range 45 mm Hg, DBP range 22 mm Hg), performed on average 17 days after the baseline survey, but that some more occurred by the time of the resurvey, on average two and half years later. This shows that technical measurement error and/or temporal variation over the short-term (e.g.

days rather than months) accounts for most of regression dilution bias for blood pressure, as least within the first few years of follow-up.

Blood pressure at baseline and resurvey was highly correlated (SBP r=0.70, DBP r=0.66; figure 4.8) and there was strong evidence for a linear association between blood pressure at baseline and resurvey (figure 4.9). The strength of these associations, as estimated by the slope of the regression line between baseline and resurvey blood pressure (with baseline blood pressure on the x-axis), was 0.65 (95% CI: 0.64-0.66) for SBP and 0.61 (0.60-0.62) for DBP (figure 4.9). The slope of these regression lines is a measure of the overall regression dilution ratio for the sample (Rosner's regression method).[89]

There was notable variation in the regression dilution ratio by age and sex, calculated using Rosner's regression method (table 4.7). Ratios were more extreme in males than females, and at older than younger ages. For SBP, the regression dilution ratios at ages 30-39 years and 70-79 years were 0.64 and 0.52, respectively, in males, and 0.70 and 0.57 in females. For DBP, the age-specific differences by sex were slightly less marked: the regression dilution ratios at ages 30-39 years and 70-79 years were 0.65 and 0.56, respectively, in males, and 0.66 and 0.57 in females. These results imply that within-person variability of real blood pressure levels, of technical measurement error, or of both, were slightly greater in males than females, and somewhat greater at older than younger ages in both sexes. Ratios were not materially changed by further adjustment for area and education. A comparison of age- and sex-specific regression dilution ratios by method of calculation found little difference in the age-and sex-specific ratios produced by Rosner's regression method,[89] the group method[91] or the intraclass correlation coefficient method[92] (table 4.8).

4.4 Completeness and accuracy of incident stroke events

4.4.1 Completeness

There were 8692 incident stroke events reported by the follow-up surveillance systems by November 2011 (table 4.9): 6043 (70%) ischaemic stroke events, 2197 (25%) intracerebral haemorrhage events, 130 (1.5%) subarachnoid haemorrhage events and 322 (3.5%) unspecified stroke events. Overall, the proportion of participants reported as loss to follow-up was small (0.2%; 857 participants). The overall crude incidence rate of stroke was 351 per 100 000 person-years. The total number of incident stroke events reported from each of the ten areas ranged from 34 in Qingdao (crude incidence rate of 20 per 100 000 person-years) to 1957 in Henan (crude incidence rate of 633 per 100 000 person-years). The number of stroke events reported from Qingdao was much lower than that for any other area: the second lowest number was for Henan, with 287 stroke events (crude incidence rate of 211 per 100 00 person-years).

There was only one stroke event reported by the mortality surveillance system to have been diagnosed by autopsy. Information on whether the diagnosis of an incident stroke event had involved imaging by CT or MRI scan was available only for events reported by the disease surveillance system (ie. not for deaths reported by the mortality surveillance system). The proportion of incident stroke events reported by the disease surveillance system varied enormously by area (table

4.10). Notably, Qingdao did not have any stroke events reported by the disease surveillance system, as it was not yet operating in this area: a fact that accounts for this area's very low number of reported incident stroke events. The proportion of stroke events reported by the disease surveillance system also varied by stroke pathological type: 97% of ischaemic stroke events were reported by the disease surveillance system, 56% of intracerebral haemorrhage events, 84% of subarachnoid haemorrhage events and 73% of unspecified stroke (table 4.10). The number of incident stroke events reported by each of the surveillance systems for each pathological type, stratified by age, by sex and by area can be found in tables C.1-C.3 in appendix C and illustrated in figure C.1 in appendix C.

Of 7439 incident stroke events reported by the disease surveillance system, 79% (5844 events) had been known to have involved imaging: 78% of ischaemic stroke events, 87% of intracerebral haemorrhage events, 84% of subarachnoid haemorrhage events and 49% of unspecified stroke. Consequently, the overall proportion of incident stroke events of each pathological type known to have involved imaging was the product of the proportion reported by the disease surveillance system and the proportion of these that were known to have involved imaging by CT or MRI scan: 75% (4556 events) of ischaemic stroke events, 71% (92) of subarachnoid haemorrhage events, but just 49% (1081) of intracerebral haemorrhage events and 36% (115) of unspecified stroke events (table 4.11, figure 4.10). As a result of these analyses, person-years of observation from Qingdao were excluded from the main prospective analyses because of the incompleteness of follow-up in this area.

4.4.2 Accuracy

The accuracy of stroke diagnoses was assessed by the adjudication sub-study. There were 1781 stroke events selected for the adjudication sub-study (table 4.12). The notes of 436 of these events could not be retrieved from the hospitals. Copies of the remaining 1345 were taken and adjudicated by the CKB team. During the adjudication process, there were 323 of these events for which either the participant information (name, sex, year of birth) or admission date (within one month) in the medical notes did not match that of the stroke event reported to the CKB study. After excluding these events, there were 1022 events on which analyses were conducted: 807 ischaemic stroke events, 139 intracerebral haemorrhage events, 21 subarachnoid haemorrhage events and 55 unspecified stroke events.

Ischaemic stroke

The overall positive predictive value of ischaemic stroke was 42% (95%CI: 39-46): table 4.13. Of the 807 ischaemic stroke events adjudicated, 341 events were adjudicated as ischaemic stroke, 15 events (2%) were adjudicated as other pathological types (14 events were intracerebral haemorrhage and one event was subarachnoid haemorrhage), 34 events (4%) were adjudicated as not stroke and 417 events (52%) were adjudicated as ‘equivocal’, as there was not sufficient information to verify or refute the diagnosis of ischaemic stroke. In this last group, there were 306 events for which there was evidence of cerebral infarction on CT or MRI scan but not sufficient clinical evidence of stroke documented during admission. It was observed informally by the adjudicator, that for most of these events, stroke was not considered the main diagnosis at discharge, implying that cerebral infarction may have been an incidental finding rather than the main cause of the presenting complaint.

For 70 ischaemic stroke events, there was a different final diagnosis in the medical notes to that assigned in the CKB study: either stroke was not reported as a final diagnosis in the notes or the pathological type of stroke was different to that reported in the CKB study. This may have been the result of some error in the process of reporting the diagnosis or the wrong admission notes had been collected. Excluding these events only slightly increased the positive predictive value of ischaemic stroke and slightly reduced the number of false positive events (those adjudicated as other pathological types or not strokes). Of 737 ‘matched’ ischaemic stroke events, 330 events (45%) were adjudicated as ischaemic stroke; 2 events (<1%) were adjudicated as other pathological types (both intracerebral haemorrhage events); 12 events (2%) were adjudicated as not strokes; and 393 events (53%) were adjudicated as equivocal (table C.5 in Appendix C).

The proportion of ischaemic stroke events adjudicated as equivocal with evidence of cerebral infarction on CT or MRI scan (‘cerebral infarction CT/MRI’), varied by surveillance system, hospital tier, area, and age at event (table 4.14). Events reported by the disease surveillance system had a higher proportion adjudicated as cerebral infarction CT/MRI (44% [95% CI: 40-48]) than those reported by the health insurance system (24% [19-30]). Tertiary level hospitals had a higher proportion (45% [95% CI: 40-51]) than primary (34% [28-40]) or secondary (32% [27-38]) level hospitals; and the proportion varied somewhat by area, ranging from 66% (95% CI: 55-75) in Harbin to 15% (8-25) in Qingdao. There was weak evidence of variation by age, with the youngest age group having a slightly lower proportion than at older ages (40-49 years: 27% [95% CI: 19-37]) than older age groups (70-79 years: 42% [34-49]). These results indicate that events adjudicated as cerebral infarction CT/MRI were not restricted to particular hospital tiers, areas or age groups that could be easily excluded from the prospective analyses to substantially improve the positive predictive value for ischaemic stroke. The overall predictive value of ischaemic stroke for ischaemic stroke and cerebral infarction CT/MRI combined was 80% (95% CI: 77-83).

Intracerebral haemorrhage

The overall positive predictive value of intracerebral haemorrhage was 85% (95% CI: 78-89): table 4.13. Of the 139 intracerebral haemorrhage events adjudicated, 118 events were adjudicated as intracerebral haemorrhage, 4 events (3%) were adjudicated as other pathological types (2 events were ischaemic stroke and 2 event were subarachnoid haemorrhage), 8 events (6%) were adjudicated as not strokes, and 9 events (6%) were adjudicated as equivocal. There were 24 events for which there was a different discharge diagnosis in the medical notes to the CKB data. Excluding these events, 112 events (97%) were adjudicated as intracerebral haemorrhage, zero events were adjudicated as other pathological types, 1 event was adjudicated as not stroke, and 2 events were adjudicated as equivocal (table C.6 in Appendix C).

Subarachnoid haemorrhage

The overall positive predictive value of subarachnoid haemorrhage was 62% (95% CI: 41-79): table 4.13. Of the 21 subarachnoid haemorrhage events adjudicated, 13 events were adjudicated as subarachnoid haemorrhage, 2 events (10%) were adjudicated as other pathological types (both intracerebral haemorrhage events), 3 events (14%) were adjudicated as not strokes, and 3 events (14%) were adjudicated as 'equivocal'. There were 7 events for which there was a different discharge diagnosis in the medical notes to that assigned in the CKB study. Excluding these events, 11 events (79%) were adjudicated as subarachnoid haemorrhage and 3 events (21%) were adjudicated as not stroke (table C.6 in Appendix C).

Sensitivity analysis

The main analyses of the adjudication sub-study were repeated using only the 416 stroke events included in the subsequent prospective analyses (tables C.7-C.8 in appendix C). The results were similar to the previous results for all stroke events. The positive predictive value of ischaemic stroke was 37% (95% CI: 32-42). Of the 340 ischaemic stroke events adjudicated, 125 events were adjudicated as ischaemic stroke, 5 events (2%) were adjudicated as other pathological types (all intracerebral haemorrhage events), 14 events (4%) were adjudicated as not strokes, and 196 events (58%) were adjudicated as 'equivocal' (157 of these events had evidence of cerebral infarction on CT/MRI scan). The variation in the proportion of ischaemic stroke events adjudicated as ischaemic stroke and cerebral infarction CT/MRI, by hospital tier, area and age (table C.8 in Appendix C) were again similar to the results for all stroke events. The overall positive predictive value of ischaemic stroke for ischaemic stroke and cerebral infarction CT/MRI combined was 83% (95% CI: 79-87). As in the analyses of all stroke events, the positive predictive value was high for both intracerebral haemorrhage

(81% [95% CI: 70-89]) and subarachnoid haemorrhage (73% [95% CI: 43-90]), and the proportion of these stroke pathological types misclassified as other pathological types was low (table C.7 in appendix C). Finally, repeating these analyses excluding 48 events with different final diagnosis in the medical notes to that assigned in the CKB study gave similar results (table C.9 in Appendix C).

4.5 Stroke incidence rates

There were 5783 stroke events known to have involved imaging by CT or MRI scan (tables 4.15 and 4.16). The main prospective analyses that follow restricted analyses to these events. Participants from Qingdao were excluded as there was substantial undercounting of stroke events imaged by CT or MRI scan in this area. Stroke events and person-years of follow-up outside of the age range 40-79 were also excluded as there were too few events at age <40 years and ≥80 years to provide reliable results for the main prospective analyses at these ages (stroke events by age and sex prior to these exclusion are shown in tables C.4 [all events] and C.5 [events imaged by CT/MRI] in appendix C). Ischaemic stroke events in the CKB study are referred to as ‘cerebral infarction’ in this and subsequent sections of the thesis, as the adjudication sub-study found that these events would more accurately be described as cerebral infarction, at present.

Among 455 438 participants (184 949 males and 270 489 females), the overall age- and sex-standardised incidence of stroke at age 40-79 years was 399 events per 100 000 person-years (standardised by taking the unweighted average of the component ten-year incidence rates in both males and females): table 4.15. The age- and sex-standardised incidence at 40-79 years varied by stroke pathological type: 313 per 100 000 person-years for cerebral infarction (4513 events), 73 per 100 000 person-years for intracerebral haemorrhage (1071 events), 5 per 100 000 person-years for subarachnoid haemorrhage (85 events) and 9 per 100 000 person-years for unspecified stroke (114 events).

There were too few events for subarachnoid haemorrhage and unspecified stroke to reliably compare incidence rates by area, age or sex. The incidence of cerebral infarction and intracerebral haemorrhage was higher at older ages in both males and females, and the age-specific rates were higher in males than females (table 4.15). The incidence of cerebral infarction and intracerebral haemorrhage approximately doubled with each decade in both males and females. The age-standardised incidence of stroke at 40-79 years was 30% higher in males than females for cerebral infarction and 88% higher in males than females for intracerebral haemorrhage.

There was substantial variation by area in the incidence of both cerebral infarction (~11-fold variation) and intracerebral haemorrhage (~14-fold variation): table 4.16. The overall crude incidence of cerebral infarction was 16% higher in urban than rural areas (222 events per 100 000 person-years in urban areas, 192 events per 100 000 person-years in rural areas), whereas the incidence of intracerebral haemorrhage was around 20 times lower in urban than rural areas (16 events per 100 000 person-years in urban areas, 351 events per 100 000 person-years in rural areas).

The variation in incidence of cerebral infarction and intracerebral haemorrhage by age, by sex and by area, was examined using cox proportional hazard models to adjust for potential confounders (table D.1 in appendix D). The associations were in keeping with the variation in incidence described above. For interest, the associations between both main stroke pathological types and potential confounders of the associations of usual blood pressure and stroke incidence are reported in appendix D (tables D.2 to D.10). These associations are not described here as they are extraneous to the main aims of the thesis.

4.6 Associations of usual blood pressure with stroke incidence

4.6.1 Cerebral infarction

At age 40-79 years, the proportional difference in risk of cerebral infarction associated with a given absolute difference in usual blood pressure was constant throughout the range of blood pressures examined (SBP 120-170 mm Hg; DBP 70-100 mm Hg): there were strong positive ‘log-linear’ associations (figure 4.11). Adjusting for age, sex, education and area (and correcting for regression dilution bias), 10 mm Hg higher usual SBP was associated with 47% (95% CI: 45-51) higher risk of cerebral infarction and 5 mm Hg higher usual DBP was associated with 42% (40-46) higher risk (table 4.17). Uncorrected for regression dilution bias, the associations were considerably shallower: 10 mm Hg higher baseline SBP was associated with 24% (95% CI: 23-26) higher risk of cerebral infarction and 5 mm Hg higher baseline DBP was associated with 22% (21-24) higher risk (table E.1 in appendix E).

Progressive adjustment for the set of major potential confounders did not materially affect the strength of these associations (table 4.17). After adjustment for potential confounders, with the exception of blood pressure-lowering medication use, 10 mm Hg higher usual SBP was associated with 45% (95% CI: 41-47) higher risk of cerebral infarction and 5 mm Hg higher usual DBP was associated with 40% (36-44) higher risk. Including blood pressure-lowering medication use in the model, only slightly reduced the strength of association for both SBP and DBP: 10 mm Hg higher usual SBP was associated with 43% (95% CI: 40-46) higher risk and 5 mm Hg higher usual DBP was associated with 38% (35-42) higher risk.

Within each decade of age at risk, between 40-79 years, there were strong positive log-linear associations between risk of cerebral infarction and both usual SBP (figure 4.12) and usual DBP (figure 4.13). At age 60-69 years, the strengths of associations were similar to the overall associations (the overall mean age at event for cerebral infarction was 64 years): 10 mm Hg higher usual SBP was associated with 48% (95% CI: 43-53) higher risk of cerebral infarction (figure 4.14) and 5 mm Hg higher usual DBP was associated with 41% (36-47) higher risk (figure 4.15). The strengths of the age-specific associations were progressively shallower at older ages: 10 mm Hg higher usual SBP was associated with 90% (95% CI: 78-103) higher risk of cerebral infarction at age 40-49 years and 27% (22-32) higher risk at age 70-79 years; 5 mm Hg higher usual DBP was associated with 75% (64-86) higher risk at age 40-49 years and 23% (18-28) higher risk at age 70-79 years. Despite this, the absolute difference in risk of cerebral infarction associated with a given increase in usual blood pressure was still much higher at older age groups, as stroke is so much more common at older ages. For example, 10 mm Hg difference in usual SBP between 130 mm Hg and 140 mm Hg was associated with an absolute difference in risk of cerebral infarction that was about four times as great at age 70-79 years than at 40-49 years.

There was strong evidence for steeper age-specific associations in males than females at all ages for SBP (figure 4.14), but only weak evidence of such differences for DBP (figure 4.15). Overall, at age 40-79 years, 10 mm Hg higher usual SBP was associated with 56% (95% CI: 51-61) higher risk of cerebral infarction in males compared to 41% (37-45) in females (figure 4.16); and 5 mm Hg higher usual DBP was associated with 46% (42-50) higher risk of cerebral infarction in males compared to 38% (34-42) in females (figure E.3 in appendix E).

Further effect modification of the association between cerebral infarction and usual SBP was examined by area (urban/rural), alcohol intake, smoking, BMI, MET hours/day, diabetes and blood pressure-lowering medication use (figures 4.16 and 4.17). There was strong evidence of effect modification by area, alcohol intake, smoking, BMI and diabetes; and no evidence of effect modification by MET hours/day ($p_{trend} = 0.1$) or blood pressure-lowering medication use ($p_{trend} = 0.2$). The associations were stronger in rural than urban areas (HR for 10 mm Hg higher usual SBP: rural 56% [95% CI: 52-60], urban 36% [32-41]); in weekly than occasional or never alcohol drinkers (weekly 69% [60-78], occasional 44% [39-49], never 40% [36-45]); in current than never smokers (current 62% [56-68] , never 41% [37-45]); at lower than higher BMI (BMI <22 kg/m^2 54% [48-60] , ≥25 kg/m^2 39% [34-44]; and in those without diabetes than with diabetes (no diabetes 48%

[45-51], diabetes 32% [23-42]). Finally, there was no evidence of any difference in the strength of association using cerebral infarction events classified as fatal (defined as events followed by death within 30 days) and non-fatal (events not followed by death within 30 days): $p_{heterogeneity} = 0.6$.

Effect modification of the association by alcohol intake, smoking, BMI, MET hours/day and area, was also analysed separately in males and females (figures E.1 and E.2 in appendix E). There was strong evidence of effect modification by alcohol intake and smoking, in males but not females; by BMI, in females but not males; by area in both sexes; and by MET hours/day in neither sex. The reduced power of these sex-specific analyses, however, means the results should be interpreted with greater caution than the overall analyses. Where there was evidence of strong effect modification in either sex, the qualitative nature of the association was consistent with the overall association. In males, associations with usual SBP were stronger in weekly than occasional or never alcohol drinkers (HR for 10 mm Hg higher usual SBP: weekly drinkers 68% [95% CI: 59-78], occasional drinkers 46% [37-55], never 52% [43-61]); in current than never smokers (current 64% [58-71], never 39% [27-52]); and in rural than urban areas (rural 64% [58-71], urban 44% [37-51]). There was no evidence of effect modification in males by BMI ($p_{trend} = 0.1$) or MET hours/day ($p_{trend} = 0.7$). In females, associations were stronger at lower than higher BMI (BMI <22 kg/m^2 51% [95% CI: 43-60], BMI ≥25 kg/m^2 33% [28-39]), and in rural than urban areas (rural 49% [44-55], urban 31% [26-37]). There was only weak evidence of effect modification in females by MET hours/day ($p_{trend} = 0.01$) and alcohol intake ($p_{heterogeneity} = 0.05$), and no evidence of effect modification by smoking ($p_{heterogeneity} = 0.5$); there were, however, wide confidence intervals about the hazard ratios for weekly drinkers and current smokers, in particular, reflecting the few stroke events in these categories.

The evidence for effect modification of the overall and sex-specific associations with usual DBP was, on the whole, consistent with that of usual SBP (figures E.3-E.6 in appendix E). The strength of the associations within categories of effect modifiers for 5 mm Hg higher usual DBP was similar to those given for 10 mm Hg higher usual SBP. Unlike the analyses for usual SBP, however, there was additional evidence for effect modification of the overall association by MET hours/day ($p_{trend} = 0.005$) and blood pressure-lowering medication use ($p_{heterogeneity} < 0.001$). The overall associations were stronger at higher than lower MET hours/day (HR for 5 mm Hg higher usual DBP: ≥30 MET hours/day 51% [95% CI: 44-59], <20 MET hours/day 39% [35-43]), and in non-users than users of blood pressure-lowering medication (non-users 42% [39-45], users 21% [12-31]). Excluding those using blood pressure-lowering medication did not materially change the strength of the main age- and sex-specific associations between usual SBP or usual DBP with either cerebral infarction (figure E.15 in appendix E) or intracerebral haemorrhage (figure E.16 in appendix E).

4.6.2 Intracerebral haemorrhage

As with cerebral infarction, there were strong positive log-linear associations between risk of intracerebral haemorrhage and both usual SBP and usual DBP, throughout the range of blood pressures (figure 4.18). Adjusting for age, sex, education and area (and correcting for regression dilution bias), 10 mm Hg higher usual SBP was associated with 82% (95% CI: 76-90) higher risk of intracerebral haemorrhage and 5 mm Hg higher usual DBP was associated with 81% (74-90) higher risk (table 4.18). Uncorrected for regression dilution bias, the associations were considerably shallower: 10 mm Hg higher baseline SBP was associated with 40% (95% CI: 37-43) higher risk of intracerebral haemorrhage and 5 mm Hg higher baseline DBP was associated with 40% (37-44) higher risk (table E.2 in appendix E). Progressive adjustment for major potential confounders did not materially affect the strength of these associations (table 4.18). After adjustment for potential confounders, including blood pressure-lowering medication use, 10 mm Hg higher usual SBP was associated with 83% (95% CI: 76-91) higher risk of cerebral infarction and 5 mm Hg higher usual DBP was associated with 82% (75-90) higher risk.

There were strong positive log-linear age-specific associations between risk of intracerebral haemorrhage and both usual SBP (figure 4.19) and usual DBP (figure 4.20) in all age groups. At age 60-69 years, the strength of associations was similar to the overall associations (the overall mean age at event for intracerebral haemorrhage was 63 years): 10 mm Hg higher usual SBP was associated with 84% (95% CI: 71-97) higher risk of intracerebral haemorrhage (figure 4.21) and 5 mm Hg higher usual DBP was associated with 85% (72-99) higher risk (figure 4.22). The strengths of the age-specific associations were progressively shallower at older ages: 10 mm Hg higher usual SBP was associated with 131% (95% CI: 110-155) higher risk of intracerebral haemorrhage at age 40-49 years and 33% (23-44) higher risk at age 70-79 years; 5 mm Hg higher usual DBP was associated with 119% (99-141) higher risk at age 40-49 years and 34% (23-45) higher risk at age 70-79 years. As with cerebral infarction, however, the absolute difference in risk of intracerebral haemorrhage associated with 10 mm Hg higher usual SBP was much higher at older age groups: 10 mm Hg difference in usual SBP between 130 mm Hg and 140 mm Hg was associated with an absolute difference in risk of intracerebral haemorrhage that was about three times as great at age 70-79 years than at 40-49 years.

The age-specific associations for intracerebral haemorrhage were stronger than for cerebral infarction for each decade of age at risk (the age-specific association for both stroke pathological types are shown on the same figures in appendix E: figure E.13 for usual SBP and figure E.14 for usual DBP). For usual SBP, the variation in strength of the age-specific associations was slightly greater for intracerebral haemorrhage than for cerebral infarction: at age 40-49 years the strength of association was greater than at age 70-79 years by 2.9 times for intracerebral haemorrhage and 2.7 times for cerebral infarction. For usual DBP, the strength of association was 2.7 times greater at age 40-49 years than at age 70-79 years for both stroke pathological types.

There was no evidence of a difference in the strength of the age-specific associations for intracerebral haemorrhage between males and females (SBP figure 4.21, DBP figure 4.22). Overall, at age 40-79 years, 10 mm Hg higher usual SBP was associated with 84% (95% CI: 75-94) higher risk of intracerebral haemorrhage in males compared to 81% (72-91) in females (figure 4.23); and 5 mm Hg higher usual DBP was associated with 78% (69-87) higher risk of intracerebral haemorrhage in males compared to 85% (75-96) in females (figure E.9 in Appendix E).

There was also no evidence of effect modification of the overall associations with usual SBP by area, alcohol intake, smoking, BMI, blood pressure-lowering medication use or fatal/non-fatal intracerebral haemorrhage events (figures 4.23 and 4.24); there was, however, strong evidence by MET hours/day and weak evidence by diabetes. The overall associations were stronger at higher than lower MET hours/day (HR for 10 mm Hg higher usual SBP: ≥30 MET hours/day 109% [95% CI: 94-125], <30 MET hours/day 85% [73-98], <20 MET hours/day 66% [57-75]); and in those without diabetes than with diabetes (without diabetes 85% [78-92], with diabetes 46% [21-76]). The mean age at event varied somewhat by level of MET hours/day: 58 years at ≥30 MET hours/day, 61 years at <30 MET hours/day and 66 years at <20 MET hours/day. Comparing these results to the age-specific hazard ratios for intracerebral haemorrhage (figure 4.21) indicates that age may account some of the effect modification by MET hours/day.

As with cerebral infarction, effect modification of the associations was also analysed separately in males and females, by alcohol intake, smoking, BMI, MET hours/day and area (figures E.7 and E.8 in appendix E). There was no evidence of effect modification by alcohol intake, smoking or area in either sex; there was weak evidence of effect modification by BMI in females but not males, and strong evidence of effect modification by MET hours/day in both sexes. In females, there were stronger associations at higher than lower BMI: 10 mm Hg higher usual SBP was associated with 103% (95% CI: 86-122) higher risk in those with BMI ≥25 kg/m^2 compared to 73% (58-90) higher risk in those with BMI <22 kg/m^2; the equivalent values for males were 88% (67-111) and 87% (73-102), for BMI ≥25 kg/m^2 and <22 kg/m^2 respectively. There was no evidence of differences between the sexes in the strength of association by level of MET hours/day.

The evidence for effect modification of the overall and sex-specific associations with usual DBP was consistent with that of usual SBP (E.9-E.12 in appendix E). The strength of the associations within categories of effect modifiers for 5 mm Hg higher usual DBP was, on the whole, similar to those given for 10 mm Hg higher usual SBP.

4.6.3 Subarachnoid haemorrhage

Adjusting for age, sex, education and area (and correcting for regression dilution bias), 10 mm Hg higher usual SBP was associated with 49% (95% CI: 29-73) higher risk of subarachnoid haemorrhage and 5 mm Hg higher usual DBP was associated with 44% (24-67) higher risk. Uncorrected for regression dilution bias, 10 mm Hg higher baseline SBP was associated with 24% (95% CI: 13-35) higher risk of subarachnoid haemorrhage and 5 mm Hg higher baseline DBP was associated with 21% (11-32) higher risk. Further adjustment for major potential confounders did not materially affect the strength of these associations. There was insufficient number of events to reliably assess the shape of the association or investigate for effect modification by age, sex or other potential effect modifiers.

4.6.4 All stroke events

The overall associations between usual blood pressure and risk of intracerebral haemorrhage were stronger than for cerebral infarction, by a factor of 1.55 for usual SBP (figure 4.25) and 1.69 for usual DBP (figure 4.25). There was no evidence of difference in the strength of the overall associations for cerebral infarction, subarachnoid haemorrhage and unspecified stroke, for either usual SBP or usual DBP.

Comparing the strengths of associations using events for which the diagnosis was known and not known to have involved a CT or MRI scan, within each stroke pathological type (SBP figure 4.25, DBP figure 4.26), found that there was no evidence of a difference for cerebral infarction, subarachnoid haemorrhage and unspecified stroke. There was, however, strong evidence of differences in the strengths of the associations for intracerebral haemorrhage for both SBP and DBP, with shallower associations for events not known to have involved imaging (where misclassification with cerebral infarction is more likely): 10 mm Hg higher usual SBP was associated with 82% (95% CI: 76-89) higher risk of intracerebral haemorrhage using events known to have involved imaging compared to 62% (56-68) higher risk using events not known to have involved imaging. The age-specific and sex-specific associations for cerebral infarction and intracerebral haemorrhage, using events not known to have involved imaging, can be found in figures E.17 and E.18 in appendix E; the associations for intracerebral haemorrhage were shallower in both sexes and for each decade age at risk, except at age 70-79 years for which there was no evidence of difference.

The overall association between usual blood pressure and incidence of all stroke events combined was much same for SBP (figure 4.25) and DBP (figure 4.26). Adjusting for age, sex, education and area (and correcting for regression dilution bias), 10 mm Hg higher usual SBP was associated with 54% (95% CI: 52-56) higher risk of stroke and 5 mm Hg higher usual DBP was associated with 49% (95% CI: 47-52) higher risk.

4.6.5 Informativeness of blood pressure indices

The comparison of the predictive power of a single measurement of each blood pressure index at baseline (as indicated by chi-squared [X^2_1] value relating blood pressure to incidence of stroke events known to have involved imaging) found mid blood pressure to be the best predictor of cerebral infarction and mean arterial pressure the best predictor of intracerebral haemorrhage (table 4.19; table E.3 in appendix E).

For the prediction of cerebral infarction incidence, the overall X^2_1 values relative to mid blood pressure were 98% for mean arterial pressure, 95% for SBP, 80% for DBP and 54% for pulse pressure (table 4.19). These percentages did not vary markedly by age or sex, except for DBP where the percentages were lower at older ages (92% at age 40-49 years and 69% at age 70-79 years).

For the prediction of intracerebral haemorrhage incidence, the overall X^2_1 values relative to mean arterial blood pressure were 99% for mid blood pressure, 91% for SBP, 88% for DBP and 49% for pulse pressure. These percentages were much the same in males and females, except for pulse pressure (males 45%, females 54%); there was also some evidence of variation by age for SBP, DBP and pulse pressure, but no clear trends.

In summary, mid blood pressure and mean arterial pressure were better predictors than either SBP or DBP of both cerebral infarction and intracerebral haemorrhage; SBP was a much better predictor than DBP of cerebral infarction (particularly at older ages) and a slightly better predictor of intracerebral haemorrhage; pulse pressure was substantial less informative than the other measures at predicting cerebral infarction or intracerebral haemorrhage.

Tables and figures: 4.1 Participant characteristics

Table 4.1: Baseline demographic characteristics, by area (among 488 789 participants)

Area	Participants, n	Proportion female, %	Mean (SD) age, years		Educated to middle school or higher, %	Location of province within China
			Male	Female		
Urban						
Qingdao	33 351	55	49 (10)	51 (10)	78	East, coastal
Harbin	49 813	60	52 (12)	52 (11)	87	Northeast, inland
Haikou	28 955	64	54 (10)	52 (12)	66	South central, coastal
Suzhou	52 177	58	52 (10)	52 (10)	38	East, coastal
Liuzhou	46 690	62	54 (11)	53 (10)	76	South central, coastal
All urban	210 986	60	52 (11)	52 (11)	68	
Rural						
Sichuan	55 017	62	53 (11)	51 (10)	35	Southwest, inland
Gansu	48 489	61	51 (11)	48 (10)	27	Northwest, inland
Henan	60 300	56	51 (11)	50 (10)	52	Central, inland
Zhejiang	56 791	59	53 (10)	52 (10)	20	East, coastal
Hunan	57 206	56	53 (11)	50 (10)	37	South central, inland
All rural	277 803	59	52 (11)	50 (10)	35	East, coastal
Overall	488 789	59	52 (11)	51 (10)	49	

Table 4.2: Other selected baseline characteristics, by sex (among 488 789 participants)

	Male		Female		All	
Participants	199 825		288 964		488 789	
	Mean (SD)					
BMI, kg/m^2	23.4	(3.2)	23.7	(3.4)	23.6	(3.3)
Waist circumference, cm	81.8	(9.7)	78.8	(9.4)	80.0	(9.6)
Hip circumference, cm	90.5	(6.7)	91.0	(6.7)	90.8	(6.7)
Waist-hip ratio, %	90.2	(6.4)	86.5	(7.0)	88.1	(7.0)
Physical activity, MET hours/day	27.2	(15.0)	25.2	(12.5)	26.0	(13.6)
	Percent					
Educated to middle school or higher	58		43		49	
Current smoking	62		2		27	
Alcohol consumed at least weekly	34		2		15	
Tea consumed at least weekly	51		21		34	
Fresh fruit consumed daily	14		21		18	
Fresh vegetable consumed daily	95		95		95	
Month of baseline survey: April to Sept.	51		52		52	
Diabetes	5		5		5	
Taking blood pressure-lowering medication	4		4		4	

Figure 4.1: Frequency distribution of baseline SBP values, by sex (among 488 789 participants)

Histogram bar width: 0.5 mm Hg; IQR = interquartile range.

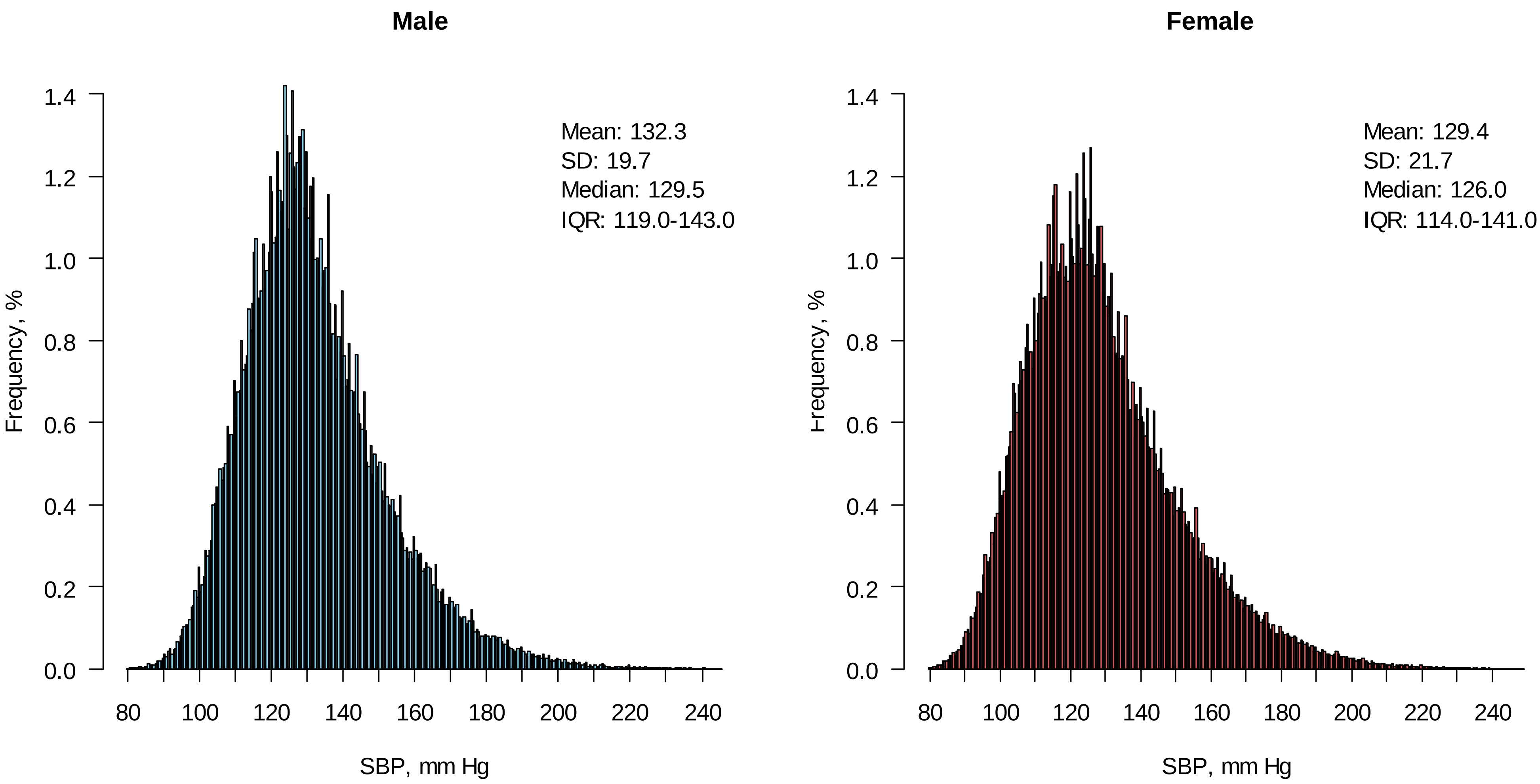
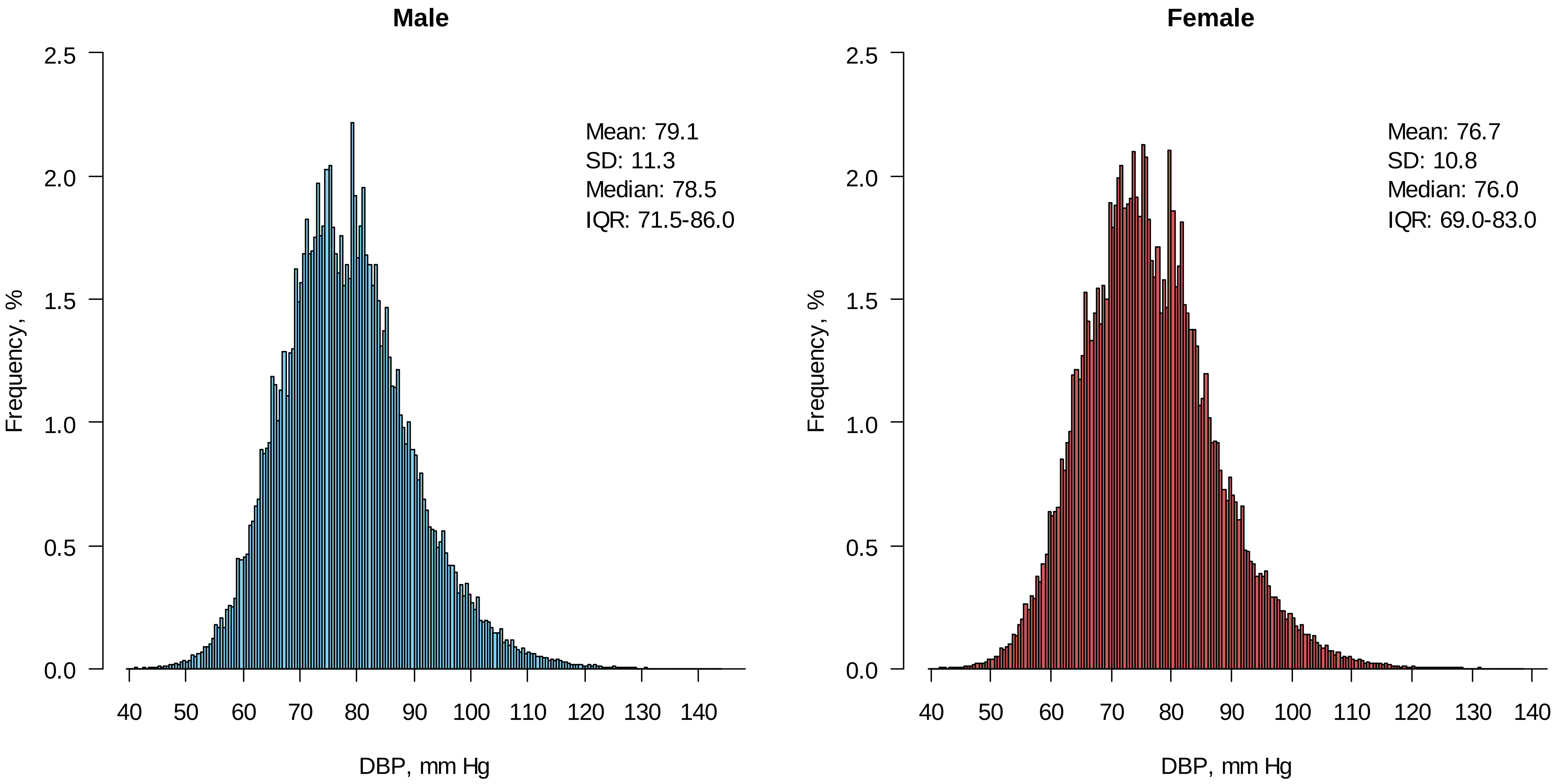


Figure 4.2: Frequency distribution of baseline DBP values, by sex (among 488 789 participants)

Histogram bar width: 0.5 mm Hg; IQR = interquartile range.



Tables and figures: 4.2 Baseline associations of blood pressure with major potential confounders

Figure 4.3: Baseline associations of blood pressure with age, by sex (among 488 789 participants)

Means adjusted for education and area.

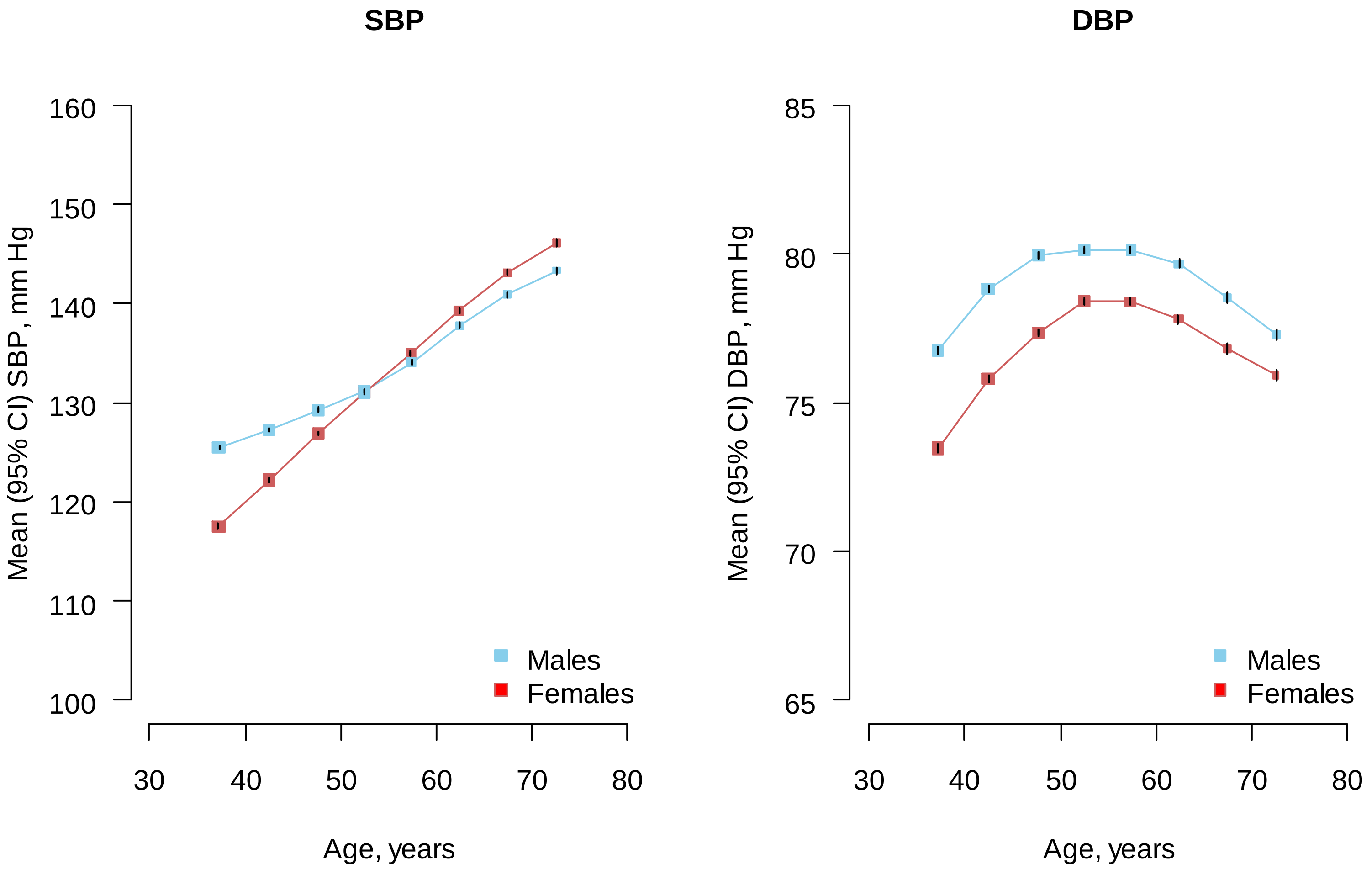


Table 4.3: Baseline associations of blood pressure with sex, education and area (among 488 789 participants)

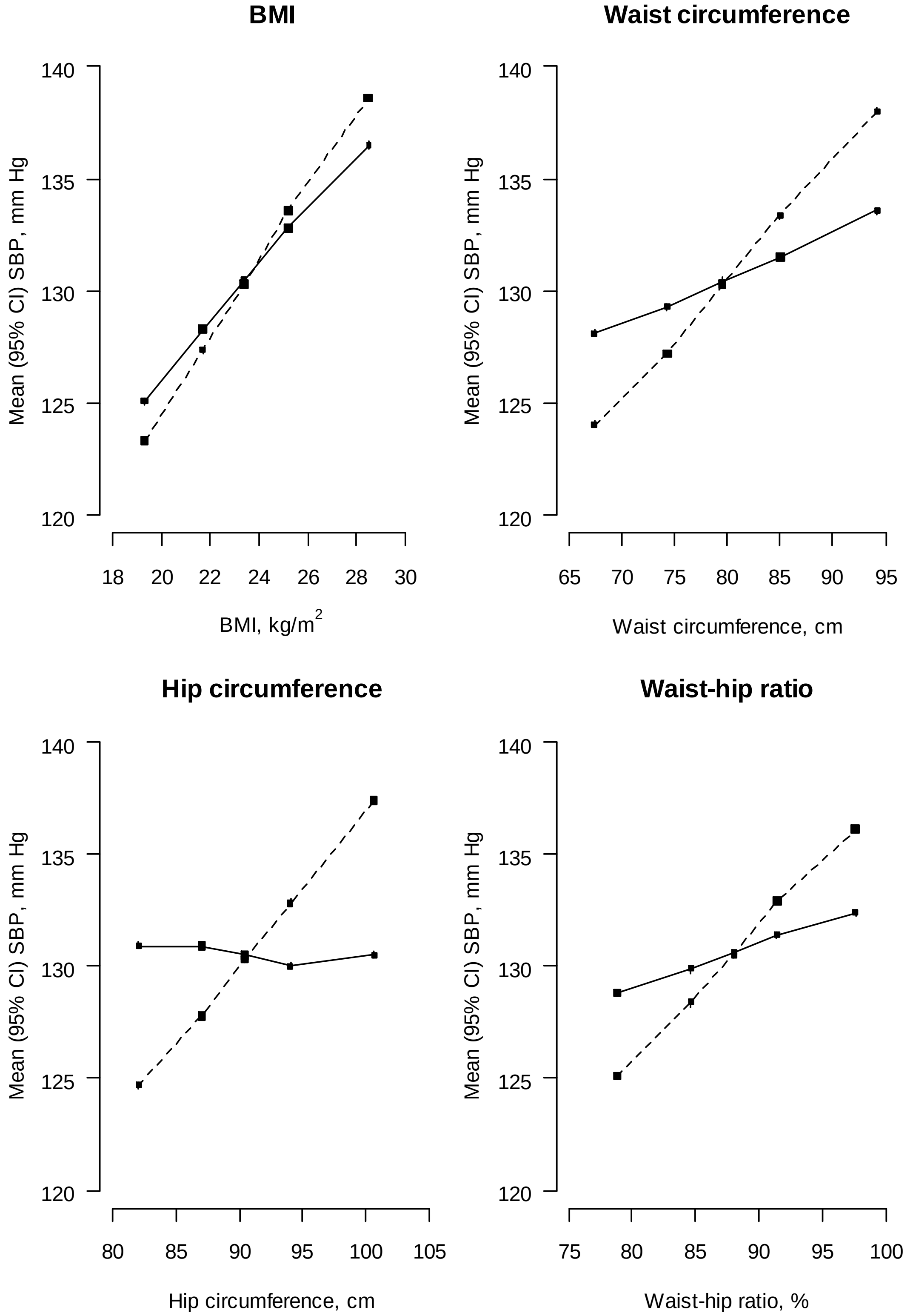
Means adjusted for other variables in the table and age.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Sex						
Male	199 825	(41)	132.0	(131.9-132.1)	79.1	(79.0-79.1)
Female	288 964	(59)	129.6	(129.5-129.6)	76.6	(76.6-76.7)
Educational level						
No formal schooling	91 143	(19)	133.0	(132.9-133.2)	78.3	(78.2-78.4)
Primary school	157 251	(32)	130.8	(130.7-130.9)	77.6	(77.6-77.7)
Middle school	138 924	(28)	130.1	(130.0-130.2)	77.6	(77.5-77.6)
High school	73 698	(15)	129.1	(129.0-129.3)	77.3	(77.2-77.4)
Tech./coll./uni.*	27 773	(6)	127.7	(127.5-128.0)	76.9	(76.8-77.1)
Area†						
Qingdao (U)	33 351	(7)	132.8	(132.6-133.0)	79.3	(79.2-79.4)
Harbin (U)	49 813	(10)	127.3	(127.1-127.5)	78.1	(78.0-78.2)
Haikou (U)	28 955	(6)	123.8	(123.6-124.1)	74.4	(74.3-74.6)
Suzhou (U)	52 177	(11)	131.8	(131.7-132.0)	78.7	(78.6-78.8)
Liuzhou (U)	46 690	(10)	127.1	(126.9-127.3)	75.1	(75.0-75.2)
Sichuan (R)	55 017	(11)	129.0	(128.9-129.2)	77.2	(77.1-77.3)
Gansu (R)	48 489	(10)	131.5	(131.4-131.7)	77.7	(77.6-77.8)
Henan (R)	60 300	(12)	134.3	(134.1-134.4)	78.4	(78.4-78.5)
Zhejiang (R)	56 791	(12)	134.0	(133.9-134.2)	80.0	(79.9-80.1)
Hunan (R)	57 206	(12)	130.6	(130.4-130.8)	76.2	(76.1-76.3)

* Technical school, technical college or university.
† (U)=urban area, (R)=rural area.

Figure 4.4: Baseline associations of SBP with measures of adiposity (among 488 789 participants)

Dashed lines (----) adjusted only for age, sex, education and area; solid lines (——) adjusted not only for age, sex, education and area, but for the other adiposity measures.*



* Blood pressure means by quintiles of BMI were further adjusted for hip circumference and waist circumference; means by quintiles of hip circumference were further adjusted for BMI and waist circumference; means by quintiles of waist circumference were further adjusted for BMI and waist circumference; and means by quintiles of waist-hip ratio were further adjusted for BMI, hip circumference and waist circumference.

Table 4.4: Baseline associations of blood pressure with dietary variables (among 488 789 participants)

Means adjusted for age, sex, education and area.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Fresh fruit consumption						
Never/rarely	30 786	(6)	132.4	(132.2-132.6)	78.3	(78.2-78.4)
Monthly	167 593	(34)	131.0	(130.9-131.1)	77.7	(77.6-77.7)
1-3 days/wk	154 896	(32)	130.7	(130.6-130.8)	77.7	(77.7-77.8)
4-6 days/wk	46 124	(9)	130.1	(129.9-130.3)	77.6	(77.5-77.7)
Daily	89 390	(18)	129.2	(129.1-129.4)	77.2	(77.1-77.3)
Fresh vegetable consumption						
Not daily	25 904	(5)	130.4	(130.2-130.7)	77.7	(77.6-77.8)
Daily	462 885	(95)	130.6	(130.5-130.6)	77.6	(77.6-77.7)
Tea intake						
Never/rarely	171 074	(35)	130.1	(130.0-130.2)	77.3	(77.2-77.3)
Occasional	134 405	(27)	130.0	(129.9-130.2)	77.4	(77.3-77.4)
Monthly	19 086	(4)	130.7	(130.4-131.0)	77.7	(77.5-77.9)
Weekly/daily	164 224	(34)	131.5	(131.4-131.6)	78.3	(78.2-78.3)

Figure 4.5: Baseline associations of blood pressure with alcohol intake (among 488 789 participants)

Means adjusted for age, sex, education, area and smoking.

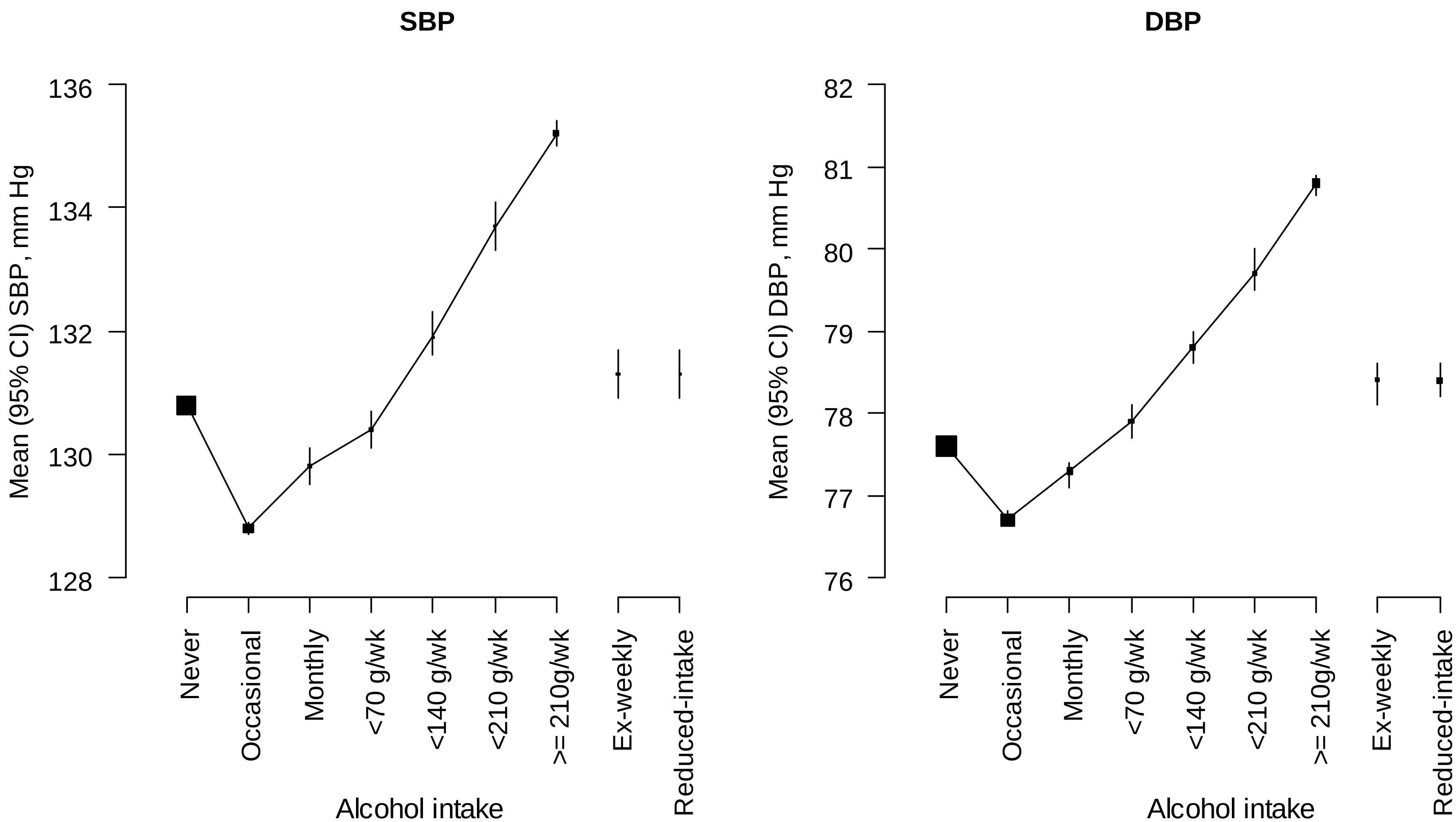


Figure 4.6: Baseline associations of blood pressure with month of baseline survey (among 488 789 participants)

Means adjusted for age, sex, education and area.

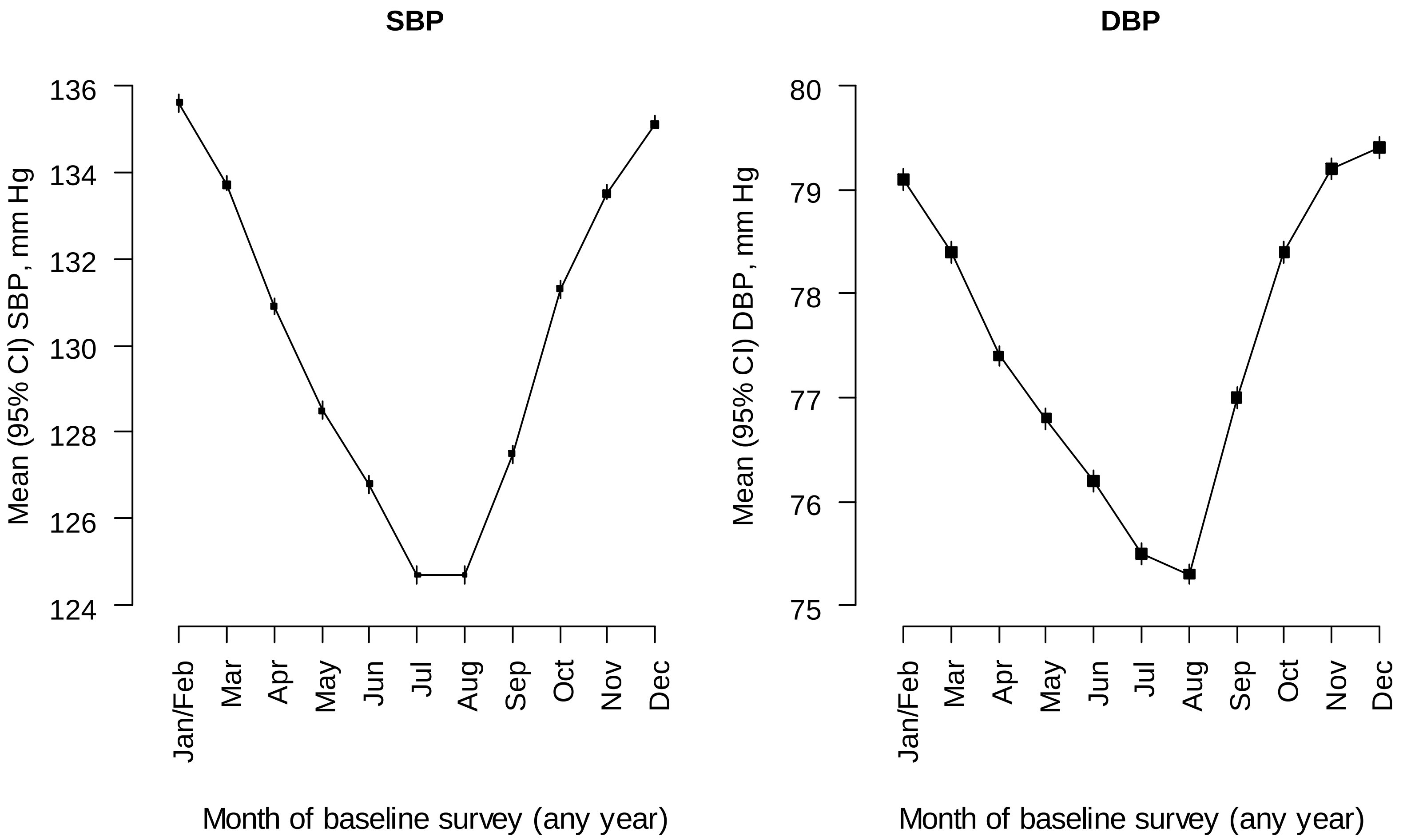


Table 4.5: Baseline associations of blood pressure with other variables (among 488 789 participants)

Means were adjusted for age, sex, education and area.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Physical activity quintiles (MET hours/day)*						
0.0 - <14.4	97 774	(20)	131.1	(131.0-131.2)	78.2	(78.1-78.2)
14.4 - <19.7	97 716	(20)	131.0	(130.9-131.2)	78.0	(77.9-78.0)
19.7 - <26.8	97 803	(20)	130.4	(130.2-130.5)	77.7	(77.6-77.7)
26.8 - <38.0	97 784	(20)	130.3	(130.1-130.4)	77.3	(77.3-77.4)
38.0 - 139.5	97 712	(20)	130.1	(130.0-130.3)	77.1	(77.0-77.2)
Per 10 units lower	488 789	(100)	0.25	(0.21-0.30)	0.29	(0.27-0.32)
Smoking†						
Never	303 127	(62)	131.5	(131.4-131.6)	78.1	(78.1-78.2)
Occasional	27 978	(6)	130.7	(130.5-131.0)	77.8	(77.7-77.9)
Ex-regular	27 236	(6)	130.5	(130.2-130.7)	78.1	(77.9-78.2)
Current	130 448	(27)	128.5	(128.4-128.7)	76.4	(76.3-76.5)
History of diabetes‡						
No	466 144	(95)	130.3	(130.3-130.4)	77.6	(77.6-77.6)
Yes	22 645	(5)	135.9	(135.6-136.1)	78.1	(78.0-78.2)
Taking BP-lowering medication§						
No	471 207	(96)	130.0	(130.0-130.1)	77.4	(77.4-77.4)
Yes	17 582	(4)	145.0	(144.7-145.3)	84.0	(83.9-84.2)

* Mean of quintiles: 10.6, 17.0, 22.9, 32.1, 47.6 MET hours/day.
† Further adjusted for alcohol intake.
‡ Further adjusted for adiposity (BMI, waist circumference, hip circumference).
§ Further adjusted for adiposity (BMI, waist circumference, hip circumference), physical activity (MET hours/day), alcohol intake, diabetes, fresh fruit consumption and fresh vegetable consumption.

Tables and figures: 4.3 Regression dilution ratios for blood pressure

Table 4.6: Baseline demographic characteristics of resurveyed participants, by area (among 18 791 participants resurveyed)

	Resurvey				Baseline survey	
Area*	Participants, n	Proportion of baseline sample, %	Proportion female, %	Mean age at baseline, years	Proportion female, %	Mean age at baseline, years
Qingdao (U)	1 270	3.8	64	53	55	50
Harbin (U)	1 792	3.6	63	52	60	52
Haikou (U)	1 068	3.7	64	52	64	53
Suzhou (U)	1 873	3.6	62	53	58	52
Liuzhou (U)	1 539	3.3	59	52	62	54
Sichuan (R)	1 909	3.5	63	51	62	51
Gansu (R)	1 979	4.1	62	49	61	49
Henan (R)	2 784	4.6	57	49	56	51
Zhejiang (R)	2 318	4.1	62	53	59	53
Hunan (R)	2 259	3.9	57	52	56	52
Overall	18 791	3.8	61	52	59	52

* (U)=urban area, (R)=rural area.

Figure 4.7: Serial changes in mean blood pressure within groups defined by baseline blood pressure quintiles (among 18 791 participants resurveyed)

Blood pressure was measured at baseline (‘B’ on plots; among 18 791 participants), at the quality control survey (‘Q’ on plots; among 14 911 participants) and at the resurvey (‘R’ on plots; among 18 791 participants).

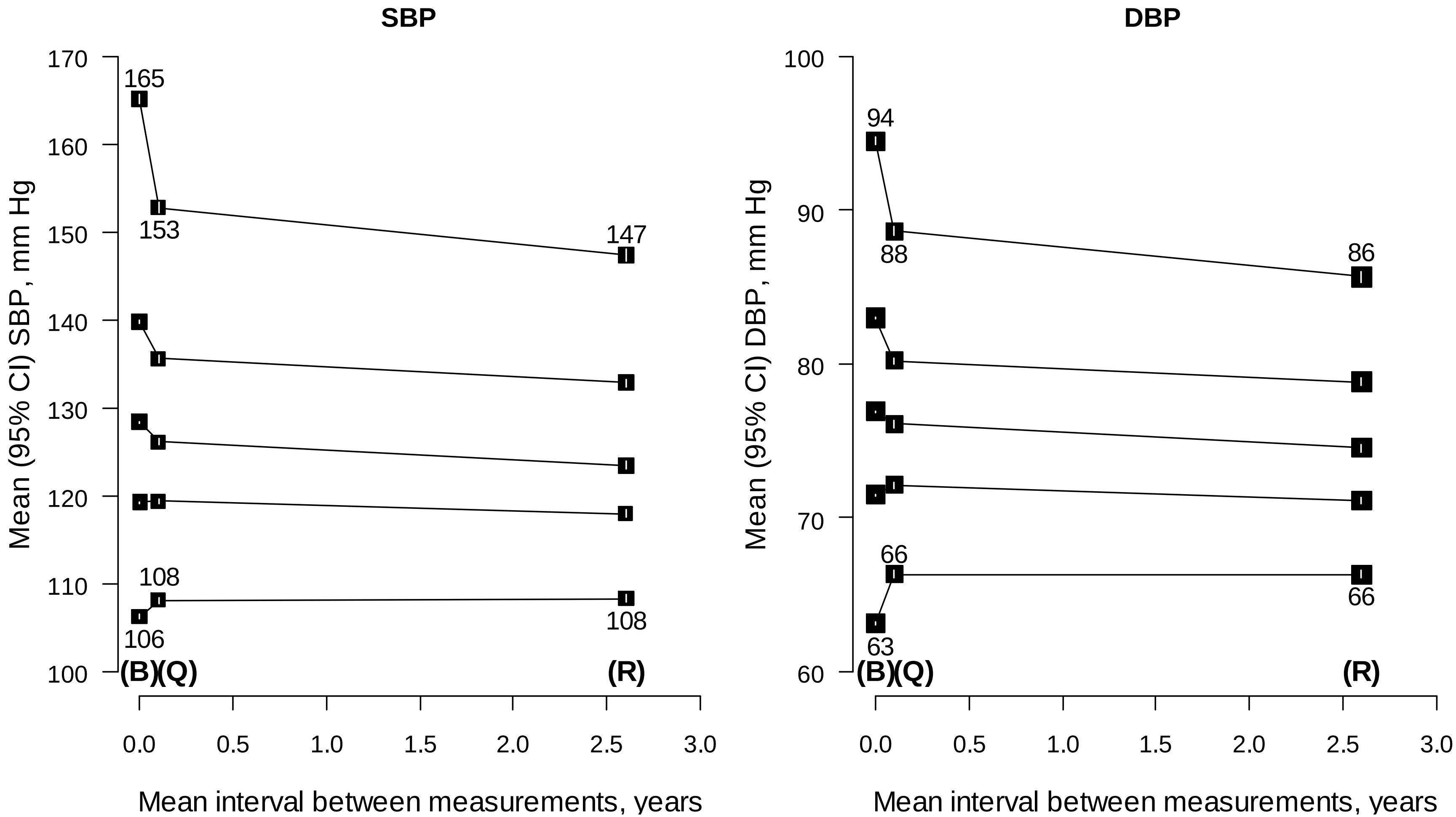


Figure 4.8: Scatter plot of resurvey blood pressure vs baseline blood pressure (among 18 791 participants resurveyed)

Pearson's correlation coefficient (r) with p-value (p) is given.

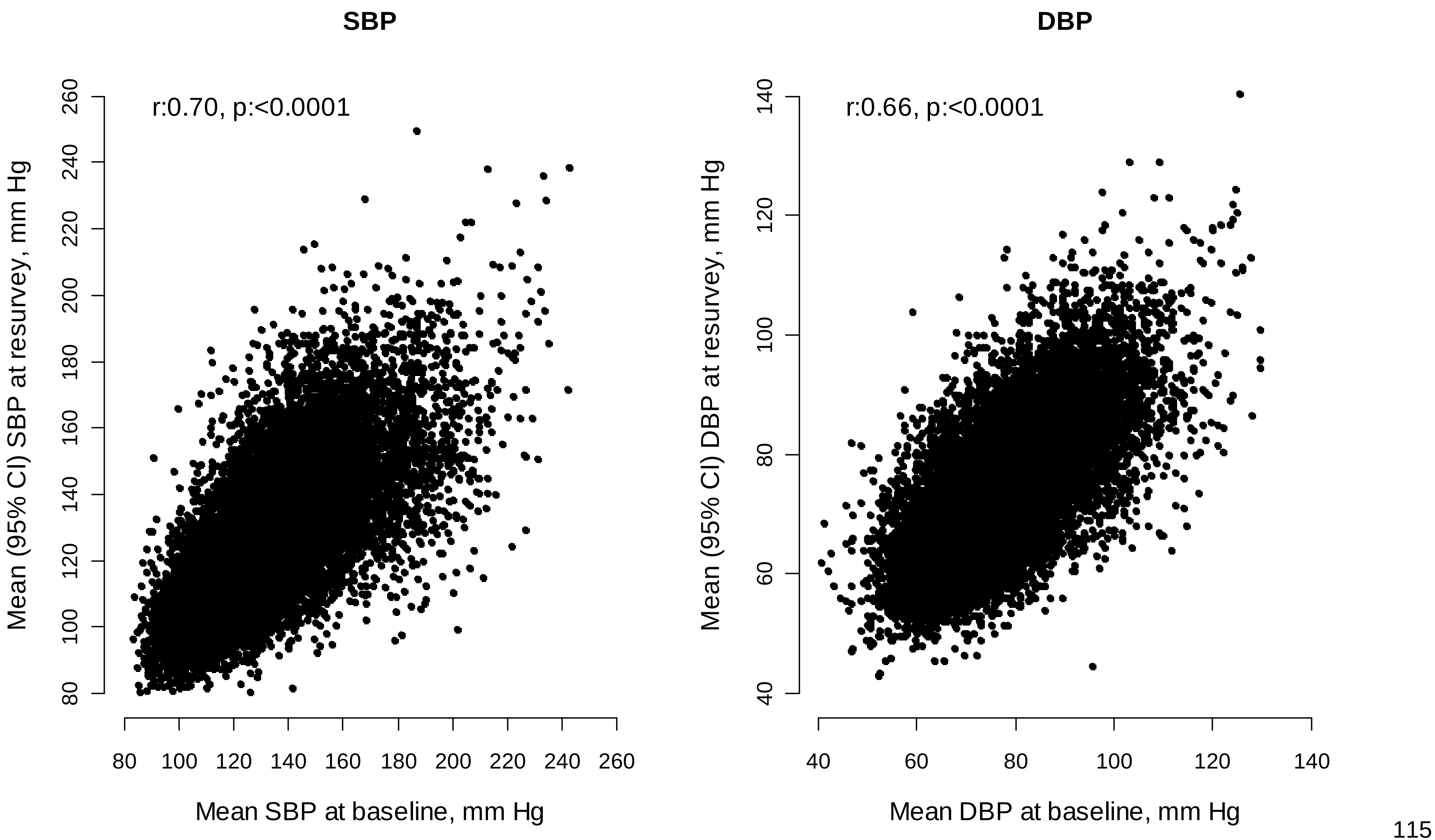


Figure 4.9: Resurvey blood pressure vs baseline blood pressure (among 18 791 resurveyed participants)

The slope (β with 95% CI) of the regression line for the association is given.

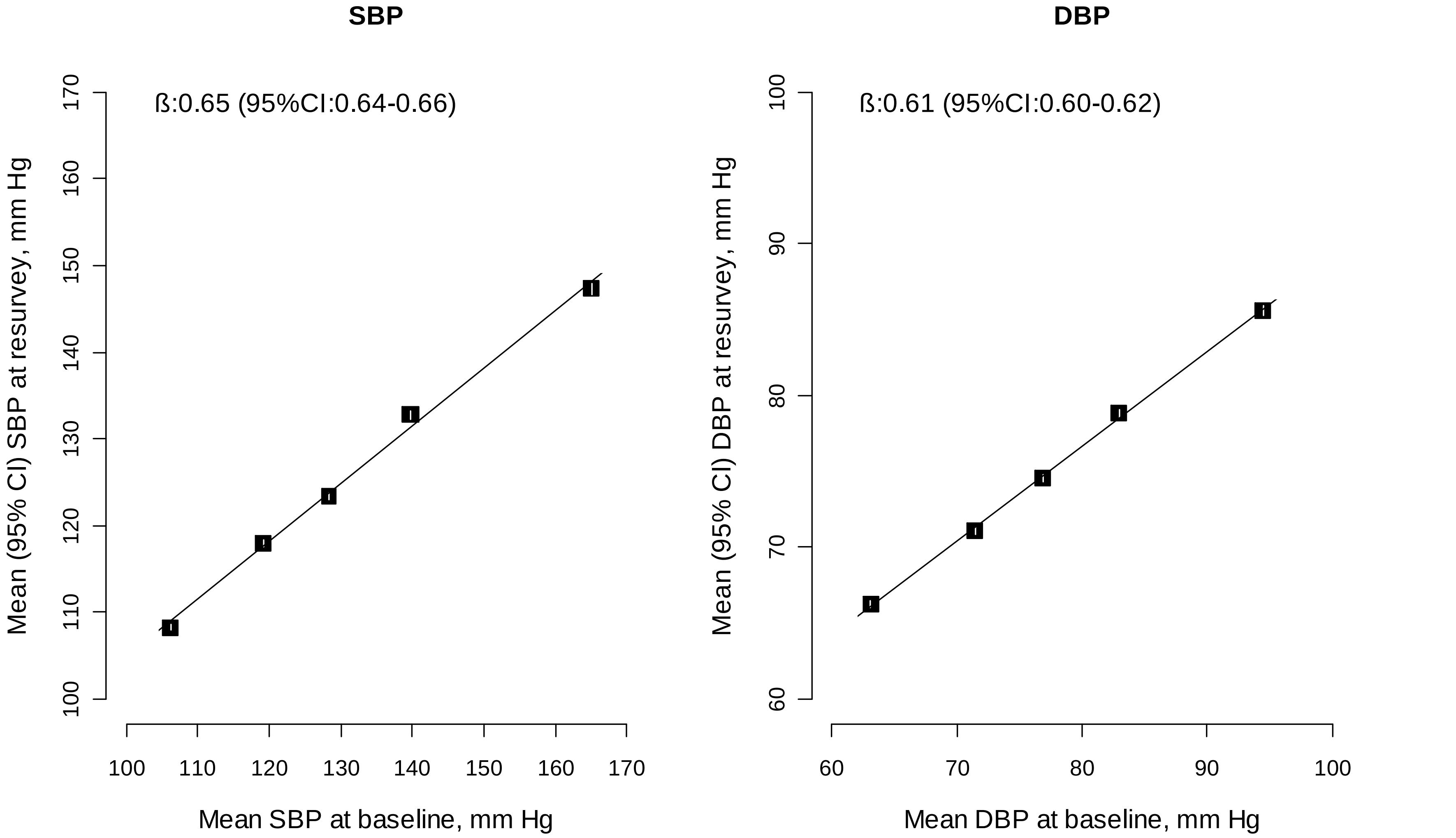


Table 4.7: Regression dilution ratios for blood pressure using Rosner's regression method,[89] by age and sex specific baseline groups (among 18 791 participants resurveyed)

Age at baseline, years	Participants, n	Mean interval between surveys,* years	Regression dilution ratio (95%CI)			
			SBP		DBP	
Male						
30-39	1105	2.6	0.64	(0.59-0.68)	0.65	(0.61-0.69)
40-49	2124	2.5	0.61	(0.58-0.64)	0.62	(0.59-0.65)
50-59	2203	2.6	0.59	(0.56-0.62)	0.56	(0.53-0.59)
60-69	1456	2.6	0.54	(0.50-0.58)	0.57	(0.53-0.61)
70-79	469	2.6	0.52	(0.45-0.59)	0.56	(0.49-0.63)
Female						
30-39	1869	2.7	0.70	(0.67-0.74)	0.66	(0.63-0.70)
40-49	3536	2.6	0.65	(0.63-0.67)	0.64	(0.61-0.66)
50-59	3692	2.6	0.63	(0.61-0.65)	0.60	(0.58-0.62)
60-69	1841	2.7	0.59	(0.56-0.62)	0.59	(0.56-0.63)
70-79	496	2.6	0.57	(0.51-0.64)	0.57	(0.51-0.64)

* Mean interval between baseline survey and resurvey

Table 4.8: Regression dilution ratios calculated using the group method[91] and intraclass correlation coefficient method,[92] by age- and sex-specific baseline groups (among 18 791 participants resurveyed)

		Regression dilution ratio			
		SBP		DBP	
Age at baseline, years	Participants, n	Group method (quintiles)	Intraclass correlation coefficient	Group method (quintiles)	Intraclass correlation coefficient
Male					
30-39	1105	0.64	0.60	0.62	0.67
40-49	2124	0.62	0.60	0.61	0.66
50-59	2203	0.59	0.60	0.57	0.61
60-69	1456	0.55	0.56	0.57	0.58
70-79	469	0.51	0.51	0.55	0.54
Female					
30-39	1869	0.69	0.67	0.65	0.67
40-49	3536	0.67	0.67	0.65	0.67
50-59	3692	0.65	0.65	0.60	0.63
60-69	1841	0.60	0.62	0.58	0.58
70-79	496	0.55	0.58	0.58	0.57

Tables and figures: 4.4 Completeness and accuracy of incident stroke events

Table 4.9: Number of incident stroke events, by area and pathological type of stroke (among 488 789 participants)

Area*	Person-years at risk ($x10^3$)	Incident stroke events, number (crude rate per 100 000 person-years)									
		Ischaemic stroke		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified		Total	
Qingdao (U)	171	11	(6)	21	(12)	2	(1)	0	(0)	34	(20)
Harbin (U)	245	1 568	(640)	126	(51)	13	(5)	28	(11)	1 735	(708)
Haikou (U)	136	262	(193)	18	(13)	1	(1)	6	(4)	287	(211)
Suzhou (U)	262	317	(121)	84	(32)	6	(2)	65	(25)	472	(180)
Liuzhou (U)	225	695	(309)	90	(40)	16	(7)	16	(7)	817	(363)
Sichuan (R)	282	180	(64)	371	(132)	16	(6)	39	(14)	606	(215)
Gansu (R)	250	176	(70)	425	(170)	1	(<1)	18	(7)	620	(248)
Henan (R)	309	1 527	(494)	349	(113)	33	(11)	48	(16)	1 957	(633)
Zhejiang (R)	303	663	(219)	219	(72)	14	(5)	27	(9)	923	(305)
Hunan (R)	295	644	(218)	494	(167)	28	(9)	75	(25)	1 241	(421)
Overall	2 478	6 043	(244)	2 197	(89)	130	(5)	322	(13)	8 692	(351)

* (U)=urban area, (R)=rural area.

Table 4.10: Number of incident stroke events reported by the disease surveillance system,* by area and pathological type of stroke (among 488 789 participants)

Area[†]	Person-years at risk (x10³)	Incident stroke events, number (% of all incident stroke events)									
		Ischaemic stroke		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified		Total	
Qingdao (U)	171	0	(0)	0	(0)	0	(0)	0	(-)	0	(0)
Harbin (U)	245	1 552	(99)	74	(59)	7	(54)	27	(96)	1 660	(96)
Haikou (U)	136	258	(98)	11	(61)	1	(100)	6	(100)	276	(96)
Suzhou (U)	262	300	(95)	54	(64)	6	(100)	13	(20)	373	(79)
Liuzhou (U)	225	669	(96)	55	(61)	13	(81)	15	(94)	752	(92)
Sichuan (R)	282	175	(97)	276	(74)	10	(63)	27	(69)	488	(81)
Gansu (R)	250	129	(73)	81	(19)	1	(100)	11	(61)	222	(36)
Henan (R)	309	1 500	(98)	319	(91)	33	(100)	48	(100)	1 900	(97)
Zhejiang (R)	303	655	(99)	188	(86)	14	(100)	21	(78)	878	(95)
Hunan (R)	295	618	(96)	182	(37)	24	(86)	66	(88)	890	(72)
Overall	2 478	5 856	(97)	1 240	(56)	109	(84)	234	(73)	7 439	(86)

***** Remainder were reported by the mortality surveillance system only.
[†] (U)=urban area, (R)=rural area.
'-' = not calculable.

Table 4.11: Number of incident stroke events known to have been imaged by CT/MRI scan, by area and pathological type of stroke (among 488 789 participants)

Area*	Person-years at risk ($x10^3$)	Incident stroke events, number (% of all incident stroke events)									
		Ischaemic stroke		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified		Total	
Qingdao (U)	171	0	(0)	0	(0)	0	(0)	0	(-)	0	(0)
Harbin (U)	245	1322	(83)	63	(50)	5	(38)	21	(75)	1411	(80)
Haikou (U)	136	136	(52)	8	(44)	1	(100)	4	(67)	149	(52)
Suzhou (U)	262	134	(42)	34	(39)	3	(50)	3	(5)	174	(36)
Liuzhou (U)	225	298	(43)	30	(33)	7	(38)	1	(6)	336	(41)
Sichuan (R)	282	156	(87)	260	(69)	10	(56)	19	(49)	445	(73)
Gansu (R)	250	114	(64)	69	(16)	1	(100)	0	(0)	184	(29)
Henan (R)	309	1328	(86)	291	(83)	32	(88)	14	(27)	1665	(84)
Zhejiang (R)	303	531	(79)	156	(71)	11	(79)	9	(33)	707	(76)
Hunan (R)	295	537	(83)	170	(34)	22	(71)	44	(59)	773	(62)
Overall	2 478	4556	(75)	1081	(49)	92	(65)	115	(35)	5844	(67)

* (U)=urban area, (R)=rural area.

Figure 4.10: Number and proportion of incident stroke events known to have been imaged by CT/MRI scan, by pathological type of stroke (among 488 789 participants)

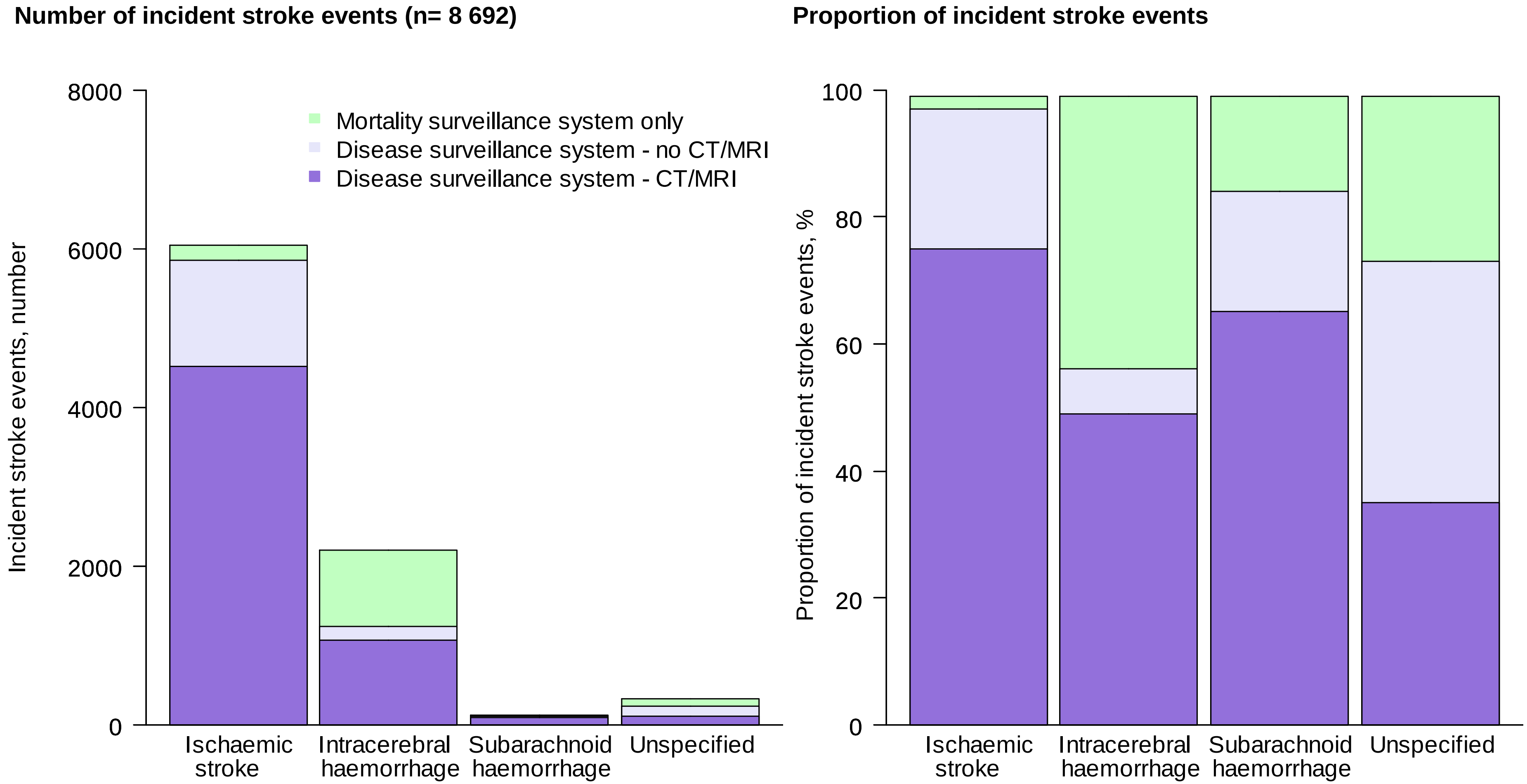


Table 4.12: Adjudication sub-study: stroke events selected, by surveillance system, hospital tier, area and stroke pathological type

	Stroke events, n		
	Selected for adjudication	Medical notes found	Notes for the correct person and admission*
Surveillance system			
Disease	1 284	898	679
Health insurance	497	447	343
Hospital tier			
Primary	484	386	258
Secondary	578	433	322
Tertiary	719	526	442
Area†			
Qingdao (U)	141	142	109
Harbin (U)	135	111	97
Haikou (U)	299	162	142
Suzhou (U)	138	105	90
Liuzhou (U)	165	122	111
Sichuan (R)	148	100	60
Gansu (R)	301	239	189
Henan (R)	194	164	91
Zhejiang (R)	119	83	70
Hunan (R)	141	117	63
Stroke pathological type			
Ischaemic stroke	1 374	1 058	807
Intracerebral haemorrhage	292	194	139
Subarachnoid haemorrhage	84	23	21
Unspecified	31	70	55
Overall	1 781	1 345	1 022

* Participant information in the medical notes matched participant information in the CKB study (name, sex, year of birth) and admission date from medical notes was within one month of stroke event date in the CKB study.

† (U)=urban area, (R)=rural area.

Table 4.13: Adjudication sub-study: comparison of CKB reported diagnoses and adjudicated diagnoses (among 1022 stroke events)

	Adjudicated diagnosis, number of events (% total)									
	Stroke pathological type			Equivocal[†]				Not stroke		
CKB reported diagnosis	Ischaemic stroke	Intracerebral haemorrhage	SAH	Cerebral infarction CT/MRI	Unspecified stroke pathological type	Old stroke	Insufficient information	TIA	Other	Total
Ischaemic stroke	341 (42) *	14 (2)	1 (<1)	306 (38)	19 (2)	40 (5)	52 (6)	3 (<1)	31 (4)	807
Intracerebral haemorrhage	2 (1)	118 (85) *	2 (1)	3 (2)	3 (2)	1 (1)	2 (1)	0 (0)	8 (6)	139
Subarachnoid haemorrhage	0 (0)	2 (10)	13 (62) *	0 (0)	0 (0)	0 (0)	3 (14)	0 (0)	3 (14)	21
Unspecified stroke type	8 (15)	2 (4)	0 (0)	16 (29)	0 (0)	1 (2)	23 (42)	3 (5)	2 (4)	55

* The positive predictive value of CKB data diagnosis for each stroke pathological type.
[†] Insufficient evidence to verify or refute diagnosis of the stroke pathological type. Cerebral infarction CT/MRI: evidence of cerebral infarction from CT/MRI report without sufficient clinical evidence of signs/symptoms of stroke documented during admission. Unspecified stroke type: evidence of signs/symptoms of stroke without sufficient evidence from CT/MRI to diagnose pathological type. Old stroke: notes report old stroke without sufficient evidence of event to diagnose stroke or sufficient evidence from CT/MRI scan. Insufficient information: insufficient clinical information to allow adjudication.
SAH = subarachnoid haemorrhage.
TIA = transient ischaemic attack.

Table 4.14: Adjudication sub-study: positive predictive value (PPV) of ischaemic stroke,* by surveillance system, hospital tier, area, age and sex (among 807 ischaemic stroke events)

	Adjudicated diagnosis		
	Ischaemic stroke (A)	Cerebral infarction CT/MRI † (B)	Cerebral infarction (A+B)
	PPV, % (95%CI)	PPV, % (95%CI)	PPV, % (95%CI)
Surveillance system			
Disease	39 (35-43)	44 (40-48)	83 (80-86)
Health insurance	50 (43-56)	24 (19-30)	74 (68-79)
Hospital tier			
Primary	40 (34-47)	34 (28-40)	74 (68-79)
Secondary	47 (41-53)	32 (27-38)	79 (74-84)
Tertiary	40 (35-45)	45 (40-51)	85 (81-89)
Area‡			
Qingdao (U)	69 (57-79)	15 (8-25)	84 (73-91)
Harbin (U)	26 (18-35)	66 (55-75)	91 (83-95)
Haikou (U)	40 (32-49)	31 (23-39)	71 (62-78)
Suzhou (U)	45 (34-57)	40 (29-51)	85 (75-91)
Liuzhou (U)	38 (30-48)	51 (41-60)	89 (82-94)
Sichuan (R)	39 (25-55)	53 (37-68)	92 (78-97)
Gansu (R)	47 (39-55)	24 (18-32)	71 (63-78)
Henan (R)	41 (31-52)	36 (26-47)	77 (66-85)
Zhejiang (R)	45 (32-59)	33 (21-47)	78 (64-87)
Hunan (R)	34 (22-48)	42 (29-56)	76 (63-86)
Age at risk (years)			
40-49	49 (39-59)	27 (19-37)	76 (66-83)
50-59	39 (33-45)	41 (35-47)	80 (75-84)
60-69	43 (37-49)	38 (32-43)	80 (75-85)
70-79	41 (34-49)	42 (34-49)	83 (76-88)
Overall	42 (39-46)	38 (35-41)	80 (77-83)

* Percentage of CKB data diagnoses of ischaemic stroke in the adjudication sub-study, adjudicated as: ischaemic stroke (A); cerebral infarction CT/MRI (B); or cerebral infarction (i.e. all events with CT/MRI evidence of cerebral infarction [A+B]).

† Evidence of cerebral infarction from CT/MRI report without sufficient clinical evidence of signs/symptoms of stroke documented during admission.

‡ (U)=urban area, (R)=rural area.

Tables and figures: 4.5 Stroke incidence rates

Table 4.15: Number and crude incidence rate of incident stroke events,* by age, sex and pathological type (among 455 438 participants†)

Age group at risk, years	Person-years at risk (x10^3)	Incident stroke events, number (crude rate per 100 000 person-years)									
		Cerebral infarction		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified		Total	
Male											
40-49	265	163	(62)	58	(22)	6	(2)	6	(2)	233	(88)
50-59	290	556	(192)	145	(50)	11	(4)	12	(4)	724	(250)
60-69	198	742	(375)	191	(96)	19	(10)	24	(12)	976	(493)
70-79	100	785	(785)	214	(214)	7	(7)	28	(28)	1 034	(1 034)
All (40-79) ‡	853	2 246	(354)	58	(96)	43	(6)	70	(12)	2 967	(466)
Female											
40-49	446	155	(35)	58	(13)	6	(1)	4	(1)	223	(50)
50-59	450	657	(146)	160	(36)	14	(3)	12	(3)	843	(187)
60-69	257	801	(312)	128	(50)	14	(5)	15	(6)	958	(373)
70-79	110	654	(595)	117	(106)	8	(7)	13	(12)	792	(720)
All (40-79) ‡	1 262	2 267	(272)	463	(51)	42	(4)	44	(6)	2 816	(333)
Overall‡	2 115	4 513	(313)	1 071	(73)	85	(5)	114	(9)	5 783	(399)

* Stroke events known to have been imaged by CT/MRI scan.
† Excluding participants from Qingdao, as there was substantial undercounting of stroke events imaged by CT/MRI scan (the disease surveillance system was not yet operating in this area), and stroke events and person-years of follow-up outside of the age range 40-79 years as there were few events outside of these ages (33 events at age 30-39 years and 28 events at 80-87 years).
‡ Age-standardised by taking the unweighted average of the component ten-year incidence rates (overall: average of age-standardised incidences of both sexes)

Table 4.16: Number and crude incidence rate of incident stroke events,* by area and pathological type of stroke (among 455 438 participants†)

Area‡	Person-years at risk (x10³)	Incident stroke events, number (crude rate per 100 000 person-years)									
		Cerebral infarction		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified		Total	
Harbin (U)	223	1 305	(585)	63	(28)	5	(2)	21	(9)	1 394	(625)
Haikou (U)	123	136	(111)	8	(7)	1	(1)	4	(3)	149	(121)
Suzhou (U)	243	132	(54)	33	(14)	3	(1)	3	(1)	171	(70)
Liuzhou (U)	215	297	(138)	30	(14)	6	(3)	1	(<1)	334	(155)
Sichuan (R)	255	156	(61)	257	(101)	9	(4)	19	(7)	441	(173)
Gansu (R)	213	112	(53)	68	(32)	1	(<1)	0	(0)	181	(85)
Henan (R)	279	1 320	(473)	288	(103)	29	(10)	13	(5)	1 650	(591)
Zhejiang (R)	292	523	(179)	155	(53)	11	(4)	9	(3)	698	(239)
Hunan (R)	273	532	(195)	169	(62)	20	(7)	44	(16)	765	(280)
Overall	2 115	4 513	(213)	1 071	(51)	85	(4)	114	(5)	5 783	(273)

* Stroke events known to have been imaged by CT/MRI scan.
† Excluding participants from Qingdao, as there was substantial undercounting of stroke events imaged by CT/MRI scan (the disease surveillance system was not yet operating in this area), and stroke events and person-years of follow-up outside of the age range 40-79 years as there were few events outside of these ages (33 events at age 30-39 years and 28 events at 80-87 years).
‡ (U)=urban area, (R)=rural area.

Tables and figures: 4.6 Associations of usual blood pressure and stroke incidence

Figure 4.11: Cerebral infarction incidence (4513 events) versus usual SBP and usual DBP (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (overall regression dilution ratio of 0.56 for SBP and 0.57 for DBP). HR are relative to lowest blood pressure group. Each closed square represents HR with area inversely proportional to the variance of the log HR. The number of stroke events in each blood pressure group is given below the square and point estimate of the HR above it. Mean age at cerebral infarction event was 64 years.

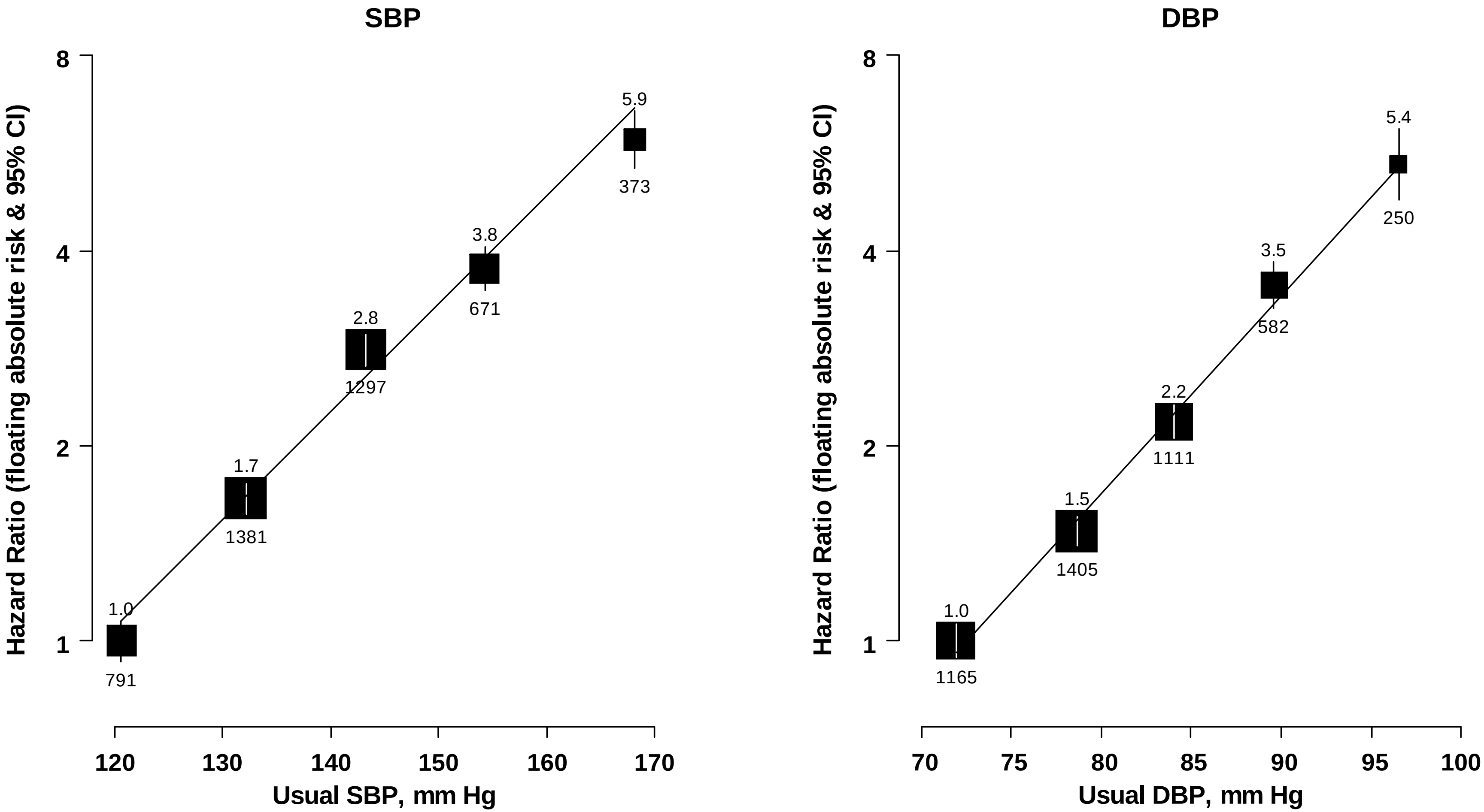


Table 4.17: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher usual SBP and 5 mm Hg higher usual DBP, progressively adjusted for major potential confounders (among 455 438 participants)

Overall regression dilution ratio of 0.56 for SBP and 0.57 for DBP. Mean age at cerebral infarction event was 64 years.

Potential confounders included in model	SBP		DBP	
	HR	**(95%CI)**	**HR**	**(95%CI)**
Age, sex and area	1.47	(1.45-1.51)	1.42	(1.40-1.46)
Plus education*	1.47	(1.45-1.51)	1.42	(1.40-1.46)
Plus month baseline survey	1.47	(1.45-1.51)	1.42	(1.40-1.46)
Plus smoking	1.49	(1.45-1.51)	1.42	(1.40-1.46)
Plus alcohol intake	1.47	(1.45-1.51)	1.42	(1.40-1.46)
Plus body-mass index	1.45	(1.43-1.49)	1.40	(1.38-1.44)
Plus waist and hip circum.	1.45	(1.43-1.49)	1.40	(1.36-1.42)
Plus physical activity	1.45	(1.43-1.49)	1.40	(1.36-1.42)
Plus history of diabetes	1.45	(1.41-1.47)	1.40	(1.36-1.42)
Plus intake of fruit, veg. and tea	1.45	(1.41-1.47)	1.40	(1.36-1.44)
Plus blood pressure-lowering medication use	1.43	(1.40-1.46)	1.38	(1.35-1.42)

* Association illustrated in Figure 4.11.

Figure 4.12: Cerebral infarction incidence (4513 events) in each decade of age at risk versus usual SBP (among 455 438 participants)

Hazard ratios (HR) adjusted sex, education and area (with floating absolute risk and 95% CI). All HR are relative to lowest blood pressure group at age 40-49 years. Each closed square represents HR with area inversely proportional to the variance of the log HR. The number of stroke events in each blood pressure group is given below the square and point estimate of the HR above it.

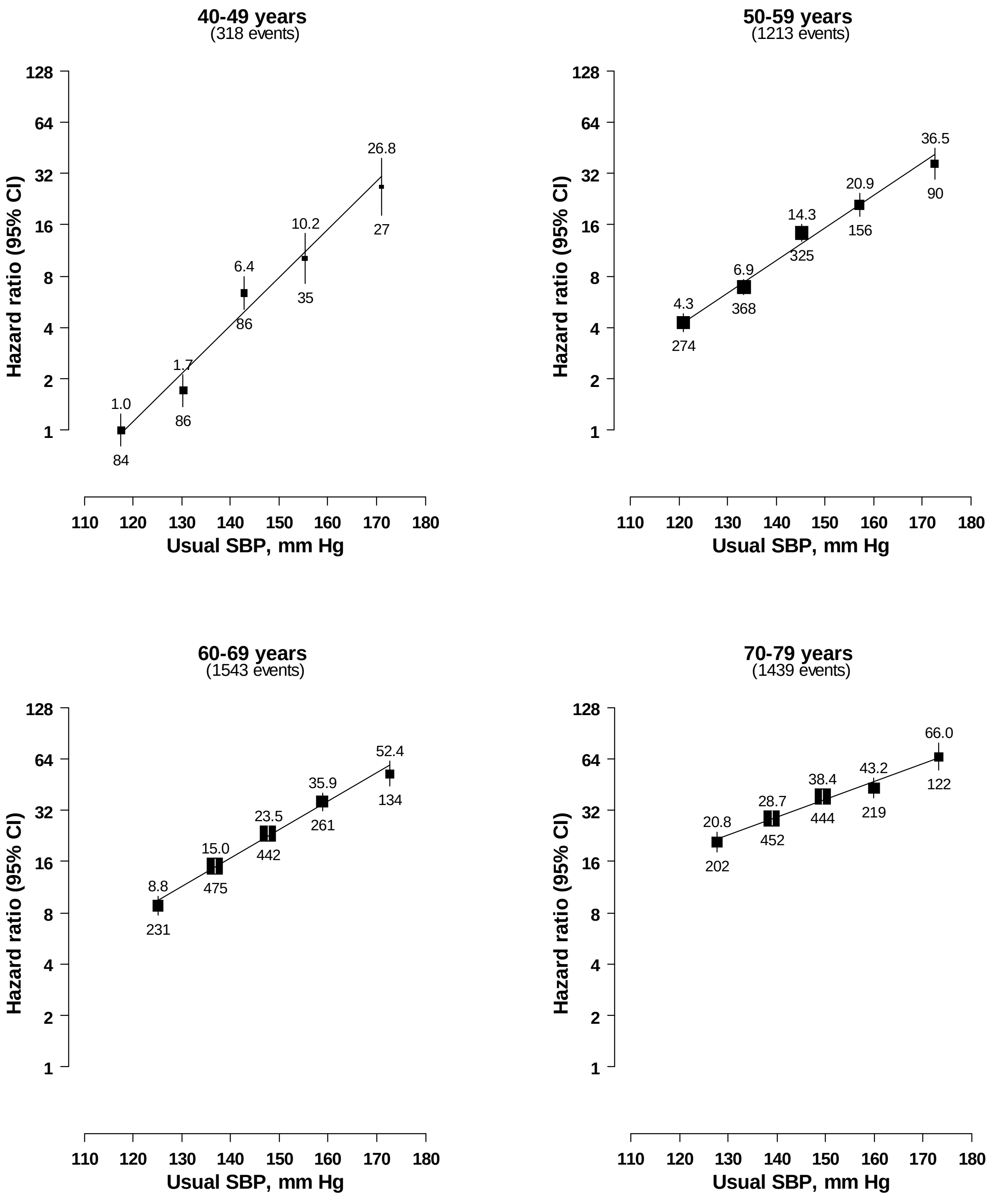


Figure 4.13: Cerebral infarction incidence (4513 events) in each decade of age at risk versus usual DBP (among 455 438 participants)

Hazard ratios (HR) adjusted sex, education and area (with floating absolute risk and 95% CI). All HR are relative to lowest blood pressure group at age 40-49 years. Each closed square represents HR with area inversely proportional to the variance of the log HR. The number of stroke events in each blood pressure group is given below the square and point estimate of the HR above it.

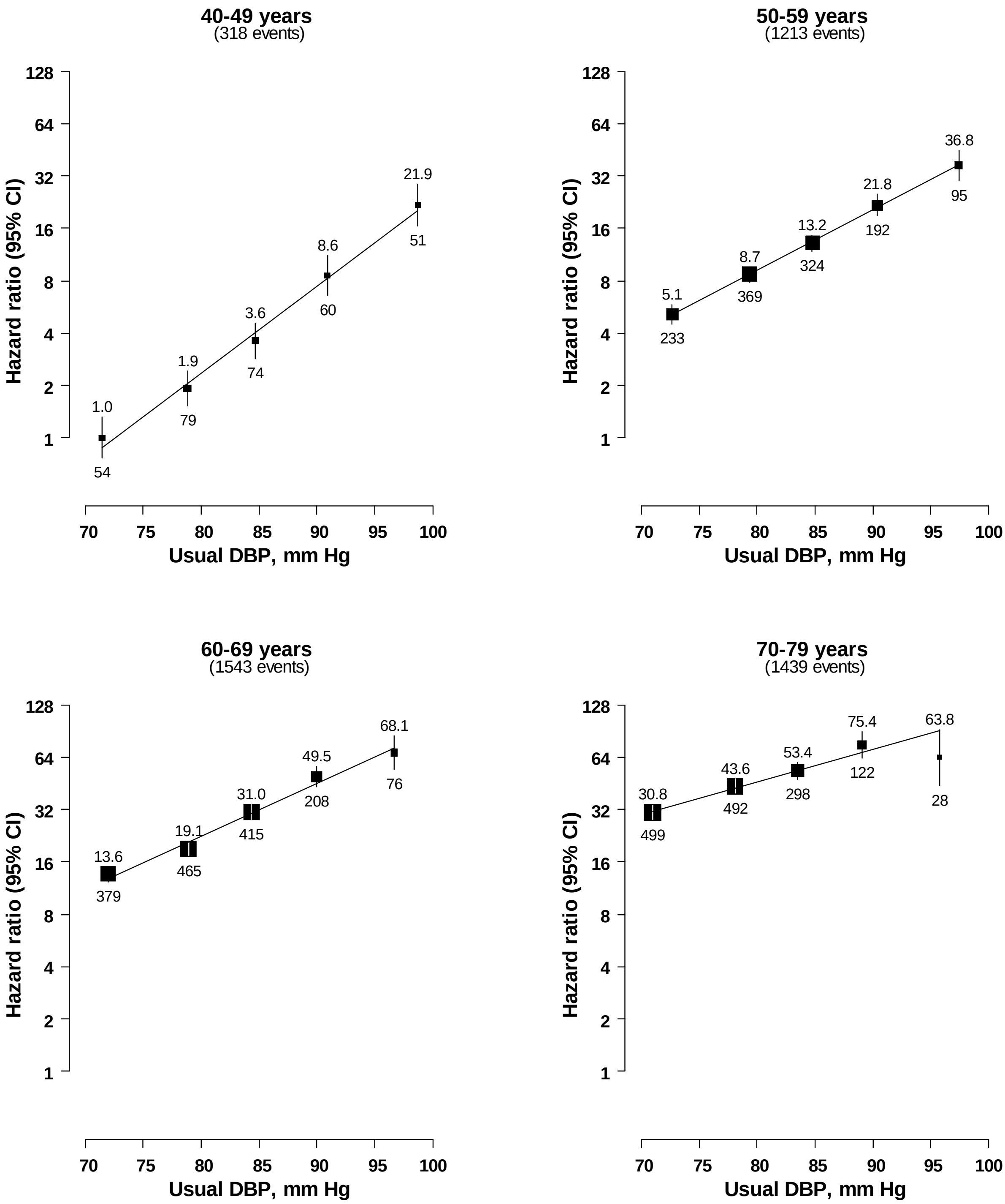


Figure 4.14: Cerebral infarction incidence (4513 events): age-specific hazard ratios for 10 mm Hg higher usual SBP, by sex (among 455 438 participants)

Hazard ratios (HR) adjusted for education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR (further adjusted for sex) and the open diamond indicates the 95% CI of the overall result.

Age at risk, years	Sex	No. of events	Hazard Ratio (95% CI)
40-49	Male	163	2.10 (1.90 - 2.32)
	Female	155	1.77 (1.62 - 1.93)
	Both	**318**	**1.90 (1.78 - 2.03)**
50-59	Male	556	1.62 (1.53 - 1.71)
	Female	657	1.47 (1.40 - 1.54)
	Both	**1213**	**1.53 (1.48 - 1.59)**
60-69	Male	742	1.59 (1.51 - 1.67)
	Female	801	1.40 (1.33 - 1.47)
	Both	**1543**	**1.48 (1.43 - 1.53)**
70-79	Male	785	1.33 (1.25 - 1.41)
	Female	654	1.22 (1.16 - 1.29)
	Both	**1439**	**1.27 (1.22 - 1.32)**

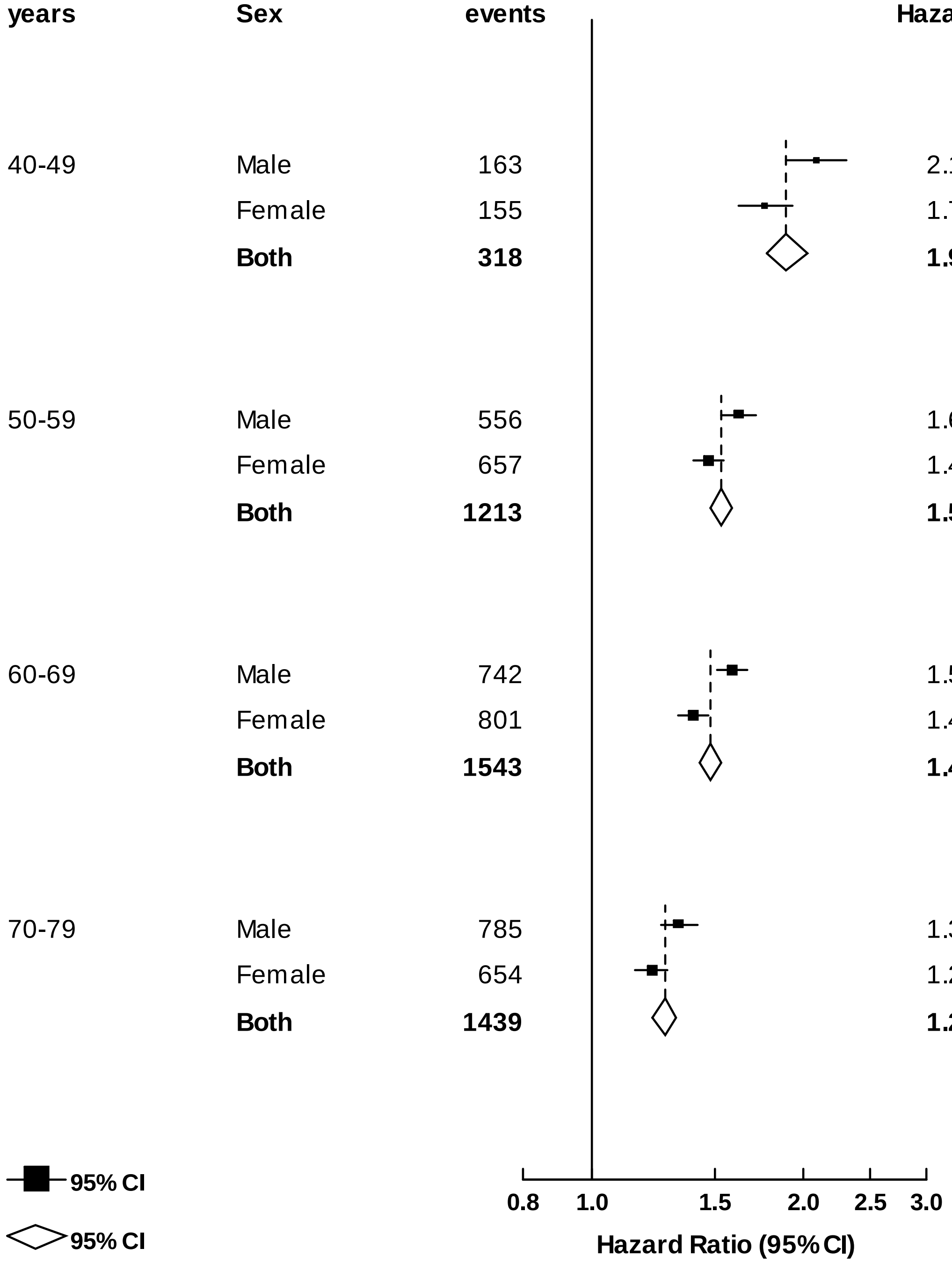


Figure 4.15: Cerebral infarction incidence (4513 events): age-specific hazard ratios for 5 mm Hg higher usual DBP, by sex (among 455 438 participants)

Hazard ratios (HR) adjusted for education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR (further adjusted for sex) and the open diamond indicates the 95% CI of the overall result.

Age at risk, years	Sex	No. of events	Hazard Ratio (95% CI)
40-49	Male	163	1.76 (1.61 - 1.92)
	Female	155	1.74 (1.59 - 1.89)
	Both	**318**	**1.75 (1.64 - 1.86)**
50-59	Male	556	1.56 (1.48 - 1.65)
	Female	657	1.45 (1.38 - 1.53)
	Both	**1213**	**1.50 (1.45 - 1.56)**
60-69	Male	742	1.48 (1.41 - 1.56)
	Female	801	1.35 (1.28 - 1.42)
	Both	**1543**	**1.41 (1.36 - 1.47)**
70-79	Male	785	1.25 (1.18 - 1.32)
	Female	654	1.21 (1.14 - 1.28)
	Both	**1439**	**1.23 (1.18 - 1.28)**

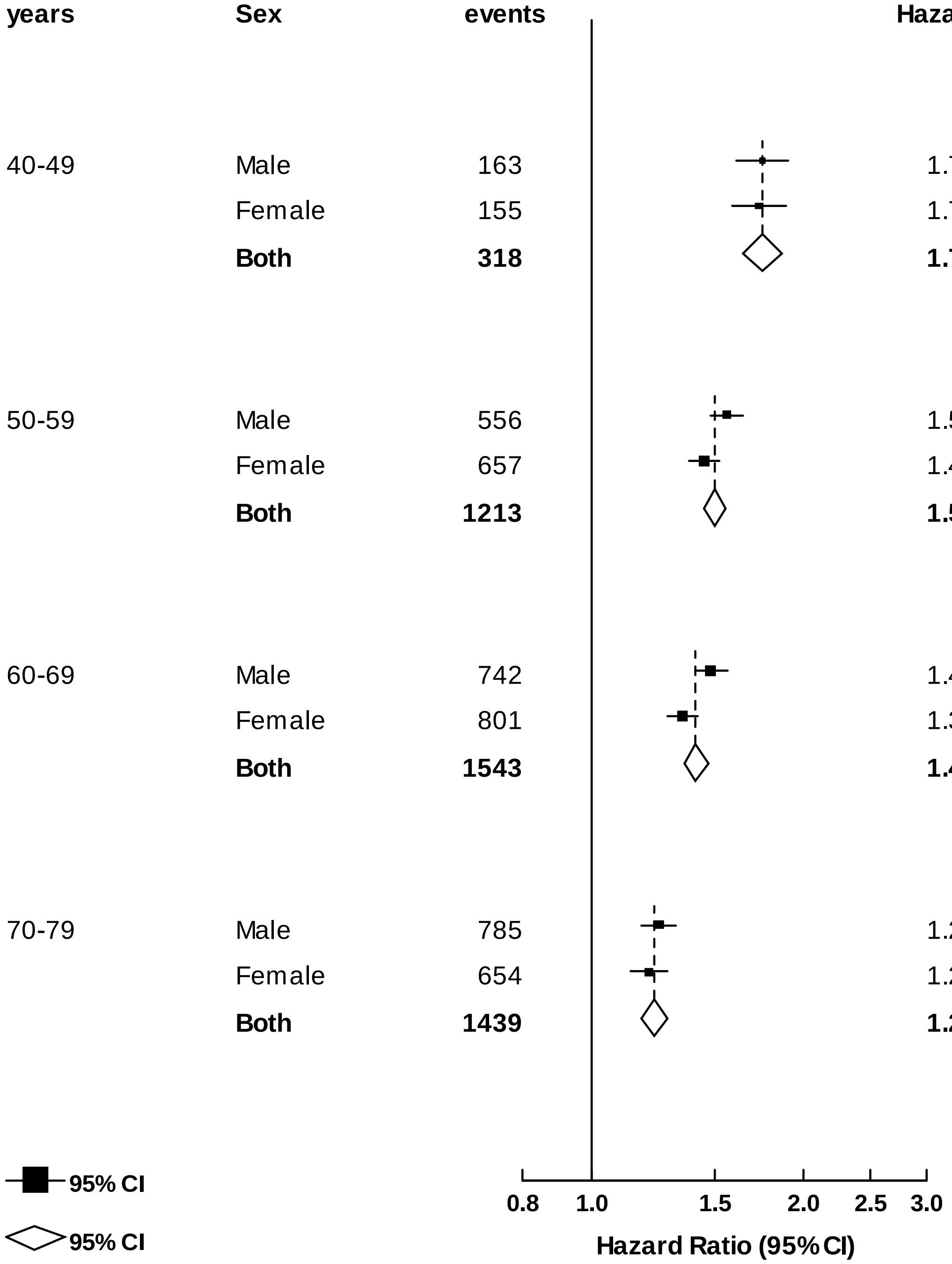
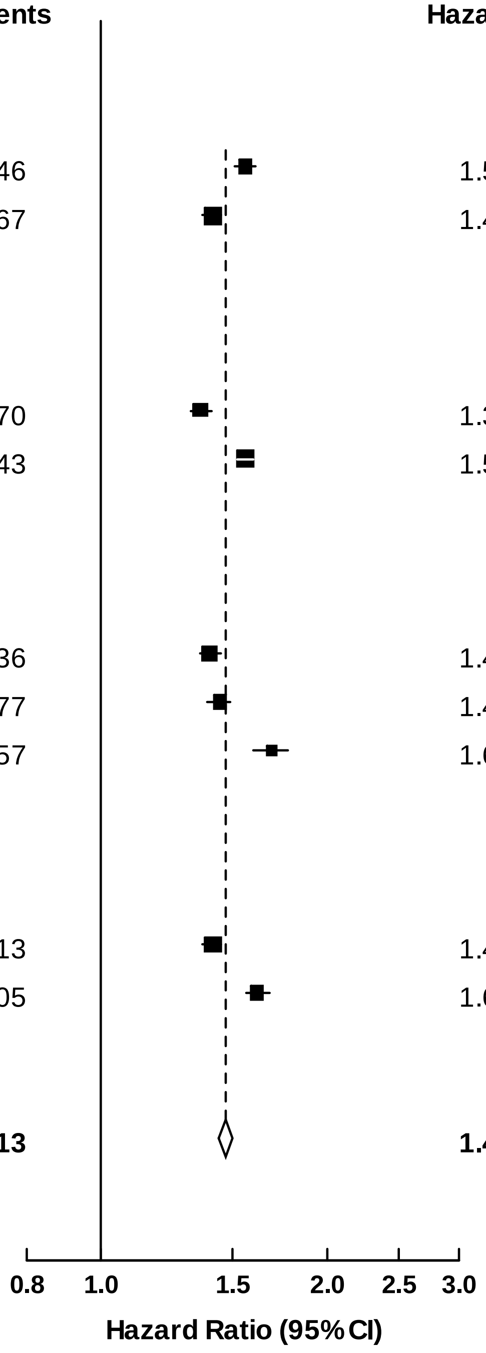
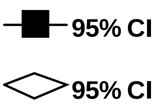


Figure 4.16: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher usual SBP, by set (I) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Sex			
Male	65	2246	1.56 (1.51 - 1.61)
Female	64	2267	1.41 (1.37 - 1.45)
Heterogeneity test: $\chi^2_1 = 21.4$ (p<0.001)			
Area			
Urban	63	1870	1.36 (1.32 - 1.41)
Rural	65	2643	1.56 (1.52 - 1.60)
Heterogeneity test: $\chi^2_1 = 41.4$ (p<0.001)			
Alcohol intake*			
Never	65	1836	1.40 (1.36 - 1.45)
Occassional	63	1477	1.44 (1.39 - 1.49)
Weekly	63	757	1.69 (1.60 - 1.78)
Heterogeneity test: $\chi^2_2 = 36.1$ (p<0.001)			
Smoking†			
Never	64	2413	1.41 (1.37 - 1.45)
Current	63	1405	1.62 (1.56 - 1.68)
Heterogeneity test: $\chi^2_1 = 34.0$ (p<0.001)			
Overall	**64**	**4513**	**1.47 (1.44 - 1.50)**



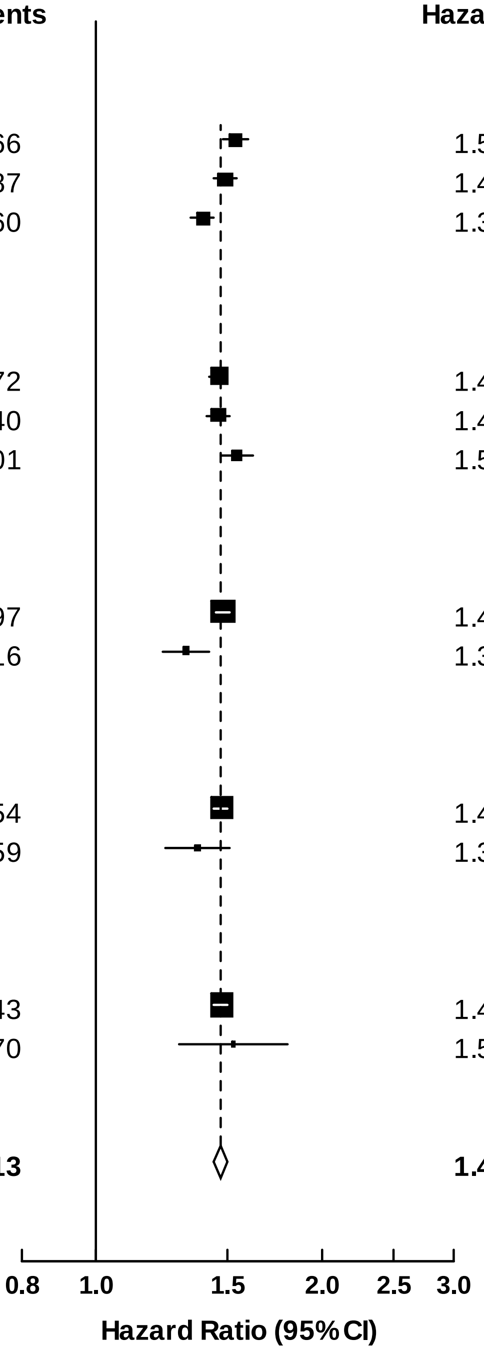


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure 4.17: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher usual SBP, by set (II) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
BMI, kg/m²			
<22	66	1166	1.54 (1.48 - 1.60)
<25	64	1487	1.49 (1.44 - 1.55)
≥25	63	1860	1.39 (1.34 - 1.44)
Trend test: $\chi^2_1 = 14.6$ (p<0.001)			
MET, hrs/day			
<20	66	2472	1.46 (1.42 - 1.50)
<30	62	1340	1.46 (1.41 - 1.51)
≥30	59	701	1.54 (1.47 - 1.62)
Trend test: $\chi^2_1 = 2.5$ (p=0.1)			
Diabetes			
No	64	3997	1.48 (1.45 - 1.51)
Yes	65	516	1.32 (1.23 - 1.42)
Heterogeneity test: $\chi^2_1 = 9.0$ (p=0.003)			
BP medication			
No	64	4054	1.47 (1.44 - 1.50)
Yes	64	459	1.37 (1.24 - 1.51)
Heterogeneity test: $\chi^2_1 = 1.9$ (p=0.2)			
Fatal event			
No	64	4443	1.47 (1.44 - 1.50)
Yes	69	70	1.53 (1.30 - 1.81)
Heterogeneity test: $\chi^2_1 = 0.2$ (p=0.6)			
Overall	**64**	**4513**	**1.47 (1.44 - 1.50)**



■ 95% CI

◇ 95% CI

Figure 4.18: Intracerebral haemorrhage incidence (1071 events) versus usual SBP and usual DBP (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (overall regression dilution ratio of 0.56 for SBP and 0.57 for DBP). HR are relative to lowest blood pressure group. Each closed square represents HR with area inversely proportional to the variance of the log HR. The number of stroke events in each blood pressure group is given below the square and point estimate of the HR above it. Mean age at intracerebral haemorrhage event was 63 years.

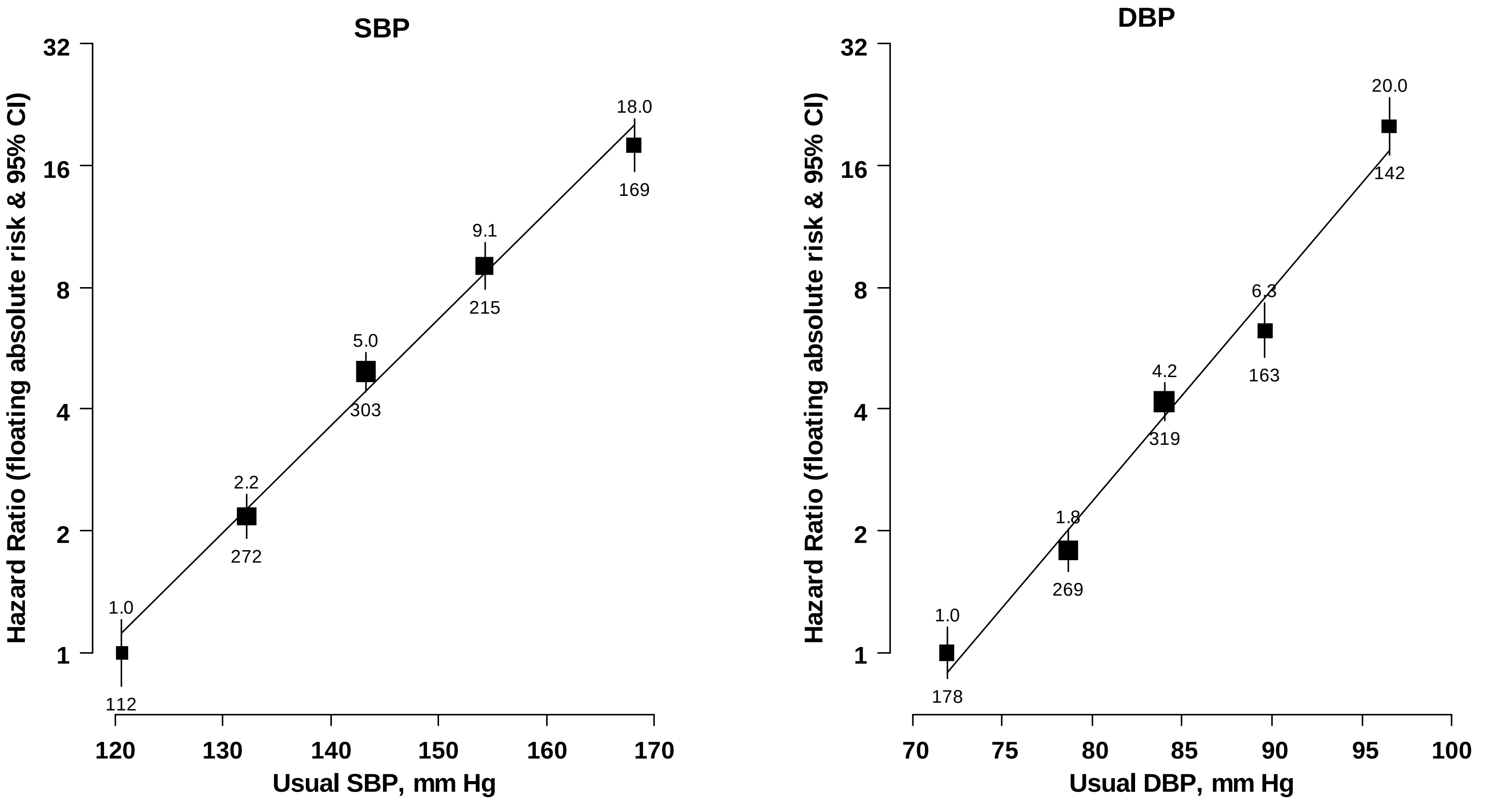


Table 4.18: Intracerebral haemorrhage incidence (1071 events): hazard ratios per 10 mm Hg higher usual SBP and 5 mm Hg usual DBP, progressively adjusted for major potential confounders (among 455 438 participants)

Overall regression dilution ratio of 0.56 for SBP and 0.57 for DBP. Mean age at intracerebral haemorrhage event was 63 years.

Potential confounders	SBP		DBP	
	HR	(95%CI)	HR	(95%CI)
Age, sex and area	1.82	(1.76-1.90)	1.81	(1.74-1.90)
Plus education*	1.82	(1.76-1.90)	1.81	(1.74-1.90)
Plus month baseline survey	1.85	(1.78-1.92)	1.83	(1.77-1.90)
Plus smoking	1.85	(1.78-1.92)	1.83	(1.77-1.90)
Plus alcohol intake	1.82	(1.76-1.92)	1.83	(1.77-1.90)
Plus body-mass index	1.87	(1.80-1.94)	1.86	(1.79-1.93)
Plus waist and hip circum.	1.87	(1.78-1.94)	1.86	(1.79-1.93)
Plus physical activity	1.85	(1.78-1.94)	1.86	(1.77-1.93)
Plus history of diabetes	1.85	(1.78-1.94)	1.86	(1.77-1.93)
Plus intake of fruit, veg. and tea	1.85	(1.78-1.92)	1.83	(1.77-1.93)
Plus blood pressure-lowering medication use	1.83	(1.76-1.91)	1.82	(1.75-1.90)

* Association illustrated in Figure 4.18.

Figure 4.19: Intracerebral haemorrhage incidence (1071 events) in each decade of age at risk versus usual SBP (among 455 438 participants)

Hazard ratios (HR) adjusted sex, education and area (with floating absolute risk and 95% CI). All HR are relative to lowest blood pressure group at age 40-49 years. Each closed square represents HR with area inversely proportional to the variance of the log HR. The number of stroke events in each blood pressure group is given below the square and point estimate of the HR above it.

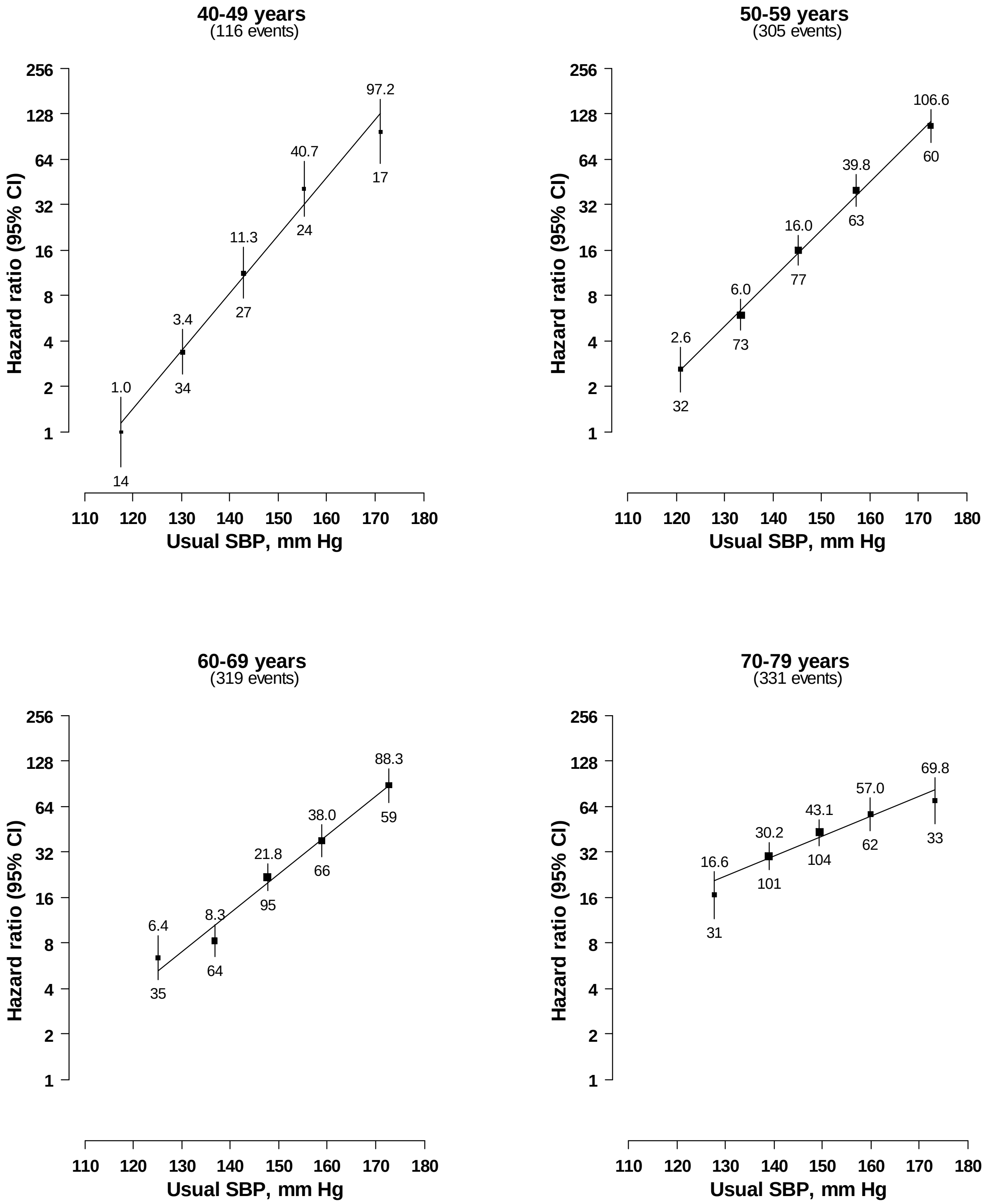


Figure 4.20: Intracerebral haemorrhage incidence (1071 events) in each decade of age at risk versus usual DBP (among 455 438 participants)

Hazard ratios (HR) adjusted sex, education and area (with floating absolute risk and 95% CI). All HR are relative to lowest blood pressure group at age 40-49 years. Each closed square represents HR with area inversely proportional to the variance of the log HR. The number of stroke events in each blood pressure group is given below the square and point estimate of the HR above it.

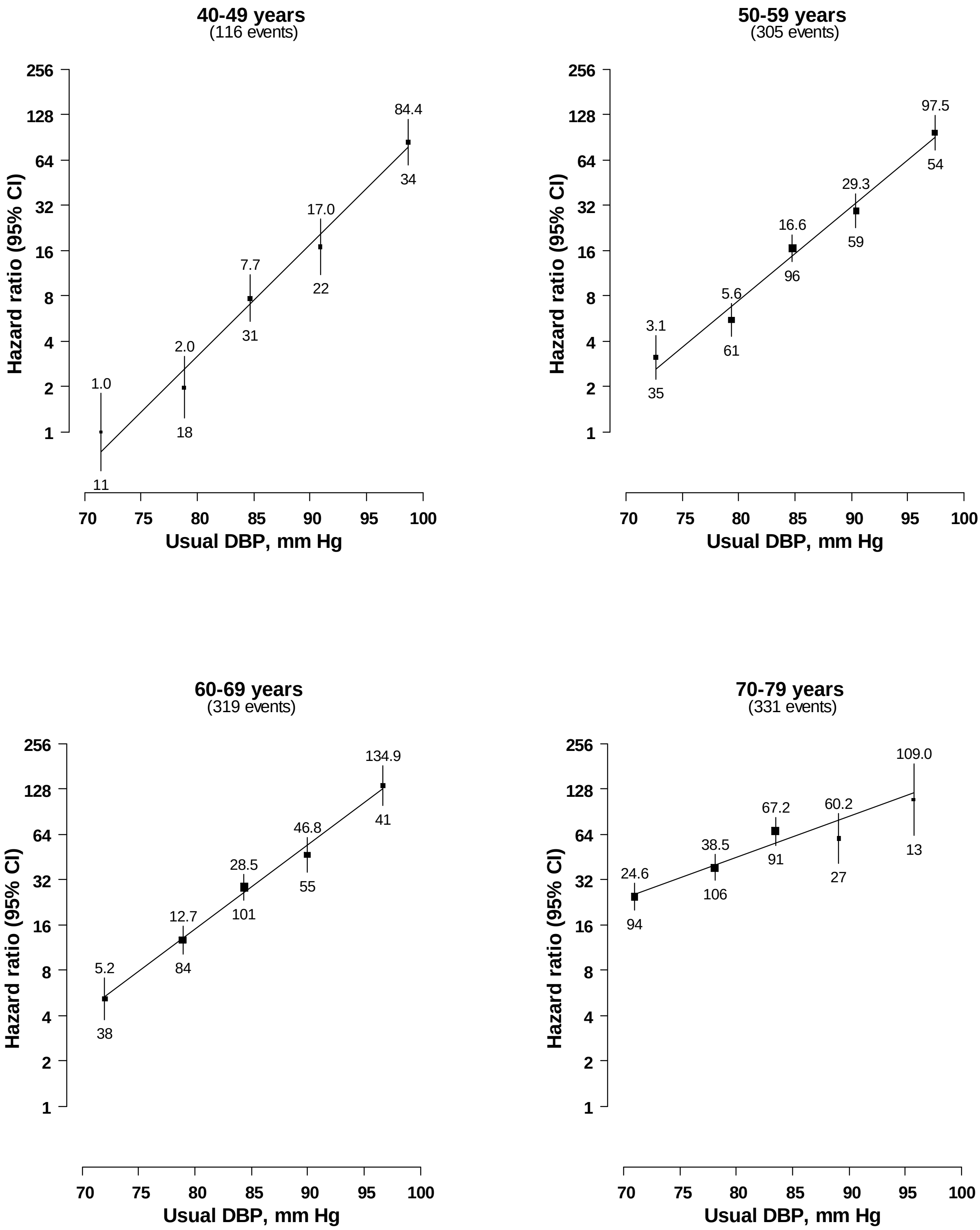


Figure 4.21: Intracerebral haemorrhage incidence (1071 events): age-specific hazard ratios for 10 mm Hg higher usual SBP, by sex (among 455 438 participants)

Hazard ratios (HR) adjusted for education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR (further adjusted for sex) and the open diamond indicates the 95% CI of the overall result.

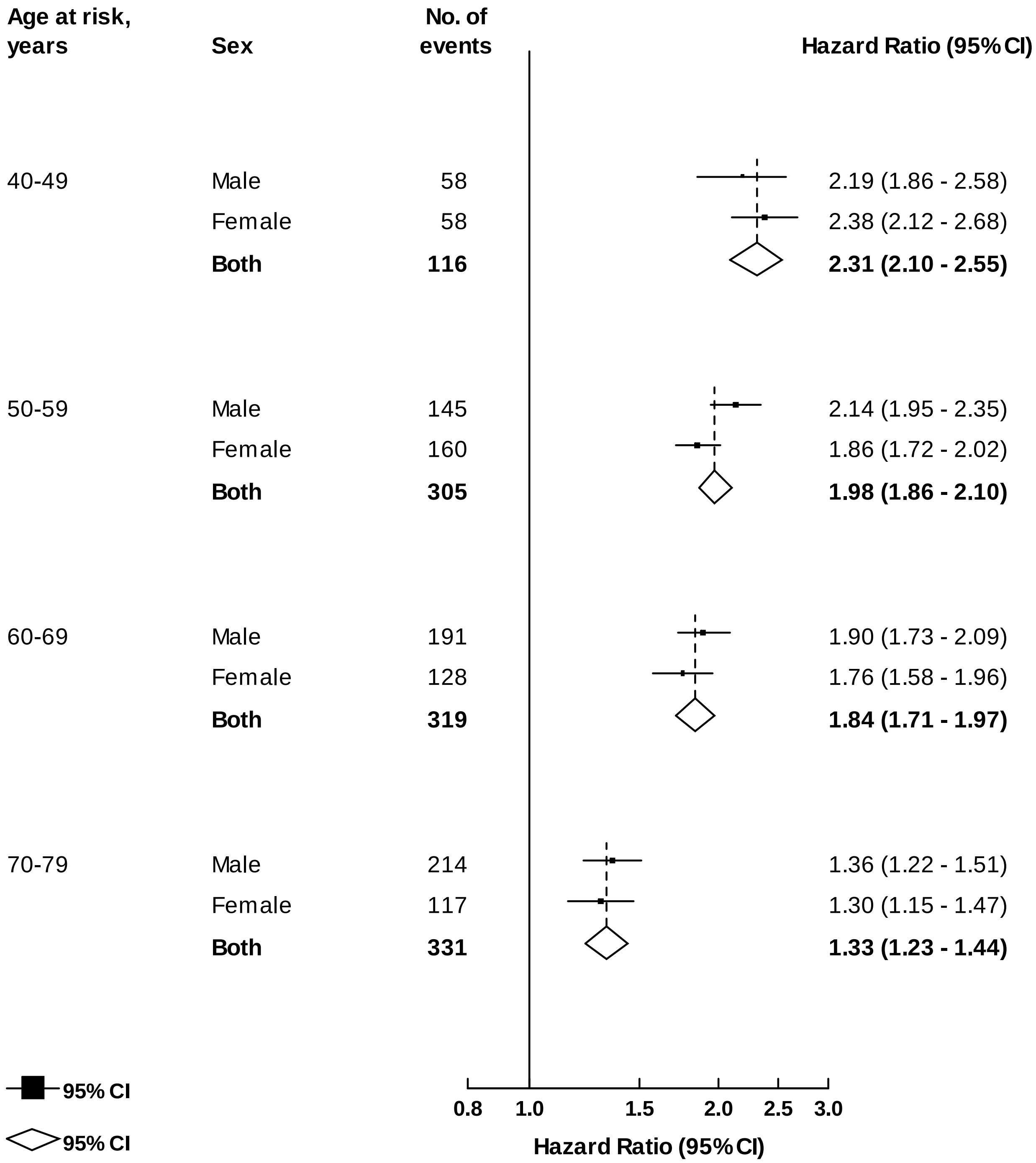


Figure 4.22: Intracerebral haemorrhage incidence (1071 events): age-specific hazard ratios for 5 mm Hg higher usual DBP, by sex (among 455 438 participants)

Hazard ratios (HR) adjusted for education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR (further adjusted for sex) and the open diamond indicates the 95% CI of the overall result.

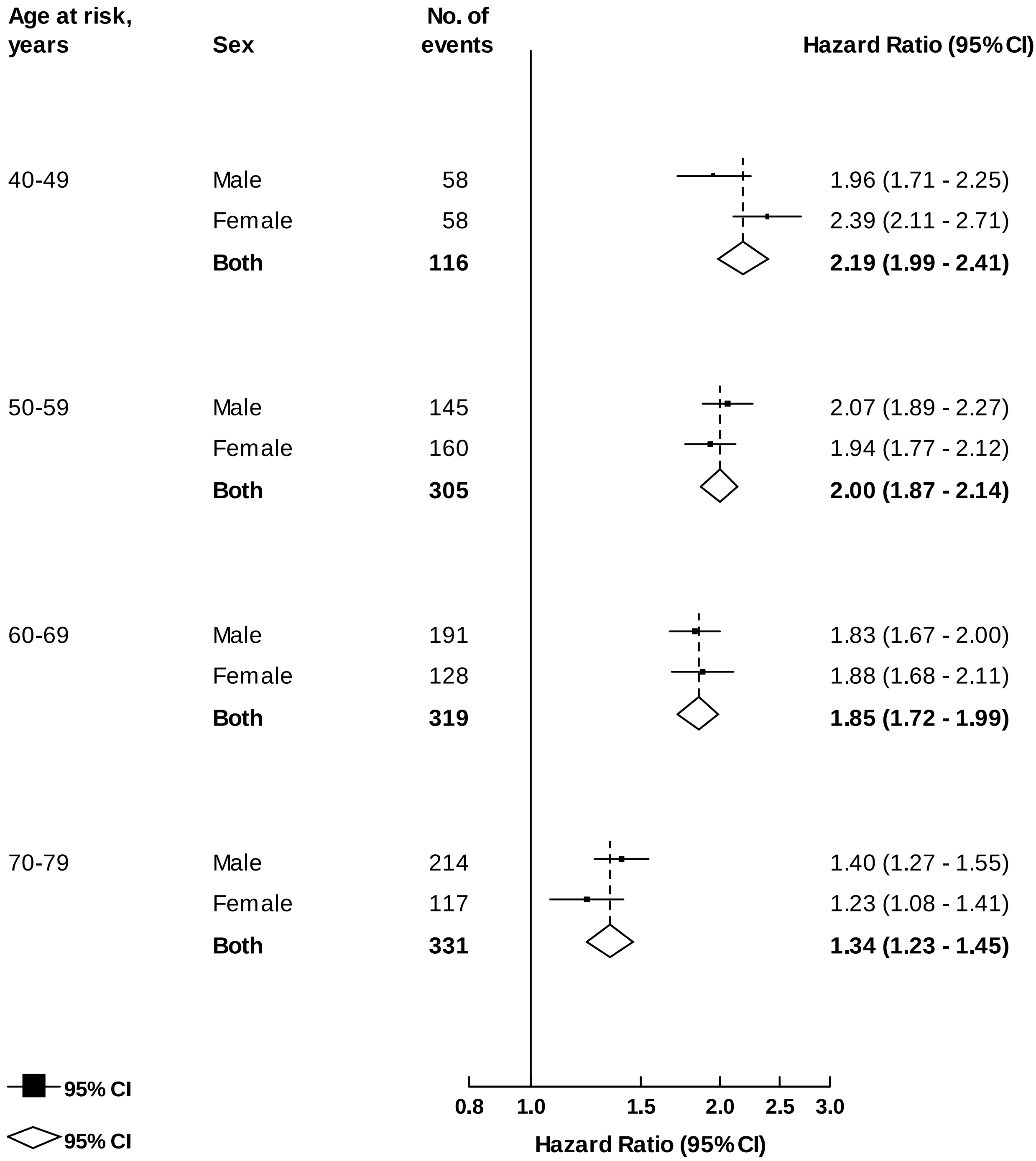
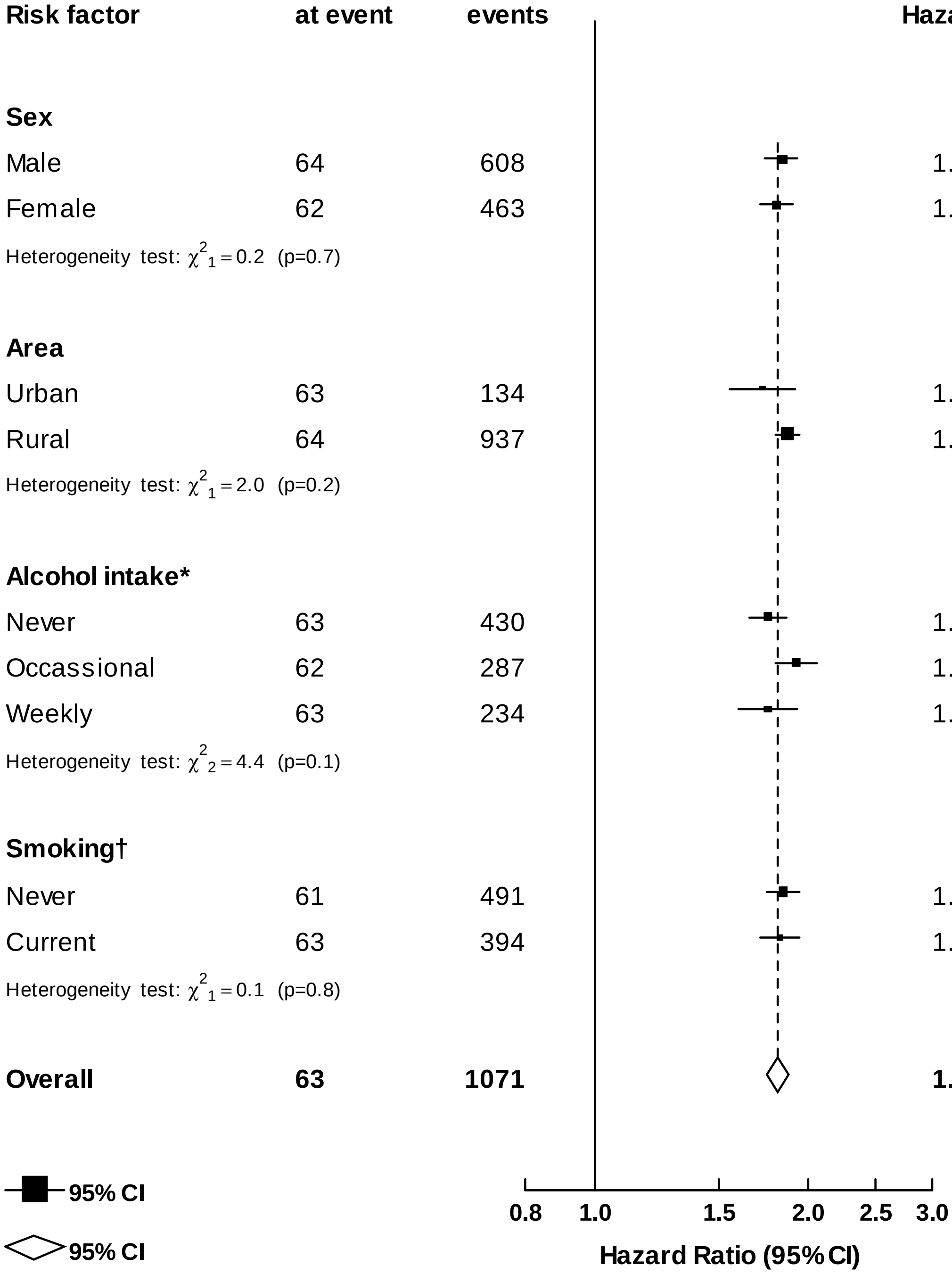


Figure 4.23: Intracerebral haemorrhage incidence (1071 events): hazard ratios for 10 mm Hg higher usual SBP, by set (I) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Sex			
Male	64	608	1.84 (1.75 - 1.94)
Female	62	463	1.81 (1.72 - 1.91)
Heterogeneity test: $\chi^2_1 = 0.2$ (p=0.7)			
Area			
Urban	63	134	1.73 (1.55 - 1.93)
Rural	64	937	1.88 (1.81 - 1.96)
Heterogeneity test: $\chi^2_1 = 2.0$ (p=0.2)			
Alcohol intake*			
Never	63	430	1.76 (1.66 - 1.87)
Occassional	62	287	1.93 (1.80 - 2.07)
Weekly	63	234	1.76 (1.60 - 1.93)
Heterogeneity test: $\chi^2_2 = 4.4$ (p=0.1)			
Smoking†			
Never	61	491	1.85 (1.76 - 1.95)
Current	63	394	1.83 (1.71 - 1.95)
Heterogeneity test: $\chi^2_1 = 0.1$ (p=0.8)			
Overall	**63**	**1071**	**1.82 (1.76 - 1.89)**

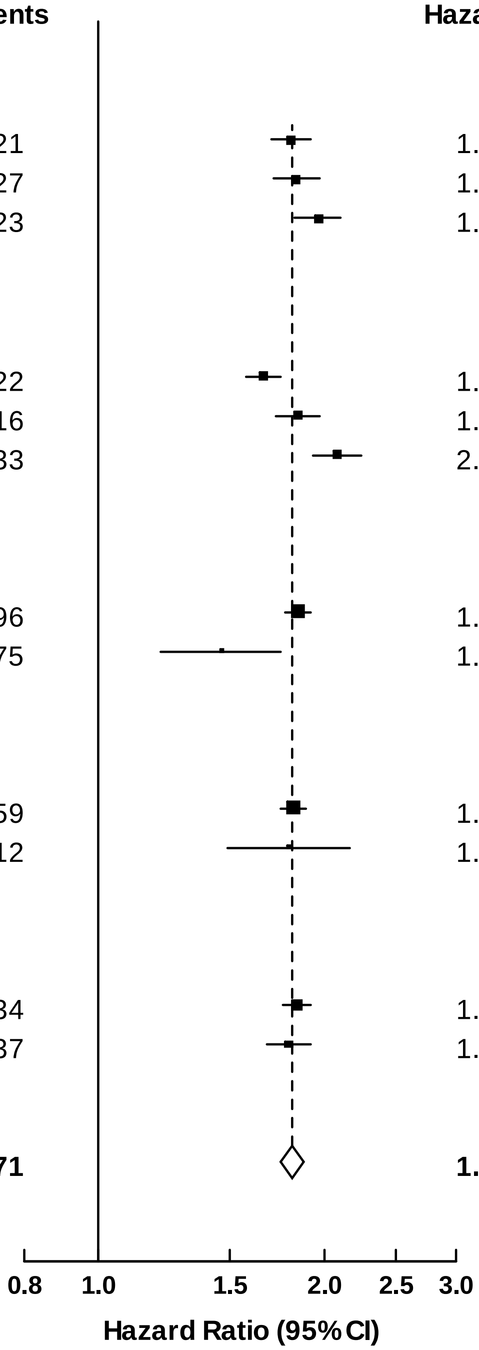


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure 4.24: Intracerebral haemorrhage incidence (1071 events): hazard ratios for 10 mm Hg higher usual SBP, by set (II) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
BMI, kg/m²			
<22	65	421	1.81 (1.71 - 1.92)
<25	63	327	1.84 (1.71 - 1.97)
≥25	60	323	1.97 (1.84 - 2.11)
Trend test: $\chi^2_1 = 3.1$ (p=0.08)			
MET, hrs/day			
<20	66	522	1.66 (1.57 - 1.75)
<30	61	316	1.85 (1.73 - 1.98)
≥30	58	233	2.09 (1.94 - 2.25)
Trend test: $\chi^2_1 = 24.6$ (p<0.001)			
Diabetes			
No	63	996	1.85 (1.78 - 1.92)
Yes	65	75	1.46 (1.21 - 1.76)
Heterogeneity test: $\chi^2_1 = 6.1$ (p=0.01)			
BP medication			
No	63	959	1.82 (1.75 - 1.89)
Yes	61	112	1.80 (1.49 - 2.18)
Heterogeneity test: $\chi^2_1 = 0.0$ (p=1)			
Fatal event			
No	62	734	1.84 (1.76 - 1.92)
Yes	65	337	1.80 (1.68 - 1.92)
Heterogeneity test: $\chi^2_1 = 0.3$ (p=0.6)			
Overall	**63**	**1071**	**1.82 (1.76 - 1.89)**



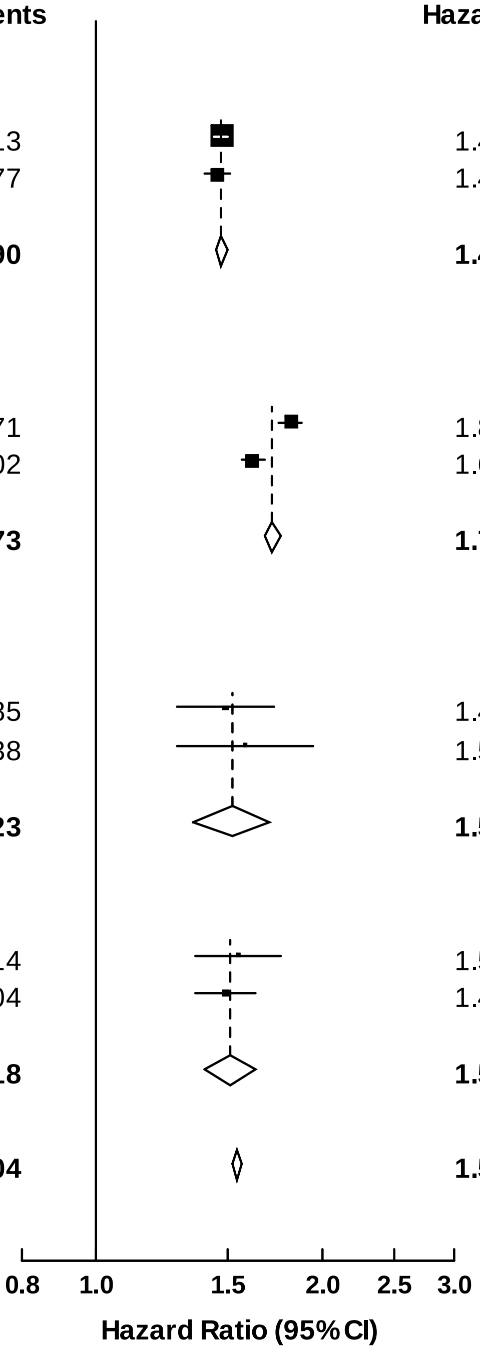
■ 95% CI

◇ 95% CI

Figure 4.25: **Stroke incidence: hazard ratios per 10 mm Hg higher usual SBP for each stroke pathological type, by diagnostic certainty of stroke events (among 455 438 participants)**

Analyses for each stroke pathological type were stratified by diagnostic certainty: firstly, using events which for which the diagnosis was known to have involved imaging with CT/MRI (labelled 'known'), as used in the main prospective analyses, and secondly, using events not known to have involved imaging with CT/MRI (labelled 'not known). Hazard ratios (HR) were adjusted for age at risk, sex, education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Imaging	Mean age at event	No. of events	Hazard Ratio (95% CI)
Cerebral infarction			
Known	64	4513	1.47 (1.44 - 1.50)
Not known	64	1477	1.45 (1.40 - 1.51)
Heterogeneity test: $\chi^2_1 = 0.4$ (p=0.5)			
Overall	**64**	**5990**	**1.47 (1.45 - 1.50)**
Intracerebral haemorrhage			
Known	63	1071	1.82 (1.76 - 1.89)
Not known	64	1102	1.62 (1.56 - 1.68)
Heterogeneity test: $\chi^2_1 = 19.7$ (p<0.001)			
Overall	**63**	**2173**	**1.72 (1.68 - 1.77)**
Subarachnoid haemorrhage			
Known	59	85	1.49 (1.29 - 1.73)
Not known	59	38	1.58 (1.28 - 1.95)
Heterogeneity test: $\chi^2_1 = 0.2$ (p=0.7)			
Overall	**59**	**123**	**1.52 (1.35 - 1.71)**
Unspecified			
Known	65	114	1.55 (1.36 - 1.76)
Not known	65	204	1.49 (1.36 - 1.63)
Heterogeneity test: $\chi^2_1 = 0.2$ (p=0.6)			
Overall	**65**	**318**	**1.51 (1.40 - 1.63)**
Overall	**64**	**8604**	**1.54 (1.52 - 1.56)**



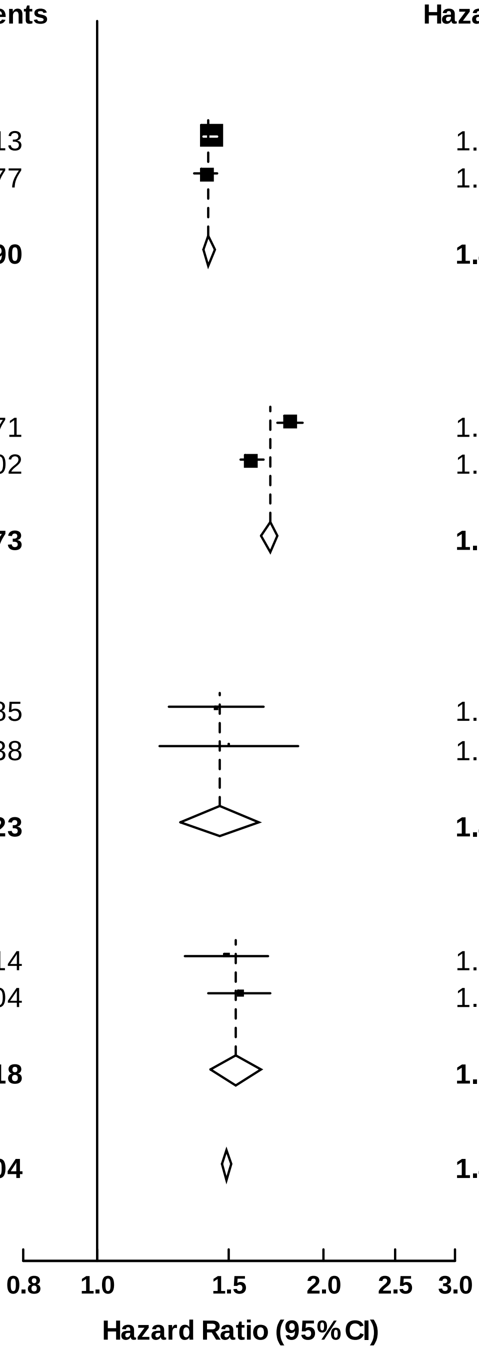
■ 95% CI

◇ 95% CI

Figure 4.26: Stroke incidence: hazard ratios per 5 mm Hg higher usual DBP for each stroke pathological type, by diagnostic certainty of stroke events (among 455 438 participants)

Analyses for each stroke pathological type were stratified by diagnostic certainty: firstly, using events which for which the diagnosis was known to have involved imaging with CT/MRI (labelled ‘known’), as used in the main prospective analyses, and secondly, using events not known to have involved imaging with CT/MRI (labelled ‘not known). Hazard ratios (HR) were adjusted for age at risk, sex, education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Imaging	Mean age at event	No. of events	Hazard Ratio (95% CI)
Cerebral infarction			
Known	64	4513	1.42 (1.39 - 1.45)
Not known	64	1477	1.40 (1.35 - 1.45)
Heterogeneity test: $\chi^2_1 = 0.4$ (p=0.5)			
Overall	**64**	**5990**	**1.41 (1.39 - 1.44)**
Intracerebral haemorrhage			
Known	63	1071	1.81 (1.74 - 1.88)
Not known	64	1102	1.61 (1.55 - 1.67)
Heterogeneity test: $\chi^2_1 = 18.2$ (p<0.001)			
Overall	**63**	**2173**	**1.70 (1.66 - 1.75)**
Subarachnoid haemorrhage			
Known	59	85	1.44 (1.24 - 1.67)
Not known	59	38	1.50 (1.21 - 1.86)
Heterogeneity test: $\chi^2_1 = 0.1$ (p=0.8)			
Overall	**59**	**123**	**1.46 (1.29 - 1.65)**
Unspecified			
Known	65	114	1.49 (1.31 - 1.69)
Not known	65	204	1.55 (1.41 - 1.71)
Heterogeneity test: $\chi^2_1 = 0.2$ (p=0.6)			
Overall	**65**	**318**	**1.53 (1.41 - 1.66)**
Overall	**64**	**8604**	**1.49 (1.47 - 1.52)**



95% CI (closed square)

95% CI (open diamond)

Table 4.19: Comparison between blood pressure indices as predictors of incidence of cerebral infarction and intracerebral haemorrhage, by age and by sex (among 455 438 participants)

Informativeness of a single measurement of a blood pressure index at baseline (as indicated by the X^2_1 values relating it to incidence of stroke known to have involved imaging with CT/MRI scan), as a percentage of the informativeness of mid blood pressure* for cerebral infarction and mean arterial pressure for intracerebral haemorrhage. The age-specific and sex-specific X^2_1 values are given in table E.3 in appendix E.

	Informative for prediction of cerebral infarction (4513 events) , %					**Informative for prediction of intracerebral haemorrhage (1071 events), %**				
	SBP	**DBP**	**Mid blood pressure**	**Mean arterial pressure**	**Pulse pressure**	**SBP**	**DBP**	**Mid blood pressure**	**Mean arterial pressure**	**Pulse pressure**
Age, years										
40-49	94	92	100	100	42	90	94	99	100	44
50-59	95	84	100	99	56	95	86	100	100	58
60-69	96	73	100	97	60	87	88	98	100	45
70-79	95	69	100	97	55	82	89	98	100	37
Sex										
Male	95	81	100	98	51	90	89	99	100	45
Female	95	79	100	98	59	92	87	99	100	54
Overall	95	80	100	98	54	91	88	99	100	49

* Mid blood pressure = 1/2SBP +1/2DBP, mean arterial pressure = 2/3SBP + 1/3DBP, and pulse pressure = SBP-DBP.

Chapter 5: Discussion

5.1 Summary of main findings

At age 40-79 years, the proportional difference in risk of both cerebral infarction and intracerebral haemorrhage associated with a given absolute difference in usual blood pressure was constant throughout the range of blood pressures examined (SBP 120-170 mm Hg; DBP 70-100 mm Hg). Overall, these proportional differences in risk were approximately 1.5-times greater for intracerebral haemorrhage than for the other stroke pathological types: 10 mm Hg higher usual SBP was associated with 82% (95% CI: 76-89) increased risk of intracerebral haemorrhage (mean age at event was 63 years); 47% (44%-50%) increased risk of cerebral infarction (mean age at event was 64 years); and 52% (95% CI: 35-71) increased risk of subarachnoid haemorrhage (mean age at event was 59 years).

There was major attenuation with age in the proportional differences in risk for both cerebral infarction and intracerebral haemorrhage. Compared with 70-79 years, the associations with usual SBP at 40-49 years were 2.7-times greater for cerebral infarction and 2.9-times greater for intracerebral haemorrhage. The absolute difference in risk for both pathological types, however, was greater in older age. The age-specific associations were slightly stronger in males than females for cerebral infarction, but similar in both sexes for intracerebral haemorrhage. For cerebral infarction, there was also strong evidence of effect modification of the overall associations with usual SBP by alcohol intake, smoking, BMI, diabetes and area. For intracerebral haemorrhage, there was strong evidence of effect modification with usual SBP by physical activity only. A single measure of SBP at baseline was found to be a better predictor of incidence of cerebral infarction and intracerebral haemorrhage than DBP, mean arterial pressure and mid blood pressure were better predictors than both SBP and DBP, and pulse pressure was substantially worse than all other measures.

5.2 Strengths and limitations of the study

Before comparing these findings to the results from other studies, the main strengths and limitations of the study are discussed.

5.2.1 Selection of participants

Participants were invited from the general population and the only exclusion criteria were age and the ability to consent – that is, participants were not selected into the CKB study on the basis of their blood pressure or disease status, and as such, selection bias is unlikely to have affected the findings. There were aspects of the selection process, however, that may affect the generalisability of the findings to China as a whole. Firstly, the areas in which the study was conducted were not selected to be representative of China as a whole, rather they were selected to maximise the potential to investigate the relationships between a broad range of exposures and common diseases. Secondly, participants who volunteer for prospective studies are often healthier than the population at large.[94] These apparent weaknesses do not, however, invalidate comparisons with China as a whole, as participants of the study are unlikely to be fundamentally different to the population at large in China with regard to the relationships examined in this thesis, never-the-less some caution is required.

5.2.2 Assessment of confounding

The broad baseline questionnaire enabled an extensive assessment of confounding of the main prospective associations in this thesis. Important potential confounders were identified in the analysis of baseline associations, including: age, sex, education, area, BMI, alcohol intake and seasonality. The qualitative nature of these associations was in keeping with the published literature for the associations with age,[95,96] sex,[96,97] education,[98,99] BMI,[43] alcohol intake[48,100] and seasonality (month of baseline survey).[101,102] As the purpose of this set of analyses was solely to describe the baseline associations, the strength of associations were not corrected for regression dilution bias and neither were participants using blood pressure-lowering medication excluded; comparisons of the strengths of the associations with the published literature should ideally be made following these amendments.

It was clear, however, that the strength of associations with BMI and seasonality, in particular, were considerably stronger than that described in studies conducted in the West: the associations with BMI were around twice as strong,[43] and the variation in blood pressure between summer and winter was around 5-times as great as that described in Europe.[101] Seasonal variation in blood pressure is considered to be due to variation in outdoor temperature. In a survey of Norwegian adults,[102] 10℃ lower outdoor temperature was associated with 1.5 mm Hg (95% CI: 0.6-2.3) higher SBP in men and 2.4 mm Hg (1.6-3.2) higher SBP in women. A report for the CKB study[84] found that above 5℃, there was a linear association with outdoor temperature, and 10℃ lowe r was associated with 5.7 mm Hg (95% CI: 5.6-5.8) higher SBP. There was no evidence, however, in the CKB study of an association at outdoor temperatures <5℃ among participants who reported having central heating in their homes. As such, it is possible that the shallower associations in European studies might be the result of a greater prevalence of central heating in Europe than China. The reason for the stronger associations with BMI in China than the West has not been established.

In spite of the strong baseline associations of a number of risk factors with blood pressure, none were found to confound the main prospective associations in this thesis. There were several vascular risk factors, however, for which baseline measurements were not available, and as such their potential confounding effect on the association between usual blood pressure and stroke incidence is unknown. In particular, there were no measures blood lipid concentrations. Unknown variables might also be confounding the association, but unlike clinical trials, these cannot be accounted for in prospective cohort studies.

5.2.3 Measurement of usual blood pressure

The procedures to ensure blood pressure was measured as accurately as possible are a major strength of the study's design. Systematic error in the measurement of blood pressure at baseline and resurvey was reduced by: standardising procedures across the ten study sites; ensuring all measurements were made by specifically trained study personnel; using a digital rather than manual sphygmomanometer, and ensuring these devices were maintained and calibrated regularly. Random error in blood pressure measurement was reduced by sampling large numbers of people at baseline and resurvey, and by measuring blood pressure more than once at each survey and using the mean blood pressure values in analyses. The reason for the digit preference for even numbers, seen in the descriptive analyses of blood pressure in the baseline data, is not clear. It could be the result of rounding by the study personnel during the surveys: blood pressure measurements were written on the back of the consent forms and entered manually into laptop computers. It might also be caused by the blood pressure device itself. There is no reason, however, to believe this affected the main findings.

The prospective nature of the study design meant that blood pressure, in those without a history of stroke at baseline, could be measured before stroke occurred. This minimised the potential for reverse causality. Stroke is known to affect blood pressure,[103] and as such, the relationship between blood pressure and stroke incidence can only be reliably investigated in studies which measure blood pressure before stroke occurrence. There may have been participants in the CKB study, however, with a history of stroke at baseline of which they were not aware or was not declared. As many of these participants are likely to experience a recurrence in the first few years after the baseline survey (which would be recorded by the study), repeating analyses with the first few years of follow-up excluded will reduce the effect, if any, of reverse causality. The follow-up to date in the CKB study was too short to reliably assess whether there has been any effect.

The large resurvey of blood pressure in this study allowed the effect of regression dilution bias on associations between blood pressure and stroke incidence to be reliably estimated. Importantly, the size of the resurvey allowed age- and sex-specific effects of regression dilution bias for blood pressure to be calculated. Using the overall regression dilution ratio, and not taking variation by age and sex into account, would have underestimated the strengths of the overall associations between blood pressure and stroke pathological types by around 15%.

Variation by age in the regression dilution ratios for blood pressure has been described in meta-analyses conducted by the Prospective Studies Collaboration and the Asia Pacific Cohort Studies Collaboration; results on variation by sex were not given in either study. Comparison between studies is complicated by the fact regression dilution ratios for each age group will tend to become more extreme in studies with longer periods between baseline and resurvey blood pressure measures. The Prospective Studies Collaboration reported similar regression dilution ratios to this thesis for SBP, despite differences between the studies in the period between baseline and resurvey blood pressure measures, particularly at older ages: 0.67 at age 40-49 years (2 year period), 0.62 at 50-59 years (4 year period), 0.58 at 60-69 years (6 year period) and 0.54 at 70-79 years (8 year period). Ratios for SBP in the Asia Pacific Studies Collaboration were slightly more extreme: 0.55 at <60 years, 0.55 at 60-69 years and 0.48 at ≥70 years (the mean follow-up period between baseline and resurvey blood pressure measures was 4 years; age-specific periods were not given).

5.2.4 Measurement of stroke incidence

The CKB study used established mortality and disease surveillance systems to identify stroke events. The surveillance systems were available in all areas, with the exception of the disease surveillance system in Qingdao which was not yet operational. There was substantial variation in the incidence of stroke by area in this study; it is unlikely that all this variation is real and some undercounting in some areas is probable. Studies of stroke incidence suggest using multiple over-lapping surveillance systems to reduce undercounting of stroke events.[104] Health insurance information, soon to be available from all ten areas, will be a further useful source of case-ascertainment, and consistency in the strengths of associations reported by different surveillance systems would be important sensitivity analyses for future prospective associations. There is no reason to suspect, however, that undercounting is related to blood pressure and, as such, should not affect the associations between blood pressure and stroke incidence.

Restricting the main analyses to stroke events for which there was evidence that a CT or MRI scan had been performed, is likely to have reduced misclassification between stroke pathological types. Random misclassification between the pathological types of stroke would have attenuated any differences in the strength of associations with blood pressure, and the low apparent misclassification rate for events reported by the disease surveillance system (assessed in the adjudication sub-study) is a significant strength of this study. It is possible, however, that in restricting the main analyses to stroke events known to have involved a CT or MRI scan, the more rapidly fatal events may have been excluded. This could bias the main analyses if rapidly fatal but accurately diagnosed events had a different association with blood pressure than other events. This hypothesis was tested by comparing the strength of associations using events which were fatal within 30 days and those which were not fatal with this period. There was no evidence of heterogeneity between these associations for either cerebral infarction or intracerebral haemorrhage, although there was substantial uncertainty about the estimates for fatal cerebral infarction, with only 70 events.

The sensitivity analyses which compared the strength of the overall associations using stroke events known and not known to have involved imaging (figures 4.25 and 4.26), indicate that restricting the main analyses to stroke events for which there was evidence that a CT or MRI scan had been performed, affected the overall associations for intracerebral haemorrhage but not the other stroke pathological types. The reason for shallower associations for intracerebral haemorrhage with stroke events not known to have involved imaging is not clear. Analyses comparing fatal and non-fatal stroke events suggest it is unlikely to be the result of differences in the severity of these events. It is possible that the misclassification rate may have been high for intracerebral haemorrhage events not known to have involved imaging; intracerebral haemorrhage is known to have a high case-fatality rate and sudden stroke deaths without prior imaging by CT or MRI scan may be more readily (but often wrongly) diagnosed by clinicians as intracerebral haemorrhage than cerebral infarction. Most intracerebral haemorrhage events that were not known to have involved imaging with CT or MRI scan were reported solely by the mortality surveillance system, and as such, it was not possible to use the adjudication sub-study to assess the extent of misclassification.

The adjudication sub-study identified that there was substantial proportion of ischaemic stroke events which could not be verified, even when restricting analyses to events known to have involved imaging with CT or MRI scan. The reason for this is not clear and it is the focus of on-going investigations. It is unknown what proportion of the events with evidence of cerebral infarction on CT or MRI scan but which could not be verified as stroke are: true stroke events for which the signs or symptoms were incompletely reported; what proportion were true stroke events that occurred in the past and are only now being reported; and what proportion are 'silent' events which were not accompanied by the signs and symptoms of stroke. A high proportion of 'silent' ischaemic events has not been described previously in stroke adjudication studies,[105,106] including those conducted in East Asia.[107] In light of these results, it was considered more appropriate at present to describe the outcome for ischaemic events using the broader term 'cerebral infarction' rather than 'ischaemic stroke'. This term is more consistent with the findings of the adjudication sub-study, but is clearly a less relevant outcome to patients and clinicians than ischaemic stroke, that is always associated with disability, of varying severity and duration.

The size of the CKB study is another of its major strengths. The study recruited a large number of participants, of which several thousand had incident stroke events during follow-up. This substantial number of stroke events increased the precision of the estimated strength of association between usual blood pressure and risk of stroke pathological types. It also allowed the strength of association to be estimated with reasonable precision by some potential effect modifiers, in particular by age and sex, known a priori to be potentially important effect modifiers.

Despite the large total number of stroke events, effect modification by some vascular risk factors should be interpreted with caution, especially those with fewer stroke events in some strata. The statistical uncertainty from few stroke events would have been compounded by uncertainty in the estimates of the regression dilution ratios, as these strata often had fewer participants resurveyed (e.g. current smokers and regular drinkers, in females). There were also insufficient strokes in particular strata of potential effect modifiers to permit further stratification of the results. For example, the number of events in diabetics was too low to permit further stratification by sex. There were several closely related variables for which a greater number of stroke events would have allowed stratification by each other, to assess the independent and combined effects of these variables. For example, the sex-specific associations for smoking would ideally have been further stratified by alcohol intake, and vice versa; as would the associations between BMI and MET hours/day. In addition, a greater number of subarachnoid haemorrhage events would have allowed the shape of associations with blood pressure to be described, as well as a more thorough assessment of confounding and effect modification.

5.2.5 Loss to follow-up

One of the potential problems with such a large study is the difficultly in accurately monitoring loss to follow-up over the long term. The CKB study undertakes periodic checks of the official records of the Public Security Bureau and surveys residential committees to identify those participants who had moved out the area. Not all participants who have moved out of the area would have been identified by these checks, but a full periodic resurvey of all participants is not practicable. At the time the analyses in this thesis were undertaken, the estimated proportion of participants loss to follow-up was very low (e.g. <1%). The relatively short follow-up period at the time of conducting the analyses for this thesis was likely to have been a benefit with regard to minimising loss to follow-up.

In summary, the main strengths of study include: the large number of stroke events that have occurred over a short period, which increased the precision of the estimated strength of the associations; the resurvey, which allowed associations with baseline blood pressure to be corrected for regression dilution bias; the low misclassification rate between stroke pathological types, as assessed in the adjudication sub-study; and the breadth of the baseline survey, which allowed the main associations to be assessed for confounding and effect modification by a range of vascular risk factors. The main limitations include: the period of follow-up, which was too short to reliably assess reverse causality; the low positive predictive value of ischaemic stroke identified in the adjudication sub-study; and the lack of blood lipid variables (the blood taken at baseline had yet to be analysed at the time of writing), which meant confounding or effect modification of the main association by blood lipid fractions could not be assessed.

5.3 Consistency with published literature

The main findings of the thesis are first compared with the prospective studies identified in the Literature Review, and then with the large meta-analyses of prospective studies conducted by the Prospective Studies Collaboration and the Asia Pacific Cohort Studies Collaboration.

5.3.1 Prospective studies of blood pressure and stroke risk in China

The positive nature of the associations between blood pressure and stroke risk described in this thesis were consistent with the results from studies identified in the Literature Review. With the exception of the Shanghai Women's Health Study,[77] however, the strength of the association between blood pressure and stroke in these studies was substantially weaker than the main findings in this thesis. The point estimate of the hazard ratio from the Shanghai Women's Health Study[77] was similar to this thesis but the confidence interval was so wide as to admit a very wide range of possibilities: 10 mm Hg higher baseline SBP was associated with 56% (95% CI: 6-128) increased risk of stroke.

Blood pressure was not corrected for regression dilution bias in any of the studies identified in the Literature Review and this is likely to be the main reason for their weaker associations. The strengths of the associations in the two larger studies identified in the Literature Review were around 50% weaker than in the analyses conducted as part of this thesis: 10 mm Hg higher baseline SBP was associated with 20% (95% CI: 19-21) higher risk of stroke in the China Prospective Study of 212 000 Men,[74] and 25% (24-26) higher risk in the China National Hypertension Survey Epidemiology Follow-up Study.[75] Without correction for regression dilution bias, 10 mm Hg higher SBP was associated with 27% (95% CI: 26-28) higher risk of overall stroke in analyses conducted for this thesis.

There were two studies identified in the Literature Review that reported results by stroke pathological type: the China Steelworkers Cohort Study[73] and the China Prospective Study of 212 000 Men.[74] Consistent with the main findings in this thesis, the China Steelworkers Cohort study found stronger associations for intracerebral haemorrhage than ischaemic stroke (although it was not possible to estimate the strength of these associations for a given increase in blood pressure from the information provided in the paper). In contrast, the China Prospective Study of 212 000 Men found no evidence of a difference in the strengths of the associations for ischaemic stroke and intracerebral haemorrhage. The reason for the discrepancy between these studies is not clear. It is possible that misclassification between stroke pathological types was greater in the China Prospective Study of 212 000 Men than either the China Steelworkers Cohort study or the analyses conducted for this thesis. The China Prospective Study of 212 000 Men used routinely collected mortality registry data to identify the pathological type of stroke death at a time when CT and MRI scans were not widespread in China, and there was no information on the death certificates as to whether a CT or MRI scan was involved in the diagnosis. The China Steelworkers Cohort study was conducted around 15 years before the China Prospective Study of 212 000 Men but the diagnostic accuracy of stroke pathological types may well have been better as hospital records for each stroke event were reviewed.

Two studies identified in the Literature Review, the China National Hypertension Survey Epidemiological Follow-up Study[75] and the China Prospective Study of 212 000 Men,[74] described effect modification of the main associations by vascular risk factors. The China National Hypertension Survey Epidemiological Follow-up

Study reported effect modification by age, BMI and smoking, and the China Prospective Study of 212 000 Men did so by smoking; no studies reported the presence or absence of effect modification by sex.

In the China National Hypertension Survey Epidemiological Follow-up Study the strengths of the associations in each strata of the potential effect modifier were shown graphically but not reported numerically. They indicated stronger associations at younger than older age, at lower than higher BMI and in smokers than non-smokers. The effect modification by age is consistent with the main finding of this thesis, as the associations for both main pathological types in this thesis were stronger at younger than older ages. Comparisons with the main findings in this thesis for the effect modification by BMI and smoking is difficult without further stratification of these analyses by stroke pathological type. Assuming most of the stroke events in the China National Hypertension Survey Epidemiological Follow-up Study were ischaemic stroke (this is likely to be case as stroke incidence including non-fatal events was measured, rather than solely stroke mortality), the results were broadly consistent with those in this thesis for ischaemic stroke, which found stronger associations at lower than higher BMI, and in current than never smokers.

The China Prospective Study of 212 000 Men described effect modification by smoking with stronger associations reported in non-smokers than smokers. These findings are not consistent with the analyses conducted for this thesis for either of the main stroke pathological types, and as the study measured stroke mortality only, it would not be reasonable to assume most events were ischaemic stroke. It could, however, be hypothesised that the shallower association in smokers is due to a higher proportion of ischaemic stroke events than intracerebral haemorrhage events in this group than in the non-smoking group: in the additional prospective analyses, conducted as part of this thesis, smoking was found to increase the risk of ischaemic stroke but not intracerebral haemorrhage (tables D.6 and D.10 in appendix D). As with the China National Hypertension Survey Epidemiological Follow-up Study, however, the number of stroke events of each pathological type in each strata of the effect modifier was not reported and the results were not stratified by stroke pathological type.

5.3.2 Large meta-analyses of prospective studies in East Asian and Western populations

The most reliable estimates to date for the age-specific associations between usual blood pressure and stroke have been produced by two large meta-analyses of prospective studies: the Prospective Studies Collaboration study[26] and the Asia Pacific Cohort Studies Collaboration study.[27] Figures 5.1 and 5.2 illustrate the results of these studies, together with main findings of this thesis. The results from the China Prospective Cohort study of 212 000 Men, discussed in the Literature Review, were added to the figures for comparison.

Consistent with the main finding of this thesis, both meta-analyses described positive log-linear associations between usual SBP and risk of cerebral infarction and intracerebral haemorrhage, with stronger age-specific associations at younger ages. In addition, there was no evidence of difference between the overall strength of association for subarachnoid haemorrhage in the analyses conducted for this thesis (mean age at event 59) and the equivalent age-specific results in either of the meta-analyses.

The strengths of the age-specific associations for cerebral infarction in the CKB study were similar to those of the Asia Pacific Cohort Studies Collaboration study. For example, at age 60-69 years, 10 mm Hg higher usual SBP was associated with 48% (95% CI: 43-53) higher risk of cerebral infarction in the main analyses of this thesis compared to 54% (45-64) higher risk in the Asia Pacific Cohort Studies Collaboration study. In both studies, the age-specific associations were stronger for intracerebral haemorrhage than cerebral infarction, but the difference in strength between the pathological types was greater in the main analyses of this thesis than in the Asia Pacific Cohort Studies Collaboration study. At age 60-69 years, 10 mm Hg higher usual SBP was associated with 84% (95% CI: 71-97) higher risk of intracerebral haemorrhage in the analyses of this thesis compared to 67% (57-77) higher risk in the Asia Pacific Cohort Studies Collaboration study.

In the Prospective Studies Collaboration study, the strengths of the age-specific associations between usual SBP and risk of cerebral infarction were again similar to the main findings in this thesis: at age 60-69 years, 10 mm Hg higher usual SBP was associated with 49% (95% CI: 34-48) higher risk of cerebral infarction. Unlike the finding in this thesis, however, the Prospective Studies Collaboration study found no evidence of any difference in the strength of the associations between the main stroke pathological types: at age 60-69 years, 10 mm Hg higher usual SBP was associated with 52% (95% CI: 45-59) higher risk of intracerebral haemorrhage.

The reason for these differences in the strengths of the associations between studies is unclear. They are unlikely to be chance finding given the large number of strokes in these studies. Unaccounted confounding or extensive misclassification between the main stroke pathological types might account for some of the differences; it could also be that some are real. These possibilities are discussed further, below.

Adjustment for potential confounders did not have a major effect on the strength of associations in any of these studies. There were a number of potential confounders assessed in the main analyses of this thesis and none had a major effect. There were some risk factors, however, which were not measured and as such their effect could not be assessed. The meta-analyses were more limited than the CKB study in the extent to which they could assess for confounding. The Asia Pacific Cohort Studies Collaboration assessed for confounding by total cholesterol, smoking and alcohol intake in the cohorts that provided data on these potential confounders, and the Prospective Studies Collaboration study assessed for confounding by total cholesterol, diabetes, smoking, alcohol intake and weight.

Meta-analyses of randomised controlled trials offer unconfounded estimates of the strength of association between usual blood pressure and risk of stroke, over the short period of a few years. One of the largest meta-analysis of trials[25] combined the results from 108 blood pressure-lowering trials (including trials targeting different blood pressure goals and those examining blood pressure medications versus placebo); almost all studies were conducted in the West. Standardised to a blood pressure reduction of 10 mm Hg SBP, the meta-analysis found 10 mm Hg lower SBP was associated with 41% (95% CI: 33-48) lower risk of stroke, equivalent to 69% (95% CI: 49-92) higher risk of stroke for 10 mm Hg higher usual SBP; the mean age of those included in these trials was 62 years and the mean duration of follow-up was 3.5 years. There was no evidence of a difference in the risk of stroke between trials categorised by different inclusion criteria (trials restricted to participants with a history of vascular disease, and those restricted to participants without a history of vascular disease). Unfortunately, the results were not given by stroke pathological type, and neither were the results from other identified large trials or meta-analyses of trials.[23,24] As such, it was not possible to use the results from blood pressure-lowering trials to assess the extent of confounding, if any, by unknown confounders of the associations by stroke pathological type. Though perhaps unlikely, given the assessment of confounding by major vascular risk factors in CKB study and the large meta-analyses of prospective studies, it is still possible that confounding might explain some of differences between these studies.

Misclassification between the main stroke pathological types was likely to be low in the main analyses conducted for this thesis, as indicated by the adjudication sub-study. The extent of misclassification in the meta-analyses of large prospective studies is less clear. Information on whether a CT or MRI scan was involved in the diagnosis of stroke was only available for around half the studies in the Asia Pacific Cohort Studies Collaboration study, and only half the strokes in these studies were known to have had scans. The proportion of strokes known to have involved a CT or MRI scan in the Prospective Studies Collaboration study is not reported, but for many of the older studies included in the analysis, the technology was simply not available. As misclassification would tend to attenuate any differences in the strengths of the associations between stroke pathological types, greater misclassification in the meta-analyses than in the CKB study may explain the greater similarity in the strengths of the associations of stroke pathological types in these studies than in the CKB study. It is also possible, however, that some of the differences between these studies are real. For example, the shallower associations for intracerebral haemorrhage reported in the Prospective Studies Collaboration study may be the result of different genetic or environmental exposures between populations in East Asia and those in the West.

There were consistencies and differences in the effect modification results in the analyses conducted for this thesis compared to those of the meta-analyses. The Prospective Studies Collaboration study described effect modification by sex for the associations between usual SBP and risk of overall stroke, with slightly weaker age-specific associations for females than males: at age 60-69 years, 10 mm Hg higher of usual SBP was associated with 46% (95% CI: 40-52) higher risk of stroke in females compared to 56% (51-60) higher risk in males. This is consistent with the findings of this thesis for cerebral infarction (figure 4.14) but not intracerebral haemorrhage (figure 4.21). By contrast, the Asia Pacific Cohort Studies Collaboration study did not find any evidence of effect modification by sex. Neither meta-analysis, unfortunately, reported effect modification by sex for each of the main stroke pathological types separately.

The Asia Pacific Cohort Studies Collaboration has published further results on effect modification of the association between blood pressure and stroke by BMI,[108] smoking[109] and total cholesterol;[110] the Prospective Studies Collaboration has not published further results on effect modification. The results of the Asia Pacific Cohort Studies Collaboration analyses for effect modification by smoking and BMI are not consistent with the findings of this thesis; effect modification by total cholesterol cannot be compared with the finding of this thesis, as cholesterol is yet to be measured in the CKB study. Unlike the findings in this thesis, the Asia Pacific Cohort Studies Collaboration[108] did not find evidence of effect modification by BMI for either ischaemic stroke ($p_{heterogeneity} = 0.24$) or intracerebral haemorrhage ($p_{heterogeneity} = 0.18$). There was evidence, however, of effect modification by BMI ($p_{heterogeneity} = 0.01$) for coronary heart disease, with stronger associations at lower than higher BMI, consistent with the effect modification findings in this thesis for cerebral infarction.

For smoking, the Asia Pacific Cohort Studies Collaboration[109] found evidence of effect modification for associations with intracerebral haemorrhage but not ischaemic stroke: 10 mm Hg higher usual SBP was association with 81% (95% CI: 73-90) higher risk of intracerebral haemorrhage in current smokers and 66% (59-73) higher risk in non-smokers. By contrast, the analyses conducted for this thesis found evidence of effect modification by smoking for associations with cerebral infarction but not intracerebral haemorrhage, with stronger associations in current than never smokers.

Analyses conducted by the Asia Pacific Cohort Studies Collaboration[110] found effect modification by total cholesterol for associations with ischaemic stroke but not for intracerebral haemorrhage. Associations with ischaemic stroke were stronger at lower than higher total cholesterol: 10 mm Hg higher usual SBP was association with 40% (95% CI: 36-43) higher risk of ischaemic stroke at total cholesterol <4.8 mmol/L compared to 29% (21%-37%) higher risk at total cholesterol ≥6.3 mmol/L. This thesis was not able to assess effect modification by lipid fractions.

5.4 Causality

The totality of evidence indicates that blood pressure is an important cause of ischaemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage. Meta-analyses of randomised clinical trials show with a higher degree of certainty than prospective cohort studies that blood pressure is a cause of stroke.[23,24,25] At present, however, clinical trials do not allow the importance of this relationship to be examined in detail by age, sex and stroke pathological type, as permitted by large prospective cohort studies.

Large prospective cohort studies have consistently found strong positive associations between blood pressure and risk of stroke in both sexes, and throughout middle and old age, for all stroke pathological types.[26,27] The prospective character of these studies, which measure blood pressure prior to stroke incidence in participants without history of vascular disease, has established the temporal nature of these associations. There is also a strong biological plausibly for the relationship with all the stroke pathological types: ischaemic stroke,[111,112] intracerebral haemorrhage[113,72] and subarachnoid haemorrhage.[71]

Strong positive associations have been described in different parts of the world where study conditions and background levels of different risk factors are likely to be very different, although there have been comparatively few studies of subarachnoid haemorrhage compared to ischaemic stroke or intracerebral haemorrhage.[114] The strengths of the associations have been reasonably consistent for ischaemic stroke in different parts of the world (figure 5.1), whereas the strength of the associations for intracerebral haemorrhage have been more varied (figure 5.2). The reason for the variation in the results for intracerebral haemorrhage is unclear. As discussed in the previous section, possible biases, including misclassification between the stroke pathological types, might explain some, or all, of this variation. It is also possible, however, that there are real differences in the strengths of associations for intracerebral haemorrhage that might have an environmental basis (for example, differences in the prevalence of other risk factors for vascular disease which might be modifying the associations) or a genetic basis (for which the evidence is weak at present[115]), or both.

There is insufficient evidence to assess whether the effect modifications of the associations by vascular risk factors investigated in analyses for this thesis (by alcohol intake, smoking, BMI, MET hours/day and area) were real. Some of the effect modification identified could well be due to chance. Consistency with other studies has also not been demonstrated (for example, no previous studies were found which investigated effect modification by physical activity or alcohol intake), and the biological plausibility of these effect modification findings are not established. These findings could also be the result of effect modification by other risk factors not investigated, such as cholesterol levels, or the result of variation in the proportion of subtypes (figure 1.1) of the stroke pathological types by strata of the effect modifiers: there is weak evidence from meta-analyses of case-control studies of an increased risk of hypertension in some subtypes compared to others (small vessel compared to non-small vessel ischaemic stroke,[116] and non-lobar compared to lobar intracerebral haemorrhage[117]).

The pathological lesions which result in stroke are known to vary by subtype of stroke pathological type.[111,72] For example, large vessel ischaemic stroke is considered to result from atherosclerosis of large arteries of the head or neck, whereas there is evidence that non-atherosclerotic arteriopathy may underlie many small vessel ischaemic strokes.[118] There is also evidence that lobar intracerebral haemorrhage may be caused by different pathological lesions to deep intracerebral haemorrhage.[72] Despite this, the extent to which the strength of association with usual blood pressure varies, if at all, by subtype of stroke pathological type is unclear.

5.5 Future research

A number of the analyses conducted for this thesis would benefit from the greater precision afforded by more stroke events, in particular, the analyses for subarachnoid haemorrhage. More stroke events would also allow some of the effect modification analyses to be further stratified by other risk factors. For example, diabetes could be stratified by sex, and some strongly associated variables could be stratified by each other (such smoking and alcohol, and BMI and physical activity). This would allow the independent and combined effects of these variables on the associations between usual blood pressure and stroke pathological types to be estimated.

Future research could also address some specific weakness of the study, identified earlier: reverse causality could be assessed by repeating the main analyses of this thesis after several more years of follow-up, excluding the first few years of follow-up; the main analyses could also be repeated after the blood lipid levels at baseline have been analyses, which would allow the main finding to this thesis to be assessed for confounding and effect modification by lipid fractions; further investigation of ischaemic stroke events in the adjudication sub-study would clarify the reason for the large proportion of these events that could not be validated, and ideally the original radiological images themselves would be reviewed together with the notes. An extension to the adjudication sub-study to assess the diagnostic accuracy of intracerebral haemorrhage events reported solely by the mortality surveillance system would be of benefit in understanding whether misclassification with ischaemic stroke could account for the weaker association with blood pressure in this group.

The relationship between blood pressure and stroke pathological types could be investigated further by replicating the main analyses using blood pressure indices other than usual SBP and usual DBP, such as mean arterial pressure, mid blood pressure and pulse pressure. A single baseline measure of mid blood pressure was found to be the best predictor of cerebral infarction and mean arterial pressure the best predictor of intracerebral haemorrhage (in part, because random measurement errors which affect just SBP or just DBP would have been reduced by calculating the average). The associations between usual levels of these other indices and stroke pathological types, however, is unknown. A description of these associations would offer an even more comprehensive assessment of the relationship between blood pressure and stroke pathological types.

Important future analyses would also include investigating the relationship between usual blood pressure and the subtypes of stroke pathological types, important for understanding the mechanisms by which blood pressure causes stroke. This would require a more detailed classification of some of the stroke events in the CKB study. This would not be straightforward, unfortunately, as most algorithms used to classify subtypes of ischaemic stroke require a Doppler ultrasound scan of the carotid arteries[119] and preliminary analyses from the adjudication sub-study suggest is performed rarely in China. Further classification would also be useful for the planned nested case-control studies, within the CKB study, which will investigate the genetic determinants of stroke (such studies require detailed phenotyping of stroke events[120]).

Lastly, it would be worthwhile comparing the results of this thesis to similar analyses of other vascular disease outcomes in the CKB study (in particular, ischaemic heart disease) and also to analyses from other large prospective studies on-going in different parts of the world. For example, the UK Biobank study[121] also has half a million participants, the baseline survey has recently been completed and stroke events are being followed-up. Any consistencies or differences in the strengths of associations between studies would offer an insight into the aetiology of stroke and how this may differ in different parts of the world.

5.6 Public health implications

The results of this thesis have important clinical and public health implications for the prevention of stroke in China. Consistent with other large analyses, there were strong continuous associations between blood pressure and stroke pathological types with no evidence of a threshold (down to at least 120 mm Hg usual SBP and 70 mm Hg usual DBP). This suggests that lowering blood pressure reduces the risk of stroke pathological types even in those considered normotensive.

The different strengths of the associations between blood pressure and stroke pathological types indicates that lowering blood pressure would have a greater effect on the risk of intracerebral haemorrhage than cerebral infarction. Assuming all of the epidemiologically expected benefit of reducing blood pressure on stroke risk is realised, at age 60-69 years, 10 mm Hg lower SBP would reduce the risk of intracerebral haemorrhage by just under a half (46%) and the risk of cerebral infarction by around a third (32%).

The absolute benefit of such changes in the relative risks, however, depends on the absolute risk of cerebral infarction and intracerebral haemorrhage. Those at greatest absolute risk would have the greatest absolute benefit from a given proportional reduction in their risk of stroke. The evidence from clinical trials suggests that the relative risk reductions for stroke are similar in those with and without a history of vascular disease. As such, those at highest absolute risk includes those with a history of vascular disease, who are at particularly high risk of stroke or recurrence of stroke, even though they were excluded from the analyses in this thesis to avoid reverse causality.

At a population level, even modest reductions in blood pressure in China would have a significant effect on stroke risk. At age 60-69 years, the results of this thesis suggest that 2 mm Hg lower SBP would reduce the risk of cerebral infarction by 8% (95% CI: 7-9) and the risk of intracerebral haemorrhage by 13% (11-15), which could be achievable, for example, by substituting conventional dietary salt for low sodium salt.[122,123] Given the high rates of stroke in China, these reductions in relative risk would have a substantial effect on the number of stroke events, especially in the parts of China with the highest absolute risk of stroke, such as the north and inland areas.

5.7 Conclusion

This study found that in Chinese adults, aged 40-79 years, usual blood pressure was strongly and positively related to risk of all stroke pathological types. The strength of association was greater for intracerebral haemorrhage than for other pathological types. There were log-linear associations between usual blood pressure and risk of both cerebral infarction and intracerebral haemorrhage, throughout the range of blood pressure observed; there were too few events to assess the shape of association for subarachnoid haemorrhage. For both cerebral infarction and intracerebral haemorrhage, there was strong evidence of major effect modification by age and to a lesser extent by a number of other vascular risk factors. The associations were shallower at older ages, although the annual absolute differences in risk were greater at older age. The strengths of these associations were much greater than estimated by previous prospective studies in China, particularly for intracerebral haemorrhage.

Figure 5.1: Cerebral infarction incidence: age-specific hazard ratios for 10 mm Hg higher usual SBP in the CKB study and other studies

Each closed square represents hazard ratio (HR) with area inversely proportional to the variance of the log HR. The age-specific results from the CKB study are presented together with the result from the Asia Pacific Cohort Studies Collaboration,[27] the Prospective Studies Collaboration[26] and the China Prospective Study of 212 000 Men.[74]

Study, by age at risk	No. of events	Hazard Ratio (95% CI)
China Kadoorie Biobank		
40-49 yrs	318	1.90 (1.78 - 2.03)
50-59 yrs	1213	1.53 (1.48 - 1.59)
60-69 yrs	1543	1.48 (1.43 - 1.53)
70-79 yrs	1439	1.27 (1.22 - 1.32)
Asia Pacific Cohort Studies Collaboration		
50-59 yrs	488	1.75 (1.63 - 1.88)
60-69 yrs	484	1.54 (1.45 - 1.64)
70-79 yrs	402	1.39 (1.30 - 1.49)
80-89 yrs	204	1.27 (1.12 - 1.44)
Prospective Studies Collaboration		
50-59 yrs	177	1.69 (1.55 - 1.85)
60-69 yrs	538	1.49 (1.41 - 1.57)
70-79 yrs	850	1.41 (1.34 - 1.48)
80-89 yrs	518	1.14 (1.07 - 1.22)
China Prospective Study of 212 000 Men		
60-69 yrs	1231	1.19 (1.16 - 1.22)

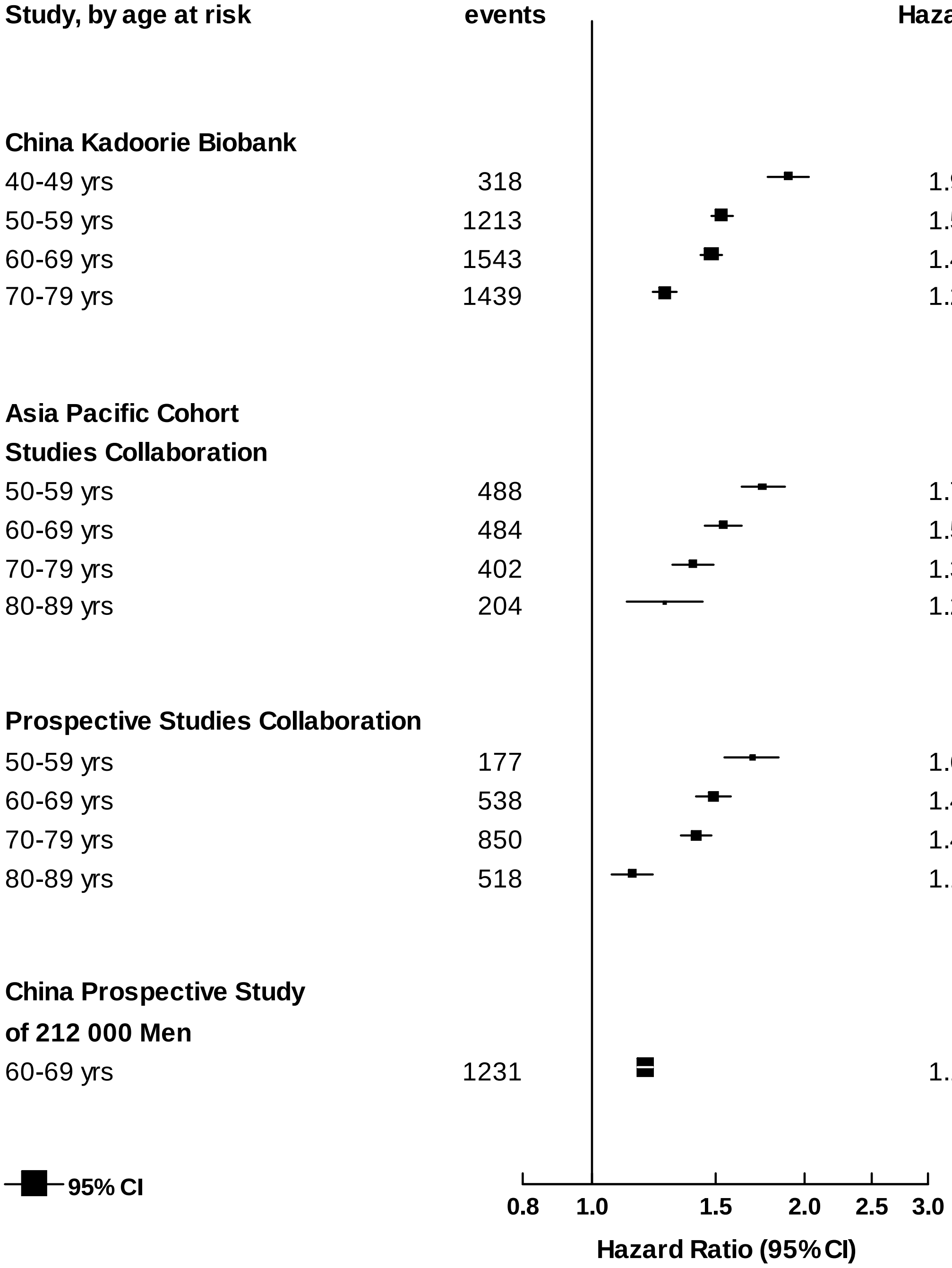
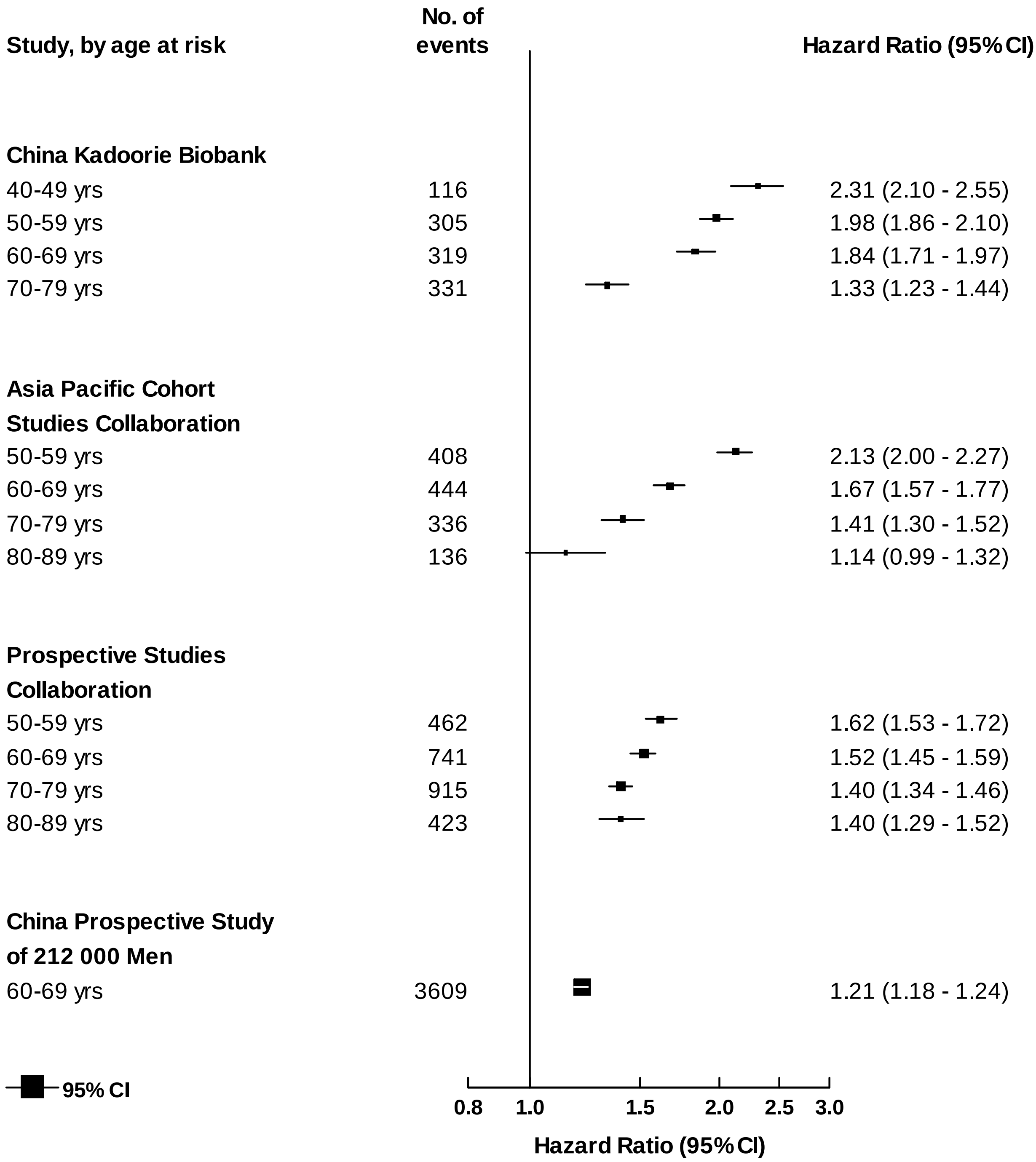


Figure 5.2: Intracerebral haemorrhage incidence: age-specific hazard ratios for 10 mm Hg higher usual SBP in the CKB study and other studies

Each closed square represents hazard ratio (HR) with area inversely proportional to the variance of the log HR. The age-specific results from the CKB study are presented together with the result from the Asia Pacific Cohort Studies Collaboration,[27] the Prospective Studies Collaboration[26] and the China Prospective Study of 212 000 Men.[74]



Appendix A: China Ecological Study results

Table A.1: Pearson's correlation coefficients of county stroke mortality at age 35-69 in 1986-88 with county level values of vascular risk factors in 1989, in 67 counties in China, by sex

Original analyses of the China Ecological Study of 69 rural counties (two counties did not report stroke mortality rates) and the 1989 Biochemistry, Diet and Lifestyle surveys. Mortality rates were age-standardised by taking the unweighted average of the component five-year mortality rates. Female correlations exclude county Longxian. Data on plasma glucose was not available for three counties. 'Percentage who were well-educated' was defined as attending 'senior middle' school or higher.

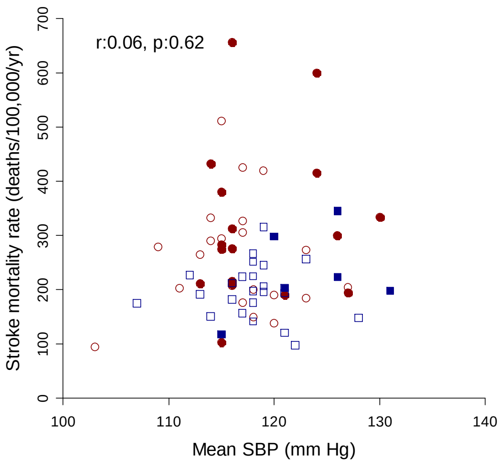
	Pearson's correlation coefficient, r (95%CI)			
Variables	**Male**		**Female**	
Systolic blood pressure (mm Hg)	0.06	(-0.18-0.30)	0.28	(0.03-0.48)*
Diastolic blood pressure (mm Hg)	0.18	(-0.07-0.40)	0.32	(0.08-0.52)*
Urinary Sodium (mg Na/ mg creatinine)	0.17	(-0.07-0.40)	-	-
Green vegetable consumption (days veg. consumed/year)	-0.19	(-0.41-0.05)	-0.40	(-0.59- -0.18)*
BMI (kg/m^2)	0.04	(-0.20-0.28)	0.40	(0.17-0.58)*
Alcohol consumption (g/day)	-0.12	(-0.35-0.13)	-0.10	(-0.34-0.14)
Total cholesterol (mg/dL)	-0.14	(-0.37-0.10)	-0.22	(-0.43-0.03)
- HDL cholesterol (mg/dL)	-0.09	(-0.32-0.16)	-0.36	(-0.55- -0.13)*
- Non-HDL cholesterol (mg/dL)	-0.11	(-0.34-0.14)	-0.05	(-0.29-0.19)
Plasma Glucose (mg/dL)	0.05	(-0.20-0.29)	-0.24	(-0.46-0.01)
Current smokers (%)	-0.05	(-0.29-0.19)	0.11	(-0.13-0.35)
Oil and fat consumption (g/day)	-0.11	(-0.34-0.13)	-0.10	(-0.34-0.14)
Fruit consumption (days fruit consumed /year)	-0.05	(-0.29-0.19)	0.12	(-0.13-0.35)
Percentage who were well-educated	-0.01	(-0.25-0.23)	0.04	(-0.20-0.28)
Household income in 1989 (100 Yuan)	0.04	(-0.21-0.27)	-0.26	(-0.47- -0.02)*

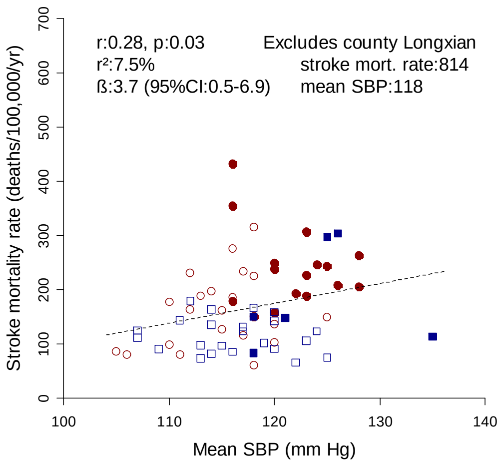
* p<0.05

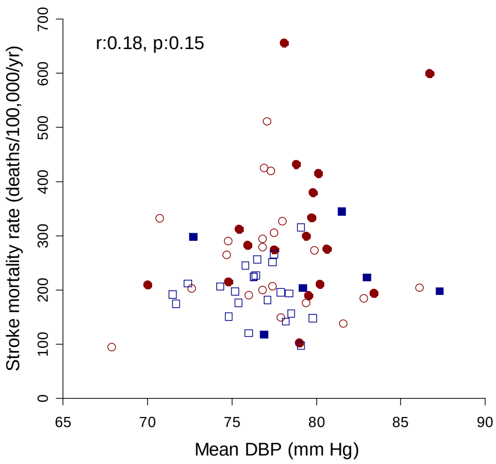
Figure A.1: Scatter plots of county stroke mortality at age 35-69 in 1986-88 with county level values of vascular risk factors in 1989, in 67 counties in China, by sex

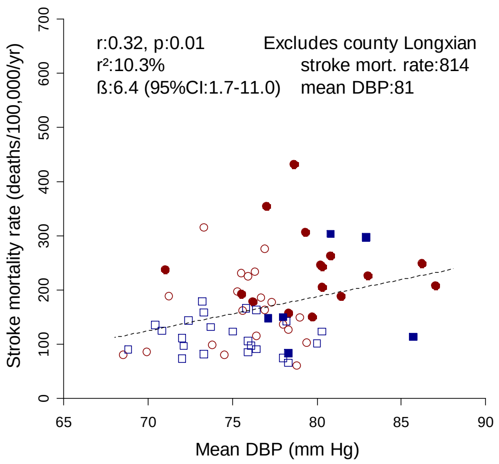
Original analyses of the China Ecological Study of 69 rural counties (two counties did not report stroke mortality rates) and the 1989 Biochemistry, Diet and Lifestyle surveys (see notes of table A.1). Where the correlation coefficient (r) between the two variables is statistically significant (p<0.05), a regression line has been drawn and the slope coefficient (β) has been calculated. Counties are presented in geographic groups, see key.

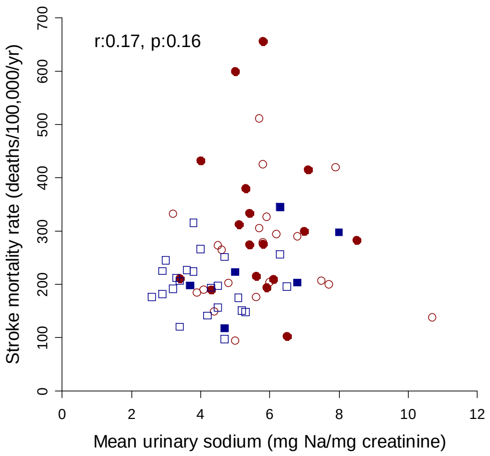
Males	**Females**











KEY FOR SCATTERPLOTS

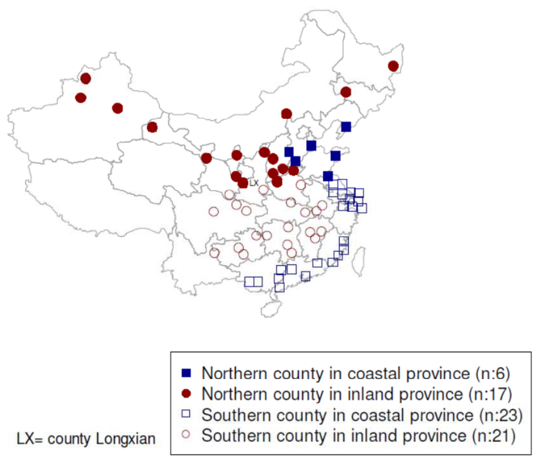


Figure continues overleaf

Figure A.1 - Continued

Males	Females

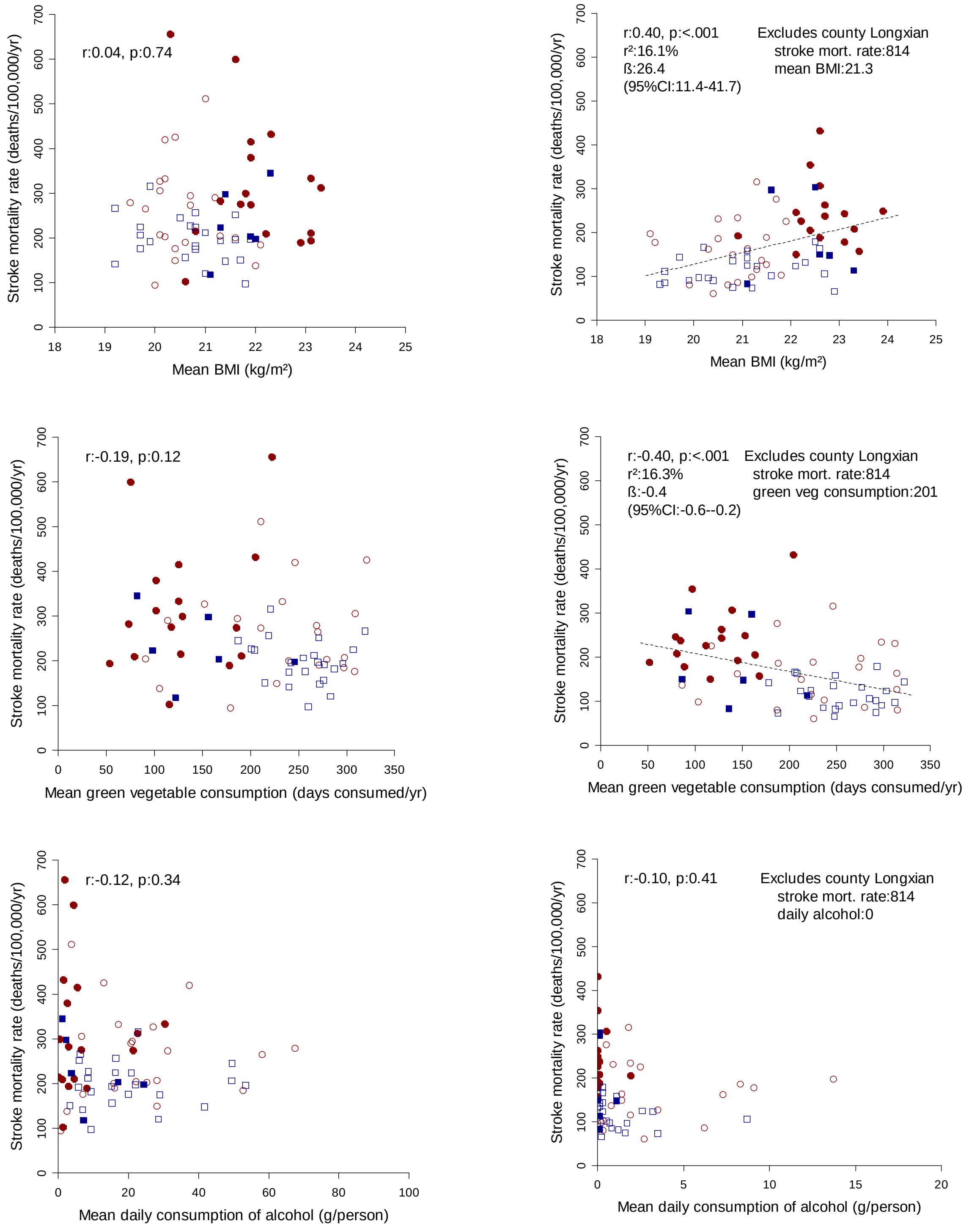
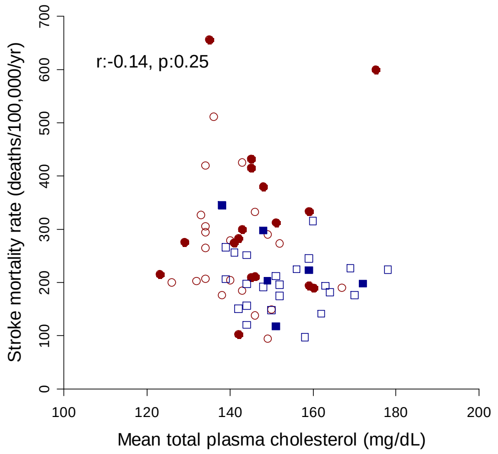
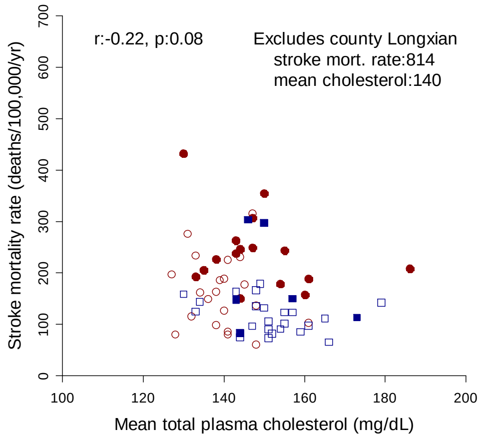


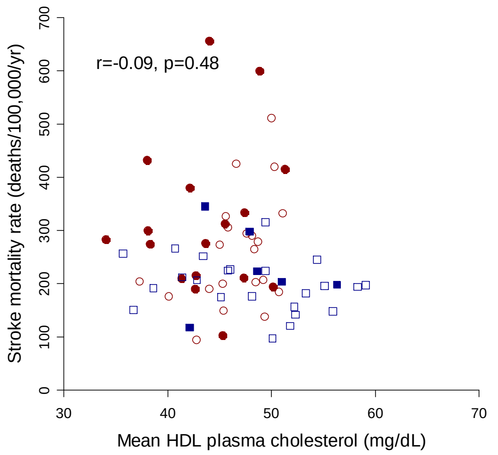
Figure continues overleaf

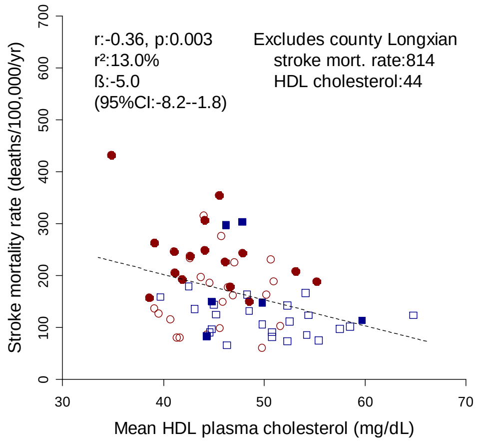
Figure A.1 - Continued

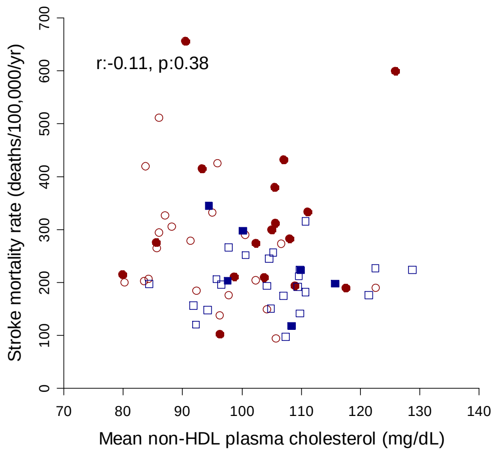
Males	Females











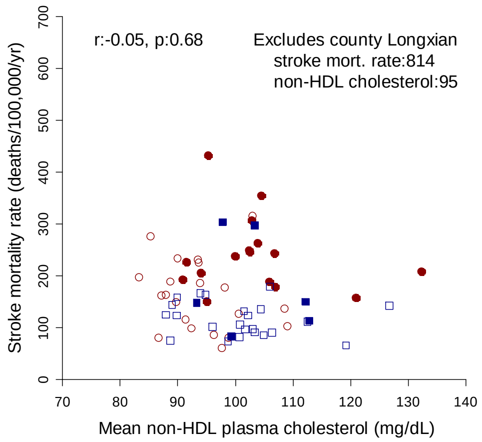


Figure continues overleaf

Figure A.1 - Continued

Males | **Females**

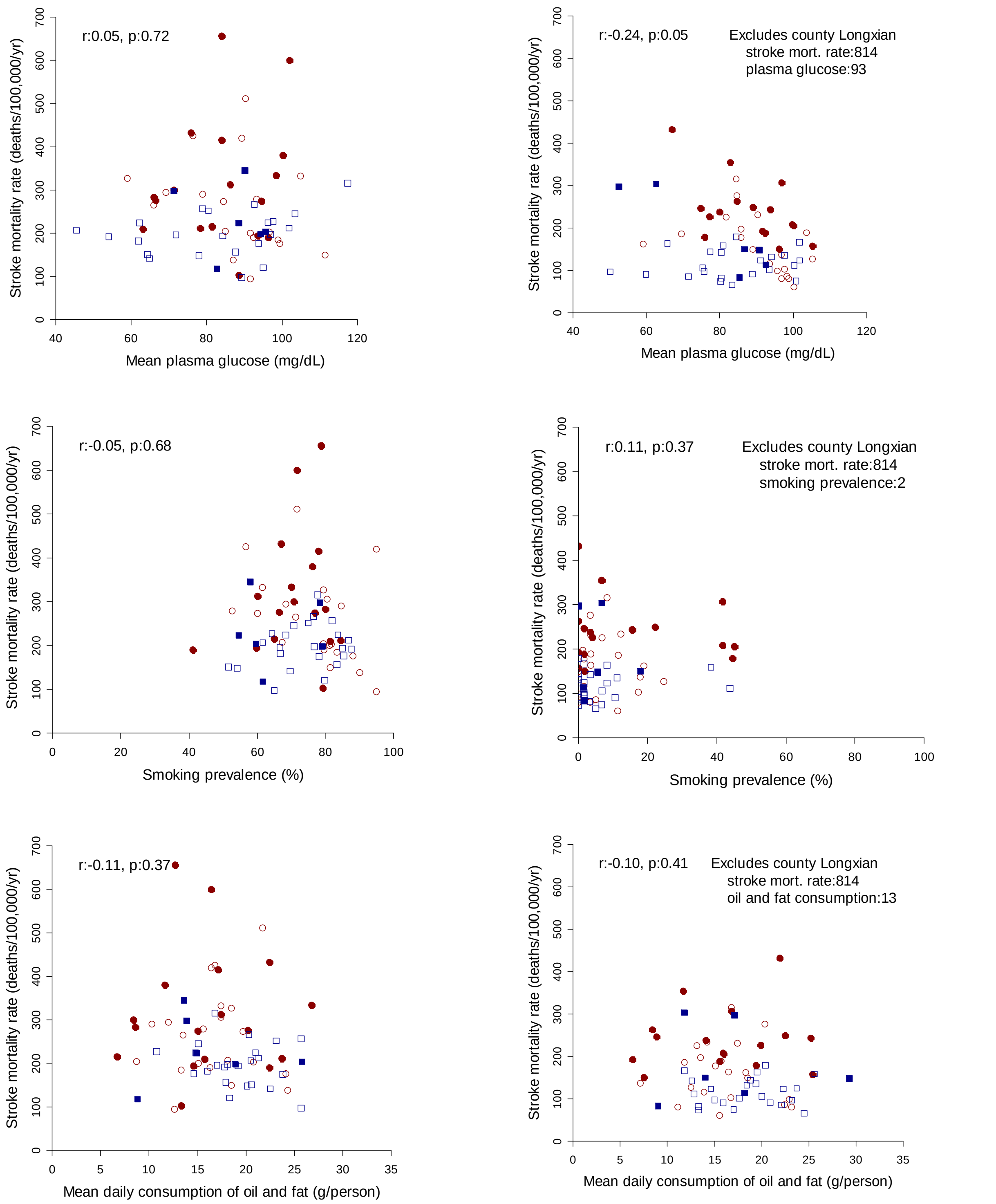


Figure continues overleaf

Figure A.1 - Continued

Males | **Females**

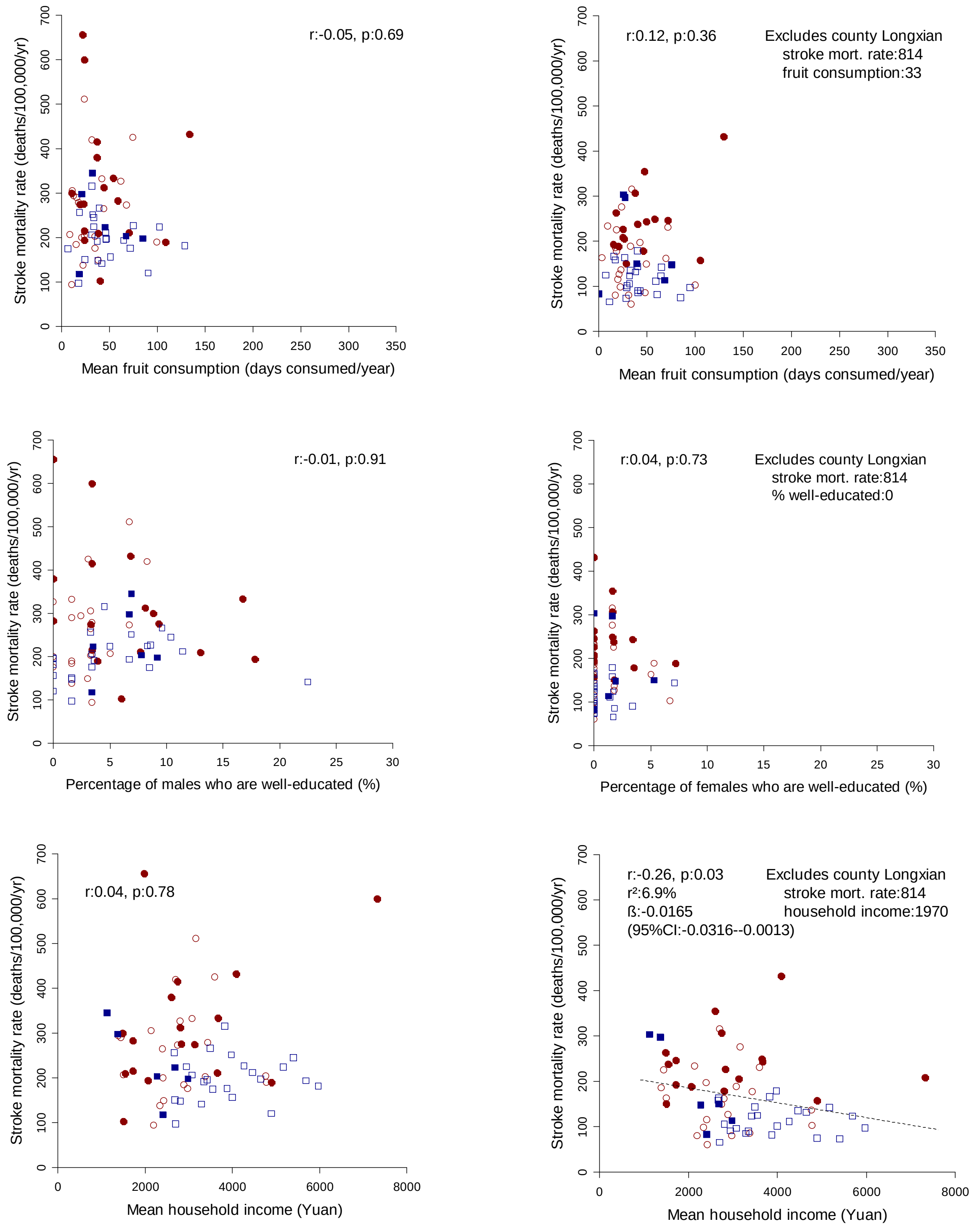


Figure continues overleaf

Table A.2: Literature Review database searches: textwords and MeSH terms

Research question of database search: What is the association between blood pressure and stroke incidence or mortality reported in prospective cohort studies conducted in China? Databases searched: MEDLINE (from 1950), Global health (from 1973) and EMBASE (from 1980). Date of search: 30/06/2010.

Key words	Textword	MeSH terms
Stroke	Stroke$ cerebrovasc$ accident$ Cerebral vasc$ accident$ Brain attack$ Brain ischemia$ Brain ischaemia$ Intracerebral hemorrhage$ Intracerebral Haemorrhage$ Intraparenchymal hemorrhage$ Intraparenchymal haemorrhage$ Subarachnoid hemorrhage$ Subarachnoid haemorrhage$	Stroke/ Intracranial Hemorrhages/ Cerebral Hemorrhage/ Subarachnoid Hemorrhage/ Cerebral Infarction/ Cerebrovascular Disorders/ Brain Ischemia/
Blood pressure	blood pressure hypertens$	Blood Pressure/ Hypertension/
Cohort studies	Cohort longitudinal prospective	Cohort Studies/
China	China$ Chinese Sino$	China/

Table A.3: Diagnostic criteria for stroke pathological types

Stroke Pathological type	Diagnostic criteria	
	Clinical criteria	**Investigations**
Ischaemic stroke	World health organisation clinical criteria for stroke[8] *	Plus at least one of the following: 1. CT or MRI scan which shows ischaemic changes of an age and in a region of the brain compatible with the clinical symptoms and signs, or is normal. The CT scan needs to have been performed within ten days of onset signs/symptoms of stroke. The MRI scan needs to have been performed within 3 months unless appropriate sequences have been used.[†] 2. Necropsy examination which shows ischaemic changes of an age and region compatible with the clinical symptoms and signs, or is normal.
Intracerebral haemorrhage	World health organisation clinical criteria for stroke[8] *	Plus at least one of the following: 1. CT or MRI scan which shows a parenchymal haemorrhage of an age and in a region of the brain compatible with the clinical symptoms and signs.[‡] 2. Necropsy examination which shows a parenchymal haemorrhage of an age and intraparenchymal region compatible with the clinical symptoms and signs.
Subarachnoid haemorrhage	World health organisation clinical criteria for stroke[8] *	Plus at least one of the following: 1. CT or MRI scan indicating blood in the subarachnoid space (eg. in the Sylvian fissure, between the frontal lobes, in the basal cistern or in the cerebral ventricles). 2. Necropsy examination with recent subarachnoid haemorrhage and an aneurysm or arteriovenous malformation. 3. CSF (liquor) bloody (>2,000 rbc per mm^3 from a non-traumatic tap at least 8 hours after onset of symptoms) and: (a) an aneurysm or an arteriovenous malformation found on angiography; (b) xanthochromic (confirmed by bilirubin spectrophotometry) and the possibility of intracerebral haemorrhage has been excluded by necropsy/CT/MRI scan; or (c) xanthochromic (confirmed by bilirubin spectrophotometry) and an appropriate clinical history.[§]

* Or a collection of signs/symptoms indicating brainstem involvement.

† CT scan should be performed within ten days (ideally within seven days) to avoid misclassification of small intracerebral haemorrhages as ischaemic strokes.[124,125] Old haemorrhages (older than 3 months[126]) may be misclassified as ischaemic lesions, or normal, using MRI unless appropriate sequences (gradient echo) are used.

‡ Evidence of haemorrhagic transformation of an infarct should be classified as ischaemic stroke.

§ Subarachnoid haemorrhage can be diagnosed on the basis of a lumbar puncture and appropriate clinical history, although ideally intracerebral haemorrhage should be excluded by CT/MRI scan.

Appendix B: CKB additional results: baseline analyses

Table B.1: Number of participants recruited at baseline and number excluded from analyses, by area

Area	Participants recruited	Participants excluded		Participants included
		History of vascular disease*	Other†	
Urban				
Qingdao	35 509	2 009	169	33 351
Harbin	57 555	7 672	90	49 813
Haikou	29 689	661	76	28 955
Suzhou	53 260	1 017	67	52 177
Liuzhou	50 173	3 423	64	46 690
All urban	226 186	14 782	466	210 986
Rural				
Sichuan	55 687	560	112	55 017
Gansu	50 041	1 342	225	48 489
Henan	63 357	3 000	63	60 300
Zhejiang	57 704	817	101	56 791
Hunan	59 916	2 628	92	57 206
All rural	286 705	8 347	593	277 803
Overall	512 891	23 129	1059	488 789

***** Participants with a self-reported history of stroke/TIA or CHD at baseline.
† Participants with outlying values in key variables (see Table B.2).

Table B.2: Criteria for excluding participants with outlying values in key variables

Variables	Lower limit (excluded if < limit)	Upper limit (excluded if > limit)	Participants outside of limits, n
Original variables:			
1st reading of SBP, mm Hg	80	250	121
2nd reading of SBP, mm Hg	80	250	110
1st reading of DBP, mm Hg	40	150	76
2nd reading of DBP, mm Hg	40	150	60
Standing height, m	1.25	1.9	68
Weight, kg*	29	115	117
Waist circumference, cm	50	125	101
Hip circumference, cm	60	130	123
Derived variables:			
BMI, kg/m^2	14	40	183
Waist-hip ratio	0.6	1.25	171
Difference between 1st and 2nd SBP reading, mm Hg	-25	30	95
Difference between 1st and 2nd DBP reading, mm Hg	-30	35	121
Difference between SBP and DBP in 1st blood pressure reading, mm Hg	10	150	39
Difference between SBP and DBP in 2nd blood pressure reading, mm Hg	10	150	30
Alcohol consumed in typical week, grams	-	2 000	32

* Two participants with missing values for weight were also excluded.

Table B.3: Baseline correlations between blood pressure, adiposity variables, and physical activity in MET hours/day (among 199 825 males and 288 964 females participants)

Pearson partial correlation coefficient x 100, adjusted for area and 5-year age groups.

		DBP	Waist circumference	Hip circumference	Waist-hip ratio	BMI	MET hours/day
SBP	Male:	77	22	17	17	28	3
	Female:	74	21	13	19	22	1
DBP		Male:	23	19	18	28	3
		Female:	13	4	16	13	4
Waist circumference			Male:	80	80	84	10
			Female:	75	77	85	3
Hip circumference				Male:	29	75	13
				Female:	17	77	11
Waist-hip ratio					Male:	60	3
					Female:	53	6
BMI						Male:	3
						Female:	2

Table B.4: Baseline associations of blood pressure with age, for males and females, minimally adjusted (among 488 789 participants)

Means adjusted for education and area.

Age group, years	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Males						
30-39	29427	(6)	125.7	(125.5-125.8)	76.8	(76.7-76.9)
40-44	31633	(6)	127.6	(127.5-127.8)	79.0	(78.9-79.1)
45-49	26695	(5)	129.5	(129.3-129.7)	80.2	(80.0-80.3)
50-54	33629	(7)	131.4	(131.2-131.6)	80.2	(80.1-80.4)
55-59	27232	(6)	134.3	(134.0-134.5)	80.1	(80.0-80.2)
60-64	20103	(4)	137.9	(137.6-138.2)	79.6	(79.5-79.8)
65-69	17033	(3)	140.6	(140.2-140.9)	78.4	(78.2-78.5)
70-79	14073	(3)	142.7	(142.4-143.1)	77.1	(76.9-77.3)
Female						
30-39	47976	(10)	117.7	(117.5-117.8)	73.4	(73.3-73.5)
40-44	51673	(11)	122.3	(122.1-122.4)	75.8	(75.7-75.9)
45-49	40490	(8)	126.8	(126.6-127.0)	77.4	(77.3-77.5)
50-54	50777	(10)	131.0	(130.8-131.2)	78.4	(78.3-78.5)
55-59	38692	(8)	135.0	(134.7-135.2)	78.4	(78.3-78.5)
60-64	25306	(5)	139.2	(138.9-139.5)	77.8	(77.7-77.9)
65-69	19644	(4)	142.4	(142.1-142.7)	76.6	(76.4-76.8)
70-79	14406	(3)	145.2	(144.8-145.6)	75.6	(75.4-75.8)

Table B.5: Baseline associations of blood pressure with measures of adiposity, with adjustment for other adiposity measures (among 488 789 participants)

Means were adjusted for age, sex, education, area and other adiposity measures.*

Adiposity variables, by quintiles	Participants, n	Mean of group at baseline	Mean (95%CI) blood pressure			
			SBP		DBP	
BMI, (kg/m^2)						
14.0 - <20.8	99 697	19	125.1	(124.9-125.2)	74.9	(74.8-75.0)
20.8 - <22.6	98 447	22	128.3	(128.2-128.4)	76.2	(76.2-76.3)
22.6 - <24.3	96 778	23	130.5	(130.3-130.6)	77.5	(77.5-77.6)
24.3 - <26.4	96 958	25	132.8	(132.7-132.9)	78.9	(78.8-79.0)
26.4 – 40.0	96 909	29	136.5	(136.3-136.7)	80.8	(80.7-80.9)
Waist circumference (cm)						
50.0 - <71.6	98 268	67	128.1	(128.0-128.3)	76.5	(76.4-76.6)
71.6 - <77.0	96 418	74	129.3	(129.1-129.4)	76.8	(76.8-76.9)
77.0 - <82.1	100 737	80	130.4	(130.3-130.6)	77.5	(77.4-77.6)
82.1 - <88.2	94 948	85	131.5	(131.4-131.6)	78.2	(78.1-78.2)
88.2 - 125.0	98 418	94	133.6	(133.4-133.7)	79.3	(79.2-79.3)
Hip circumference, (cm						
60.0 - <85.1	99 636	82	130.9	(130.8-131.1)	77.8	(77.7-77.9)
85.1 - <88.8	96 005	87	130.9	(130.8-131.0)	77.7	(77.6-77.8)
88.8 - <92.1	99 090	90	130.5	(130.4-130.6)	77.6	(77.5-77.7)
92.1 - <96.2	95 355	94	130.0	(129.9-130.2)	77.4	(77.4-77.5)
96.2 - 129.0	98 703	101	130.5	(130.4-130.7)	77.7	(77.6-77.8)
Waist-hip ratio (%)						
59.6 - <82.5	107 280	79	128.8	(128.7-128.9)	76.8	(76.7-76.9)
82.5 - <86.5	96 841	85	129.9	(129.7-130.0)	77.2	(77.2-77.3)
86.5 - <89.5	82 227	88	130.6	(130.4-130.7)	77.6	(77.5-77.6)
89.5 - <93.5	95 637	91	131.4	(131.2-131.5)	77.9	(77.9-78.0)
93.5 - 125.4	106 804	98	132.4	(132.2-132.5)	78.6	(78.5-78.7)

* Blood pressure means by quintiles of BMI were further adjusted for hip circumference and waist circumference; means by quintiles of hip circumference were further adjusted for BMI and waist circumference; means by quintiles of waist circumference were further adjusted for BMI and waist circumference; and means by quintiles of waist-hip ratio were further adjusted for BMI, hip circumference and waist circumference.

Table B.6: Baseline associations of blood pressure with alcohol intake, with adjustment for smoking (among 488 789 participants)

Means adjusted for age, sex, education, area and smoking.

Alcohol intake	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Never	223 364	(46)	131.0	(130.9-131.1)	77.6	(77.6-77.7)
Ex-weekly	7 922	(2)	131.3	(130.9-131.7)	78.4	(78.2-78.7)
Reduced-intake	10 578	(2)	131.1	(130.7-131.5)	78.3	(78.1-78.5)
Occasional	156 339	(32)	128.9	(128.8-129.0)	76.7	(76.7-76.8)
Monthly drinker	16 902	(3)	129.6	(129.4-129.9)	77.2	(77.0-77.3)
Weekly: <70g/wk	14 163	(3)	130.2	(129.9-130.6)	77.8	(77.6-78.0)
Weekly: <140g/wk	14 429	(3)	131.7	(131.3-132.0)	78.7	(78.5-78.9)
Weekly: <210g/wk	9 144	(2)	133.3	(132.9-133.7)	79.5	(79.3-79.7)
Weekly: >210g/wk	35 948	(7)	134.7	(134.5-135.0)	80.5	(80.4-80.6)

Table B.7: Baseline associations of blood pressure with measures of adiposity, minimally adjusted (among 488 789 participants)

Means were adjusted for age, sex, education and area.

Adiposity variables by quintiles	Participants, n	Mean of group at baseline	Mean (95%CI) blood pressure			
			SBP		DBP	
BMI, (kg/m^2)						
14.0 - <20.8	99 697	19	123.3	(123.2-123.4)	73.9	(73.8-74.0)
20.8 - <22.6	98 447	22	127.4	(127.2-127.5)	75.7	(75.6-75.7)
22.6 - <24.3	96 778	23	130.3	(130.2-130.4)	77.4	(77.4-77.5)
24.3 - <26.4	96 958	25	133.6	(133.5-133.7)	79.4	(79.3-79.4)
26.4 – 40.0	96 909	29	138.6	(138.5-138.7)	82.0	(81.9-82.0)
Waist circumference (cm)						
50.0 - <71.6	98 268	67	124.7	(124.5-124.8)	74.5	(74.4-74.6)
71.6 - <77.0	96 418	74	127.8	(127.7-127.9)	76.0	(76.0-76.1)
77.0 - <82.1	100 737	80	130.3	(130.2-130.4)	77.4	(77.4-77.5)
82.1 - <88.2	94 948	85	132.8	(132.7-133.0)	78.9	(78.9-79.0)
88.2 - 125.0	98 418	94	137.4	(137.3-137.5)	81.3	(81.3-81.4)
Hip circumference, (cm)						
60.0 - <85.1	99 636	82	124.0	(123.9-124.2)	74.3	(74.2-74.3)
85.1 - <88.8	96 005	87	127.2	(127.1-127.3)	75.7	(75.6-75.7)
88.8 - <92.1	99 090	90	130.3	(130.2-130.4)	77.4	(77.3-77.5)
92.1 - <96.2	95 355	94	133.4	(133.2-133.5)	79.2	(79.1-79.3)
96.2 - 129.0	98 703	101	138.0	(137.9-138.2)	81.7	(81.6-81.8)
Waist-hip ratio (%)						
59.6 - <82.5	107 280	79	125.1	(125.0-125.2)	74.8	(74.8-74.9)
82.5 - <86.5	96 841	85	128.4	(128.2-128.5)	76.4	(76.4-76.5)
86.5 - <89.5	82 227	88	130.5	(130.4-130.7)	77.5	(77.5-77.6)
89.5 - <93.5	95 637	91	132.9	(132.8-133.0)	78.8	(78.7-78.8)
93.5 - 125.4	106 804	98	136.1	(136.0-136.2)	80.6	(80.6-80.7)

Table B.8: Baseline associations of blood pressure with alcohol intake and month of baseline survey, minimally adjusted (among 488 789 participants)

Means adjusted for age, sex, education and area.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Alcohol intake						
Never	223 364	(46)	130.8	(130.8-130.9)	77.6	(77.5-77.6)
Ex-weekly	7 922	(2)	131.3	(130.9-131.7)	78.4	(78.1-78.6)
Reduced-intake	10 578	(2)	131.3	(130.9-131.7)	78.4	(78.2-78.6)
Occasional	156 339	(32)	128.8	(128.7-128.9)	76.7	(76.7-76.8)
Monthly drinker	16 902	(3)	129.8	(129.5-130.1)	77.3	(77.1-77.4)
Weekly: <70g/wk	14 163	(3)	130.4	(130.1-130.7)	77.9	(77.7-78.1)
Weekly: <140g/wk	14 429	(3)	131.9	(131.6-132.3)	78.8	(78.6-79.0)
Weekly: <210g/wk	9 144	(2)	133.7	(133.3-134.1)	79.7	(79.5-80.0)
Weekly: >210g/wk	35 948	(7)	135.2	(135.0-135.4)	80.8	(80.7-80.9)
Month of baseline survey						
January/February	46 960	(10)	135.6	(135.4-135.8)	79.1	(79.0-79.2)
March	50 859	(10)	133.7	(133.6-133.9)	78.4	(78.3-78.5)
April	49 798	(10)	130.9	(130.7-131.1)	77.4	(77.3-77.5)
May	46 294	(9)	128.5	(128.3-128.7)	76.8	(76.7-76.9)
June	44 449	(9)	126.8	(126.6-127.0)	76.2	(76.1-76.3)
July	37 155	(8)	124.7	(124.5-124.9)	75.5	(75.4-75.6)
August	38 296	(8)	124.7	(124.5-124.9)	75.3	(75.2-75.4)
September	36 215	(7)	127.5	(127.3-127.7)	77.0	(76.9-77.1)
October	36 550	(7)	131.3	(131.1-131.5)	78.4	(78.3-78.5)
November	50 490	(10)	133.5	(133.4-133.7)	79.2	(79.1-79.3)
December	51 723	(11)	135.1	(135.0-135.3)	79.4	(79.3-79.5)

Table B.9: Baseline associations of blood pressure with other selected variables, minimally adjusted (among 488 789 participants)

Means were adjusted for age, sex, education and area.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Smoking						
Never	30 3127	(62)	131.3	(131.2-131.4)	78.0	(77.9-78.0)
Occasional	27 978	(6)	130.3	(130.1-130.5)	77.6	(77.5-77.7)
Ex-regular	27 236	(6)	130.7	(130.5-131.0)	78.3	(78.2-78.4)
Current	130 448	(27)	129.0	(128.8-129.1)	76.7	(76.6-76.8)
History of diabetes						
No	466 144	(95)	130.2	(130.2-130.3)	77.6	(77.5-77.6)
Yes	22 645	(5)	137.9	(137.6-138.1)	79.2	(79.1-79.3)
Taking blood pressure-lowering medication						
No	471 207	(96)	129.9	(129.9-130.0)	77.3	(77.3-77.4)
Yes	17 582	(4)	148.0	(147.8-148.3)	85.5	(85.4-85.7)

Table B.10: Baseline associations of blood pressure with measures of adiposity, extensively adjusted (among 488 789 participants)

Means were adjusted for age, sex, education, area, other measures of adiposity,* and other selected variables (MET hours/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, smoking, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

Adiposity variables, by quintiles	Participants, n	Mean of group at baseline	Mean (95%CI) blood pressure			
			SBP		DBP	
BMI, (kg/m^2)						
14.0 - <20.8	99 697	19	125.4	(125.3-125.6)	75.0	(74.9-75.1)
20.8 - <22.6	98 447	22	128.4	(128.2-128.5)	76.3	(76.2-76.3)
22.6 - <24.3	96 778	23	130.4	(130.3-130.5)	77.5	(77.4-77.6)
24.3 - <26.4	96 958	25	132.6	(132.5-132.7)	78.8	(78.8-78.9)
26.4 - 40.0	96 909	29	136.3	(136.1-136.4)	80.7	(80.6-80.8)
Waist circumference (cm)						
50.0 - <71.6	98 268	67	127.4	(127.3-127.6)	76.2	(76.2-76.3)
71.6 - <77.0	96 418	74	128.9	(128.8-129.0)	76.7	(76.6-76.8)
77.0 - <82.1	100 737	80	130.4	(130.3-130.5)	77.5	(77.4-77.5)
82.1 - <88.2	94 948	85	131.8	(131.7-132.0)	78.3	(78.2-78.3)
88.2 - 125.0	98 418	94	134.4	(134.2-134.6)	79.5	(79.4-79.6)
Hip circumference, (cm						
60.0 - <85.1	99 636	82	131.4	(131.2-131.5)	77.9	(77.8-78.0)
85.1 - <88.8	96 005	87	131.1	(131.0-131.3)	77.8	(77.7-77.9)
88.8 - <92.1	99 090	90	130.6	(130.5-130.7)	77.6	(77.6-77.7)
92.1 - <96.2	95 355	94	129.9	(129.8-130.0)	77.4	(77.3-77.5)
96.2 - 129.0	98 703	101	129.9	(129.7-130.0)	77.5	(77.4-77.6)
Waist-hip ratio (%)						
0.60 - <0.83	107 280	79	128.1	(128.0-128.3)	76.6	(76.5-76.7)
0.83 - <0.87	96 841	85	129.7	(129.5-129.8)	77.2	(77.1-77.3)
0.87 - <0.90	82 227	88	130.6	(130.5-130.7)	77.6	(77.5-77.7)
0.90 - <0.94	95 637	91	131.6	(131.5-131.7)	78.0	(78.0-78.1)
0.94 - 1.25	106 804	98	133.0	(132.8-133.1)	78.8	(78.7-78.9)

* Blood pressure means by quintiles of BMI were further adjusted for hip circumference and waist circumference; means by quintiles of hip circumference were further adjusted for BMI and waist circumference; means by quintiles of waist circumference were further adjusted for BMI and waist circumference; and means by quintiles of waist-hip ratio were further adjusted for BMI, hip circumference and waist circumference.

Table B.11: Baseline associations of blood pressure with dietary variables, extensively adjusted (among 488 789 participants)

Means were adjusted for age, sex, education, area and other selected variables (BMI, hip circumference, waist circumference, MET hours/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, smoking, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Fresh fruit consumption						
Never/rarely	30 786	(6)	132.3	(132.1-132.5)	78.4	(78.3-78.5)
Monthly	167 593	(34)	131.2	(131.1-131.3)	77.8	(77.8-77.9)
1-3 days/wk	154 896	(32)	130.6	(130.5-130.6)	77.6	(77.6-77.7)
4-6 days/wk	46 124	(9)	129.9	(129.7-130.0)	77.4	(77.3-77.5)
Daily	89 390	(18)	129.2	(129.0-129.3)	77.1	(77.0-77.2)
Fresh vegetable consumption						
Not daily	25 904	(5)	130.9	(130.6-131.1)	78.0	(77.8-78.1)
Daily	462 885	(95)	130.6	(130.5-130.6)	77.6	(77.6-77.7)
Tea intake						
Never/rarely	171 074	(35)	130.3	(130.2-130.4)	77.4	(77.3-77.5)
Occasional	134 405	(27)	130.3	(130.2-130.4)	77.5	(77.4-77.6)
Monthly	19 086	(4)	130.5	(130.2-130.7)	77.6	(77.5-77.8)
Weekly/daily	164 224	(34)	131.1	(131.0-131.2)	78.0	(78.0-78.1)

Table B.12: Baseline associations of blood pressure with alcohol intake and month of baseline survey, extensively adjusted (among 488 789 participants)

Means were adjusted for age, sex, education, area and other selected variables (BMI, hip circumference, waist circumference, MET hrs/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, smoking, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Alcohol intake						
Never	223 364	(46)	130.9	(130.8-131.0)	77.6	(77.6-77.7)
Ex-weekly	7 922	(2)	131.0	(130.6-131.4)	78.3	(78.0-78.5)
Reduced-intake	10 578	(2)	130.2	(129.9-130.6)	77.8	(77.6-78.0)
Occasional	156 339	(32)	129.2	(129.1-129.3)	76.8	(76.8-76.9)
Monthly drinker	16 902	(3)	129.8	(129.5-130.0)	77.2	(77.1-77.4)
Weekly: <70g/wk	14 163	(3)	130.1	(129.8-130.4)	77.7	(77.5-77.9)
Weekly: <140g/wk	14 429	(3)	131.4	(131.1-131.7)	78.5	(78.4-78.7)
Weekly: <210g/wk	9 144	(2)	132.7	(132.3-133.1)	79.3	(79.0-79.5)
Weekly: >210g/wk	35 948	(7)	134.3	(134.1-134.5)	80.4	(80.3-80.5)
Month of baseline survey						
January/February	46 960	(10)	135.7	(135.6-135.9)	79.2	(79.1-79.3)
March	50 859	(10)	133.5	(133.3-133.6)	78.2	(78.1-78.3)
April	49 798	(10)	130.7	(130.5-130.9)	77.3	(77.2-77.4)
May	46 294	(9)	128.3	(128.2-128.5)	76.8	(76.7-76.9)
June	44 449	(9)	126.7	(126.6-126.9)	76.2	(76.1-76.3)
July	37 155	(8)	124.6	(124.4-124.8)	75.5	(75.4-75.6)
August	38 296	(8)	124.8	(124.6-125.0)	75.4	(75.3-75.5)
September	36 215	(7)	127.5	(127.3-127.7)	77.0	(76.9-77.1)
October	36 550	(7)	131.4	(131.2-131.6)	78.5	(78.4-78.6)
November	50 490	(10)	133.7	(133.6-133.9)	79.3	(79.2-79.4)
December	51 723	(11)	135.4	(135.2-135.5)	79.5	(79.4-79.6)

Table B.13: Baseline associations of blood pressure with other variables, extensively adjusted (among 488 789 participants)

Means were adjusted for age, sex, education, area and other selected variables (BMI, hip circumference, waist circumference, MET hrs/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, smoking, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

	Participants, n (%)		Mean (95%CI) baseline blood pressure			
			SBP		DBP	
Physical activity quintiles (MET hours/day)*						
0.0 - <14.4	97 774	(20)	131.2	(131.0-131.3)	78.2	(78.1-78.2)
14.4 - <19.7	97 716	(20)	131.1	(130.9-131.2)	78.0	(77.9-78.0)
19.7 - <26.8	97 803	(20)	130.4	(130.3-130.5)	77.7	(77.6-77.7)
26.8 - <38.0	97 784	(20)	130.2	(130.1-130.3)	77.3	(77.3-77.4)
38.0 - 139.5	97 712	(20)	130.0	(129.9-130.2)	77.1	(77.0-77.1)
Smoking						
Never	303 127	(62)	131.3	(131.2-131.4)	78.0	(78.0-78.1)
Occasional	27 978	(6)	130.2	(130.0-130.5)	77.6	(77.4-77.7)
Ex-regular	27 236	(6)	129.7	(129.5-129.9)	77.7	(77.5-77.8)
Current	130 448	(27)	129.1	(129.0-129.3)	76.7	(76.6-76.8)
History of diabetes						
No	466 144	(95)	130.3	(130.3-130.4)	77.6	(77.6-77.7)
Yes	22 645	(5)	135.6	(135.4-135.9)	78.0	(77.8-78.1)
Taking blood pressure lowering medication†						
No	471 207	(96)	130.0	(130.0-130.1)	77.4	(77.4-77.4)
Yes	17 582	(4)	144.9	(144.6-145.2)	84.0	(83.8-84.1)

* Mean of quintiles: 10.6, 17.0, 22.9, 32.1, 47.6 MET hours/day.
† Adjusted for all other selected variables.

Appendix C: CKB additional results: incident stroke events

Table C.1: Number of incident stroke events, by age, by sex and by area (among 488 789 participants)

	Person-years at risk (x10^3)	Stroke events, n				
		Ischaemic stroke	Intracerebral haemorrhage	Subarachnoid haemorrhage	Unspecified	Total
Age at risk (years)						
30-39	205	21	14	7	3	45
40-49	774	408	204	20	18	650
50-59	797	1 562	528	35	79	2 204
60-69	480	2 056	690	46	106	2 898
70-79	222	1 964	752	22	115	2 853
80-87	3	32	9	0	1	42
Sex						
Male	1 003	2 968	1 227	61	171	4 427
Female	1 475	3 075	970	69	151	4 265
Area						
Qingdao	171	11	21	2	0	34
Harbin	245	1 568	126	13	28	1 735
Haikou	136	262	18	1	6	287
Suzhou	262	317	84	6	65	472
Liuzhou	225	695	90	16	16	817
Sichuan	282	180	371	16	39	606
Gansu	250	176	425	1	18	620
Henan	309	1 527	349	33	48	1 957
Zhejiang	303	663	219	14	27	923
Hunan	295	644	494	28	75	1 241
Overall	2 478	6 043	2 197	130	322	8 692

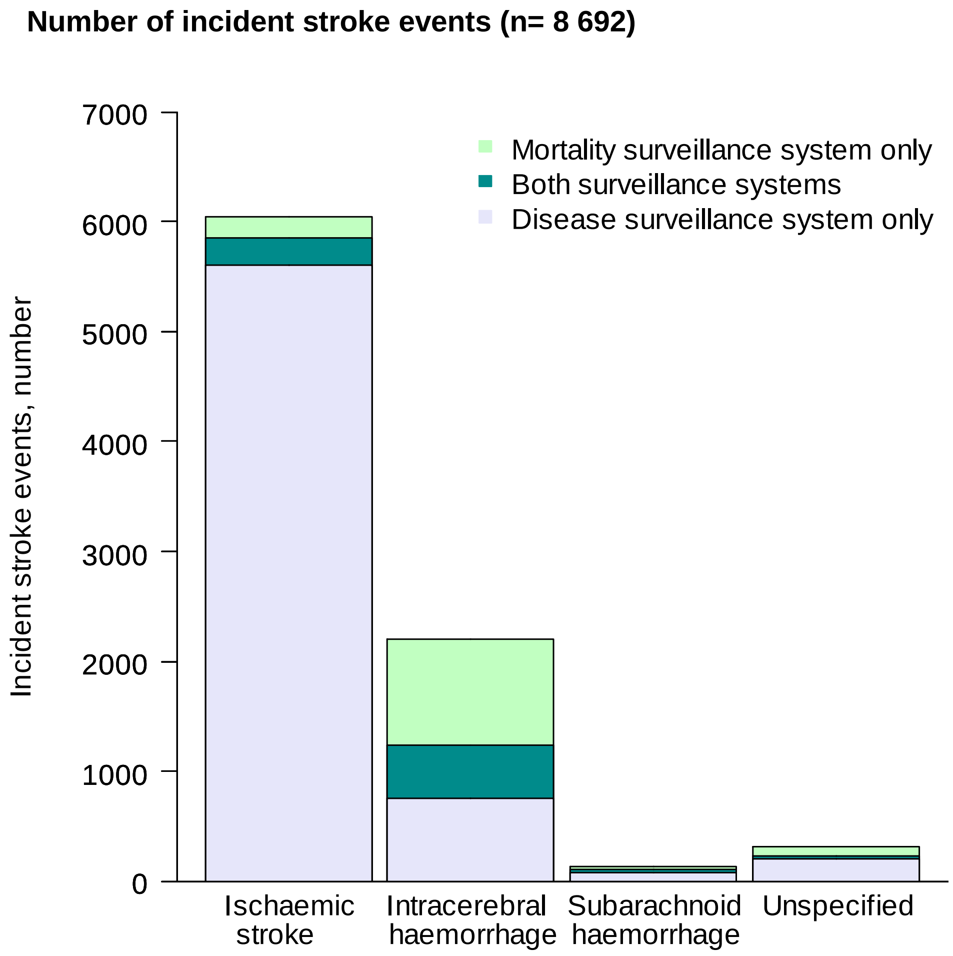
Table C.2: Number of incident stroke events reported by the disease surveillance system, by age, by sex and by area (among 488 789 participants)

	Person-years at risk ($x10^3$)	Stroke events, n				
		Ischaemic stroke	Intracerebral haemorrhage	Subarachnoid haemorrhage	Unspecified	Total
Age at risk (years)						
30-39	205	21	7	7	3	38
40-49	774	401	137	18	15	571
50-59	797	1 535	340	29	69	1 973
60-69	480	2 009	376	37	75	2 497
70-79	222	1 861	375	18	71	2 325
80-87	3	29	5	0	1	35
Sex						
Male	1 003	2 860	696	57	125	3 738
Female	1 475	2 996	544	52	109	3 701
Area						
Qingdao	171	0	0	0	0	0
Harbin	245	1 552	74	7	27	1 660
Haikou	136	258	11	1	6	276
Suzhou	262	300	54	6	13	373
Liuzhou	225	669	55	13	15	752
Sichuan	282	175	276	10	27	488
Gansu	250	129	81	1	11	222
Henan	309	1 500	319	33	48	1 900
Zhejiang	303	655	188	14	21	878
Hunan	295	618	182	24	66	890
Overall	2 478	5 856	1 240	109	234	7 439

Table C.3: Number of stroke deaths reported by the mortality surveillance system, by age, by sex and by area (among 488 789 participants)

	Person-years at risk ($x10^3$)	Stroke deaths, n				
		Ischaemic stroke	Intracerebral haemorrhage	Subarachnoid haemorrhage	Unspecified	Total
Age at risk (years)						
30-39	205	0	7	0	0	7
40-49	775	12	111	2	3	128
50-59	801	44	292	7	16	359
60-69	485	108	506	17	38	669
70-79	227	202	593	10	59	864
80-87	3	5	7	0	0	12
Sex						
Male	1 011	210	868	11	62	1 151
Female	1 483	161	648	25	54	888
Area						
Qingdao	171	11	21	2	0	34
Harbin	249	26	64	8	1	99
Haikou	137	5	7	0	0	12
Suzhou	262	27	45	0	59	131
Liuzhou	227	35	49	6	2	92
Sichuan	282	19	282	7	25	333
Gansu	250	52	368	0	8	428
Henan	313	99	190	6	0	295
Zhejiang	305	45	110	1	12	168
Hunan	297	52	380	6	9	447
Overall	2 494	371	1 516	36	116	2 039

Figure C.1: Number and proportion of incident stroke events reported by each surveillance system, by stroke pathological type (among 488 789 participants)



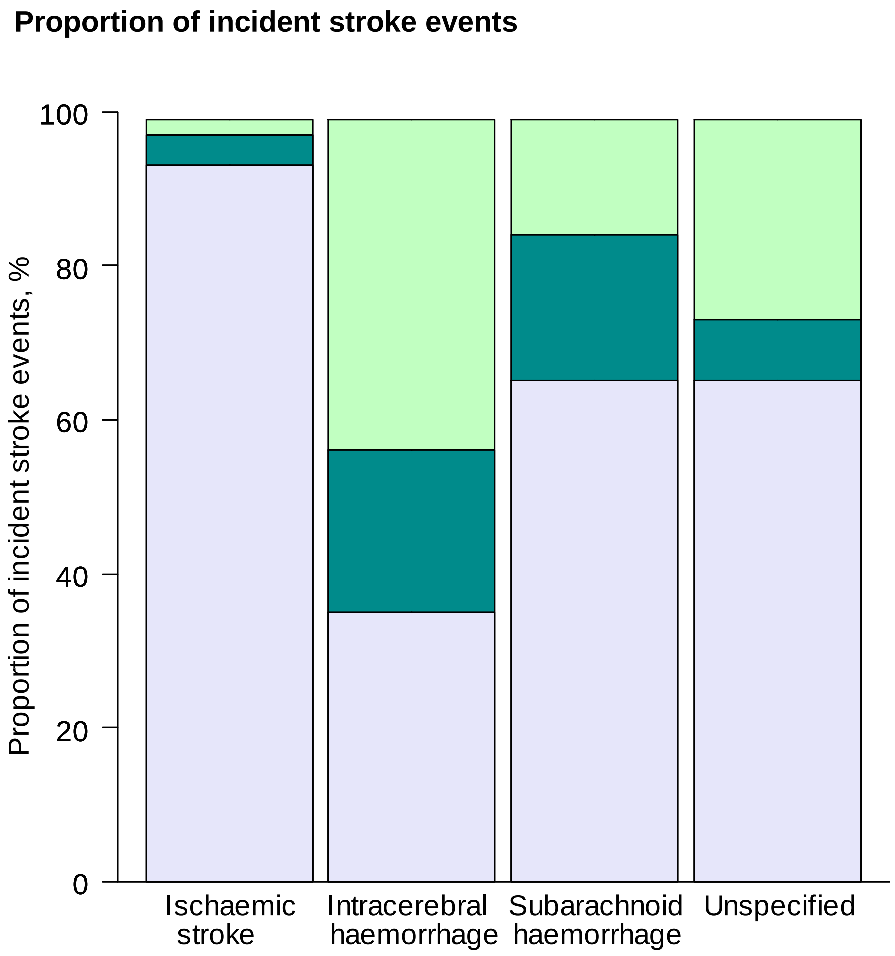


Table C.4: Number of incident events of each stroke pathological type, by age and sex (among 488 789 participants)

Age group at risk, by sex	Person-years at risk (x10^3)	Incident stroke events, n (crude rate per 100 000 person-years)									
		Ischaemic stroke		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified		Total	
Male, years											
33-40	77	15	(19)	4	(5)	4	(5)	2	(3)	25	(32)
40-49	295	212	(72)	104	(35)	10	(3)	10	(3)	336	(114)
50-59	317	694	(219)	259	(82)	15	(5)	40	(13)	1 008	(318)
60-69	207	989	(478)	404	(195)	23	(11)	51	(25)	1 467	(709)
70-79	105	1 044	(994)	453	(431)	9	(9)	67	(64)	1 573	(1 498)
80-87	1	14	(1 400)	3	(300)	0	(0)	1	(100)	18	(1 800)
All (40-79)*	1 003	2 968	(441)	1 227	(186)	61	(7)	171	(26)	4 427	(660)
Female, years											
33-40	127	6	(5)	10	(8)	3	(2)	1	(1)	20	(16)
40-49	478	196	(41)	100	(21)	10	(2)	8	(2)	314	(66)
50-59	480	868	(181)	269	(56)	20	(4)	39	(8)	1 196	(249)
60-69	272	1 067	(392)	286	(105)	23	(8)	55	(20)	1 431	(526)
70-79	117	920	(786)	299	(256)	13	(11)	48	(41)	1 280	(1 094)
80-87	2	18	(900)	6	(300)	0	(0)	0	(0)	24	(1 200)
All (40-79)*	1 475	3 075	(350)	970	(109)	69	(6)	151	(18)	4 265	(484)
Overall (40-79)*	2 478	6 043	(395)	2 197	(148)	130	(7)	322	(22)	8 692	(572)

* Age-standardised by taking the unweighted average of the component ten-year incidence rates (overall: average of age-standardised incidences of both sexes)

Table C.5: Number of incident stroke events of each pathological type known to have been imaged by CT/MRI scan, by age and sex (among 488 789 participants)

		Incident stroke events imaged by CT/MRI scan, n (% of all incident stroke events)									
Age group at risk, by sex	Person-years at risk (x10^3)	Ischaemic stroke		Intracerebral haemorrhage		Subarachnoid haemorrhage		Unspecified		Total	
Male, years											
33-40	77	12	(80)	1	(25)	4	(100)	1	(50)	18	(72)
40-49	295	163	(76)	58	(57)	6	(60)	6	(60)	233	(69)
50-59	317	556	(80)	145	(56)	11	(73)	12	(30)	724	(72)
60-69	207	742	(75)	191	(47)	19	(83)	24	(47)	976	(67)
70-79	105	785	(75)	214	(47)	7	(78)	28	(42)	1034	(66)
80-87	1	8	(57)	1	(33)	0	(-)	0	(0)	9	(50)
All (33-87)	1 003	2266	(76)	610	(50)	47	(77)	71	(42)	2994	(68)
Female, years											
33-40	127	6	(100)	6	(60)	3	(100)	0	(0)	15	(75)
40-49	478	155	(79)	58	(58)	6	(60)	4	(50)	223	(71)
50-59	480	657	(76)	160	(59)	14	(70)	12	(31)	843	(70)
60-69	272	801	(75)	128	(45)	14	(61)	15	(27)	958	(67)
70-79	117	654	(71)	117	(39)	8	(62)	13	(27)	792	(62)
80-87	2	17	(94)	2	(33)	0	(-)	0	(-)	19	(79)
All (33-87)	1 475	2290	(74)	471	(49)	45	(65)	44	(29)	2850	(67)
Overall	2 478	4555	(75)	1081	(49)	92	(71)	115	(36)	5844	(67)

'-' = not calculable

Table C.6: Adjudication sub-study: comparison of CKB data diagnoses and the adjudicated diagnoses in 902 'matched' stroke events

Excludes 120 events with a different discharge diagnosis in the medical notes to the CKB data.

	Adjudicated diagnosis, number of events (% total)									
	Stroke pathological type			Equivocal[†]				Not stroke		
CKB study diagnosis	Ischaemic stroke	Intracerebral haemorrhage	SAH	Cerebral infarction CT/MRI	Unspecified stroke pathological type	Old stroke	Insufficient information	TIA	Other	Total
Ischaemic stroke	330 (45)	2 (0)	0 (0)	293 (40)	19 (3)	35 (5)	46 (6)	3 (<1)	9 (1)	737
Intracerebral haemorrhage	0 (0)	112 (97)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	1 (1)	115
Subarachnoid haemorrhage	0 (0)	0 (0)	11 (79)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (21)	14
Unspecified stroke type	2 (6)	0 (0)	0 (0)	9 (25)	0 (0)	0 (0)	20 (56)	3 (8)	2 (6)	36

* The positive predictive value of CKB study diagnosis for stroke pathological type.
[†] Insufficient evidence to verify or refute diagnosis of the stroke pathological type. Cerebral infarction CT/MRI: evidence of cerebral infarction from CT/MRI report without sufficient clinical evidence of signs/symptoms of stroke documented during admission. Unspecified stroke type: evidence of signs/symptoms of stroke without sufficient evidence from CT/MRI to diagnose pathological type. Old stroke: notes report old stroke without sufficient evidence of event to diagnose stroke or sufficient evidence from CT/MRI scan. Insufficient information: insufficient clinical information to allow adjudication.
SAH = subarachnoid haemorrhage.
TIA = transient ischaemic attack.

Table C.7: Adjudication sub-study: comparison of CKB data diagnoses and adjudicated diagnoses, restricted to events used in subsequent prospective analyses (among 416 ischaemic stroke events)

	Adjudicated diagnosis, number of events (% total)									
	Stroke pathological type			Equivocal[†]				Not stroke		
CKB study diagnosis	Ischaemic stroke	Intracerebral haemorrhage	SAH	Cerebral infarction CT/MRI	Unspecified stroke pathological type	Old stroke	Insufficient information	TIA	Other	Total
Ischaemic stroke	125 (37)*	5 (1)	0 (0)	157 (46)	3 (1)	20 (6)	16 (5)	1 (<1)	13 (4)	340
Intracerebral haemorrhage	0 (0)	48 (81)*	2 (3)	1 (2)	2 (3)	1 (2)	2 (3)	0 (0)	3 (5)	59
Subarachnoid haemorrhage	0 (0)	1 (9)	8 (73)*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (18)	11
Unspecified stroke type	2 (33)	1 (17)	0 (0)	2 (33)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	6

* The positive predictive value of CKB study diagnosis for stroke pathological type.
[†] Insufficient evidence to verify or refute diagnosis of the stroke pathological type. Cerebral infarction CT/MRI: evidence of cerebral infarction from CT/MRI report without sufficient clinical evidence of signs/symptoms of stroke documented during admission. Unspecified stroke type: evidence of signs/symptoms of stroke without sufficient evidence from CT/MRI to diagnose pathological type. Old stroke: notes report old stroke without sufficient evidence of event to diagnose stroke or sufficient evidence from CT/MRI scan. Insufficient information: insufficient clinical information to allow adjudication.
SAH = subarachnoid haemorrhage.
TIA = transient ischaemic attack.

Table C.8: Adjudication sub-study: positive predictive value (PPV) of ischaemic stroke,* by surveillance system, hospital tier, area, age and sex; restricted to events used in subsequent prospective analyses (among 416 ischaemic stroke events)

	Adjudicated diagnosis					
	Ischaemic stroke (A)		Cerebral infarction CT/MRI † (B)		Cerebral infarction (A+B)	
	PPV, % (95%CI)		PPV, % (95%CI)		PPV, % (95%CI)	
Hospital tier						
Primary	40	(31-50)	46	(37-56)	86	(78-92)
Secondary	38	(29-48)	41	(32-51)	79	(71-86)
Tertiary	33	(26-41)	50	(42-58)	83	(76-88)
Area‡						
Harbin (U)	23	(14-35)	67	(55-78)	90	(80-95)
Haikou (U)	26	(16-38)	43	(31-56)	69	(56-79)
Suzhou (U)	50	(31-69)	38	(21-57)	88	(69-96)
Liuzhou (U)	47	(31-64)	47	(31-64)	94	(80-98)
Sichuan (R)	34	(20-53)	55	(38-72)	90	(74-96)
Gansu (R)§	-		-		-	
Henan (R)	44	(32-57)	39	(28-52)	83	(72-91)
Zhejiang (R)	50	(34-66)	32	(19-49)	82	(66-92)
Hunan (R)	36	(23-51)	40	(27-56)	76	(61-87)
Age at risk (years)						
40-49	54	(38-69)	43	(29-59)	97	(86-100)
50-59	31	(23-40)	50	(41-59)	81	(72-87)
60-69	38	(30-47)	45	(37-54)	83	(75-89)
70-79	34	(24-45)	45	(35-57)	79	(69-87)
Sex						
Male	38	(31-45)	46	(38-53)	83	(77-88)
female	36	(29-43)	47	(40-54)	83	(76-88)
Overall	37	(32-42)	46	(41-51)	83	(79-87)

* Percentage of CKB study diagnoses of ischaemic stroke in the adjudication sub-study, adjudicated as: ischaemic stroke (A); Cerebral infarction CT/MRI (B); or cerebral infarction (i.e. all events with CT/MRI evidence of cerebral infarction [A+B]).

† Evidence of cerebral infarct from CT/MRI report without sufficient clinical evidence of signs/symptoms of stroke documented during admission.

‡ (U)=urban area, (R)=rural area.

§ There was one event selected for Gansu and it was adjudicated as ischaemic stroke.

Table C.9: Adjudication sub-study: comparison of CKB data diagnoses and the adjudicated diagnoses in 362 stroke events known to have been imaged by CT/MRI scan

Analysis restricted to stroke events used in subsequent prospective analyses. Excludes 48 events with a different discharge diagnosis in the medical notes to the CKB study.

	Adjudicated diagnosis, number of events (% total)																		
	Stroke pathological type						**Equivocal[†]**								**Not stroke**				
CKB study diagnosis	**Ischaemic stroke**		**Intracerebral haemorrhage**		**SAH**		**Cerebral infarction CT/MRI**		**Unspecified stroke pathological type**		**Old stroke**		**Insufficient information**		**TIA**		**Other**		**Total**
Ischaemic stroke	123	(39)	1	(0)	0	(0)	152	(48)	3	(1)	17	(5)	15	(5)	1	(<1)	2	(1)	314
Intracerebral haemorrhage	0	(0)	45	(98)	0	(0)	0	(0)	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)	46
Subarachnoid haemorrhage	0	(0)	0	(0)	6	(75)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	2	(25)	8
Unspecified stroke type	0	(-)	0	(-)	0	(-)	0	(-)	0	(-)	0	(-)	0	(-)	0	(-)	0	(-)	0

* The positive predictive value of CKB study diagnosis for stroke pathological type.
[†] Insufficient evidence to verify or refute diagnosis of the stroke pathological type. Cerebral infarction CT/MRI: evidence of cerebral infarction from CT/MRI report without sufficient clinical evidence of signs/symptoms of stroke documented during admission. Unspecified stroke type: evidence of signs/symptoms of stroke without sufficient evidence from CT/MRI to diagnose pathological type. Old stroke: notes report old stroke without sufficient evidence of event to diagnose stroke or sufficient evidence from CT/MRI scan. Insufficient information: insufficient clinical information to allow adjudication.
SAH = subarachnoid haemorrhage.
TIA = transient ischaemic attack.
'-' = not calculable.

Appendix D: CKB additional results: prospective analyses (I)

Table D.1: Associations of stroke incidence with age, sex, education and area, by main stroke pathological types (among 455 438 participants)

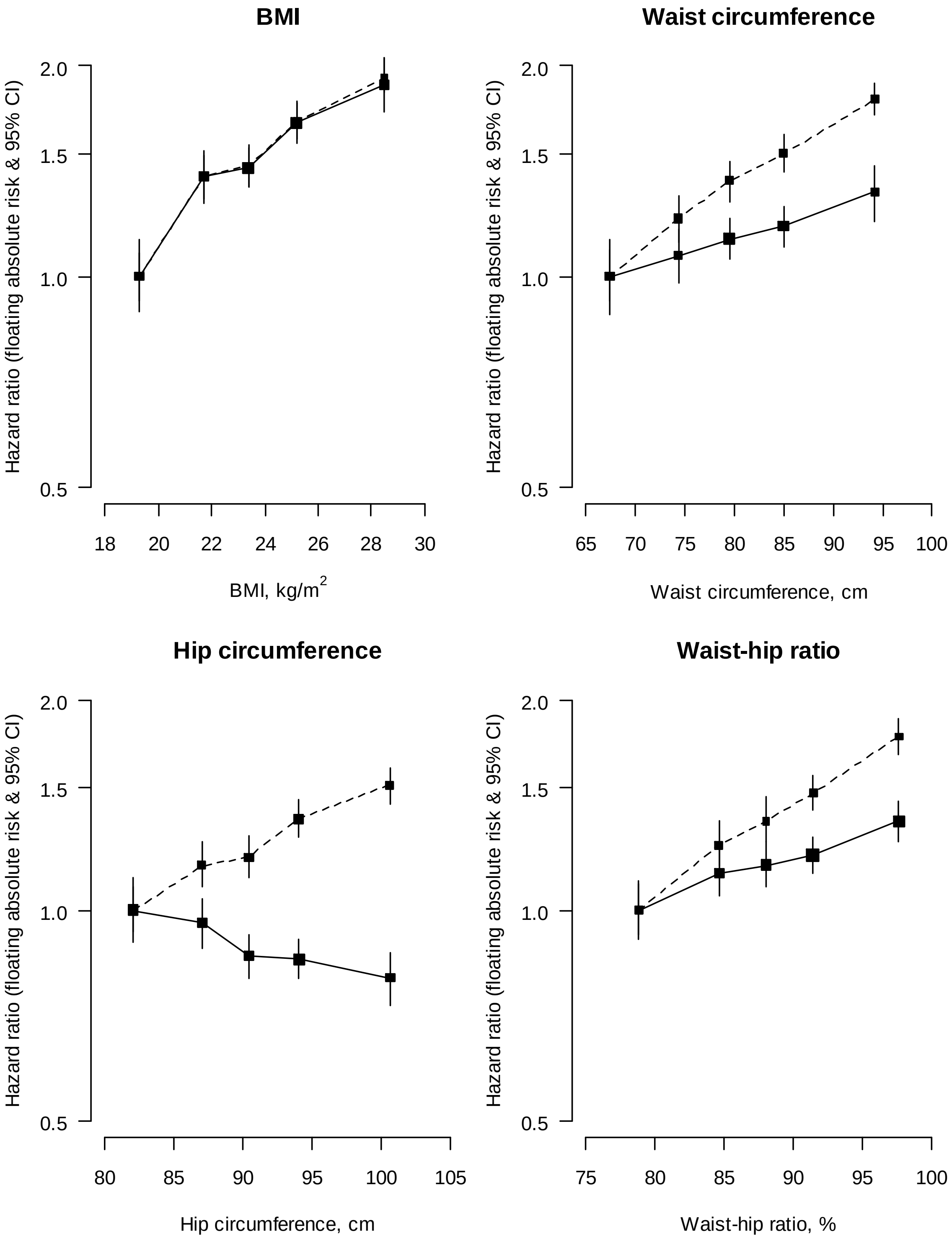
Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education and area (where appropriate)

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	HR	(95%CI)	Events	HR	(95%CI)
Age at baseline, years						
40-49	542	1.00	(0.91-1.09)	171	1.00	(0.85-1.18)
50-59	1 396	2.68	(2.54-2.83)	320	1.55	(1.39-1.73)
60-69	1 620	5.72	(5.45-6.00)	355	3.11	(2.81-3.45)
70-79	901	8.96	(8.35-9.62)	210	5.61	(4.85-6.49)
Sex						
Male	2 246	1.00	(-)	608	1.00	(-)
Female	2 267	0.76	(0.71-0.80)	463	0.56	(0.49-0.64)
Educational level						
No formal	1 029	1.00	(0.92-1.08)	317	1.00	(0.87-1.15)
Primary school	1 640	0.96	(0.91-1.01)	505	0.94	(0.86-1.03)
Middle school	1 005	0.94	(0.88-1.00)	169	0.71	(0.60-0.84)
High school	546	0.85	(0.78-0.93)	61	0.52	(0.40-0.69)
Tech./Coll./Uni.	293	0.77	(0.68-0.88)	19	0.50	(0.31-0.80)
Area*						
Harbin (U)	1 305	3.08	(2.87-3.29)	63	0.56	(0.43-0.74)
Haikou (U)	136	0.51	(0.43-0.60)	8	0.11	(0.05-0.21)
Suzhou (U)	132	0.27	(0.23-0.32)	33	0.21	(0.15-0.30)
Liuzhou (U)	297	0.68	(0.61-0.77)	30	0.25	(0.18-0.37)
Sichuan (R)	156	0.32	(0.27-0.37)	257	1.67	(1.47-1.88)
Gansu (R)	112	0.30	(0.25-0.36)	68	0.55	(0.43-0.70)
Henan (R)	1 320	2.68	(2.54-2.83)	288	1.87	(1.67-2.10)
Zhejiang (R)	523	0.91	(0.83-0.99)	155	0.81	(0.69-0.96)
Hunan (R)	532	1.00	(0.92-1.09)	169	1.00	(0.86-1.17)

* (U)=urban area, (R)=rural area.
'-' = not calculable.

Figure D.1: Associations of cerebral infarction (4 513 events) with measures of adiposity at baseline (among 455 438 participants)

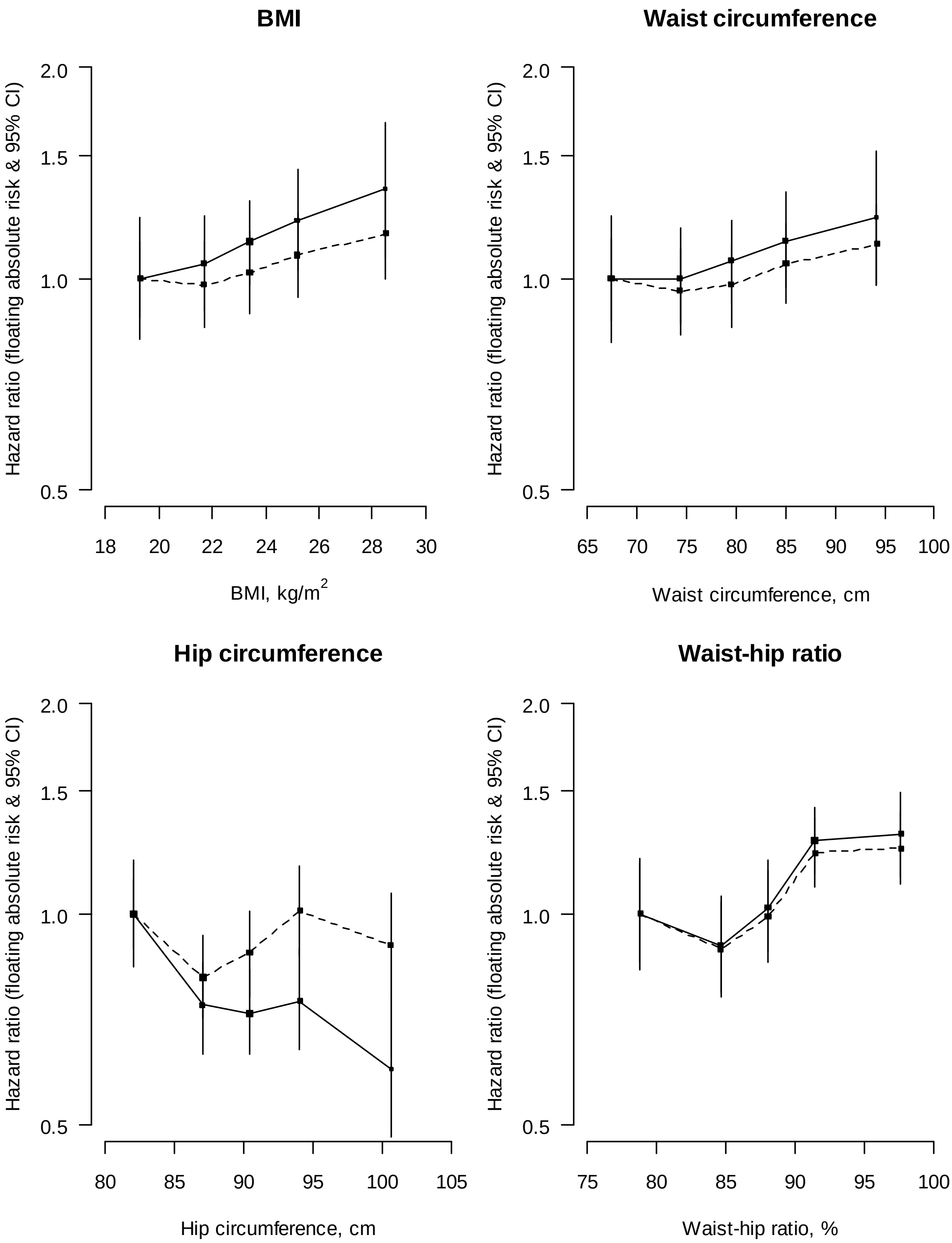
Dashed lines (----) adjusted for age at risk, sex, education, smoking and area; solid lines (——) adjusted for age at risk, sex, education, smoking, area and other adiposity measures.*



* Blood pressure means by quintiles of BMI were further adjusted for hip circumference and waist circumference; means by quintiles of hip circumference were further adjusted for BMI and waist circumference; means by quintiles of waist circumference were further adjusted for BMI and waist circumference; and means by quintiles of waist-hip ratio were further adjusted for BMI, hip circumference and waist circumference.

Figure D.2: Associations of intracerebral haemorrhage (1 071 events) with measures of adiposity at baseline (among 455 438 participants)

Dashed lines (----) adjusted for age at risk, sex, education, smoking and area; solid lines (——) adjusted for age at risk, sex, education, smoking, area and other adiposity measures.*



*Blood pressure means by levels of BMI were further adjusted for hip circumference and waist circumference; means by levels of hip circumference were further adjusted for BMI and waist circumference; means by levels of waist circumference were further adjusted for BMI and waist circumference; and means by levels of waist-hip ratio were further adjusted for BMI, hip circumference and waist circumference.

Table D.2: Associations of stroke incidence with measures of adiposity at baseline, by main stroke pathological types (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education, smoking and area.

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	**HR**	**(95%CI)**	**Events**	**HR**	**(95%CI)**
BMI, (kg/m^2)						
14.0 - <20.8	625	1.00	(0.92-1.08)	262	1.00	(0.88-1.13)
20.8 - <22.6	740	1.39	(1.29-1.49)	202	0.98	(0.85-1.13)
22.6 - <24.3	824	1.44	(1.34-1.54)	200	1.02	(0.89-1.17)
24.3 - <26.4	1 027	1.67	(1.57-1.78)	202	1.08	(0.94-1.24)
26.4 – 40.0	1 297	1.93	(1.83-2.05)	205	1.16	(1.00-1.33)
Waist circumference (cm)						
50.0 - <71.6	559	1.00	(0.92-1.09)	226	1.00	(0.87-1.14)
71.6 - <77.0	682	1.21	(1.12-1.30)	204	0.96	(0.83-1.10)
77.0 - <82.1	848	1.37	(1.28-1.46)	204	0.98	(0.85-1.12)
82.1 - <88.2	1 020	1.50	(1.41-1.60)	211	1.05	(0.92-1.20)
88.2 - 125.0	1 404	1.79	(1.70-1.89)	226	1.12	(0.98-1.28)
Hip circumference, (cm)						
60.0 - <85.1	747	1.00	(0.93-1.08)	356	1.00	(0.89-1.12)
85.1 - <88.8	740	1.16	(1.08-1.25)	198	0.81	(0.71-0.93)
88.8 - <92.1	772	1.19	(1.11-1.28)	185	0.88	(0.76-1.01)
92.1 - <96.2	905	1.35	(1.27-1.44)	180	1.01	(0.87-1.17)
96.2 - 129.0	1 349	1.51	(1.42-1.60)	152	0.90	(0.76-1.07)
Waist-hip ratio (%)						
59.6 - <82.5	612	1.00	(0.92-1.09)	156	1.00	(0.85-1.18)
82.5 - <86.5	760	1.24	(1.16-1.34)	155	0.89	(0.76-1.04)
86.5 - <89.5	727	1.34	(1.25-1.45)	168	0.99	(0.85-1.15)
89.5 - <93.5	1 214	1.47	(1.39-1.56)	308	1.22	(1.09-1.37)
93.5 - 125.4	1 200	1.77	(1.67-1.88)	284	1.24	(1.10-1.40)

Table D.3: Associations of stroke incidence with measures of adiposity at baseline, additionally adjusted for other measures of adiposity (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education, smoking, area and other adiposity measures.*

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	HR	(95%CI)	Events	HR	(95%CI)
BMI, (kg/m^2)						
14.0 - <20.8	625	1.00	(0.89-1.13)	262	1.00	(0.82-1.22)
20.8 - <22.6	740	1.39	(1.27-1.51)	202	1.05	(0.90-1.23)
22.6 - <24.3	824	1.43	(1.34-1.53)	200	1.13	(0.98-1.29)
24.3 - <26.4	1 027	1.66	(1.55-1.77)	202	1.21	(1.03-1.43)
26.4 – 40.0	1 297	1.88	(1.72-2.05)	205	1.34	(1.07-1.67)
Waist circumference (cm)						
50.0 - <71.6	559	1.00	(0.90-1.11)	226	1.00	(0.84-1.19)
71.6 - <77.0	682	0.96	(0.88-1.04)	204	0.74	(0.63-0.85)
77.0 - <82.1	848	0.86	(0.80-0.92)	204	0.72	(0.63-0.83)
82.1 - <88.2	1 020	0.85	(0.80-0.91)	211	0.75	(0.64-0.89)
88.2 - 125.0	1 404	0.80	(0.73-0.87)	226	0.60	(0.48-0.76)
Hip circumference, (cm						
60.0 - <85.1	747	1.00	(0.88-1.13)	356	1.00	(0.81-1.23)
85.1 - <88.8	740	1.07	(0.98-1.17)	198	1.00	(0.86-1.18)
88.8 - <92.1	772	1.13	(1.06-1.21)	185	1.06	(0.92-1.21)
92.1 - <96.2	905	1.18	(1.10-1.26)	180	1.13	(0.97-1.33)
96.2 - 129.0	1 349	1.32	(1.20-1.44)	152	1.22	(0.98-1.52)
Waist-hip ratio (%)						
59.6 - <82.5	612	1.00	(0.91-1.10)	156	1.00	(0.83-1.20)
82.5 - <86.5	760	1.13	(1.05-1.22)	155	0.90	(0.77-1.06)
86.5 - <89.5	727	1.16	(1.08-1.25)	168	1.02	(0.88-1.19)
89.5 - <93.5	1 214	1.20	(1.13-1.27)	308	1.27	(1.14-1.42)
93.5 - 125.4	1 200	1.34	(1.25-1.43)	284	1.30	(1.13-1.49)

* Blood pressure means by levels of BMI were further adjusted for hip circumference and waist circumference; means by levels of hip circumference were further adjusted for BMI and waist circumference; means by levels of waist circumference were further adjusted for BMI and waist circumference; and means by levels of waist-hip ratio were further adjusted for BMI, hip circumference and waist circumference.

Table D.4: Associations of stroke incidence with dietary variables at baseline, by main stroke pathological types (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education and area.

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	HR	(95%CI)	Events	HR	(95%CI)
Fresh fruit consumption						
Never/rarely	466	1.00	(0.91-1.10)	157	1.00	(0.85-1.18)
Monthly	1 727	0.98	(0.92-1.04)	505	0.77	(0.70-0.84)
1-3 days/wk	1 173	0.95	(0.90-1.01)	293	0.67	(0.60-0.75)
4-6 days/wk	294	0.97	(0.87-1.09)	59	0.64	(0.49-0.83)
Daily	853	0.90	(0.83-0.98)	57	0.43	(0.32-0.58)
Fresh vegetable consumption						
Not daily	132	1.00	(-)	43	1.00	(-)
Daily	4 381	1.05	(0.87-1.26)	1 028	1.03	(0.75-1.42)
Tea intake						
Never/rarely	2 192	1.00	(0.95-1.05)	449	1.00	(0.89-1.13)
Occasional	1 009	0.95	(0.89-1.00)	262	0.82	(0.73-0.92)
Monthly	139	1.00	(0.85-1.18)	26	0.67	(0.46-0.99)
Weekly/daily	1 173	1.03	(0.96-1.11)	334	0.75	(0.65-0.86)

'-' = not calculable.

Figure D.3: Associations of stroke incidence with alcohol intake at baseline, by main stroke pathological types (among 455 438 participants)

Hazard ratios relative to never drinkers, adjusted for age at risk, sex, education, smoking and area.

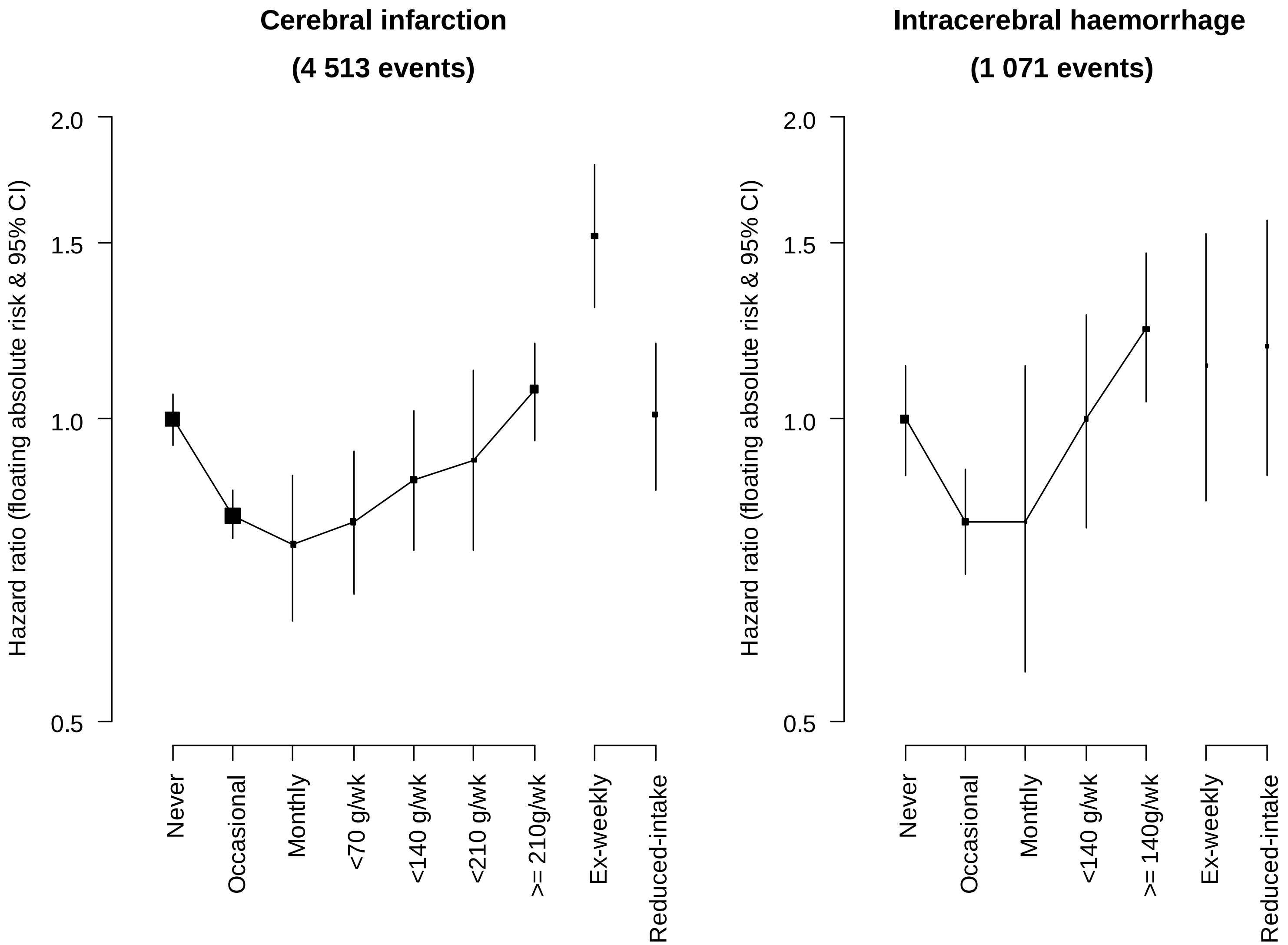


Figure D.4: Associations of stroke incidence with month of baseline survey, by main stroke pathological types (among 455 438 participants)

Hazard ratios relative to month of baseline survey in Jan/Feb, adjusted for age at risk, sex, education and area.

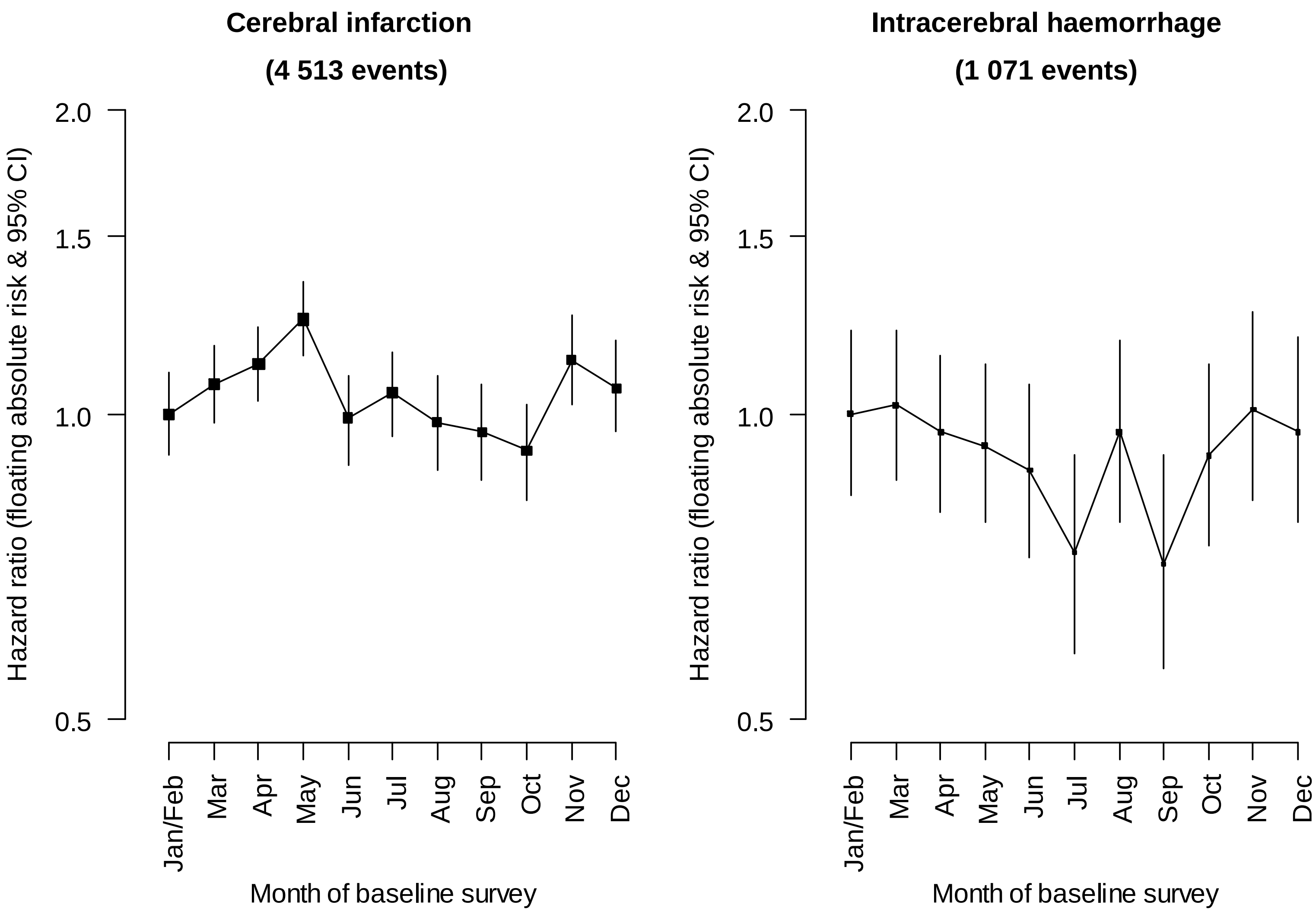


Table D.5: Associations of stroke incidence with alcohol intake at baseline and month of baseline survey, by stroke pathological type (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education and area.

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	HR	(95%CI)	Events	HR	(95%CI)
Alcohol intake*						
Never	1 836	1.00	(0.94-1.06)	430	1.00	(0.88-1.13)
Ex-weekly	151	1.52	(1.29-1.79)	43	1.13	(0.83-1.53)
Reduced-intake	146	1.01	(0.85-1.19)	46	1.18	(0.88-1.58)
Occasional	1 477	0.80	(0.76-0.85)	287	0.79	(0.70-0.89)
Monthly drinker	145	0.75	(0.63-0.88)	31	0.79	(0.56-1.13)
Weekly: <70g/wk	150	0.79	(0.67-0.93)	31	0.95	(0.67-1.36)
Weekly: <140g/wk	160	0.87	(0.74-1.02)	37	1.04	(0.75-1.44)
Weekly: <210g/wk	93	0.91	(0.74-1.12)	20	0.87	(0.56-1.35)
Weekly: >210g/wk	355	1.07	(0.95-1.19)	146	1.31	(1.09-1.57)
Month of baseline survey						
January/February	414	1.00	(0.91-1.10)	111	1.00	(0.83-1.21)
March	502	1.07	(0.98-1.17)	131	1.02	(0.86-1.21)
April	508	1.12	(1.03-1.22)	124	0.96	(0.80-1.14)
May	537	1.24	(1.14-1.35)	112	0.93	(0.78-1.12)
June	400	0.99	(0.89-1.09)	101	0.88	(0.72-1.07)
July	419	1.05	(0.95-1.15)	76	0.73	(0.58-0.91)
August	340	0.98	(0.88-1.09)	90	0.96	(0.78-1.18)
September	313	0.96	(0.86-1.07)	64	0.71	(0.56-0.91)
October	333	0.92	(0.82-1.02)	90	0.91	(0.74-1.12)
November	365	1.13	(1.02-1.25)	84	1.01	(0.82-1.26)
December	382	1.06	(0.96-1.18)	88	0.96	(0.78-1.19)

* Further adjusted for smoking.

Table D.6: Associations of stroke incidence with other variables at baseline, by main stroke pathological types (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education and area.

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	HR	(95%CI)	Events	HR	(95%CI)
Physical activity quintiles (MET hours/day)*						
0.0 - <14.4	1 811	1.00	(0.95-1.05)	355	1.00	(0.89-1.13)
14.4 - <19.7	1 204	0.94	(0.89-1.00)	252	0.88	(0.78-1.00)
19.7 - <26.8	692	0.88	(0.81-0.95)	193	0.77	(0.67-0.89)
26.8 - <38.0	436	0.83	(0.75-0.91)	132	0.62	(0.52-0.74)
38.0 - 139.5	370	0.71	(0.63-0.79)	139	0.74	(0.62-0.88)
Smoking†						
Never	2 413	1.00	(0.92-1.08)	491	1.00	(0.84-1.18)
Occasional	255	0.98	(0.87-1.11)	77	0.96	(0.77-1.20)
Ex-regular	440	1.05	(0.95-1.15)	109	0.97	(0.80-1.17)
Current	1 405	1.22	(1.15-1.29)	394	0.93	(0.83-1.04)
History of diabetes‡						
No	3 997	1.00	(-)	996	1.00	(-)
Yes	516	1.64	(1.49-1.80)	75	1.42	(1.12-1.81)
Taking blood pressure lowering medication‡						
No	4 054	1.00	(-)	959	1.00	(-)
Yes	459	1.80	(1.63-1.99)	112	2.56	(2.08-3.14)

* Mean of quintiles: 10.6, 17.0, 22.9, 32.1, 47.6 MET hours/day.
† Further adjusted for alcohol .
‡ Further adjusted for adiposity (BMI, waist circum. and hip circum. where appropriate).
§ Further adjusted for adiposity (BMI, waist circumference, hip circumference), physical activity (METs), alcohol intake, diabetes, fresh fruit consumption and fresh vegetable consumption.
'-' = not calculable.

Table D.7: Associations of stroke incidence with measures of adiposity at baseline, extensively adjusted (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education, smoking, area and adiposity;* and other selected variables (MET hrs/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, smoking, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	HR	(95%CI)	Events	HR	(95%CI)
BMI, (kg/m^2)						
14.0 - <20.8	625	1.00	(0.89-1.13)	262	1.00	(0.82-1.22)
20.8 - <22.6	740	1.38	(1.27-1.51)	202	1.05	(0.90-1.23)
22.6 - <24.3	824	1.43	(1.34-1.53)	200	1.14	(0.99-1.30)
24.3 - <26.4	1 027	1.65	(1.54-1.77)	202	1.23	(1.05-1.45)
26.4 – 40.0	1 297	1.86	(1.70-2.04)	205	1.37	(1.10-1.70)
Waist circumference (cm)						
50.0 - <71.6	559	1.00	(0.90-1.11)	226	1.00	(0.84-1.19)
71.6 - <77.0	682	0.95	(0.88-1.03)	204	0.75	(0.64-0.87)
77.0 - <82.1	848	0.85	(0.79-0.91)	204	0.74	(0.64-0.85)
82.1 - <88.2	1 020	0.84	(0.78-0.90)	211	0.77	(0.65-0.91)
88.2 - 125.0	1 404	0.78	(0.71-0.85)	226	0.62	(0.49-0.78)
Hip circumference, (cm						
60.0 - <85.1	747	1.00	(0.88-1.13)	356	1.00	(0.81-1.23)
85.1 - <88.8	740	1.08	(0.99-1.18)	198	1.00	(0.86-1.18)
88.8 - <92.1	772	1.15	(1.07-1.23)	185	1.05	(0.92-1.20)
92.1 - <96.2	905	1.21	(1.13-1.29)	180	1.13	(0.96-1.33)
96.2 - 129.0	1 349	1.36	(1.24-1.49)	152	1.21	(0.97-1.51)
Waist-hip ratio (%)						
59.6 - <82.5	612	1.00	(0.91-1.10)	156	1.00	(0.83-1.20)
82.5 - <86.5	760	1.15	(1.06-1.23)	155	0.91	(0.77-1.07)
86.5 - <89.5	727	1.18	(1.10-1.27)	168	1.02	(0.88-1.19)
89.5 - <93.5	1 214	1.23	(1.16-1.30)	308	1.27	(1.14-1.42)
93.5 - 125.4	1 200	1.38	(1.29-1.48)	284	1.29	(1.12-1.48)

* Blood pressure means by levels of BMI were further adjusted for hip circumference and waist circumference; means by levels of hip circumference were further adjusted for BMI and waist circumference; means by levels of waist circumference were further adjusted for BMI and waist circumference; and means by levels of waist-hip ratio were further adjusted for BMI, hip circumference and waist circumference.

Table D.8: Associations of stroke incidence with dietary variables at baseline, extensively adjusted (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education, smoking and area; and other selected variables (BMI, hip circumference, waist circumference, MET hrs/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

Baseline level of variables	**Cerebral infarction (4 513 events)**			**Intracerebral haemorrhage (1 071 events)**		
	Events	**HR**	**(95%CI)**	**Events**	**HR**	**(95%CI)**
Fresh fruit consumption						
Never/rarely	466	1.00	(0.91-1.10)	157	1.00	(0.85-1.18)
Monthly	1 727	1.04	(0.98-1.10)	505	0.81	(0.74-0.89)
1-3 days/wk	1 173	1.01	(0.95-1.07)	293	0.71	(0.63-0.80)
4-6 days/wk	294	1.04	(0.92-1.17)	59	0.68	(0.53-0.89)
Daily	853	0.98	(0.90-1.07)	57	0.46	(0.35-0.62)
Fresh vegetable consumption						
Not daily	132	1.00	(-)	43	1.00	(-)
Daily	4 381	1.06	(0.88-1.27)	1 028	1.06	(0.77-1.47)
Tea intake						
Never/rarely	2 192	1.00	(0.95-1.06)	449	1.00	(0.88-1.13)
Occasional	1 009	0.95	(0.90-1.01)	262	0.84	(0.75-0.95)
Monthly	139	0.98	(0.83-1.15)	26	0.67	(0.45-0.98)
Weekly/daily	1 173	0.98	(0.91-1.06)	334	0.74	(0.64-0.85)

'-' = not calculable.

Table D.9: Associations of stroke incidence with alcohol intake at baseline and month of baseline survey, extensively adjusted (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education, smoking and area; and other selected variables (BMI, hip circumference, waist circumference, MET hrs/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	**HR**	**(95%CI)**	**Events**	**HR**	**(95%CI)**
Alcohol intake						
Never	1 836	1.00	(0.94-1.06)	430	1.00	(0.88-1.13)
Ex-weekly	151	1.45	(1.23-1.71)	43	1.13	(0.83-1.53)
Reduced-intake	146	0.96	(0.81-1.13)	46	1.23	(0.92-1.65)
Occasional	1 477	0.82	(0.78-0.87)	287	0.84	(0.74-0.95)
Monthly drinker	145	0.77	(0.65-0.90)	31	0.88	(0.62-1.26)
Weekly: <70g/wk	150	0.80	(0.68-0.95)	31	1.05	(0.73-1.49)
Weekly: <140g/wk	160	0.87	(0.75-1.03)	37	1.10	(0.80-1.53)
Weekly: <210g/wk	93	0.90	(0.73-1.11)	20	0.93	(0.60-1.44)
Weekly: >210g/wk	355	1.05	(0.94-1.18)	146	1.38	(1.15-1.66)
Month of baseline survey						
January/February	414	1.00	(0.91-1.10)	111	1.00	(0.83-1.21)
March	502	1.07	(0.98-1.17)	131	1.02	(0.86-1.21)
April	508	1.12	(1.03-1.22)	124	0.96	(0.81-1.15)
May	537	1.22	(1.12-1.33)	112	0.92	(0.77-1.11)
June	400	0.96	(0.87-1.06)	101	0.86	(0.71-1.05)
July	419	1.03	(0.93-1.13)	76	0.71	(0.57-0.89)
August	340	0.96	(0.86-1.07)	90	0.93	(0.76-1.15)
September	313	0.94	(0.84-1.05)	64	0.70	(0.55-0.89)
October	333	0.91	(0.81-1.01)	90	0.89	(0.72-1.09)
November	365	1.11	(1.00-1.24)	84	1.01	(0.81-1.25)
December	382	1.05	(0.95-1.17)	88	0.96	(0.77-1.18)

Table D.10: Associations of stroke incidence with other variables at baseline, extensively adjusted (among 455 438 participants)

Hazard ratios (HR) with floating absolute risk, adjusted for age at risk, sex, education, smoking and area; and other selected variables (BMI, hip circumference, waist circumference, MET hrs/day, alcohol intake, tea intake, fresh fruit consumption, fresh vegetable consumption, month of baseline survey and history of diabetes) except where the variable is on the causal pathway between exposure and blood pressure, see Figure 1.3.

Baseline level of variables	Cerebral infarction (4 513 events)			Intracerebral haemorrhage (1 071 events)		
	Events	HR	(95%CI)	Events	HR	(95%CI)
Physical activity quintiles (MET hours/day)*						
0.0 - <14.4	1 811	1.00	(0.95-1.05)	355	1.00	(0.89-1.13)
14.4 - <19.7	1 204	0.95	(0.89-1.00)	252	0.89	(0.79-1.01)
19.7 - <26.8	692	0.89	(0.82-0.96)	193	0.78	(0.68-0.90)
26.8 - <38.0	436	0.84	(0.76-0.92)	132	0.62	(0.52-0.75)
38.0 - 139.5	370	0.71	(0.64-0.80)	139	0.75	(0.62-0.89)
Smoking						
Never	2 413	1.00	(0.92-1.08)	491	1.00	(0.85-1.18)
Occasional	255	0.98	(0.87-1.11)	77	0.95	(0.76-1.19)
Ex-regular	440	1.02	(0.93-1.12)	109	0.98	(0.81-1.18)
Current	1 405	1.30	(1.23-1.38)	394	0.95	(0.85-1.06)
History of diabetes						
No	3 997	1.00	(-)	996	1.00	(-)
Yes	516	1.59	(1.44-1.75)	75	1.34	(1.05-1.70)
Taking blood pressure lowering medication†						
No	4 054	1.00	(-)	959	1.00	(-)
Yes	459	1.80	(1.63-1.99)	112	2.59	(2.11-3.18)

* Mean of quintiles: 10.6, 17.0, 22.9, 32.1, 47.6 MET hours/day.
† Adjusted for all other selected variables.

Appendix E: CKB additional results: prospective analyses (II)

Table E.1: Cerebral infarction incidence (4513 events): hazard ratios for 10 mm Hg higher baseline SBP and 5 mm Hg higher baseline DBP, progressively adjusted for major potential confounders (among 455 438 participants)

.

Potential confounders included in model	SBP		DBP	
	HR	(95%CI)	HR	(95%CI)
Age, sex and area	1.24	(1.23-1.26)	1.22	(1.21-1.24)
Plus education	1.24	(1.23-1.26)	1.22	(1.21-1.24)
Plus month baseline survey	1.24	(1.23-1.26)	1.22	(1.21-1.24)
Plus smoking	1.25	(1.23-1.26)	1.22	(1.21-1.24)
Plus alcohol intake	1.24	(1.23-1.26)	1.22	(1.21-1.24)
Plus body-mass index	1.23	(1.22-1.25)	1.21	(1.20-1.23)
Plus waist and hip circum.	1.23	(1.22-1.25)	1.21	(1.19-1.22)
Plus physical activity	1.23	(1.22-1.25)	1.21	(1.19-1.22)
Plus history of diabetes	1.23	(1.21-1.24)	1.21	(1.19-1.22)
Plus intake of fruit, veg. and tea	1.23	(1.21-1.24)	1.21	(1.19-1.23)
Plus blood pressure-lowering medication	1.22	(1.21-1.24)	1.20	(1.19-1.22)

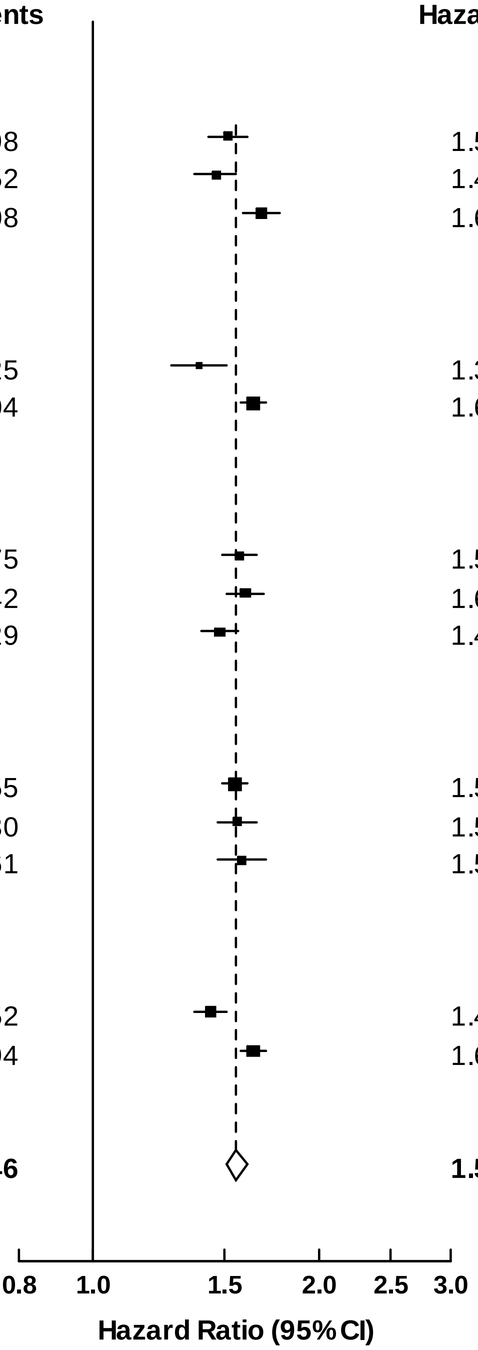
Table E.2: Intracerebral haemorrhage incidence (1071 events): hazard ratios for 10 mm Hg higher baseline SBP and 5 mm Hg higher baseline DBP, progressively adjusted for major potential confounders (among 455 438 participants)

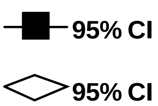
Potential confounders included in model	SBP		DBP	
	HR	**(95%CI)**	**HR**	**(95%CI)**
Age, sex and area	1.40	(1.37-1.43)	1.40	(1.37-1.44)
Plus education	1.40	(1.37-1.43)	1.40	(1.37-1.44)
Plus month baseline survey	1.41	(1.38-1.44)	1.41	(1.38-1.44)
Plus smoking	1.41	(1.38-1.44)	1.41	(1.38-1.44)
Plus alcohol intake	1.40	(1.37-1.44)	1.41	(1.38-1.44)
Plus body-mass index	1.42	(1.39-1.45)	1.42	(1.39-1.45)
Plus waist and hip circum.	1.42	(1.38-1.45)	1.42	(1.39-1.45)
Plus physical activity	1.41	(1.38-1.45)	1.42	(1.38-1.45)
Plus history of diabetes	1.41	(1.38-1.45)	1.42	(1.38-1.45)
Plus intake of fruit, veg. and tea	1.41	(1.38-1.44)	1.41	(1.38-1.45)
Plus blood pressure- lowering medication	1.40	(1.37-1.43)	1.40	(1.37-1.44)

Figure E.1: Male: cerebral infarction incidence (2246 events): hazard ratios for 10 mm Hg higher usual SBP, by potential effect modifiers (among 184 949 male participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	68	498	1.52 (1.43 - 1.61)
Occassional	64	652	1.46 (1.37 - 1.55)
Weekly	63	708	1.68 (1.59 - 1.78)
Heterogeneity test: $\chi^2_2 = 11.8$ (p=0.003)			
Smoking†			
Never	67	325	1.39 (1.27 - 1.52)
Current	63	1304	1.64 (1.58 - 1.71)
Heterogeneity test: $\chi^2_1 = 11.6$ (p<0.001)			
BMI, kg/m²			
<22	66	675	1.57 (1.49 - 1.66)
<25	65	742	1.60 (1.51 - 1.70)
≥25	63	829	1.48 (1.40 - 1.56)
Trend test: $\chi^2_1 = 2.3$ (p=0.1)			
MET, hrs/day			
<20	67	1355	1.55 (1.49 - 1.61)
<30	62	530	1.56 (1.47 - 1.66)
≥30	60	361	1.58 (1.46 - 1.70)
Trend test: $\chi^2_1 = 0.2$ (p=0.7)			
Area			
Urban	65	852	1.44 (1.37 - 1.51)
Rural	64	1394	1.64 (1.58 - 1.71)
Heterogeneity test: $\chi^2_1 = 16.5$ (p<0.001)			
Overall	**65**	**2246**	**1.56 (1.51 - 1.61)**



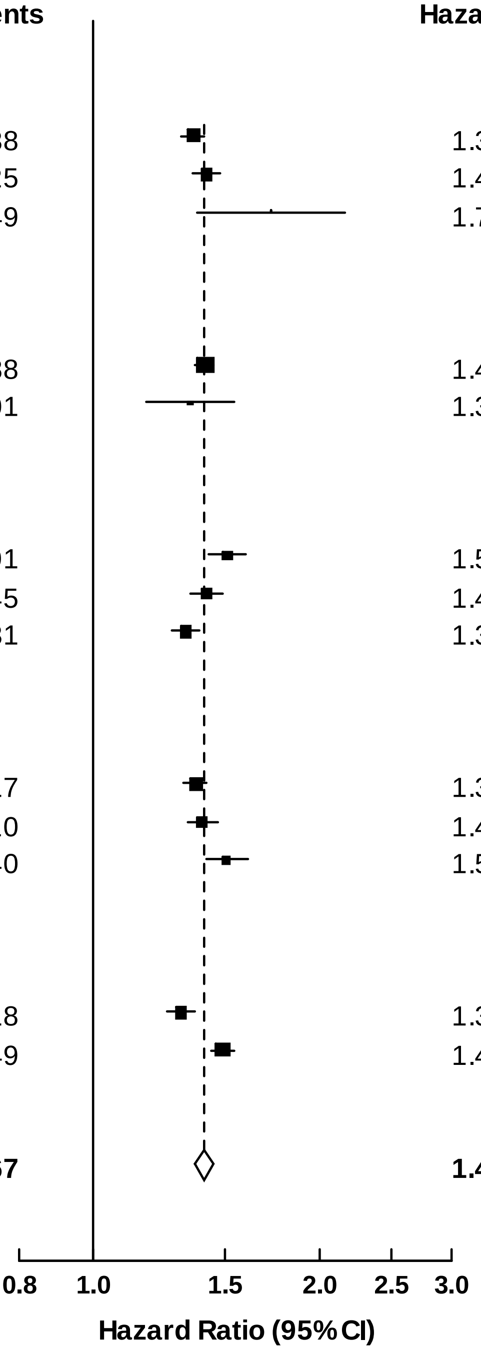


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.2: Female: cerebral infarction incidence (2267 events): hazard ratios for 10 mm Hg higher usual SBP, by potential effect modifiers (among 270 489 female participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	65	1338	1.36 (1.31 - 1.41)
Occassional	62	825	1.42 (1.36 - 1.48)
Weekly	65	49	1.73 (1.38 - 2.17)
Heterogeneity test: $\chi^2_2 = 5.9$ (p=0.05)			
Smoking†			
Never	63	2088	1.41 (1.37 - 1.45)
Current	68	101	1.35 (1.18 - 1.55)
Heterogeneity test: $\chi^2_1 = 0.4$ (p=0.5)			
BMI, kg/m²			
<22	65	491	1.51 (1.43 - 1.60)
<25	63	745	1.42 (1.35 - 1.49)
≥25	63	1031	1.33 (1.28 - 1.39)
Trend test: $\chi^2_1 = 13.1$ (p<0.001)			
MET, hrs/day			
<20	66	1117	1.37 (1.32 - 1.42)
<30	63	810	1.40 (1.34 - 1.47)
≥30	59	340	1.51 (1.42 - 1.61)
Trend test: $\chi^2_1 = 6.1$ (p=0.01)			
Area			
Urban	65	1018	1.31 (1.26 - 1.37)
Rural	62	1249	1.49 (1.44 - 1.55)
Heterogeneity test: $\chi^2_1 = 20.3$ (p<0.001)			
Overall	**64**	**2267**	**1.41 (1.37 - 1.45)**



■ 95% CI

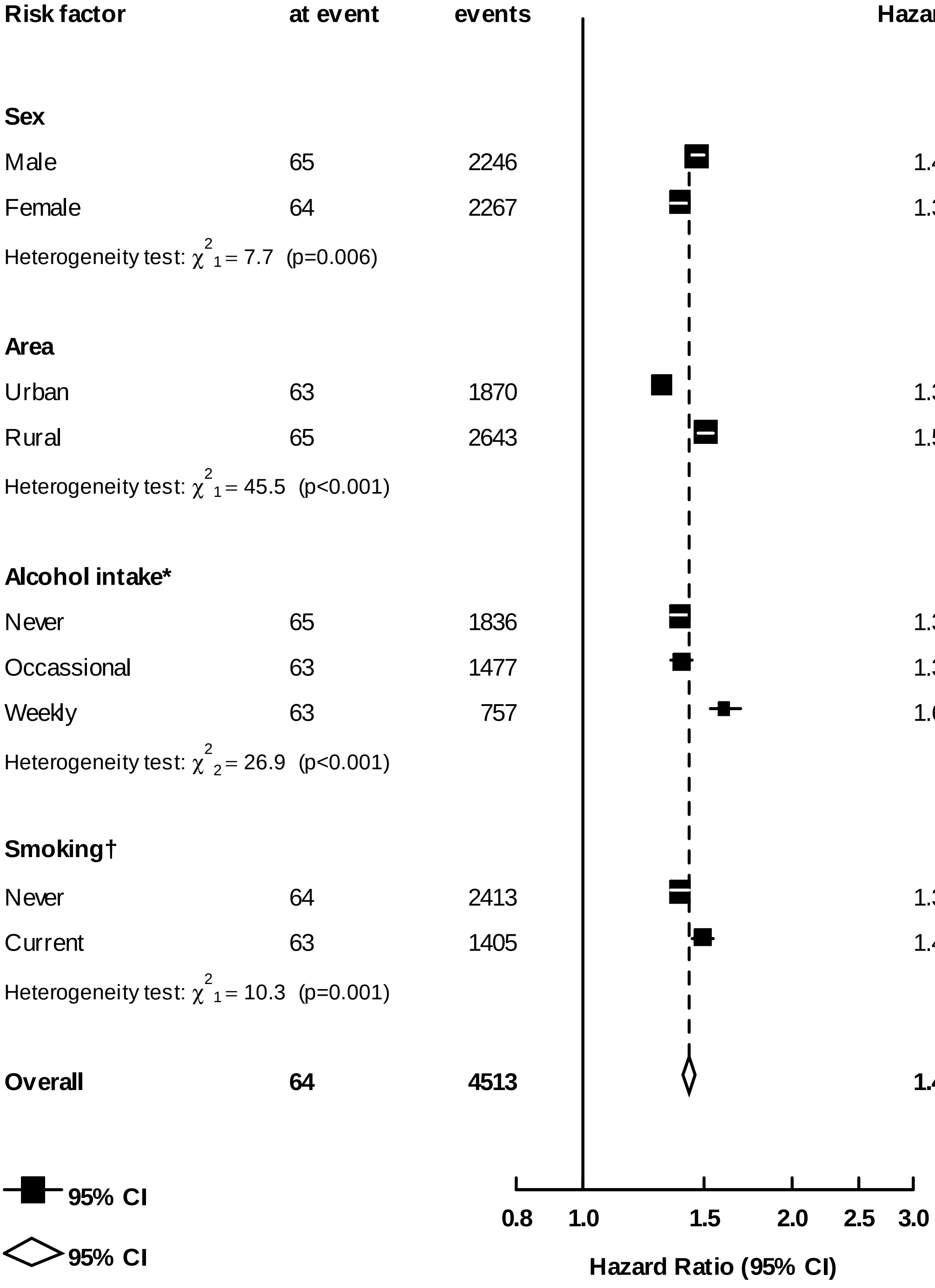
◇ 95% CI

* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.3: Overall: cerebral infarction incidence (4513 events): hazard ratios for 5 mm Hg higher usual DBP, by set (I) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Sex			
Male	65	2246	1.46 (1.42 - 1.50)
Female	64	2267	1.38 (1.34 - 1.42)
Heterogeneity test: $\chi^2_1 = 7.7$ (p=0.006)			
Area			
Urban	63	1870	1.30 (1.26 - 1.35)
Rural	65	2643	1.51 (1.47 - 1.55)
Heterogeneity test: $\chi^2_1 = 45.5$ (p<0.001)			
Alcohol intake*			
Never	65	1836	1.38 (1.34 - 1.42)
Occassional	63	1477	1.39 (1.34 - 1.44)
Weekly	63	757	1.60 (1.52 - 1.68)
Heterogeneity test: $\chi^2_2 = 26.9$ (p<0.001)			
Smoking†			
Never	64	2413	1.38 (1.34 - 1.42)
Current	63	1405	1.49 (1.44 - 1.55)
Heterogeneity test: $\chi^2_1 = 10.3$ (p=0.001)			
Overall	**64**	**4513**	**1.42 (1.39 - 1.45)**

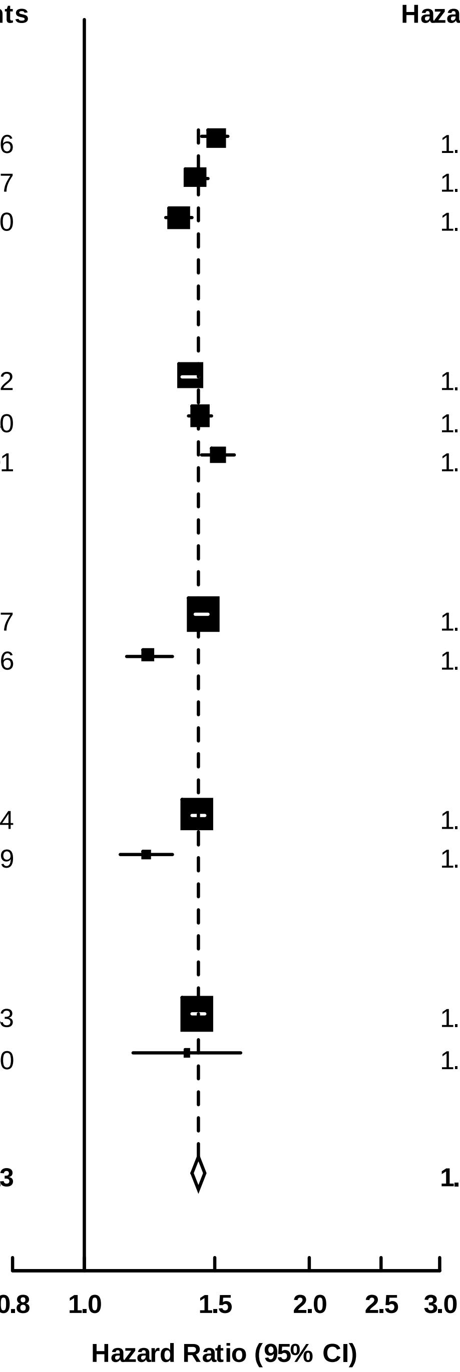


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.4: Overall: cerebral infarction incidence (4513 events): hazard ratios for 5 mm Hg higher usual DBP, by set (II) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
BMI, kg/m²			
<22	66	1166	1.50 (1.44 - 1.56)
<25	64	1487	1.41 (1.36 - 1.46)
≥25	63	1860	1.34 (1.29 - 1.39)
Trend test: $\chi^2_1 = 16.3$ (p<0.001)			
MET, hrs/day			
<20	66	2472	1.39 (1.35 - 1.43)
<30	62	1340	1.43 (1.38 - 1.49)
≥30	59	701	1.51 (1.44 - 1.59)
Trend test: $\chi^2_1 = 7.8$ (p=0.005)			
Diabetes			
No	64	3997	1.44 (1.41 - 1.47)
Yes	65	516	1.22 (1.14 - 1.31)
Heterogeneity test: $\chi^2_1 = 20.1$ (p<0.001)			
BP medication			
No	64	4054	1.42 (1.39 - 1.45)
Yes	64	459	1.21 (1.12 - 1.31)
Heterogeneity test: $\chi^2_1 = 14.9$ (p<0.001)			
Fatal event			
No	64	4443	1.42 (1.39 - 1.45)
Yes	69	70	1.37 (1.16 - 1.62)
Heterogeneity test: $\chi^2_1 = 0.2$ (p=0.7)			
Overall	**64**	**4513**	**1.42 (1.39 - 1.45)**



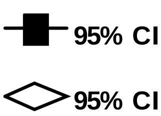
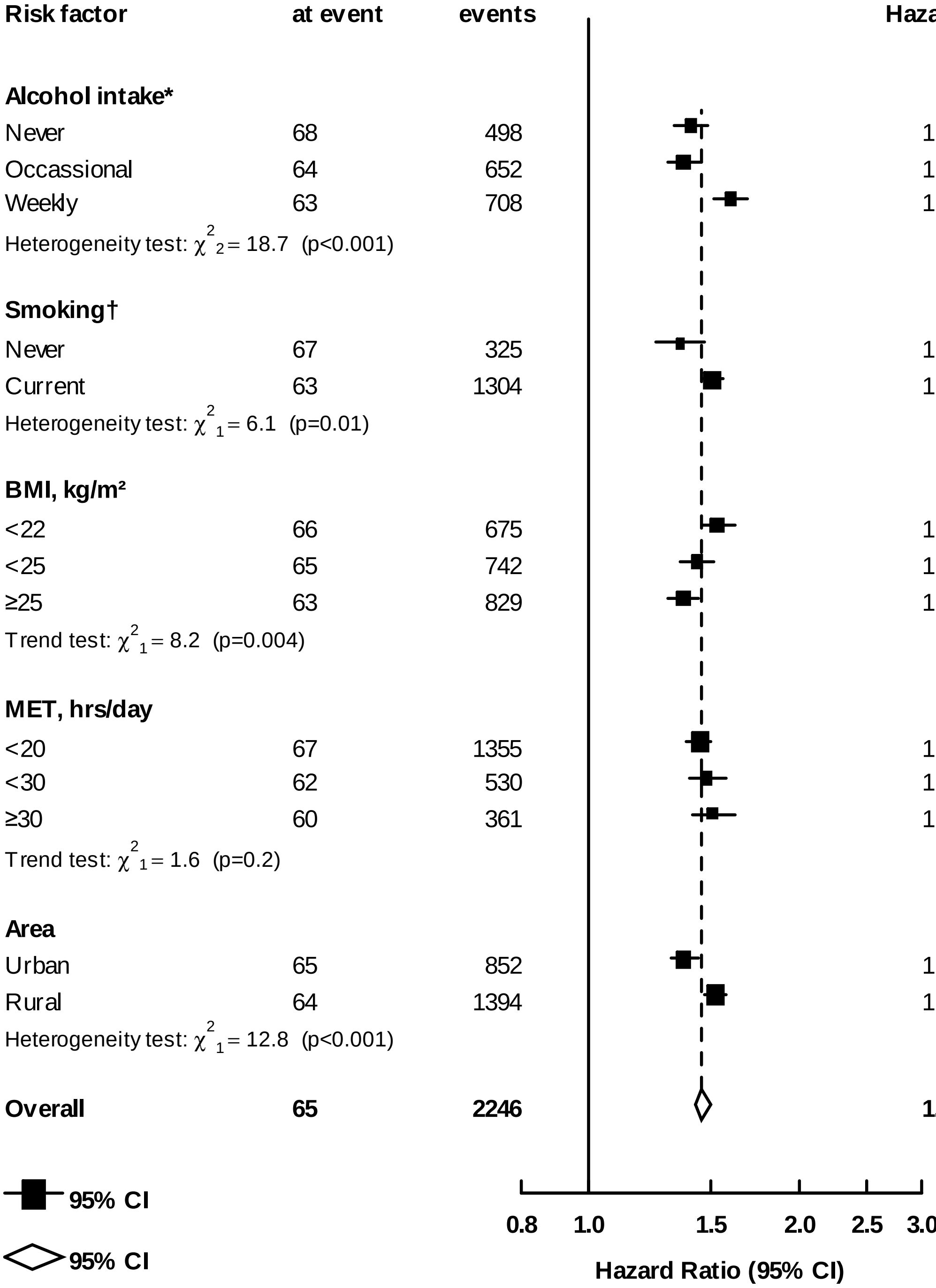


Figure E.5: Male: cerebral infarction incidence (2246 events): hazard ratios for 5 mm Hg usual DBP, by potential effect modifiers (among 184 949 male participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	68	498	1.40 (1.32 - 1.48)
Occassional	64	652	1.37 (1.30 - 1.45)
Weekly	63	708	1.60 (1.52 - 1.69)
Heterogeneity test: $\chi^2_2 = 18.7$ (p<0.001)			
Smoking†			
Never	67	325	1.35 (1.24 - 1.46)
Current	63	1304	1.51 (1.46 - 1.57)
Heterogeneity test: $\chi^2_1 = 6.1$ (p=0.01)			
BMI, kg/m²			
<22	66	675	1.53 (1.45 - 1.62)
<25	65	742	1.43 (1.36 - 1.51)
≥25	63	829	1.37 (1.30 - 1.44)
Trend test: $\chi^2_1 = 8.2$ (p=0.004)			
MET, hrs/day			
<20	67	1355	1.44 (1.39 - 1.50)
<30	62	530	1.48 (1.39 - 1.57)
≥30	60	361	1.51 (1.41 - 1.62)
Trend test: $\chi^2_1 = 1.6$ (p=0.2)			
Area			
Urban	65	852	1.37 (1.31 - 1.43)
Rural	64	1394	1.52 (1.47 - 1.58)
Heterogeneity test: $\chi^2_1 = 12.8$ (p<0.001)			
Overall	**65**	**2246**	**1.46 (1.42 - 1.50)**

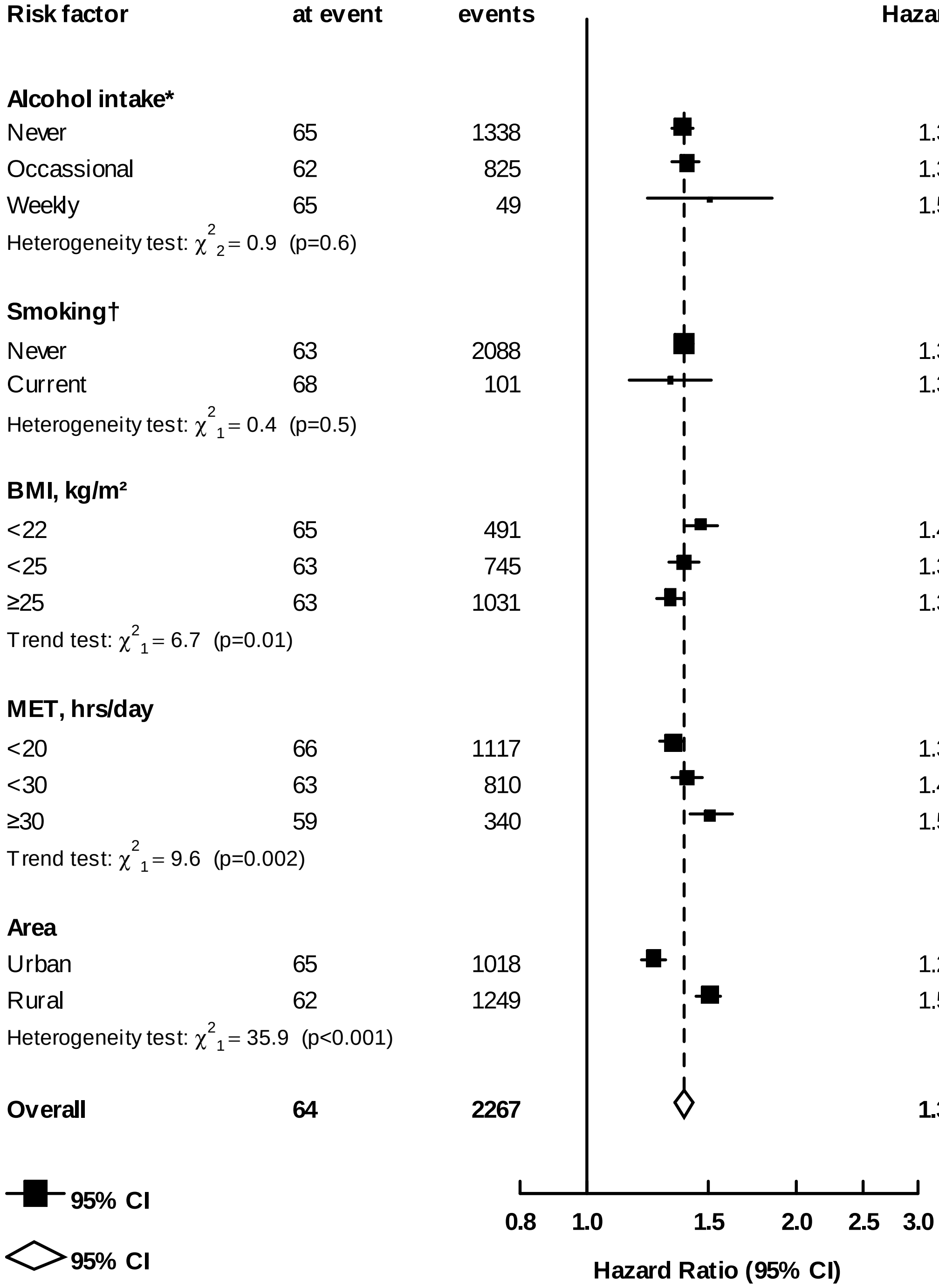


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.6: Female: cerebral infarction incidence (2267 events): hazard ratios for 5 mm Hg usual DBP, by potential effect modifiers (among 270 489 female participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	65	1338	1.37 (1.32 - 1.42)
Occassional	62	825	1.39 (1.33 - 1.46)
Weekly	65	49	1.50 (1.22 - 1.84)
Heterogeneity test: $\chi^2_2 = 0.9$ (p=0.6)			
Smoking†			
Never	63	2088	1.38 (1.34 - 1.43)
Current	68	101	1.32 (1.16 - 1.51)
Heterogeneity test: $\chi^2_1 = 0.4$ (p=0.5)			
BMI, kg/m²			
<22	65	491	1.46 (1.38 - 1.55)
<25	63	745	1.38 (1.31 - 1.45)
≥25	63	1031	1.32 (1.26 - 1.39)
Trend test: $\chi^2_1 = 6.7$ (p=0.01)			
MET, hrs/day			
<20	66	1117	1.33 (1.28 - 1.39)
<30	63	810	1.40 (1.33 - 1.47)
≥30	59	340	1.51 (1.41 - 1.62)
Trend test: $\chi^2_1 = 9.6$ (p=0.002)			
Area			
Urban	65	1018	1.25 (1.20 - 1.31)
Rural	62	1249	1.50 (1.44 - 1.56)
Heterogeneity test: $\chi^2_1 = 35.9$ (p<0.001)			
Overall	**64**	**2267**	**1.38 (1.34 - 1.42)**

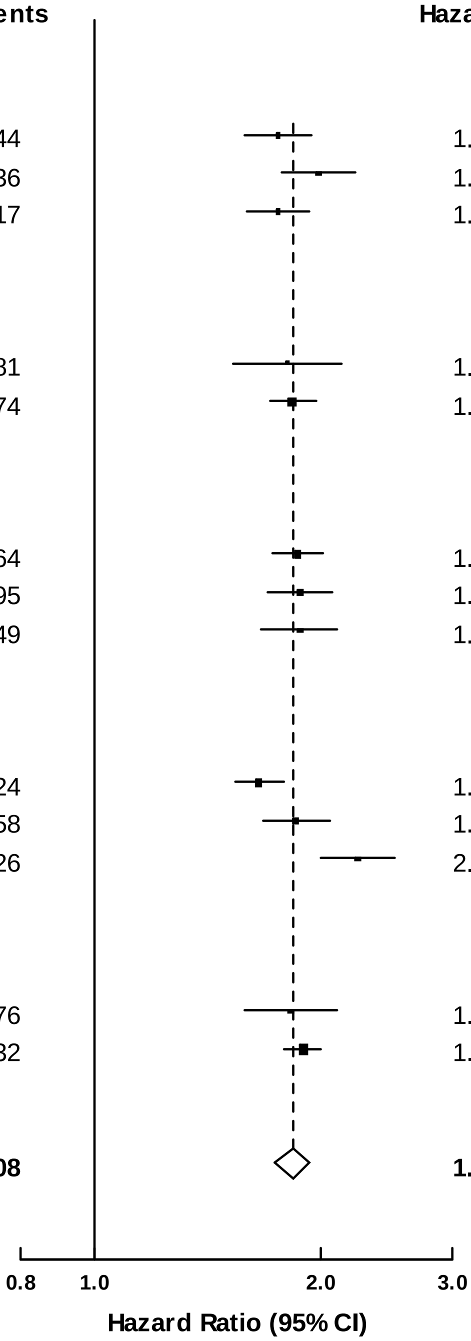


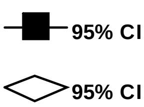
* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.7: Male: intracerebral haemorrhage incidence (608 events): hazard ratios for 10 mm Hg usual SBP, by potential effect modifiers (among 184 949 male participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	66	144	1.76 (1.59 - 1.95)
Occassional	64	136	1.99 (1.77 - 2.23)
Weekly	63	217	1.76 (1.59 - 1.94)
Heterogeneity test: $\chi^2_2 = 3.1$ (p=0.2)			
Smoking†			
Never	66	81	1.81 (1.54 - 2.13)
Current	63	374	1.84 (1.71 - 1.97)
Heterogeneity test: $\chi^2_1 = 0.0$ (p=0.9)			
BMI, kg/m²			
<22	66	264	1.87 (1.73 - 2.02)
<25	64	195	1.88 (1.70 - 2.08)
≥25	61	149	1.88 (1.67 - 2.11)
Trend test: $\chi^2_1 = 0.0$ (p=1)			
MET, hrs/day			
<20	67	324	1.66 (1.54 - 1.79)
<30	63	158	1.86 (1.68 - 2.06)
≥30	58	126	2.25 (2.01 - 2.52)
Trend test: $\chi^2_1 = 19.0$ (p<0.001)			
Area			
Urban	64	76	1.83 (1.59 - 2.11)
Rural	64	532	1.90 (1.79 - 2.01)
Heterogeneity test: $\chi^2_1 = 0.2$ (p=0.6)			
Overall	**65**	**608**	**1.84 (1.75 - 1.94)**



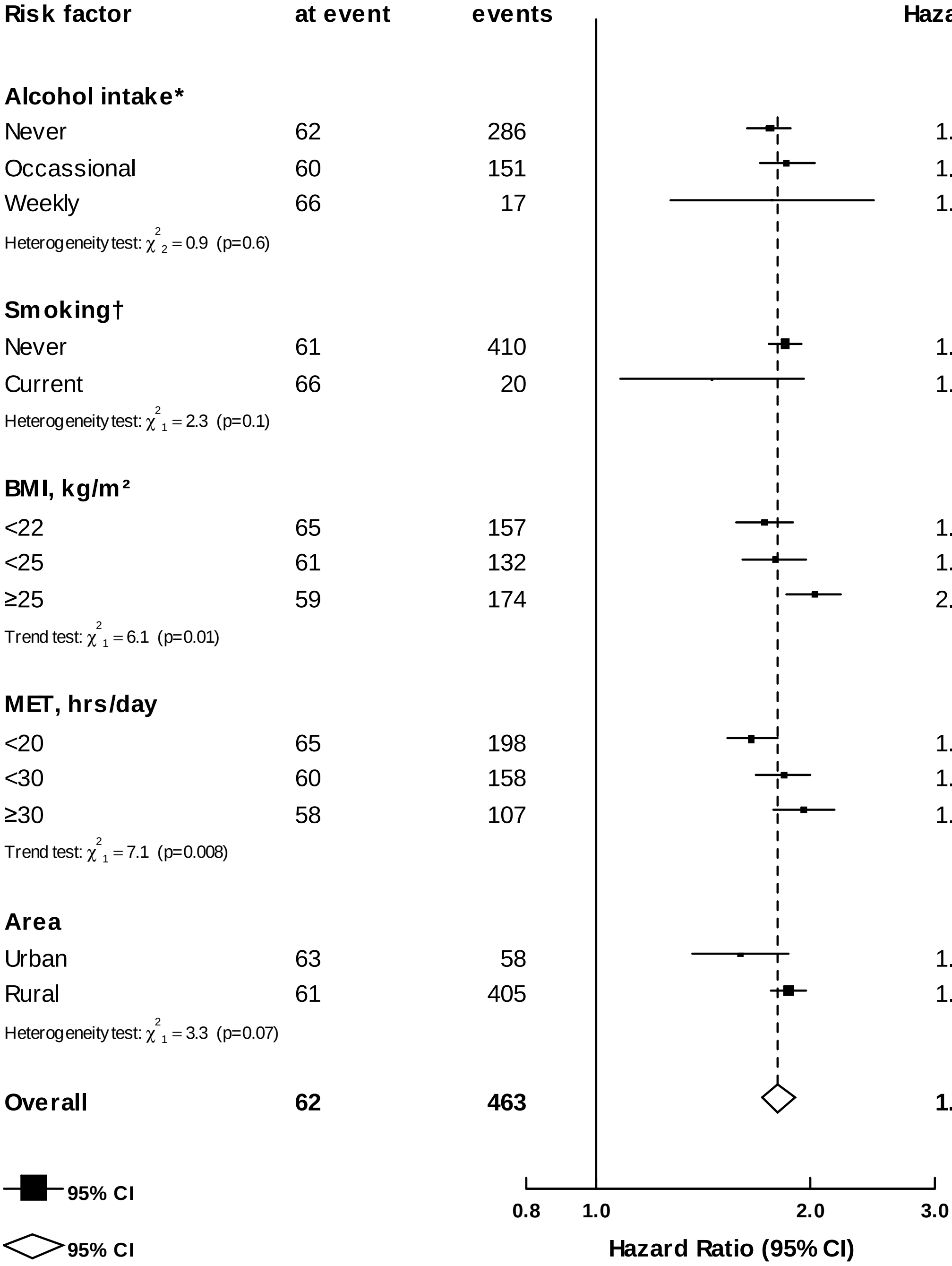


* Additionally adjusted for smoking (excludes ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes occasional and ex-regular groups).

Figure E.8: Female: intracerebral haemorrhage incidence (463 events): hazard ratios for 10 mm Hg usual SBP, by potential effect modifiers (among 270 489 female participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	62	286	1.76 (1.64 - 1.89)
Occassional	60	151	1.86 (1.70 - 2.03)
Weekly	66	17	1.77 (1.27 - 2.46)
Heterogeneity test: $\chi^2_2 = 0.9$ (p=0.6)			
Smoking†			
Never	61	410	1.85 (1.75 - 1.95)
Current	66	20	1.46 (1.08 - 1.97)
Heterogeneity test: $\chi^2_1 = 2.3$ (p=0.1)			
BMI, kg/m²			
<22	65	157	1.73 (1.58 - 1.90)
<25	61	132	1.79 (1.61 - 1.99)
≥25	59	174	2.03 (1.86 - 2.22)
Trend test: $\chi^2_1 = 6.1$ (p=0.01)			
MET, hrs/day			
<20	65	198	1.66 (1.53 - 1.80)
<30	60	158	1.84 (1.68 - 2.01)
≥30	58	107	1.97 (1.78 - 2.18)
Trend test: $\chi^2_1 = 7.1$ (p=0.008)			
Area			
Urban	63	58	1.60 (1.37 - 1.87)
Rural	61	405	1.87 (1.77 - 1.98)
Heterogeneity test: $\chi^2_1 = 3.3$ (p=0.07)			
Overall	**62**	**463**	**1.81 (1.72 - 1.91)**

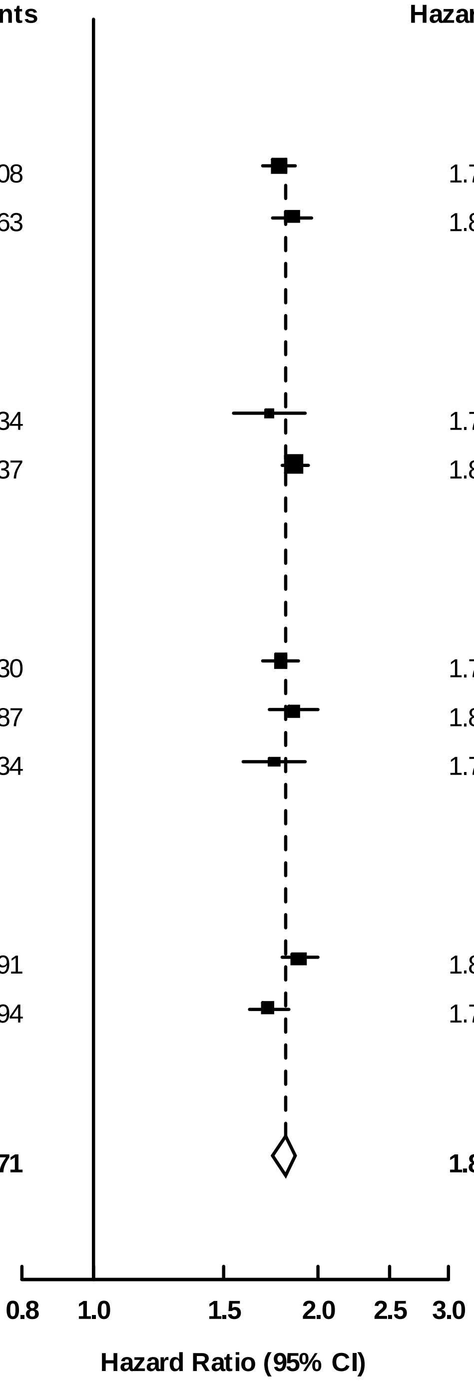


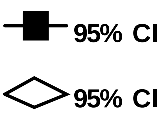
* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.9: Overall: intracerebral haemorrhage incidence (1071 events): hazard ratios for 5 mm Hg usual DBP, by set (I) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Sex			
Male	64	608	1.78 (1.69 - 1.87)
Female	62	463	1.85 (1.75 - 1.96)
Heterogeneity test: $\chi^2_1 = 1.0$ (p=0.3)			
Area			
Urban	63	134	1.73 (1.55 - 1.93)
Rural	64	937	1.86 (1.79 - 1.94)
Heterogeneity test: $\chi^2_1 = 1.5$ (p=0.2)			
Alcohol intake*			
Never	63	430	1.79 (1.69 - 1.89)
Occassional	62	287	1.86 (1.72 - 2.01)
Weekly	63	234	1.75 (1.59 - 1.92)
Heterogeneity test: $\chi^2_2 = 1.1$ (p=0.6)			
Smoking†			
Never	61	491	1.89 (1.79 - 2.00)
Current	63	394	1.72 (1.62 - 1.83)
Heterogeneity test: $\chi^2_1 = 5.0$ (p=0.02)			
Overall	**63**	**1071**	**1.81 (1.75 - 1.88)**



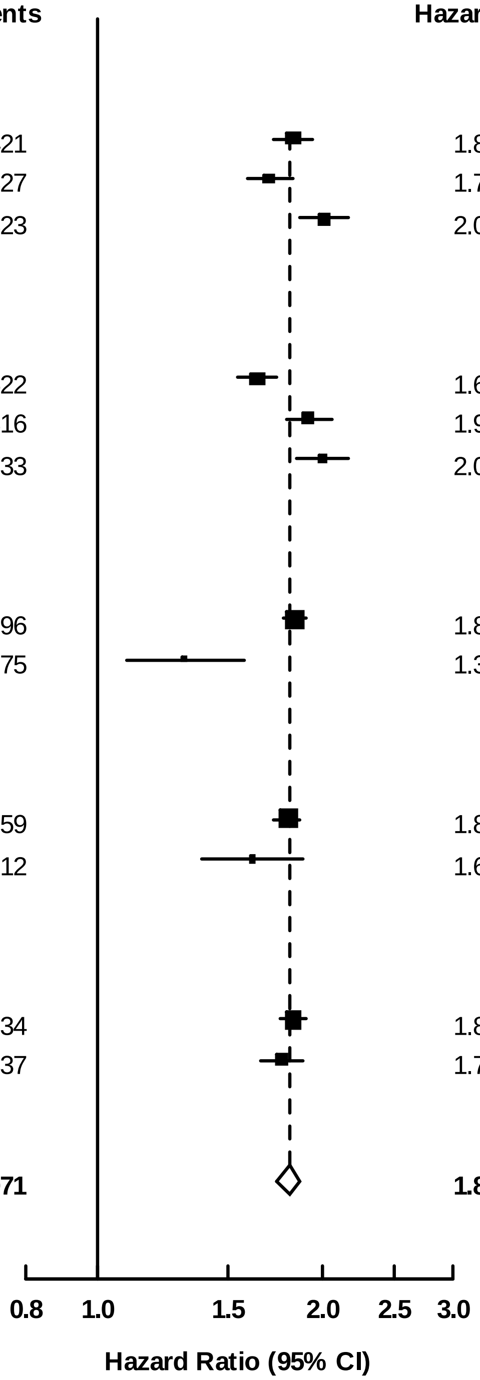


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.10: Overall: intracerebral haemorrhage incidence (1071 events): hazard ratios for 5 mm Hg usual DBP, by set (II) of potential effect modifiers (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
BMI, kg/m²			
<22	65	421	1.83 (1.72 - 1.94)
<25	63	327	1.70 (1.58 - 1.82)
≥25	60	323	2.01 (1.87 - 2.17)
Trend test: $\chi^2_1 = 2.6$ (p=0.1)			
MET, hrs/day			
<20	66	522	1.64 (1.55 - 1.74)
<30	61	316	1.92 (1.79 - 2.06)
≥30	58	233	2.01 (1.86 - 2.18)
Trend test: $\chi^2_1 = 18.9$ (p<0.001)			
Diabetes			
No	63	996	1.84 (1.77 - 1.91)
Yes	65	75	1.31 (1.09 - 1.57)
Heterogeneity test: $\chi^2_1 = 12.8$ (p<0.001)			
BP medication			
No	63	959	1.80 (1.73 - 1.87)
Yes	61	112	1.61 (1.38 - 1.88)
Heterogeneity test: $\chi^2_1 = 1.8$ (p=0.2)			
Fatal event			
No	62	734	1.83 (1.75 - 1.91)
Yes	65	337	1.77 (1.65 - 1.89)
Heterogeneity test: $\chi^2_1 = 0.7$ (p=0.4)			
Overall	**63**	**1071**	**1.81 (1.75 - 1.88)**



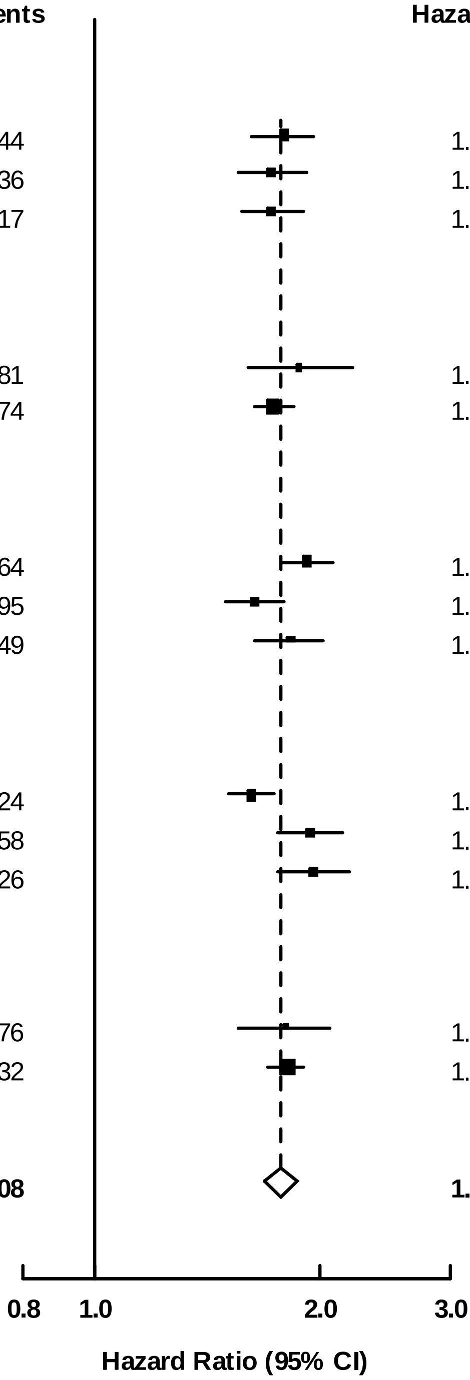
95% CI (closed square)

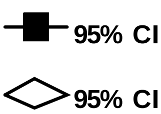
95% CI (open diamond)

Figure E.11: Male: intracerebral haemorrhage incidence (608 events): hazard ratios for 5 mm Hg higher usual DBP, by potential effect modifiers (among 184 949 male participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	66	144	1.79 (1.63 - 1.97)
Occassional	64	136	1.73 (1.56 - 1.92)
Weekly	63	217	1.73 (1.57 - 1.91)
Heterogeneity test: $\chi^2_2 = 0.3$ (p=0.9)			
Smoking†			
Never	66	81	1.88 (1.60 - 2.21)
Current	63	374	1.74 (1.63 - 1.85)
Heterogeneity test: $\chi^2_1 = 0.8$ (p=0.4)			
BMI, kg/m²			
<22	66	264	1.93 (1.79 - 2.09)
<25	64	195	1.64 (1.49 - 1.80)
≥25	61	149	1.83 (1.65 - 2.03)
Trend test: $\chi^2_1 = 1.5$ (p=0.2)			
MET, hrs/day			
<20	67	324	1.62 (1.50 - 1.74)
<30	63	158	1.94 (1.76 - 2.14)
≥30	58	126	1.96 (1.76 - 2.19)
Trend test: $\chi^2_1 = 10.2$ (p=0.001)			
Area			
Urban	64	76	1.80 (1.56 - 2.07)
Rural	64	532	1.81 (1.71 - 1.91)
Heterogeneity test: $\chi^2_1 = 0.0$ (p=0.9)			
Overall	**65**	**608**	**1.78 (1.69 - 1.87)**



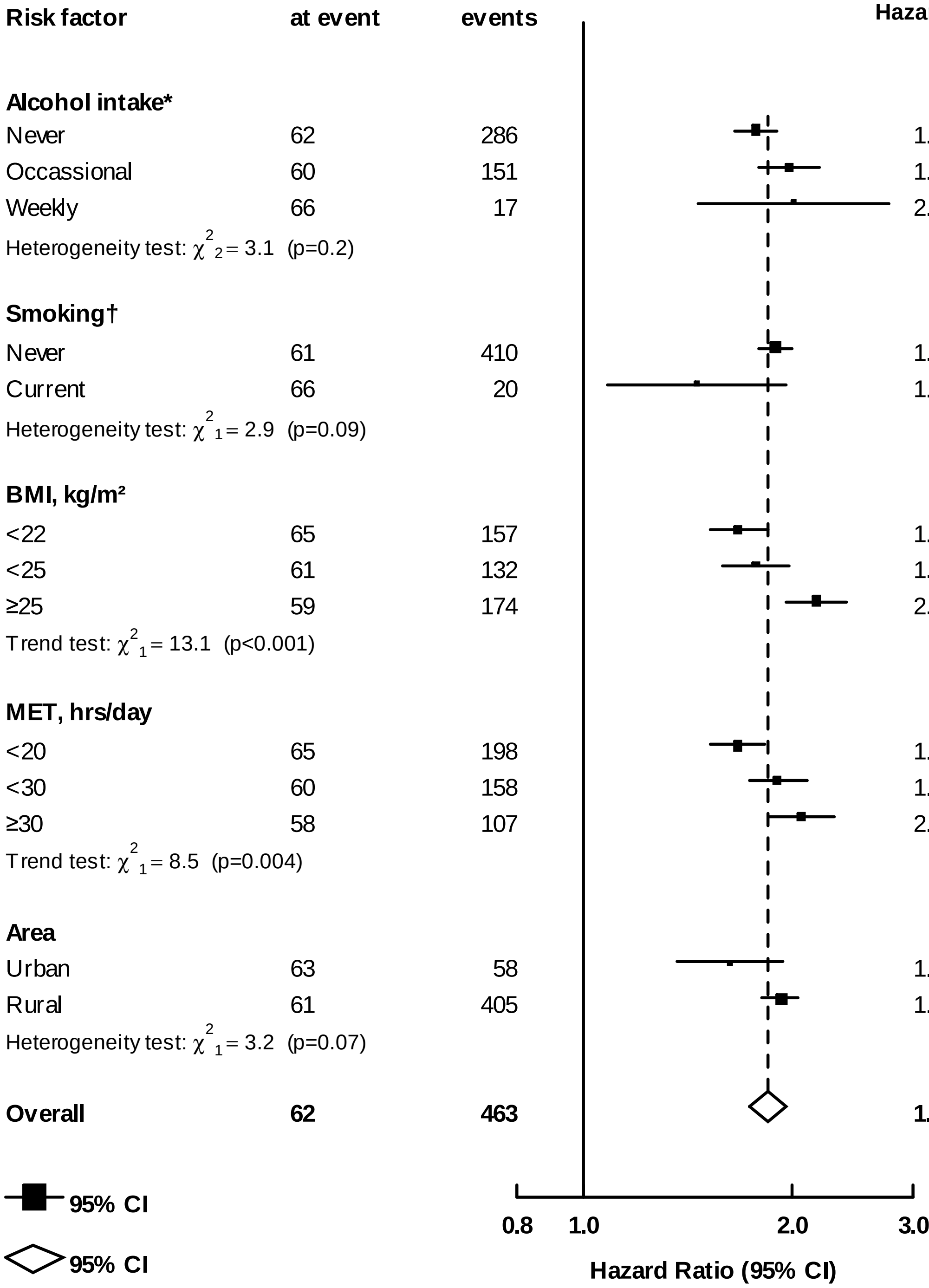


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.12: Female: intracerebral haemorrhage incidence (463 events): hazard ratios for 5 mm Hg higher usual DBP, by potential effect modifiers (among 270 489 female participants)

Hazard ratios (HR) adjusted for age at risk, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Risk factor	Mean age at event	No. of events	Hazard Ratio (95% CI)
Alcohol intake*			
Never	62	286	1.78 (1.66 - 1.91)
Occassional	60	151	1.98 (1.79 - 2.19)
Weekly	66	17	2.01 (1.46 - 2.76)
Heterogeneity test: $\chi^2_2 = 3.1$ (p=0.2)			
Smoking†			
Never	61	410	1.90 (1.79 - 2.01)
Current	66	20	1.46 (1.08 - 1.97)
Heterogeneity test: $\chi^2_1 = 2.9$ (p=0.09)			
BMI, kg/m²			
<22	65	157	1.68 (1.52 - 1.85)
<25	61	132	1.78 (1.60 - 1.99)
≥25	59	174	2.18 (1.97 - 2.41)
Trend test: $\chi^2_1 = 13.1$ (p<0.001)			
MET, hrs/day			
<20	65	198	1.67 (1.52 - 1.83)
<30	60	158	1.91 (1.73 - 2.10)
≥30	58	107	2.06 (1.84 - 2.30)
Trend test: $\chi^2_1 = 8.5$ (p=0.004)			
Area			
Urban	63	58	1.63 (1.37 - 1.94)
Rural	61	405	1.93 (1.81 - 2.05)
Heterogeneity test: $\chi^2_1 = 3.2$ (p=0.07)			
Overall	**62**	**463**	**1.85 (1.75 - 1.96)**

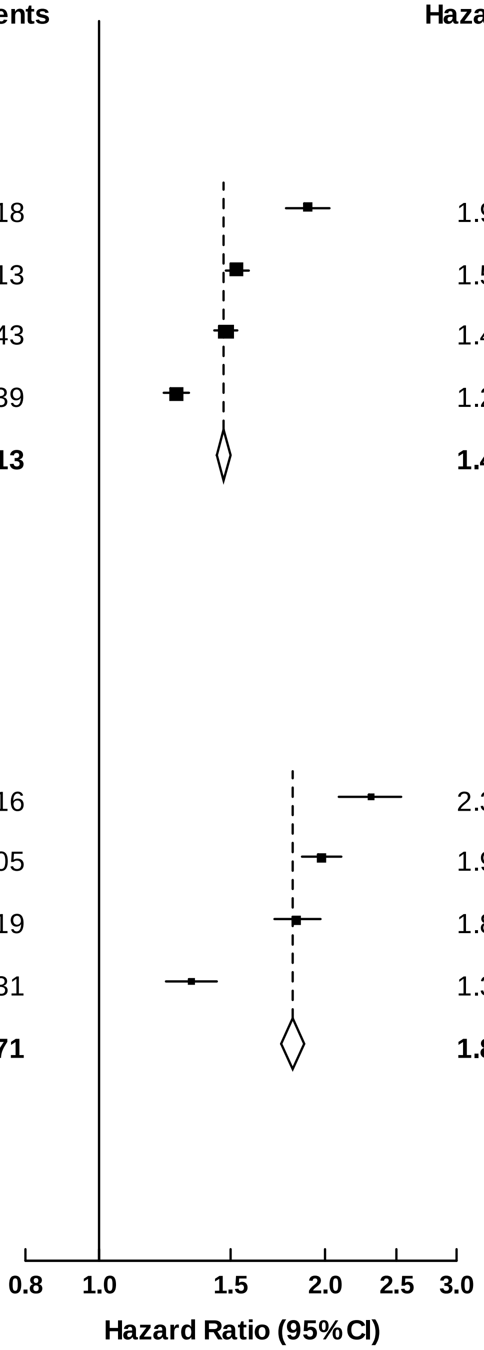


* Additionally adjusted for smoking (excludes strokes in ex-weekly, reduced-intake and monthly groups).
† Additionally adjusted for alcohol intake (excludes strokes in occasional and ex-regular groups).

Figure E.13: Stroke incidence: age-specific hazard ratios for 10 mm Hg higher usual SBP, by main stroke pathological types (among 455 438 participants)

Hazard ratios (HR) adjusted for sex, education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Age at risk, years	Mean age at event	No. of events	Hazard Ratio (95% CI)
Cerebral infarction			
40-49	46	318	1.90 (1.78 - 2.03)
50-59	56	1213	1.53 (1.48 - 1.59)
60-69	65	1543	1.48 (1.43 - 1.53)
70-79	74	1439	1.27 (1.22 - 1.32)
Overall	**64**	**4513**	**1.47 (1.44 - 1.50)**
Trend test: $\chi^2_1 = 103.3$ (p<0.001)			
Intracerebral haemorrhage			
40-49	46	116	2.31 (2.10 - 2.55)
50-59	56	305	1.98 (1.86 - 2.10)
60-69	65	319	1.84 (1.71 - 1.97)
70-79	74	331	1.33 (1.23 - 1.44)
Overall	**63**	**1071**	**1.82 (1.76 - 1.89)**
Trend test: $\chi^2_1 = 82.6$ (p<0.001)			



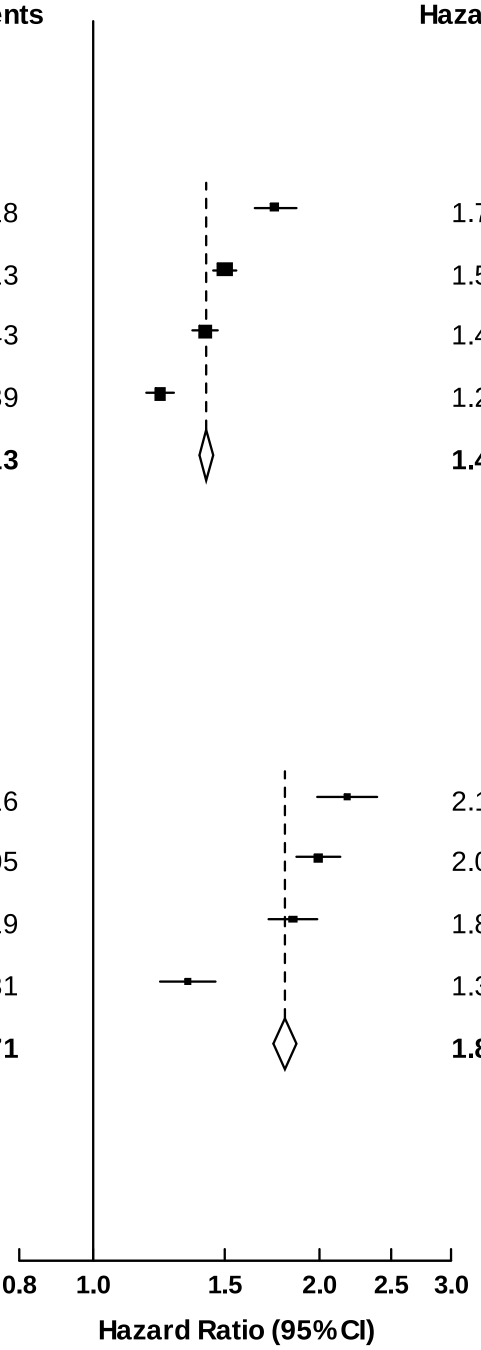
■ 95% CI

◇ 95% CI

Figure E.14: Stroke incidence: age-specific hazard ratios for 5 mm Hg higher usual DBP, by main stroke pathological types (among 455 438 participants)

Hazard ratios (HR) adjusted for sex, education and area. Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

Age at risk, years	Mean age at event	No. of events	Hazard Ratio (95% CI)
Cerebral infarction			
40-49	46	318	1.75 (1.64 - 1.86)
50-59	56	1213	1.50 (1.45 - 1.56)
60-69	65	1543	1.41 (1.36 - 1.47)
70-79	74	1439	1.23 (1.18 - 1.28)
Overall	**64**	**4513**	**1.42 (1.39 - 1.45)**
Trend test: $\chi^2_1 = 95.6$ (p<0.001)			
Intracerebral haemorrhage			
40-49	46	116	2.19 (1.99 - 2.41)
50-59	56	305	2.00 (1.87 - 2.14)
60-69	65	319	1.85 (1.72 - 1.99)
70-79	74	331	1.34 (1.23 - 1.45)
Overall	**63**	**1071**	**1.81 (1.75 - 1.88)**
Trend test: $\chi^2_1 = 65.4$ (p<0.001)			



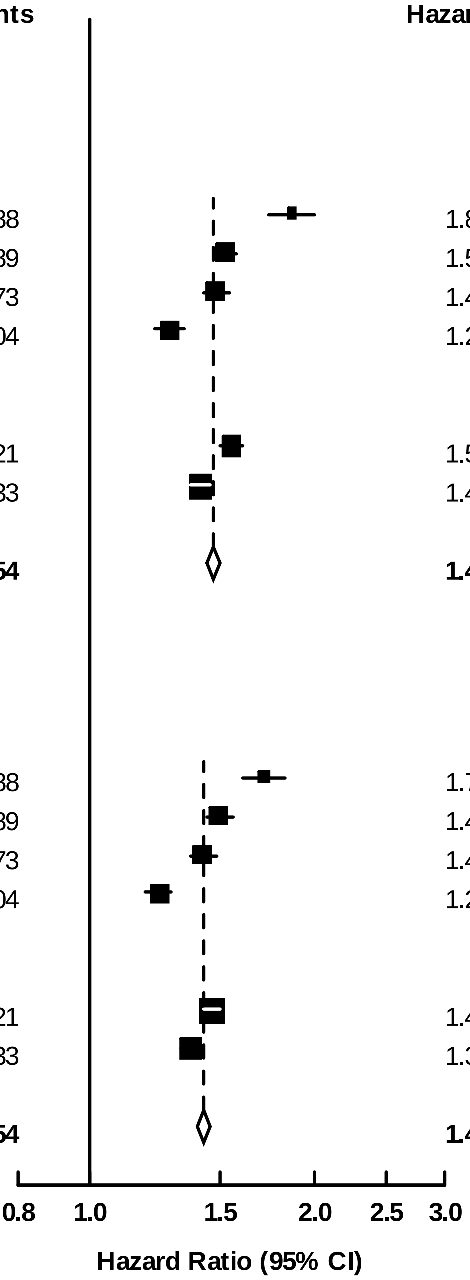
■ 95% CI

◇ 95% CI

Figure E.15: Excluding participants taking blood pressure medication: cerebral infarction incidence (4054 events): age-specific and sex-specific hazard ratios for 10 mm Hg higher usual SBP and 5 mm Hg higher usual DBP (among 438 837 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

	Mean age at event	No. of events	Hazard Ratio (95% CI)
Usual SBP			
Age at risk, years			
40-49	46	288	1.87 (1.74 - 2.01)
50-59	56	1089	1.52 (1.46 - 1.58)
60-69	65	1373	1.48 (1.43 - 1.54)
70-79	74	1304	1.28 (1.23 - 1.34)
Sex			
Male	65	2021	1.55 (1.50 - 1.60)
Female	64	2033	1.41 (1.37 - 1.45)
Overall	**64**	**4054**	**1.47 (1.44 - 1.50)**
Usual DBP			
Age at risk, years			
40-49	47	288	1.71 (1.60 - 1.83)
50-59	56	1089	1.49 (1.43 - 1.55)
60-69	65	1373	1.42 (1.37 - 1.48)
70-79	74	1304	1.24 (1.19 - 1.29)
Sex			
Male	65	2021	1.46 (1.42 - 1.50)
Female	63	2033	1.37 (1.33 - 1.42)
Overall	**64**	**4054**	**1.42 (1.39 - 1.45)**



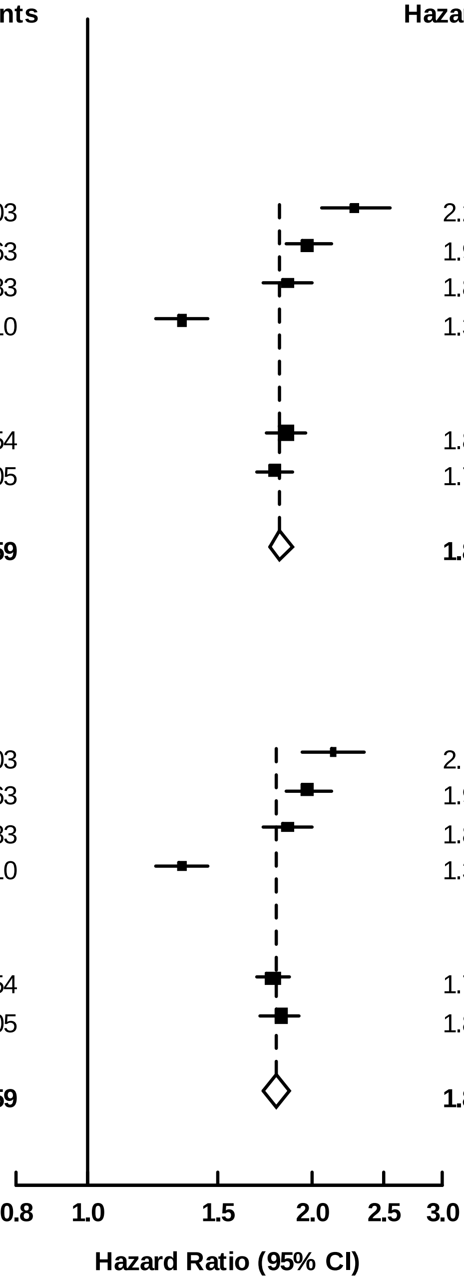
95% CI (closed square)

95% CI (open diamond)

Figure E.16: Excluding participants taking blood pressure medication: intracerebral haemorrhage incidence (959 events): age-specific and sex-specific hazard ratios for 10 mm Hg higher usual SBP and 5 mm Hg higher usual DBP (among 438 837 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

	Mean age at event	No. of events	Hazard Ratio (95% CI)
Usual SBP			
Age at risk, years			
40-49	46	103	2.29 (2.06 - 2.55)
50-59	56	263	1.98 (1.85 - 2.12)
60-69	65	283	1.86 (1.72 - 2.01)
70-79	74	310	1.34 (1.23 - 1.45)
Sex			
Male	64	554	1.85 (1.75 - 1.96)
Female	62	405	1.79 (1.69 - 1.89)
Overall	**63**	**959**	**1.82 (1.75 - 1.89)**
Usual DBP			
Age at risk, years			
40-49	45	103	2.14 (1.94 - 2.37)
50-59	56	263	1.98 (1.85 - 2.12)
60-69	65	283	1.86 (1.72 - 2.01)
70-79	74	310	1.34 (1.23 - 1.45)
Sex			
Male	65	554	1.78 (1.69 - 1.88)
Female	63	405	1.82 (1.71 - 1.93)
Overall	**64**	**959**	**1.80 (1.73 - 1.87)**



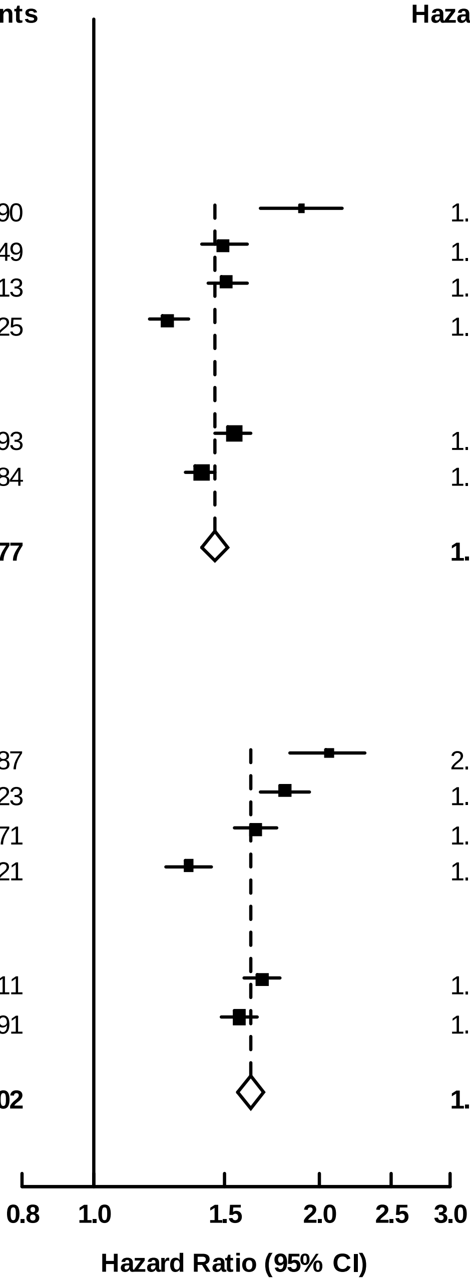
■ 95% CI

◇ 95% CI

Figure E.17: Restricted to stroke events not known to involve imaging with CT/MRI scan: stroke incidence: age-specific and sex-specific hazard ratios for 10 mm Hg higher usual SBP, by main stroke pathological types (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

	Mean age at event	No. of events	Hazard Ratio (95% CI)
Cerebral infarction			
Age at risk, years			
40-49	46	90	1.90 (1.68 - 2.15)
50-59	56	349	1.49 (1.39 - 1.60)
60-69	65	513	1.51 (1.42 - 1.60)
70-79	74	525	1.26 (1.18 - 1.34)
Sex			
Male	65	693	1.54 (1.46 - 1.63)
Female	64	784	1.39 (1.33 - 1.46)
Overall	**64**	**1477**	**1.45 (1.40 - 1.51)**
Intracerebral haemorrhage			
Age at risk, years			
40-49	46	87	2.06 (1.84 - 2.31)
50-59	56	223	1.80 (1.67 - 1.94)
60-69	65	371	1.65 (1.54 - 1.76)
70-79	74	421	1.34 (1.25 - 1.43)
Sex			
Male	65	611	1.68 (1.59 - 1.77)
Female	63	491	1.57 (1.49 - 1.66)
Overall	**64**	**1102**	**1.62 (1.56 - 1.68)**



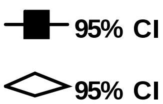
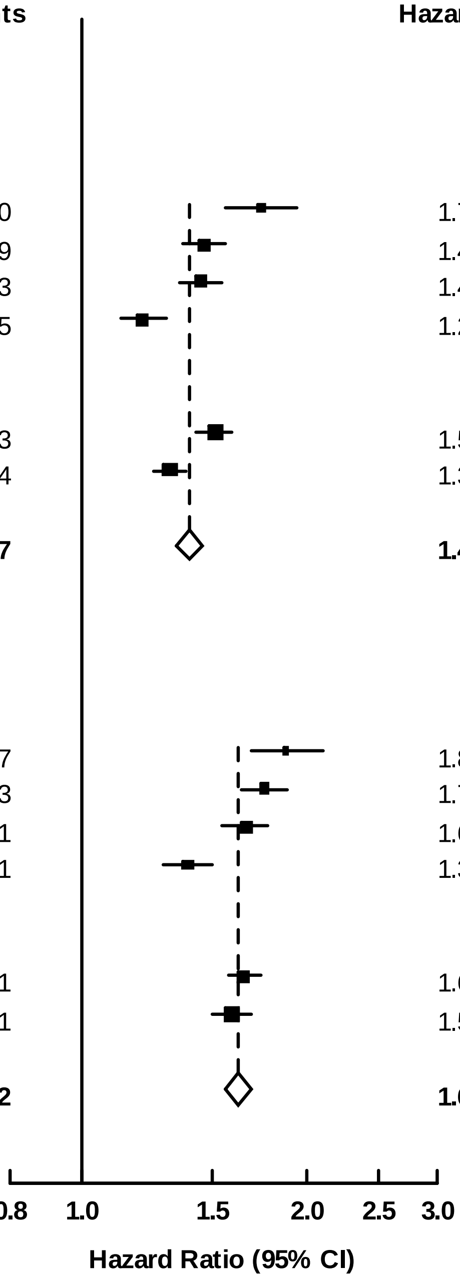


Figure E.18: Restricted to stroke events not known to involve imaging with CT/MRI scan: stroke incidence: age-specific and sex-specific hazard ratios for 5 mm Hg higher usual DBP, by main stroke pathological types (among 455 438 participants)

Hazard ratios (HR) adjusted for age at risk, sex, education and area (where appropriate). Each closed square represents HR with area inversely proportional to the variance of the log HR. The dotted vertical line indicates the overall HR and the open diamond indicates the 95% CI of the overall result.

	Mean age at event	No. of events	Hazard Ratio (95% CI)
Cerebral infarction			
Age at risk, years			
40-49	46	90	1.74 (1.55 - 1.95)
50-59	56	349	1.46 (1.36 - 1.56)
60-69	65	513	1.44 (1.35 - 1.54)
70-79	74	525	1.21 (1.13 - 1.30)
Sex			
Male	65	693	1.51 (1.43 - 1.60)
Female	64	784	1.31 (1.25 - 1.38)
Overall	**64**	**1477**	**1.40 (1.35 - 1.46)**
Intracerebral haemorrhage			
Age at risk, years			
40-49	46	87	1.88 (1.68 - 2.10)
50-59	56	223	1.76 (1.64 - 1.89)
60-69	65	371	1.66 (1.55 - 1.78)
70-79	74	421	1.39 (1.29 - 1.49)
Sex			
Male	65	611	1.65 (1.57 - 1.74)
Female	63	491	1.59 (1.50 - 1.68)
Overall	**64**	**1102**	**1.62 (1.56 - 1.69)**



■ 95% CI

◇ 95% CI

Table E.3: Comparison between blood pressure indices as predictors of incidence of cerebral infarction and intracerebral haemorrhage, by age and by sex (among 455 438 participants)

Informativeness of a single measurement of a blood pressure index at baseline (as indicated by X^2_1 statistic relating it to incidence of stroke known to have involved imaging with CT/MRI scan).

	Informative for prediction of cerebral infarction, X^2_1 values					Informative for prediction of intracerebral haemorrhage, X^2_1 values				
	SBP	**DBP**	**Mid blood pressure**	**Mean arterial pressure**	**Pulse pressure**	**SBP**	**DBP**	**Mid blood pressure**	**Mean arterial pressure**	**Pulse pressure**
Age, years										
40-49	276	271	295	296	125	212	223	233	236	104
50-59	461	406	486	480	271	381	345	404	402	232
60-69	445	338	462	449	279	246	247	277	282	126
70-79	138	100	145	141	80	47	51	56	57	21
Sex										
Male	748	643	789	777	403	443	442	489	494	220
Female	572	473	599	589	352	443	423	481	484	263
Overall	1320	1116	1388	1366	755	886	865	970	978	483

Appendix F: CKB adjudication sub-study stroke adjudication form

Figure F.1: CKB event adjudication form for stroke

1 General Information from the medical notes

1.1 Participant ID [ ][ ][ ][ ][ ][ ][ ][ ][ ]

1.2 Sex ☐ M ☐ F

1.3 Date of birth [Y][Y][Y][Y] [M][M] [D][D]

1.4 Date of admission [Y][Y][Y][Y] [M][M] [D][D]

1.5 Date of discharge or death [Y][Y][Y][Y] [M][M] [D][D]

1.6 Match checklist information? ☐ Yes ☐ No

1.7 Same person? ☐ Yes ☐ No *If no, **STOP HERE***

1.1 Stroke/TIA somewhere in the notes? ☐ Yes ☐ No *If no, **STOP HERE***

1.8 Legibility of the medical records ☐ Good ☐ Fair ☐ Poor

1.9 Hospital department ☐ Neuro ☐ Internal ☐Other, specify here [________________]

2 Discharge summary diagnoses

2.1 Is the discharge summary available? ☐ Yes ☐ No **If no, go to section 3**

2.2 Is stroke the main diagnosis? ☐ Yes ☐ No If no, what is? [________________]

2.3 Subclassification of stroke reported?

☐ Acute stroke

- 2.3.1 ☐ Ischaemic
- 2.3.1 ☐ Ischaemic (lacunar)
- 2.3.1 ☐ Intracerebral haemorrhage
- 2.3.1 ☐ Subarachnoid haemorrhage
- 2.3.1 ☐ Other/unknown

☐ Old stroke

☐ Silent infarct

☐ TIA

☐ Stroke does not appear in the summary

2.4 Are there any other diagnoses reported?

	Yes	**No**
IHD	☐	☐
DM	☐	☐
Cancer	☐	☐
COPD	☐	☐

3 Prior medical history

3.1 Prior history of stroke? ☐ Yes ☐ No
If No, go to section 4

3.1.1 What subtype?
☐ Ischaemic stroke
☐ Intracerebral haemorrhage
☐ Subarachnoid haemorrhage
☐ Other/unknown

3.1.2 How long ago did the stroke occur? _____ yrs _____ months (enter 99 if unknown)

4 Signs and symptoms

4.1 Any neurological signs or symptoms reported? ☐ Yes ☐ No
If No, go to section 5

4.2 Date of stroke event | Y | Y | Y | Y | M | M | D | D |
Or, time prior to admission: | M | M | D | D |

	Yes	No
4.3 Was a formal neurological exam performed?	☐	☐
4.4 Did the patient have any of the following:		
4.4.1 acute focal symptoms consistent with a stroke	☐	☐
4.4.2 acute focal signs consistent with a stroke	☐	☐
4.4.3 deep coma	☐	☐
4.4.4 non-focal symptoms/signs consistent with a SAH	☐	☐
4.5 Duration of the signs/symptoms >24 hours (or surgery/death)?	☐	☐
4.6 Non-vascular cause for the symptoms/signs, e.g. trauma/tumour?	☐	☐

*Note:*____

____

____

5 Investigations

5.1 Were any of the following diagnostic investigations performed?	Yes	No
5.1.1 CT scan	☐	☐
5.1.2 MRI scan	☐	☐
5.1.3 Lumbar puncture	☐	☐
5.1.4 Angiography	☐	☐

If answer 'yes' to CT and/or MRI scan, please continue with section 5, otherwise go to section 6. Where possible please select CT scans performed within ten days of onset signs/symptoms of stroke and MRI scan performed within 3 months.

CT Scan

5.2 Is the report available? ☐ Yes ☐ No

If No, go to section on MRI scan

5.3 Radiological? ☐ Yes ☐ No

Note: ____

____

5.4 Date of scan? Y Y Y Y M M D D (enter 99 if unknown)

5.5 Did the CT scan report any of the following abnormalities?

	Yes	No
5.5.1 Ischaemic change	☐	☐
5.5.2 Ischaemic change (lacunar)	☐	☐
5.5.3 Intracerebral haemorrhage	☐	☐
5.5.4 Blood in the subarachnoid space	☐	☐
5.5.5 Normal	☐	☐
5.5.6 Other diagnosis	☐	☐

5.6 Abnormalities consistent in age and site to the clinical presentation?

	Yes	No
5.6.1 Ischaemic change	☐	☐
5.6.2 Ischaemic change (lacunar)	☐	☐
5.6.3 Intracerebral haemorrhage	☐	☐
5.6.4 Blood in the subarachnoid space	☐	☐

MRI scan

5.7 Is the report available? ☐ Yes ☐ No

If No, go to section 6

5.8 Radiological? ☐ Yes ☐ No

Note: ____

____

5.9 Date of scan? Y Y Y Y M M D D (enter 99 if unknown)

5.10 Did the MRI scan report any of the following abnormalities?

	Yes	No
5.10.1 Ischaemic change	☐	☐
5.10.2 Ischaemic change (lacunar)	☐	☐
5.10.3 Intracerebral haemorrhage	☐	☐
5.10.4 Blood in the subarachnoid space	☐	☐
5.10.5 Normal	☐	☐
5.10.6 Other diagnosis	☐	☐

5.11 Abnormalities consistent in age and site to the clinical presentation?

	Yes	No
5.11.1 Ischaemic change	☐	☐
5.11.2 Ischaemic change (lacunar)	☐	☐
5.11.3 Intracerebral haemorrhage	☐	☐
5.11.4 Blood in the subarachnoid space	☐	☐

6 Medications

6.1 Were any of the following given in hospital?	**Yes**	**No**
6.1.1 Aspirin	☐	☐
6.1.2 Clopidogrel	☐	☐
6.1.3 Anticoagulant drugs	☐	☐
6.1.4 Thrombolysis	☐	☐
6.1.5 Statin	☐	☐
6.1.6 Any TCM	☐	☐
6.1.7 Other medications	☐	☐

7 Vital status at discharge

7.1 Patient's vital status at discharge from hospital?
- ☐ Alive
- ☐ Dead
- ☐ Unknown

7.1.1 If the patient died, was an autopsy performed?
- ☐ Yes
- ☐ No/Unknown

8 Reviewer diagnosis

8.1 Is there sufficient evidence to support the diagnosis of stroke?
- ☐ Yes, definitely
- ☐ Yes, possible
- ☐ No, very unlikely
- ☐ No, definitely

8.1.1 If yes, what in your opinion is the most likely pathological type of stroke?
- ☐ Ischaemic
- ☐ Ischaemic (lacunar)
- ☐ Intracerebral haemorrhage
- ☐ Subarachnoid haemorrhage
- ☐ Insufficient data

8.1.1.1 Level of evidence to support the diagnosis of pathological type?
- ☐ Yes, definitely
- ☐ Yes, possible
- ☐ No, very unlikely
- ☐ No, definitely

8.1.2 If no, is another diagnosis more likely?
- ☐ TIA
- ☐ Silent infarct
- ☐ Old stroke
- ☐ Insufficient evidence
- ☐ Other condition, please specify: _______________

8.2 Does the case need further review by an expert panel? ☐ Yes ☐ No

If ischaemic stroke or intracerebral haemorrhage selected in question 8.1.1, please complete section 9 otherwise go to section 10

9 Additional questions: Information to subtype stroke events

Extended information on ischaemic stroke events

		Yes	No
Do the notes from the neurological exam allow the pattern of neurological deficit to be described?		☐	☐
9.1	What was the pattern of neurological deficit		
9.1.1	Unilateral weakness (and/or sensory deficit) affecting face	☐	☐
9.1.2	Unilateral weakness (and/or sensory deficit) affecting arm or hand	☐	☐
9.1.3	Unilateral weakness (and/or sensory deficit) affecting leg or foot	☐	☐
9.1.4	Dysphasia	☐	☐
9.1.5	Homonymous hemianopia	☐	☐
9.1.6	Visuospatial disorder	☐	☐
9.1.7	Brainstem or cerebellar signs (e.g. nystagmus or ataxia)	☐	☐
9.1.8	Other neurological deficit	☐	☐
9.1.9	Pattern of neurological deficit unclear	☐	☐
9.2	Did the patient undergo imaging of their internal carotid arteries?	☐	☐
9.2.1	If yes, was ≥70% internal carotid artery stenosis noted on the same side as the lesion which caused the stroke?	☐	☐
	If no, go to section 10		
9.3	Did the patient have a post-stroke ECG?	☐	☐
9.3.1	If yes, is there evidence that the patient had atrial fibrillation?	☐	☐
9.4	Did the patient receive a post-stroke echocardiogram?	☐	☐
9.4.1	If yes, is there evidence that the patient had cardiac valve disease?	☐	☐
9.5	Do the notes indicate that the patient had a history of atrial fibrillation or cardiac valve disease?		
9.5.1	Atrial fibrillation	☐	☐
9.5.2	Cardiac value disease	☐	☐

Extended information on intracerebral haemorrhage events

9.6 Did the CT/MRI scan locate the haemorrhage to any of the following regions?

☐ Lobar ☐ Deep ☐ Lobar and deep ☐ Infratentorial ☐ Other ☐ Not noted ☐ Insufficient data

10 Reviewer's remarks

If checklist USS box ticked but report not available, please tick here ☐

Reviewer's name: **Date of review:**

References

1. The Global Burden of Disease: 2004 update. World Health Organization, 2008. (Accessed 01/11/12, at http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/index.html.)

2. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. Lancet 2002;360:1347-60.

3. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH, Kong LZ. Stroke in China: epidemiology, prevention, and management strategies. Lancet neurology 2007;6:456-64.

4. Aho K, Harmsen P, Hatano S, Marquardsen J, Smirnov VE, Strasser T. Cerebrovascular disease in the community: results of a WHO collaborative study. Bulletin of the World Health Organization 1980;58:113-30.

5. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke; a journal of cerebral circulation 2009;40:2276-93.

6. Caplan LR. Transient ischemic attack with abnormal diffusion-weighted imaging results: what's in a name? Archives of neurology 2007;64:1080-2.

7. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet 2008;371:1612-23.

8. WHO STEPS Stroke manual: the WHO STEPwise approach to stroke surveillanceWorld Health Organization. World Health Organisation, 2006. (Accessed 01/05/2012, at http://www.who.int/chp/steps/Manual.pdf)

9. Jiang B, Wang WZ, Chen H, et al. Incidence and trends of stroke and its subtypes in China: results from three large cities. Stroke; a journal of cerebral circulation 2006;37:63-8.

10. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke; a journal of cerebral circulation 1995;26:361-7.

11. Wu Z, Yao C, Zhao D, et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part i: morbidity and mortality monitoring. Circulation 2001;103:462-8.

12. He J, Klag MJ, Wu Z, Whelton PK. Stroke in the People's Republic of China. I. Geographic variations in incidence and risk factors. Stroke; a journal of cerebral circulation 1995;26:2222-7.

13. Xue GB, Yu BX, Wang XZ, Wang GQ, Wang ZY. Stroke in urban and rural areas of China. Chinese medical journal 1991;104:697-704.

14. Mortality, Biochemistry, Diet and Lifestyle in Rural China. Oxford University Press, 2006. (Accessed 01/11/12, at http://www.ctsu.ox.ac.uk/~china/monograph/index.htm.)

15. Zhao D, Liu J, Wang W, et al. Epidemiological transition of stroke in China: twenty-one-year observational study from the Sino-MONICA-Beijing Project. Stroke; a journal of cerebral circulation 2008;39:1668-74.

16. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. Journal of neurology, neurosurgery, and psychiatry 1990;53:16-22.

17. Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA. Incidence of the major stroke subtypes: initial findings from the North East Melbourne stroke incidence study (NEMESIS). Stroke; a journal of cerebral circulation 2001;32:1732-8.

18. World Population Prospects, the 2010 Revision. United Nations, 2012. (Accessed 01/11/12, at http://esa.un.org/unpd/wpp/Excel-Data/population.htm.)

19. Yang QD, Niu Q, Zhou YH, et al. Incidence of cerebral hemorrhage in the Changsha community. A prospective study from 1986 to 2000. Cerebrovasc Dis 2004;17:303-13.

20. Zhang LF, Yang J, Hong Z, et al. Proportion of different subtypes of stroke in China. Stroke; a journal of cerebral circulation 2003;34:2091-6.

21. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. Stroke; a journal of cerebral circulation 1997;28:491-9.

22. Ingall T, Asplund K, Mahonen M, Bonita R. A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study. Stroke; a journal of cerebral circulation 2000;31:1054-61.

23. Blood Pressure Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527-35.

24. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke; a journal of cerebral circulation 2004;35:1024.

25. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.

26. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360:1903-13.

27. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. Journal of hypertension 2003;21:707-16.

28. Clarke R, Shipley M, Lewington S, et al. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. American journal of epidemiology 1999;150:341-53.

29. Carandang R, Seshadri S, Beiser A, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA : the journal of the American Medical Association 2006;296:2939-46.

30. Goldacre MJ, Duncan M, Griffith M, Rothwell PM. Mortality rates for stroke in England from 1979 to 2004: trends, diagnostic precision, and artifacts. Stroke; a journal of cerebral circulation 2008;39:2197-203.

31. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke; a journal of cerebral circulation 2011;42:517-84.

32. Lindekleiv H, Sandvei MS, Njolstad I, et al. Sex differences in risk factors for aneurysmal subarachnoid hemorrhage: a cohort study. Neurology 2011;76:637-43.

33. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519.

34. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ 1989;298:789-94.

35. Asia Pacific Cohort Studies Collaboration. A comparison of the associations between risk factors and cardiovascular disease in Asia and Australasia. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology 2005;12:484-91.

36. Asia Pacific Cohort Studies Collaboration. Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. Stroke; a journal of cerebral circulation 2005;36:1360-5.

37. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.

38. Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370:1829-39.

39. Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. JAMA : the journal of the American Medical Association 2009;302:1993-2000.

40. Lewington S, Bragg F, Clarke R. A review on metaanalysis of biomarkers: promises and pitfalls. Clinical chemistry 2012;58:1192-204.

41. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117-25.

42. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet 2012;380:601-10.

43. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083-96.

44. Asia Pacific Cohort Studies Collaboration. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. International journal of epidemiology 2004;33:751-8.

45. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obesity research 1998;6 Suppl 2:51S-209S.

46. Emberson JR, Bennett DA. Effect of alcohol on risk of coronary heart disease and stroke: causality, bias, or a bit of both? Vascular health and risk management 2006;2:239-49.

47. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: a meta-analysis. JAMA : the journal of the American Medical Association 2003;289:579-88.

48. Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension 2001;38:1112-7.

49. Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. BMJ 1999;319:1523-8.

50. Lee CD, Folsom AR, Blair SN. Physical activity and stroke risk: a meta-analysis. Stroke; a journal of cerebral circulation 2003;34:2475-81.

51. Wendel-Vos GC, Schuit AJ, Feskens EJ, et al. Physical activity and stroke. A meta-analysis of observational data. International journal of epidemiology 2004;33:787-98.

52. Press V, Freestone I, George CF. Physical activity: the evidence of benefit in the prevention of coronary heart disease. QJM : monthly journal of the Association of Physicians 2003;96:245-51.

53. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA : the journal of the American Medical Association 2006;295:655-66.

54. He K, Merchant A, Rimm EB, et al. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. BMJ 2003;327:777-82.

55. Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. BMJ 1997;314:112-7.

56. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567.

57. Alam S, Johnson AG. A meta-analysis of randomised controlled trials (RCT) among healthy normotensive and essential hypertensive elderly patients to

determine the effect of high salt (NaCl) diet of blood pressure. Journal of human hypertension 1999;13:367-74.

58. He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. Journal of human hypertension 2002;16:761-70.

59. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. Lancet 2006;367:320-6.

60. Ascherio A, Hennekens C, Willett WC, et al. Prospective study of nutritional factors, blood pressure, and hypertension among US women. Hypertension 1996;27:1065-72.

61. John JH, Ziebland S, Yudkin P, Roe LS, Neil HA. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. Lancet 2002;359:1969-74.

62. Svetkey LP, Simons-Morton D, Vollmer WM, et al. Effects of dietary patterns on blood pressure: subgroup analysis of the Dietary Approaches to Stop Hypertension (DASH) randomized clinical trial. Archives of internal medicine 1999;159:285-93.

63. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895-905.

64. International Stroke Genetics Consortium. (Accessed 01/11/12, at http://www.strokegenetics.org/.)

65. Traylor M, Farrall M, Holliday EG, et al. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE Collaboration): a meta-analysis of genome-wide association studies. Lancet neurology 2012;11:951-62.

66. Biffi A, Sonni A, Anderson CD, et al. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. Annals of neurology 2010;68:934-43.

67. Flossmann E, Schulz UG, Rothwell PM. Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke. Stroke; a journal of cerebral circulation 2004;35:212-27.

68. People's Republic of China, Ministry of Health. China Health Statistics Yearbook 2009. Beijing: Peking Union Medical College Press; 2009.

69. World Health Organisation mortality statistics. World Health Organisation, 2009. (Accessed 01/12/2012, at http://www.who.int/whosis/mort/download/en/index.html.)

70. Adams HP, Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke; a journal of cerebral circulation 1993;24:35-41.

71. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet 2007;369:306-18.

72. Auer RN, Sutherland GR. Primary intracerebral hemorrhage: pathophysiology. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques 2005;32 Suppl 2:S3-12.

73. Zhang XF, Attia J, D'Este C, Yu XH. Prevalence and magnitude of classical risk factors for stroke in a cohort of 5092 Chinese steelworkers over 13.5 years of follow-up. Stroke; a journal of cerebral circulation 2004;35:1052-6.

74. Zhou M, Offer A, Yang G, et al. Body mass index, blood pressure, and mortality from stroke: a nationally representative prospective study of 212,000 Chinese men. Stroke; a journal of cerebral circulation 2008;39:753-9.

75. Gu D, Kelly TN, Wu X, et al. Blood pressure and risk of cardiovascular disease in Chinese men and women. American journal of hypertension 2008;21:265-72.

76. Qiu D, Mei J, Tanihata T, Kawaminami K, Minowa M. A cohort study on cerebrovascular disease in middle-aged and elderly population in rural areas in Jiangxi Province, China. Journal of epidemiology / Japan Epidemiological Association 2003;13:149-56.

77. Dorjgochoo T, Shu XO, Zhang X, et al. Relation of blood pressure components and categories and all-cause, stroke and coronary heart disease mortality in urban Chinese women: a population-based prospective study. Journal of hypertension 2009;27:468-75.

78. Chen Z, Lee L, Chen J, et al. Cohort profile: the Kadoorie Study of Chronic Disease in China (KSCDC). International journal of epidemiology 2005;34:1243-9.

79. Yang G, Hu J, Rao KQ, Ma J, Rao C, Lopez AD. Mortality registration and surveillance in China: History, current situation and challenges. Population health metrics 2005;3:3.

80. International Classification of Diseases (ICD-10). World Health Organization, 2012. (Accessed 14/11/12, at http://www.who.int/classifications/icd/en/.)

81. Wang L, Kong L, Wu F, Bai Y, Burton R. Preventing chronic diseases in China. Lancet 2005;366:1821-4.

82. Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CD, Heuschmann PU. Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. Journal of neurology, neurosurgery, and psychiatry 2009;80:1012-8.

83. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. Stroke; a journal of cerebral circulation 2011;42:1489-94.

84. Lewington S, Li L, Sherliker P, et al. Seasonal variation in blood pressure and its relationship with outdoor temperature in 10 diverse regions of China: the China Kadoorie Biobank. Journal of hypertension 2012;30:1383-91.

85. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Medicine and science in sports and exercise 2011;43:1575-81.

86. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. World Health Organisation, 2006. (Accessed 14/11/2012, at http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/index.html.)

87. Victora CG, Huttly SR, Fuchs SC, Olinto MT. The role of conceptual frameworks in epidemiological analysis: a hierarchical approach. International journal of epidemiology 1997;26:224-7.

88. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC medical research methodology 2008;8:70.

89. Rosner B, Willett WC, Spiegelman D. Correction of logistic regression relative risk estimates and confidence intervals for systematic within-person measurement error. Statistics in medicine 1989;8:1051-69; discussion 71-3.

90. Fibrinogen Studies Collaboration. Regression dilution methods for meta-analysis: assessing long-term variability in plasma fibrinogen among 27,247 adults in 15 prospective studies. International journal of epidemiology 2006;35:1570-8.

91. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective

observational studies corrected for the regression dilution bias. Lancet 1990;335:765-74.

92. Knuiman MW, Divitini ML, Buzas JS, Fitzgerald PE. Adjustment for regression dilution in epidemiological regression analyses. Annals of epidemiology 1998;8:56-63.

93. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. Statistics in medicine 1991;10:1025-35.

94. Lindsted KD, Fraser GE, Steinkohl M, Beeson WL. Healthy volunteer effect in a cohort study: temporal resolution in the Adventist Health Study. Journal of clinical epidemiology 1996;49:783-90.

95. Wolf-Maier K, Cooper RS, Banegas JR, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA : the journal of the American Medical Association 2003;289:2363-9.

96. Franklin SS, Gustin Wt, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96:308-15.

97. Martins D, Nelson K, Pan D, Tareen N, Norris K. The effect of gender on age-related blood pressure changes and the prevalence of isolated systolic hypertension among older adults: data from NHANES III. The journal of gender-specific medicine : JGSM : the official journal of the Partnership for Women's Health at Columbia 2001;4:10-3, 20.

98. Loucks EB, Abrahamowicz M, Xiao Y, Lynch JW. Associations of education with 30 year life course blood pressure trajectories: Framingham Offspring Study. BMC public health 2011;11:139.

99. Strand BH, Tverdal A. Trends in educational inequalities in cardiovascular risk factors: a longitudinal study among 48,000 middle-aged Norwegian men and women. European journal of epidemiology 2006;21:731-9.

100. Marmot MG, Elliott P, Shipley MJ, et al. Alcohol and blood pressure: the INTERSALT study. BMJ 1994;308:1263-7.

101. Barnett AG, Sans S, Salomaa V, Kuulasmaa K, Dobson AJ. The effect of temperature on systolic blood pressure. Blood pressure monitoring 2007;12:195-203.

102. Madsen C, Nafstad P. Associations between environmental exposure and blood pressure among participants in the Oslo Health Study (HUBRO). European journal of epidemiology 2006;21:485-91.

103. Robinson TG, Potter JF. Blood pressure in acute stroke. Age and ageing 2004;33:6-12.

104. Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: what makes studies comparable? Stroke; a journal of cerebral circulation 1996;27:550-8.

105. Leppala JM, Virtamo J, Heinonen OP. Validation of stroke diagnosis in the National Hospital Discharge Register and the Register of Causes of Death in Finland. European journal of epidemiology 1999;15:155-60.

106. Ninomiya T, Donnan G, Anderson N, et al. Effects of the end point adjudication process on the results of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). Stroke; a journal of cerebral circulation 2009;40:2111-5.

107. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. Pharmacoepidemiology and drug safety 2011;20:236-42.

108. Asia Pacific Cohort Studies Collaboration. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. International journal of epidemiology 2004;33:751-8.

109. Asia Pacific Cohort Studies Collaboration. Cigarette smoking, systolic blood pressure, and cardiovascular diseases in the Asia-Pacific region. Stroke; a journal of cerebral circulation 2008;39:1694-702.

110. Asia Pacific Cohort Studies Collaboration. Joint effects of systolic blood pressure and serum cholesterol on cardiovascular disease in the Asia Pacific region. Circulation 2005;112:3384-90.

111. Hisham NF, Bayraktutan U. Epidemiology, Pathophysiology, and Treatment of Hypertension in Ischaemic Stroke Patients. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2012.

112. Lammie GA. Pathology of small vessel stroke. British medical bulletin 2000;56:296-306.

113. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet 2009;373:1632-44.

114. Feigin VL, Rinkel GJ, Lawes CM, et al. Risk factors for subarachnoid hemorrhage: an updated systematic review of epidemiological studies. Stroke; a journal of cerebral circulation 2005;36:2773-80.

115. Markus HS. Stroke genetics. Human molecular genetics 2011;20:R124-31.

116. Jackson C, Sudlow C. Are lacunar strokes really different? A systematic review of differences in risk factor profiles between lacunar and nonlacunar infarcts. Stroke; a journal of cerebral circulation 2005;36:891-901.

117. Jackson CA, Sudlow CL. Is hypertension a more frequent risk factor for deep than for lobar supratentorial intracerebral haemorrhage? Journal of neurology, neurosurgery, and psychiatry 2006;77:1244-52.

118. Jackson CA, Hutchison A, Dennis MS, et al. Differing risk factor profiles of ischemic stroke subtypes: evidence for a distinct lacunar arteriopathy? Stroke; a journal of cerebral circulation 2010;41:624-9.

119. Jackson CA, Hutchison A, Dennis MS, Wardlaw JM, Lewis SC, Sudlow CL. Differences between ischemic stroke subtypes in vascular outcomes support a distinct lacunar ischemic stroke arteriopathy: a prospective, hospital-based study. Stroke; a journal of cerebral circulation 2009;40:3679-84.

120. Traylor M, Farrall M, Holliday EG, et al. Genetic risk factors for ischaemic stroke and its subtypes (the METASTROKE collaboration): a meta-analysis of genome-wide association studies. Lancet neurology 2012;11:951-62.

121. Collins R. What makes UK Biobank special? Lancet 2012;379:1173-4.

122. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ 2013;346:f1325.

123. China Salt Substitute Study Collaborative G. Salt substitution: a low-cost strategy for blood pressure control among rural Chinese. A randomized, controlled trial. Journal of hypertension 2007;25:2011-8.

124. Keir SL, Wardlaw JM, Warlow CP. Stroke epidemiology studies have underestimated the frequency of intracerebral haemorrhage. A systematic review of imaging in epidemiological studies. Journal of neurology 2002;249:1226-31.

125. Wardlaw JM, Keir SL, Dennis MS. The impact of delays in computed tomography of the brain on the accuracy of diagnosis and subsequent management

in patients with minor stroke. Journal of neurology, neurosurgery, and psychiatry 2003;74:77-81.

126. Dimigen M, Keir S, Dennis M, Wardlaw J. Long-term visibility of primary intracerebral hemorrhage on magnetic resonance imaging. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association 2004;13:104-8.