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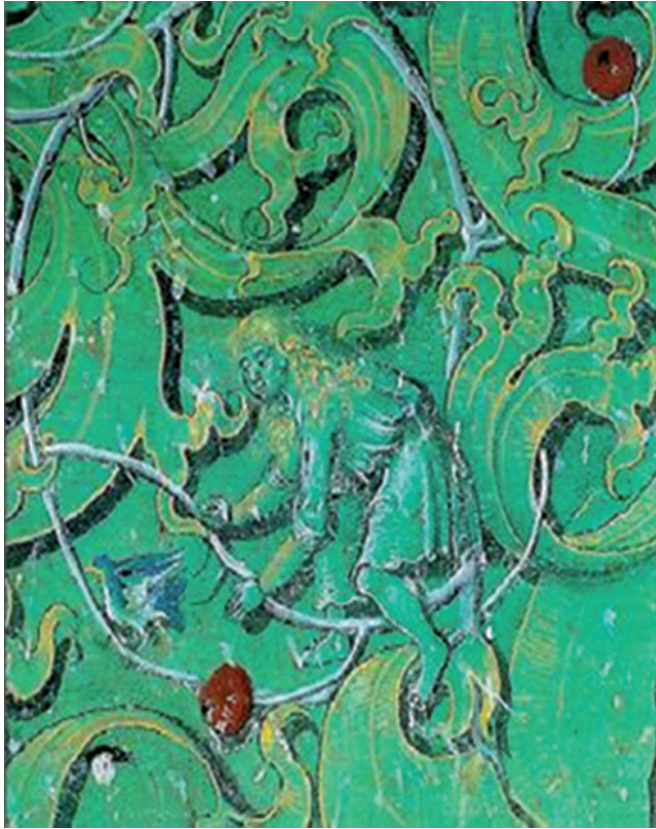
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# The Epidemiology of Intracerebral Haemorrhage

Risk Factors and Prognosis

Elisabet Zia

Lund University

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## Risk Factors and Prognosis

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# The Epidemiology of Intracerebral Haemorrhage

## Risk Factors and Prognosis

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**LUND UNIVERSITY**  
Faculty of Medicine

### **Doctoral dissertation**

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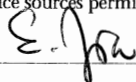
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Title and subtitle The epidemiology of intracerebral haemorrhage. Risk factors and prognosis.		
<p>Abstract</p> <p>The present thesis explored the epidemiology of intracerebral haemorrhage (ICH), i.e., factors associated to incidence and prognosis.</p> <p>In the population of Malmö (Malmö 1990 cohort), it was shown that immigrants from China/Vietnam and the Former Soviet Union had higher risk of ICH than citizens born in Sweden.</p> <p>Although hypertension is a well-known risk factor for stroke, the relation between blood pressure (BP) levels and stroke subtypes is less clear. In the Malmö Diet and Cancer cohort increasing BP was strongly associated with higher incidence of cerebral infarction, as measured by the crude and standardised incidence rates. However, in terms of relative risks (RR), the risk was highest for primary ICH (PICH), especially for nonlobar PICH.</p> <p>The results of previous studies have indicated differences in pathology and genetics between PICH subtypes by bleeding location. In the Malmö Preventive Project cohort, systolic BP and smoking were found to be associated with increased risk of lobar PICH. Systolic BP, psychiatric morbidity and diabetes were found to be associated with nonlobar PICH.</p> <p>Of 474 patients with PICH (Malmö Stroke Registry), 26% died within 28 days and 49% within three years. Male sex predicted 28-day and 3-year mortality, largely explained by high 28-day mortality in male patients older than 75 years.</p> <p>In conclusion, the incidence of ICH varies by country of birth. The impact of high BP, in terms of RR, is highest for nonlobar PICH. Smoking is associated with lobar PICH, and diabetes with nonlobar PICH. Female PICH patients have better survival than men.</p>		
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- I. Khan FA, Zia E, Janzon L, Engström G: Incidence of stroke and stroke subtypes in Malmö, Sweden, 1990-2000. Marked differences between groups defined by birth country. *Stroke* 2004;35:2054-2058.
- II. Zia E, Hedblad B, Pessah-Rasmussen H, Berglund G, Janzon L, Engström G: Blood pressure in relation to the incidence of cerebral infarction and intracerebral hemorrhage. Hypertensive hemorrhage: debated nomenclature is still relevant. *Stroke* 2007;38:2681-2685.
- III. Zia E, Pessah-Rasmussen H, Khan FA, Norrving B, Janzon L, Berglund G, Engström G: Risk factors for primary intracerebral hemorrhage: a population-based nested case-control study. *Cerebrovasc Dis* 2006;21:18-25.
- IV. Zia E, Engström G, Svensson P J, Norrving B, Pessah-Rasmussen H: Three-Year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage. *Stroke*, published on-line September 3, 2009.

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# SAMMANFATTNING

Enligt siffror från Riks-Stroke (nationellt kvalitetsregister för strokesjukvård), insjuknar ca 30 000 personer i stroke varje år i Sverige. Stroke kan indelas i huvudsakligen tre subtyper; 1) hjärninfarkt (cerebral infarkt), som oftast orsakas av ett eller flera blodkärl i hjärnan täpps till av en blodpropp, 2) hjärnblödning (intracerebralt hematoma), som orsakas av att ett blodkärl i hjärnan brister och leder till blödning i hjärnvävnaden och 3) hjärnhinneblödning (subarachnoidalblödning), där blödningen sker under spindelvävshinnan (arachnoidea). Antalet som insjuknar i stroke varje år, liksom andelen hjärnblödning, skiljer sig åt mellan olika länder och mellan olika etniska grupper.

Hjärnblödning utgör endast ca 10 % av alla stroke, men karakteriseras av dålig prognos. Utöver operation i utvalda fall, saknas det i nuläget effektiva behandlingsalternativ. Endast fyra tidigare större studier från Europa har rapporterat om prognos, och dödligheten efter en månad varierade mellan 31 och 51 %. Kunskap om prognos och prognostiska faktorer har betydelse för främst den enskilde patienten och dennes närstående, men även för planering av vårdinsatser. Det finns, i jämförelse med för t ex hjärninfarkt, förhållandevis få studier som belyser vilka faktorer som är förknippade med ökad risk för hjärnblödning. Förhöjt blodtryck är en välkänd riskfaktor, medan det är oklart om andra påverkbara faktorer som exempelvis diabetes och rökning ger ökad risk för hjärnblödning.

I denna avhandling studeras dels vilka faktorer som har samband med ökad risk för insjuknande i hjärnblödning, dels hur prognosen ser ut efter insjuknande, och vilka faktorer som har betydelse för kort- och långtidsöverlevnad samt återinsjuknande.

Det finns data som tyder på att hjärnblödning är en heterogen grupp, med skillnader i exempelvis genetiska faktorer beroende på blödningslokalisering. Lobär blödning drabbar loberna i storhjärnan och begreppet icke-lobär innefattar blödning i lillhjärnan samt mer djupliggande strukturer (hjärnstam, thalamus och basala ganglierna). Denna uppdelning har använts då vi velat belysa betydelsen av hjärnblödningens lokalisering i olika avseende.

I delarbete 1 fann vi att risken att insjukna i stroke varierade med födelseland. I undersökningen ingick alla registerade invånare i Malmö 1990 i åldrarna 40-89 år (118 134 personer). Under tio års uppföljning, drabbades 6082 av stroke, varav 615 var hjärnblödningar. Jämfört med personer födda i Sverige, hade immigranter från före detta Jugoslavien och Ungern, högre risk att insjukna i stroke (samtliga subtyper), efter att hänsyn tagits för ålder, kön, civilstånd och socioekonomiska faktorer. Risken att insjukna i hjärnblödning var högre hos personer födda i Kina/Vietnam och före detta Sovjetunionen. Den ökade risken för hjärnblödning hos immigranter från Kina/Vietnam överensstämmer med den, i jämförelse med väst, högre frekvensen av hjärnblödning i Asien, vilket delvis anses bero på hög frekvens av högt blodtryck. Från tidigare studier i Malmö vet vi att risken för insjuknande i stroke är högre i stadsdelar

med låg socioekonomisk status. Den ökade risken för hjärnblödning varierar således med födelse-land och tycks kvarstå efter emigration. Det är oklart till vilken grad riskfaktorer för kärlsjukdom (som hypertoni, rökning, diabetes), genetiska faktorer respektive socioekonomiska faktorer bidrar till detta.

Även om högt blodtryck är en välkänd riskfaktor för insjuknande i stroke, är sambandet mellan graden av blodtryck och risken för respektive stroke subtyp inte lika klarlagt. I delarbete 2 ingick deltagare från Malmö Kost Cancer studie (27 702 personer). Under uppföljningstiden (medel 7.5 år) drabbades 701 personer av stroke, varav 88 var hjärnblödning. Vi fann att i absoluta tal var risken att insjukna i hjärninfarkt högre än för hjärnblödning i alla blodtrycksgrupper, vilket är viktigt ur folkhälsoperspektiv. Den relativa risken att insjukna i förhållande till stigande blodtryck, var emellertid högst för hjärnblödning, och främst för icke-lobär hjärnblödning. För denna grupp, var den relativa risken att insjukna 26 gånger större vid blodtrycksvärden på 180/110 mmHg, och däröver, jämfört med blodtryck på 140/90 mmHg. Motsvarande riskökning för hjärninfarkt var 3. Hjärnblödning är, i förhållandevis till hjärninfarkt, ovanligt vid normalt blodtryck vilket kan förklara den med stigande blodtryck branta ökningen för hjärnblödning.

I delarbete 3 fann vi att, utöver förhöjt blodtryck, var diabetes oberoende riskfaktor för icke-lobär hjärnblödning, medan rökning var förknippat med ökad risk för lobär hjärnblödning. Diabetes förekom hos ca 10 % av personerna som drabbades av icke-lobär hjärnblödning, i jämförelse med 2 % vid lobär blödning. Rökning medförde fördubblad risk att drabbas av lobär hjärnblödning. Det är tidigare känt att depression är riskfaktor för stroke, men sambandet mellan depression och hjärnblödning var inte klarlagt. Vi fann att psykiatrisk morbiditet medförde ökad risk att drabbas av icke-lobär hjärnblödning. I studien ingick deltagare från Malmö Förebyggande Medicin studie. Under uppföljningsperioden (medel 14 år), insjuknade 147 personer i hjärnblödning.

I sista delarbetet utvärderades prognosen hos 474 patienter (Malmöbor) som drabbats av hjärnblödning mellan 1993-2000. Vi fann att kvinnor hade bättre kort- och långtidsöverlevnad än män. Skillnaden var mest uttalad hos äldre personer ( $\geq 75$  år). I denna åldersgrupp avled 26 % av kvinnorna inom en månad efter insjuknande, jämfört med 41 % av männen. Efter tre år hade ungefär hälften av patienterna avlidit. Utöver manligt kön, var blödningslokalisering (central och hjärnstam), förekomst av blod i ventriklar, stor blödningsvolym och låg medvetandegrad vid ankomst till sjukhus förenat med ökad risk att avlida. 12 % av patienterna drabbades av en ny stroke inom tre år. Ålder över 65 år var förenat med ökad risk för ny stroke.

Sammanfattningsvis visar dessa studier från Malmö att risken att insjukna i hjärnblödning varierar med födelse-land. Betydelsen av förhöjt blodtryck, avseende relativa risken att insjukna i stroke, är störst för hjärnblödning, och främst med icke-lobär blödningslokalisering. Diabetes har samband med insjuknande i icke-lobär hjärnblödning medan rökning medför ökad risk för lobär hjärnblödning. Kvinnor har bättre överlevnad än män efter hjärnblödning.

# ABBREVIATIONS

BMI	Body mass index
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CI	Confidence interval
CT	Computed tomography
DBP	Diastolic blood pressure
HR	Hazard risk
HT	Hypertensive
ICH	Intracerebral haemorrhage
MDC	Malmö Diet and Cancer
MPP	Malmö Preventive Project
MRI	Magnetic resonance imaging
NT	Normotensive
OAT	Oral anticoagulation treatment
OR	Odds risk
PICH	Primary intracerebral haemorrhage
RLS 85	Reaction level scale 85
RR	Relative risk
SBP	Systolic blood pressure
STROMA	Malmö Stroke Registry
SVD	Small vessel disease
tPA	Tissue plasminogen activator

# INTRODUCTION

## Stroke – general aspects

Every year, approximately 30 000 people suffer a stroke in Sweden<sup>1</sup>. Within one year from stroke onset, 1/3 of the patients die,<sup>2-4</sup> and of the survivors about 10 % will have a second stroke<sup>2</sup>. Globally, there are wide regional differences in stroke incidence<sup>5</sup>. Bearing in mind the large variation between the abilities of different countries to make accurate diagnosis of, and record, strokes,<sup>6</sup> a recent review showed a 100 % increase of the overall stroke incidence in low-to middle income countries, compared with a 42 % decrement in high-income countries during the last forty years.<sup>7</sup>

According to the definition established by the World Health Organisation, stroke is rapidly developed clinical signs of focal or global deficits of cerebral function, lasting more than 24 hours, or until death, with no apparent non-vascular cause<sup>8</sup>. In practice, stroke is a heterogeneous disorder consisting of three types which differ in risk profiles, management and prognosis.<sup>9-11</sup>

The three types are 1) cerebral infarction (or called ischemic stroke), mostly caused by an occlusion of a cerebral vessel, 2) intracerebral haemorrhage (ICH), caused by a ruptured cerebral vessel and bleeding into the cerebral parenchyma, and 3) subarachnoidal haemorrhage, a bleeding into the subarachnoidal space. ICH and subarachnoidal haemorrhage are together sometimes mentioned as haemorrhagic stroke, however these subtypes differ in vasculopathy,<sup>12</sup> incidence,<sup>13, 14</sup> risk factors<sup>15</sup> and prognosis,<sup>12</sup> and they are usually differentiated in epidemiological studies.

In western communities, cerebral infarction accounts for approximately 75 % of all stroke events<sup>16-23</sup> and is associated with overall better survival than the other types.<sup>11</sup> Cerebral infarction is also the most studied subtype in terms of risk factors, prognosis, and management,<sup>11, 24</sup> which has contributed to land breaking treatment possibilities.<sup>25, 26</sup> Of the clinically verified stroke cases, 5-10 % do not undergo the diagnostic procedures for sub-classification. Subarachnoidal haemorrhage accounts for ≈ 5 % and ICH for the remaining 10 %.<sup>16-23</sup>

Epidemiology [Gr. *epidēmios* prevalent], is the science concerned with the study of the factors determining and influencing the frequency and distribution of a disease, injury and other health-related events and their causes in a defined human population.<sup>27</sup> This thesis has focus on risk factors and prognosis of ICH in the city of Malmö, Sweden, even though the other stroke subtypes are discussed and handled in some aspects.

# Intracerebral haemorrhage

## *Definition and types*

Spontaneous ICH is a bleeding into the brain parenchyma without trauma or surgery. If the vessel rupture in ICH occurs close to the cortical surface, or deep in the hemisphere, an associated bleeding into the subarachnoid space and brain ventricles may arise. Spontaneous ICH may be divided into primary respectively secondary haemorrhages, depending on the underlying cause of the bleeding. However, the terminology varies considerably, and the usage of 'spontaneous ICH' equivalent to 'primary ICH' is not uncommon.

Primary intracerebral haemorrhage (PICH) accounts for ~80% of all ICH. In general, PICH is considered when the bleeding occurs *without* provocation of trauma or a number of anatomical, haemodynamic, pharmacological and hemostatic factors related to secondary intracerebral haemorrhage. Nevertheless, there are wide variations in to what extent the investigators exclude cases with these provoking factors in epidemiological studies. Warfarin treatment is often included as a possible risk factor or predictor of outcome after PICH, and the case-exclusion procedures is mostly restricted to haemorrhages related to vascular malformations, aneurysm, tumor, tPA treatment, and cerebral infarction. These latter criteria were applied in defining PICH in this thesis.

## PICH vascular pathology

Two main vascular pathologies have been identified in association to PICH; cerebral amyloid angiopathy and small vessel disease. In sporadic cerebral amyloid angiopathy (CAA) there is an infiltration by  $\beta$ -amyloid protein in the vessel wall of small and medium-sized predominantly cortical and leptomeningal blood vessels, which induce vessel wall fragility and risk of rupture.<sup>28, 29</sup> In consecutive autopsies the prevalence of CAA was 23-49% and increased with age.<sup>29-31</sup> An association to intracerebral haemorrhage was first described in the 1960s.<sup>32</sup> Bleeding from the cortical and leptomeningal vessels give rise to so called **lobar haemorrhage** localised in the cerebral cortex or subcortical white matter substance.<sup>28</sup> CAA as verified by autopsy has later been observed in 11-49 % of cases with intracerebral haemorrhage.<sup>30, 33-35</sup> In ICH cases with hypertension, CAA-lesions were never found in the basal ganglia region, rarely in the cerebellum and most frequent in the occipital and frontoparietal cerebral lobes.<sup>34</sup>

A correlation has been found between apolipoprotein E polymorphism  $\epsilon 4$ <sup>33</sup> respectively  $\epsilon 2$ <sup>36</sup> and ICH related to CAA ( $\epsilon 3$  is the 'normal' genotype). These studies were performed on North American populations, and in an European study, no such association was found.<sup>37</sup> Definite diagnosis of cerebral amyloid angiopathy require neuropathologic examination, however clinical diagnosis of possible respectively probable CAA-related ICH according to the Boston Criteria<sup>33, 38</sup> has high accuracy.<sup>39</sup>

Small vessel disease (SVD) comprise a numerous of different vasculopathies.<sup>40, 41</sup> SVD-related haemorrhages arise in particular from the perforating arterioles, terminal



vessels, which supply the basal ganglia, thalamus, brainstem and the cerebellum. Vessel rupture in these brain locations gives rise to **non-lobar haemorrhages**. Rupture mostly occurs at distal vessel bifurcation sites<sup>42</sup>. Lipohyalinosis, or ‘complex small vessel disease’<sup>43</sup> was first described in association to lacunar infarction,<sup>44</sup> and later in relation to ICH.<sup>45</sup> Lipohyalinosis is characterised by loss of the normal vessel wall architecture (segmental wall thickening and thinning), collagenous sclerosis and mural foam cell infiltration,<sup>44</sup> and in its acute form, so called fibrinoid necrosis.<sup>43, 46-48</sup> Most of the pathological studies included exclusively ICH-cases with hypertension.<sup>34, 42, 45-47</sup> In a later conducted autopsy study, which included both normo- and hypertensive cases of SVD in association to various cerebral conditions, including ICH,<sup>49</sup> lipohyalinosis or fibrinoid necrosis were rarely observed. Instead, the small-vessel morphology, which was identical in normo- and hypertensive cases, corresponded to the so called hyaline arteriolosclerosis, or ‘simple small vessel disease’.<sup>43</sup> In arteriolosclerosis, the smooth muscle cells first hypertrophies, and then are replaced by fibroblasts and deposits of collagens, resulting in a homogenous vessel wall thickening, and lumen narrowing.<sup>50</sup> Arteriolosclerosis appears in various degrees with increasing age.<sup>51</sup> It was suggested that the nature of cerebral SVD have changed since the original description<sup>44</sup> as a consequence of diminished proportion of SVD related to hypertension.<sup>49</sup>

The vascular pathology in lobar respectively nonlobar PICH may still not be as distinct as described above. In CAA-related bleedings, 84 % were lobar and 16 % nonlobar bleeding location.<sup>30</sup> The major histological difference between cases with CAA-related lobar haemorrhage, and cases who had CAA *without* haemorrhage, was the co-presence of SVD in cases with haemorrhage.<sup>52</sup> Additionally, CAA- affected vessels was suggested to indirectly induce nonlobar PICH, by impairment of the auto-regulation.<sup>34</sup> However, in one study, the vessel wall of cortical branches had normal histological appearance in cases with hypertension and non-lobar ICH attributed to lipohyalinosis.<sup>42</sup>

In summary, both CAA and SVD were observed in lobar PICH, whereas mainly SVD seems related to nonlobar PICH. However, pathological studies on PICH are rare, and none included unselected cases.

## Incidence and risk factors

### *Demographic aspects*

The age-standardised annual incidence of PICH per 100 000 person-years has been estimated to 28-33 in Europe,<sup>14, 53</sup> versus for example 47 in Japan.<sup>54</sup> The incidence of PICH is higher among men than women, and increases with age.<sup>55</sup> Population-based western studies show both stable<sup>56, 57</sup> and decreasing<sup>4, 23</sup> ICH incidence in the last decades. However, worldwide, in low-to middle-income countries, the current age-adjusted incidence rate of ICH and the frequency of ICH as stroke subtype, have been reported to be almost twice those reported in high-income countries.<sup>58</sup>

Ethnicity appears to influence on the incidence of ICH regardless of the country of residence. The incidence of ICH is twice among African Americans in USA<sup>59,60</sup> and Asians in New Zealand<sup>61</sup>, as that among Whites in the respective populations. The distribution of stroke subtypes also differs between patients with different ethnic origin. Out of all stroke, approximately 20 % are ICH in populations with Asian,<sup>61-64</sup> Black<sup>65-68</sup> and Hispanic<sup>66,69,70</sup> ethnicity, compared with 10 % in White populations.<sup>16-22</sup> Non-lobar PICH is also more common in Black<sup>59,71</sup> and Hispanic<sup>71</sup> patients than in White patients. However, it should be borne in mind that comparison of ICH incidence and stroke subtype ratios between populations in different countries is complicated by differences in methodological and diagnostic procedures<sup>7</sup>. Only a few studies have included multiple comparative ethnic subgroups within the same local study population.<sup>61,66</sup>

### *Blood pressure*

Elevated blood pressure is a well established risk factor for the incidence of both PICH and cerebral infarction,<sup>55,72</sup> and there is a linear relationship between the increment of blood pressure value and the relative risk of stroke.<sup>73</sup> In a Korean study, the relationship with increasing blood pressure was found to be stronger for PICH than for ischemic stroke,<sup>74</sup> however it is not known whether this is also true in Western populations. The term ‘hypertensive haemorrhages’ has been used to describe PICH with nonlobar location,<sup>45</sup> and mainly derives from the fact that autopsy studies at the time were mostly carried out on cases with hypertension and a high rate of the haemorrhages were nonlobar. Although the importance of hypertension in lobar bleeding has been demonstrated<sup>75</sup>, results on the relation between hypertension and PICH subtypes in case-control studies are inconsistent<sup>76</sup>.

### *Metabolic risk factors*

In those aged 35-74, individuals with diabetes have been found to have five (men) to eight (women) times higher risk of stroke than non-diabetics.<sup>77</sup> The association to cerebral infarction is well known<sup>72,78-80</sup> whereas the relationship between diabetes and PICH is less clear. Diabetes has been found to be a risk factor for PICH in young patients<sup>81</sup> and in men,<sup>72</sup> However, in a recent meta-analysis of 8 case-control studies<sup>55</sup> diabetes was not a risk factor for PICH and it has been suggested that diabetes is inversely related to PICH.<sup>82</sup>

Elevated total cholesterol levels are positively related to an increased risk of cerebral infarction,<sup>83-86</sup> in particular atherosclerosis- and small vessel disease,<sup>87</sup> but the results are inconsistent.<sup>11</sup> The relationship between cholesterol and the risk of PICH seems to be inverse<sup>72,87-91</sup> or u-shaped.<sup>85</sup> Other reported no association<sup>92,93</sup> or only in elderly men.<sup>94</sup> Low cholesterol values seem more common in cases with nonlobar haemorrhages, compared with cases with lobar haemorrhages<sup>90</sup>. Some biological explanations of why lower cholesterol levels could induce PICH are weakening of the endothelial wall due to smooth muscle cell necrosis,<sup>47</sup> reduction of platelet aggregability<sup>95</sup> and increase in the osmotic fragility of the erythrocyte cell

membrane.<sup>96,97</sup> An indirect relation, for example when low cholesterol levels are primary related to other disorders, as chronic liver disease, has also been suggested.<sup>98</sup> Elevated non-fasting triglycerides levels<sup>85,99</sup> and body mass index (BMI),<sup>100-103</sup> have been found to be associated with an increased risk of cerebral infarction, whereas the relationship to haemorrhagic stroke appear to be inconsistent for both triglycerides<sup>85,88,104</sup> and BMI.<sup>100-103</sup>

### *Smoking*

Some have found no association between smoking and PICH<sup>104-107</sup> while others have found positive relations,<sup>72,108-110</sup> in contrast to cerebral infarction, in particular the subtype related to large vessel atherosclerosis.<sup>10</sup> It is not known if smoking has different impact on lobar respectively nonlobar PICH.

### *Alcohol*

An increasing risk of PICH with ‘moderate’<sup>55,72,111</sup> to ‘heavy’ alcohol-intake,<sup>55,112</sup> as compared with non-drinkers, have been reported, taking into accounts differences in cut off points of alcohol consumption between the studies. However, one study showed no association<sup>104</sup> and another only to lobar PICH.<sup>107</sup> Some potential mechanisms by which alcohol could provoke PICH are a) enhancement of hypertension b) direct vasoconstriction and increased intracellular calcium-levels, inducing endothelial damage and c) haematological effects as thrombocytopenia and decreased platelet aggregation.<sup>113</sup>

### *Depressive disorder*

Depression is commonly diagnosed *after* stroke,<sup>114</sup> but it is difficult to establish whether the depression also pre-dated the stroke. Cerebrovascular lesions (without clinical signs of stroke) on brain images are related to the development of depressive symptoms over time.<sup>115</sup> On the other hand, individuals with depressive symptoms have an increased risk of suffering a cerebral infarction later on.<sup>116-119</sup> Both behavioural and vascular risk factors<sup>120,121</sup> as well as vascular impairment<sup>122</sup> may explain this increased stroke risk. In one study, the association was restricted to fatal stroke, suggesting that psychological distress could be associated with more severe strokes, or that the patients recovery potential might have been impaired by psychological problems and/or comorbidities (i e cardiac or other severe illnesses).<sup>117</sup> It is not known whether there is any relation between psychological distress and PICH.

### *Socioeconomic circumstances*

Groups with low socioeconomic status, as measured by levels of education and/or occupation, income, profession, migration rate or dependency of social welfare support,<sup>123-126</sup> have an increased risk of stroke overall, as well as ICH.<sup>127</sup> A higher prevalence of vascular risk factors (for example hypertension, diabetes and smoking) in groups with low socioeconomic status, partly explains this relationship.<sup>124,126</sup>

However adjustment for vascular, lifestyle or psychosocial risk factors did not change the relationship between stroke and socioeconomic status.<sup>125</sup>

Σ

Hypothetically, relating to potential differences in vascular pathology, the above mentioned risk factors might have different impact on the incidence of lobar respectively nonlobar PICH. To the best of our knowledge, no prospective study with pre-event established risk factors, has reported on risk factors of PICH subtypes.

## Prognosis

Recent studies have reported considerable variation in outcome after ICH, with one-month case fatality rates between 13 and 51 %, <sup>18, 53, 54, 128-132</sup> the lowest rates being found in Japan.<sup>54, 132</sup> After one year 47-61 % of the patients had died <sup>18, 53, 128-130, 133, 134</sup>, after three year 52 % <sup>18</sup> and after 10 year 76 %.<sup>53</sup> Only two of these studies concerned the survival of patients treated in a single hospital,<sup>18, 131</sup> the others included patients from multiple centres.<sup>53, 54, 128, 130, 132-134</sup> Considering the number of patients included in the respective study and the length of the study period, this means that each centre handled few PICH-cases, which may have had a negative impact on outcome.<sup>135</sup>

## Risk factors for mortality

### *Age and sex*

Increasing age is a well established predictor of high mortality following PICH <sup>136</sup>. The mean age at the time of stroke is higher in women than men,<sup>137</sup> Whether the age-corrected mortality rates are different for men and women with PICH is unclear. It has been reported that older men had higher one-month age-adjusted mortality after stroke overall, as compared to women,<sup>138, 139</sup> but the results are not consistent. <sup>18, 140, 141</sup> Few studies reported on mortality rates after PICH in men and women separately.<sup>128-130, 142</sup> Male sex was found to be an independent risk factor for long-term mortality in patients who survived the first month after PICH.<sup>129</sup> A different study showed a higher mortality rate in women, but after adjustment for other risk factors, female sex was not a predictive factor for death.<sup>130</sup>

### *Haemorrhagic characteristics*

Already twenty years ago, it was shown that one month mortality rates depended highly on the brain damage caused by the haemorrhage, i.e. on the haemorrhage volume and extension of the haemorrhage to the cerebral ventricles.<sup>143, 144</sup>

Intraventricular haemorrhage is most common in haemorrhage in the thalamus, nucleus caudatus and cerebellum.<sup>54</sup> Haemorrhage volume and intraventricular haemorrhage, together with age and the clinical condition of the patient on admission, as measured by level of consciousness, are the main items in prognostic grading scales.<sup>145, 146</sup> However, few studies with unselected PICH cases have verified the

impact on mortality, after adjustment for all these factors, as well as other potential predictors, for example haemorrhage site,<sup>54, 130, 147</sup> and the results are inconsistent. In 20-40% of the ICH events, the haemorrhage volume expands during the first hours after onset<sup>148, 149</sup> and this volume growth is independently related to the baseline volume<sup>150, 151</sup> and higher mortality.<sup>151</sup> The relationship between haemorrhage volume and outcome varies by haemorrhage location, with less difference in lethal versus non-lethal volume in cerebellar and brainstem haemorrhages, as compared to lobar respectively central haemorrhages.<sup>54, 147</sup> Brainstem haemorrhage has the highest one-month case fatality rate, 53-80%,<sup>54, 128, 130</sup> while the corresponding rate in lobar haemorrhage is 11-46%.<sup>54, 128, 130</sup>

### *Oral anticoagulation treatment*

At the University Hospital in Malmö, the three most common indications for OAT are atrial fibrillation, venous thromboembolism and mechanical valve prosthesis. Patients with oral anticoagulation treatment (OAT) have approximately 10 times higher risk of intracerebral haemorrhage as compared with the general population.<sup>152</sup> One-month fatality in OAT-related haemorrhages in unselected groups has been reported to be 44-55%.<sup>130, 131, 152, 153</sup> Although those receiving OAT showed significantly higher one-month fatality than those without treatment, OAT was not independently related to short-term mortality after adjustment for haematoma volume.<sup>130</sup> The results of studies on whether OAT is associated with larger baseline haemorrhage volume are inconsistent,<sup>154, 155</sup> but haematoma expansion in the acute phase seems to be more pronounced in patients on OAT, independent of baseline volume.<sup>154, 155</sup> The studies described included patients with previous stroke, and the impact of OAT on mortality in unselected first-ever PICH is unknown.

### *Management and outcome*

There are several modifiable factors associated with increased mortality in patients with PICH. High blood pressure predispose for enlargement of the bleeding<sup>156, 157</sup> which might explain why elevated blood pressure on admission is a predictor of short term mortality, independently of the presence of hypertension prior PICH event<sup>158</sup>. In 45 330 patients admitted to emergency departments, 75 % had systolic blood pressure (SBP) > 140 mmHg.<sup>159</sup> It was reported that enlargement occurs in 9 % of the patients with blood pressure target of SBP ≤ 150 mmHg, versus 30 % in patients with SBP ≤ 160 mmHg,<sup>157</sup> and pharmacological treatment of high blood pressure (SBP 150-220 mmHg) in the acute phase with blood pressure target of SBP 140 mmHg seems to be related to decreased haemorrhage growth.<sup>160</sup>

High blood glucose on admission seems to be associated with more severe bleeding.<sup>158, 161</sup> However, if it is related to early death, independently of diabetes, is not clear.<sup>158, 161</sup> In approximately 50 % of the cases with haemorrhagic stroke some abnormality on ECG is observed in the first 24 hours. Sinus tachycardia, ST-depression and inverted T-waves predicted increased three month mortality, independent of age, stroke severity and pre-stroke handicap.<sup>162</sup> These specific changes are believed to be related to the stroke per se, as opposed to for example atrial

fibrillation which is a sign of a manifest cardiac disease. It is, however, not known if pharmacological treatment of the tachycardia would improve outcome.

According to the recommendations of the American Heart Association/American Stroke Council from 2007, patients with cerebellar haemorrhage > 3 cm with neurological deterioration or who have brain stem compression and/or hydrocephalus from ventricular obstruction, should have surgical removal of the haemorrhage. In addition, patient with lobar haemorrhage within 1 cm of the brain surface, might be considered for surgical evacuation by standard craniotomy (as opposed to other surgical techniques).<sup>163</sup> However, the surgical frequency varies largely between centres. For example, in some hospitals in Japan<sup>54</sup> the surgical frequency was 36 % as compared with 10 % in the USA.<sup>128</sup>

Care in acute stroke unit improves short-term survival after stroke,<sup>164</sup> including PICH.<sup>165, 166</sup> Although there probably are large differences in local praxis, assessment in intensive-care units is not uncommon. It has been estimated that approximately 30 % of patients with supratentorial haemorrhage and almost all patients with brainstem or cerebellar haemorrhage, require intubation in the acute phase.<sup>167</sup> In severely ill patients, do-not-resuscitate orders (DNR) may be appropriate. A DNR indicates that no resuscitation should be attempted in case of cardiopulmonary arrest. It was shown, however, that DNR not only have implications in case of cardiopulmonary arrest. Hospitals with high rate of early DNR in patients with ICH, also had lower rates of aggressive management and treatment of the disease, and these hospitals also had higher in-hospital mortality after ICH.<sup>168</sup>

## Recurrence rate

In a review of hospital- and community based studies, the recurrence rates from pooled data were 4 and 6 % per patient-year, respectively. Approximately half of the recurrent events were haemorrhagic.<sup>169</sup> In the same review, recurrence was more frequent among cases with lobar PICH as first event. In lobar ICH, apolipoprotein E polymorphism  $\epsilon 4$  and  $\epsilon 2$  are predictors for recurrent haemorrhage.<sup>170</sup> Two main patterns have been described, with respect to the relationship of the first and the recurrent haemorrhage; ganglionic-ganglionic and lobar-lobar, where the first pattern is more common in Asia<sup>171, 172</sup> and the second in Europe.<sup>173-175</sup> In persons with former stroke (within five years) a blood pressure reduction of an average of 9,0/4,9 mmHg (systolic/diastolic BP) with antihypertensive treatment reduced the stroke recurrence risk by approximately 30 %. The risk reduction was highest for those with previous ICH as stroke subtype.<sup>176</sup> Although the value of antihypertensive treatment after stroke is well-established, the knowledge of specific secondary prevention strategies after PICH is limited.

# AIMS

1. To investigate the incidence of stroke subtypes in relation to country of birth (paper I)
2. To explore the relationship between blood pressure and the incidence of cerebral infarction, PICH and PICH with lobar and nonlobar location (paper II)
3. To investigate the impact of vascular and environmental factors on the risk of PICH and PICH with lobar and nonlobar location (paper III)
4. To investigate the survival and stroke recurrence after PICH in relation to demographic, clinical and haemorrhagic characteristics (paper IV)

# SUBJECTS AND METHODS

*General introduction- an overview of the methods employed in each study*

**Paper I**      Prospective cohort study

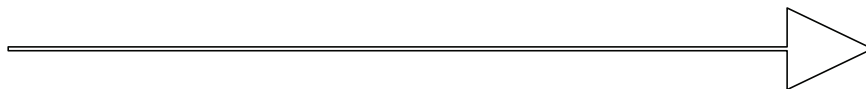
*Malmö 1990 cohort*

**screening**

1990

**incidence of stroke**

until dec 31, 2000



**Paper II**      Prospective cohort study

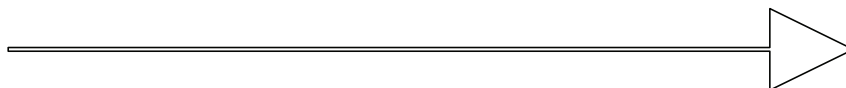
*Malmö Diet and Cancer cohort*

**screening**

1991-1996

**incidence of  
cerebral infarction and PICH**

until dec 31, 2001



**Paper III**      Nested case-control study

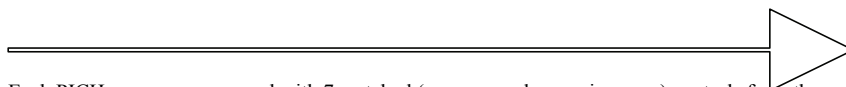
*Malmö Preventive Project cohort*

**screening**

1974-1992

**incidence of PICH**

until dec 31, 1999



Each PICH case was compared with 7 matched (age, sex and screening-year) controls from the same cohort.

**Paper IV**      Prospective cohort study of PICH patients

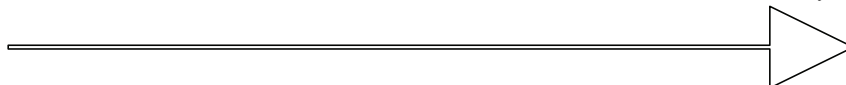
*Malmö Stroke Register PICH cohort*

**PICH event**

1993-2000

**incidence of death and recurrent stroke**

within 3 years





# Study populations

## Paper I

### *Malmö 1990*

This population-based cohort consists of all Malmö residents between 40 and 89 years of age, according to the Population Census Data from 1990,<sup>177</sup> in total 118 134 individuals (52 877 men and 65 257 women). The register included information on country of birth, marital status, type of housing (rented and owned), and annual income, based on information from a mailed questionnaire (response rate 97.5%) and data from other population registers. Only immigrants from countries with total follow-up times of  $\approx >2500$  person years were included in the analysis. Participants with missing information on birth country (n=51, 0.04 %) were excluded. In total 113 662 persons were included in this study, of whom 98 961 were born in Sweden and 14 701 in other countries.

## Paper II

### *The Malmö Diet and Cancer study*

The Malmö Diet and Cancer study (MDC) is a prospective population-based study, with the main objective of evaluating diet-related risk factors for cancer.<sup>178</sup> However, the investigation also included a number of items related to cardio- and cerebrovascular diseases. All men born between 1923-1945 and all women born between 1923 and 1950, residing in Malmö in 1991(n=74 138), were invited by letter or through newspaper advertisement to participate in the study. Reading and writing skills in the Swedish language were criteria for eligibility. 1 975 persons were excluded due to language problems or mental incapacity, and 3 258 persons died or moved out before completing the baseline examination. In all, 28 449 persons participated, out of an eligible population of 68 905 persons (participation rate 40.6 %)<sup>179</sup>.

Baseline examinations were undertaken between 1991 and 1996. The participants were first invited to a screening centre at Malmö University Hospital, where they were asked to fill in a written paper-questionnaire covering socioeconomic, demographic and lifestyle factors as well as information on previous and current diseases and medication, and diseases among relatives, in total 141 questions. Research nurses conducted various measurements including blood pressure, height and weight, and collected assorted blood samples. On a second visit occasion, individual interviews regarding detailed diet history were performed by trained dietary interviewers. In our study, those reporting a previous stroke at screening (n=324), and those for which information on blood pressure (n=44), BMI (n=46), smoking (n=324) and/or alcohol consumption (n=323) was lacking were excluded from the present study, resulting in a cohort of 27 702 subjects.

### **Paper III**

#### *Malmö Preventive Project*

The Malmö Preventive Project (MPP) was organised and carried out by the Department of Medicine at the Malmö University Hospital, with the aim of identifying individuals at high risk of cardio- and cerebrovascular diseases in a population-based cohort.<sup>180</sup> Complete birth cohorts (1921, 1926-1942, 1944, 1946, 1948-1949 for men and 1926, 1928, 1930, 1932-1936, 1938, 1941-42, 1949 for women) of registered residents of the city of Malmö were invited by letter to a health examination. The participation rate was 71%, and in total 22 444 men and 10 902 women participated. Their age ranged from 27 to 61, and the mean age was 47 years. The screening program, performed at Malmö university hospital between 1974 and 1992 (1974-1983 for men and 1976-1992 for women), comprised a physical examination, a panel of laboratory tests and a computerised self-administered questionnaire. Subjects in whom diseases or risk factors were detected at screening (~30%) were referred to the appropriate clinic for medical care and further evaluation and/or intervention. Subjects reporting myocardial infarction or stroke before the baseline examination were excluded from the present study (n=341).

### **Paper IV**

#### *Malmö Stroke Register PICH cohort*

This patient cohort includes all cases of PICH (n=474), as described below, registered in the Malmö Stroke Register (STROMA) between January 1, 1993 and December 31, 2000.

## Case retrieval

### **Paper I-IV**

#### *Malmö Stroke Register - STROMA*

The STROMA register contains information on cases of stroke since 1989<sup>181</sup> both first and recurrent stroke events according to the same case ascertainment procedure. Recurrent stroke cases are registered in a separate recurrence register if first ever stroke occurred before 1989. Only stroke cases in Malmö residents are included in STROMA. Case identification is carried out by a specialised research nurse, and consists of a continuous broad search among patients admitted to the emergency and admission department, the neurological wards and ambulatory department, as well as other relevant hospital wards, for neurological symptoms and diagnosis that could indicate stroke. Patients initially hospitalised for other initially reasons, are also included in the case identification procedure. All possible stroke cases were validated by reviewing the patients' records under the supervision of a senior stroke physician.

Malmö University Hospital is the only hospital serving the population of Malmö. Primary care and nursing homes work in collaboration with the University Hospital, and patients with symptoms of stroke at those healthcare facilities are routinely referred to the hospital for further examination and are thus included in the case identification process. The WHO's definition of stroke is used.<sup>8</sup> In the database, stroke subtypes are coded according to ICD 9 (434, 430, 431 and 436).<sup>182</sup>

#### *Other sources of case retrieval*

The National Patient register 183 was used to find cases among the participants in the MPP and MDC' cohorts who moved out from the city of Malmö during the follow-up period (paper II and III). The Swedish Causes of Death register 184 was used to provide information of death and cause of death (paper I-IV). In this case search procedure, International Classification of diseases (ICD) revision 9 and 10182 was used, ie 434.0-9 / I63.0-9 for cerebral infarction, 431.0-9 / I61.0-9 for intracerebral haemorrhage, 430.0-9 / I60.0-9 for subarachnoidal haemorrhage and 436.0-9 / I64.0-9 for unspecified stroke, according to the established endpoints in the respective studies. In paper II-IV, cases with ICD codes indicating ICH or undefined stroke underwent the same diagnosis validation procedures as for STROMA. In paper III (MPP), cases with ICH and undefined stroke before 1989 were retrieved from the national registers and the recurrence register in STROMA.

## Ascertainment of PICH diagnosis, classification and haemorrhage characteristics

Intracerebral haemorrhage was diagnosed when CT, MRI, or autopsy showed intraparenchymal blood in the brain. Angiography was carried out in selected cases with haemorrhagic stroke, i.e., when haemorrhage location, age or clinical status was suggestive of a vascular malformation. In all verified cases of intracerebral haemorrhage, the CT images were reviewed with the assistance of a neuroradiologist (Dr. Toivo Matilainen), with regard to haemorrhage volume, the presence of intraventricular haemorrhage, and the location of the haemorrhage. Cases were excluded if the haemorrhage was considered to be secondary (e.g. caused by arteriovenous malformation/aneurysm, thrombolysis of acute myocardial infarction, haemorrhagic infarction or tumor).

Haemorrhage location was classified into four regions; lobar (predominantly cortical or subcortical white matter), central (predominantly basal ganglia, internal capsule, periventricular white matter), cerebellum and brainstem. In the studies described in paper II and III, central, brainstem and cerebellar locations were categorised as one PICH subtype (nonlobar), whereas in the study presented in paper IV, they were analysed separately. The volume of the haemorrhage was calculated using the formula  $AxBxC/2$ .<sup>185</sup> Intraventricular haemorrhage was assessed as present or absent.

## Assessment and definition of risk factors

### **Paper I (Malmö 1990)**

#### *Country of birth*

The participants in the Malmö 90 cohort provided information on their country of birth in a self-administered questionnaire. This information was lacking for 51 participants (0.04%) in the Malmö 90 cohort. Only immigrants from countries with total follow-up times of  $\geq 2500$  person years were included in the analysis.

#### *Marital and Socioeconomic status*

The total income in 1990 of each individual, was divided into six categories: 0-49 000, 50 000-99 000, 100 000-149 000, 150 000-199 000, 200 000-249 000 and  $\geq 250 000$  Swedish crowns (SEK) per year (1 USD  $\approx$  6 in 1SEK in 1990). Information on housing, tenant or house-owner, was included in the assessment of socioeconomic status. Marital status was assessed as married or unmarried.

### **Paper II (MCD)**

#### *Blood pressure*

Blood pressure was measured twice, with a mercury sphygmomanometer, in the right arm after a 10 minutes rest and the average value was used. The blood pressure values were grouped according to the guidelines of the European Society of Hypertension and European Society of Cardiology from 2003,<sup>186</sup> i.e.  $<140/<90$  mmHg (normal blood pressure), systolic blood pressure (SBP) 140-159 and/or diastolic blood pressure (DBP) 90-99 mmHg, SBP 160-179 and/or DBP 100-109 mmHg and SBP  $\geq 180$  and/or DBP  $\geq 110$  mmHg as hypertension grades I-III, respectively.

#### *Metabolic factors*

Diabetes was defined as having anti-diabetic medication (both insulin and non-insulin) or self-reported diabetes according to questionnaire. Hyperlipidemia was defined as use of lipid-lowering drug treatment. Weight was measured to the nearest kilogram using balance-beam scale with subjects wearing light clothing and no shoes. Height was measured with a fix stadiometer calibrated in centimetres. Body mass index (BMI) was calculated as  $\text{weight}/\text{height}^2$ , and assessed in  $\text{kg}/\text{m}^2$ .

#### *Smoking and drinking habits*

Smoking was defined as current smoking, daily or regularly. High alcohol consumption was defined as  $> 40$  g/ day for men and  $> 30$  g/ day for women,<sup>187</sup> according to the consumption reported in the menu book.

### **Paper III (MPP)**

#### *Blood pressure*

Blood pressure was measured as described above for the MDC.

Hypertension was defined as having blood pressure  $\geq 160/95$  mmHg and/or treatment for hypertension.

#### *Metabolic factors*

Blood samples for analysis of blood glucose, serum total cholesterol and triglycerides were taken after an overnight fast, and analyzed as non-frozen samples at the department of clinical chemistry at Malmö University Hospital.

Diabetes was defined as fasting whole blood glucose  $\geq 6.7$  mmol/l, according to the World Health Organization definition from 1980,<sup>188</sup> or self-reported diabetes according to the questionnaire. Weight and height was measured in the same manner as in the MCDS (see above).

#### *Life-style related factors*

Smoking was defined as current smoker, according to the questionnaire. Alcohol abuse was defined as having a history of problematic alcohol behaviour according to the questionnaire, or by means of the results according to the modified shortened version of the Michigan Alcoholism Screening Test.<sup>189</sup> This test included nine questions (included in the MPP questionnaire), and subjects with more two or more affirmative answers were considered to be high-consumers of alcohol.

Subjects who reported that they were mostly engaged in sedentary activities in their spare time, for example with watching TV, reading or going to cinema, were categorised as physically inactive. Information about cohabiting status, defined as living without partner or not, was retrieved from The National Swedish Censuses investigations in 1975, 1980, 1985 and 1990.<sup>177</sup> Information from the year closest to the year of the participant's screening year was used.

#### *Psychiatric morbidity*

History of psychiatric morbidity was based on the responses to the question '*Have you ever received treatment or care for nervous or psychiatric problems, ?*', Yes or No.

### **Paper IV (Malmö Stroke Register PICH cohort)**

#### *Vascular risk factors*

Data on vascular risk factors at the time of PICH were retrieved from the patient records. Data were collected on the following risk factors; ischemic heart disease (i.e. history of angina pectoris and/or cardiac infarction), treatment for hypertension, current or former smoking, and diabetes mellitus (previously known or newly diagnosed). Hypertension, smoking and diabetes were defined according to the corresponding items registered in the Swedish Stroke Register.<sup>190</sup>

Data on vascular risk factors was missing as follow; treatment for hypertension n=79, smoking n=191, ischemic heart disease n=77 and diabetes n=83. These were coded in a separate category, in order not to lose them in the multivariate models.

#### *Oral anticoagulation treatment*

Information on oral anticoagulation treatment (OAT), i.e. warfarin treatment, at the time of PICH, was collected from the patient records and from the patient register at the Anticoagulation Clinic at Malmö University Hospital.

#### *Level of consciousness*

The level of consciousness on admission to the hospital was assessed according to the Reaction Level Scale (RLS 85).<sup>191</sup> This is an eight graded scale. Data were collected from the patients' records and the RLS scores were categorised into three groups; 1 (alert), 2-3 (drowsy) and 4-8 (unconscious). Information was not available in 5 cases.

## Statistical methods

The expected number of stroke cases in the immigrants groups was calculated by standardisation for age (5-year groups) and sex using the indirect method. Cox proportional hazards model was used to compare incidence rates with adjustments for age, sex, marital status and socioeconomic indicators (Paper I).

In paper II, the incidence (per 1000 person-years, py) was standardised for sex and age (5-year groups) using direct standardisation, and was weighted for the age-distribution of the MDC cohort. Confidence intervals were calculated assuming a Poisson distribution. Cox's regression model was used to calculate the relative risks, with adjustment for age, sex and other risk factors for stroke (BMI, diabetes, lipid lowering drug, smoking, high alcohol consumption). Oneway analysis of variance (ANOVA) with the Bonferroni post hoc test was used to compare continuous variables between the diagnostic groups. Logistic regression was used for categorical variables.

In paper III, the Students T-test, the Mann-Whitney u-test and the Pearson chi-square test were used to compare the distribution of risk factors in PICH cases and controls. A backward stepwise conditional logistic regression (p removal: 0.10) was used to adjust the relations between risk factors and PICH for potential confounders.

In paper IV, logistic regression, with sex as the dependent variable, was used to compare baseline characteristics in men and women. Logistic regression model, with fatal outcome as dependent variable, was used to explore risk factors for 28-day case fatality. The various risk factors were first entered individually. Age, gender and risk factors with  $p < 0.2$  were considered to be potential confounders, and were entered in the multivariate model. Cox's proportional hazards model was used to study risk factors for 3-year mortality and stroke recurrence rates. The proportional hazards

assumption was confirmed by plotting the hazards rates for the various risk factors as a function of time.

## Ethical approvals

The studies have been approved by the local ethic committee (LU 78-02 and LU 238-03).

# RESULTS

## Incidence of stroke subtypes in relation to country of birth

This study (paper I) was performed with participants from the Malmö 90 cohort. All Malmö citizens born in Sweden, aged 40-89 years, were compared to immigrants, aged 40-89 years, from countries with total follow-up times of  $\approx >2500$  person years. In total, 113 662 persons were included in the analysis.

In total, 6082 cases of stroke were identified during the follow-up period, and 615 of these were classified as ICH. The relative risk of stroke (all types), after adjustment for age, sex, marital status and socioeconomic indicators, was higher for immigrants from Hungary and former Yugoslavia, while immigrants from Denmark, Norway, Germany, Chile, Czechoslovakia and Poland had approximately the same stroke risk as those born in Sweden (Paper I, table 2). A higher risk of PICH was observed in immigrants from China/Vietnam (Relative risk (RR), 4.2; 95% confidence interval (CI) 1.7-10.4) and former Soviet Union (RR 2.7, 95% CI 1.01-7.3).

### *Conclusion*

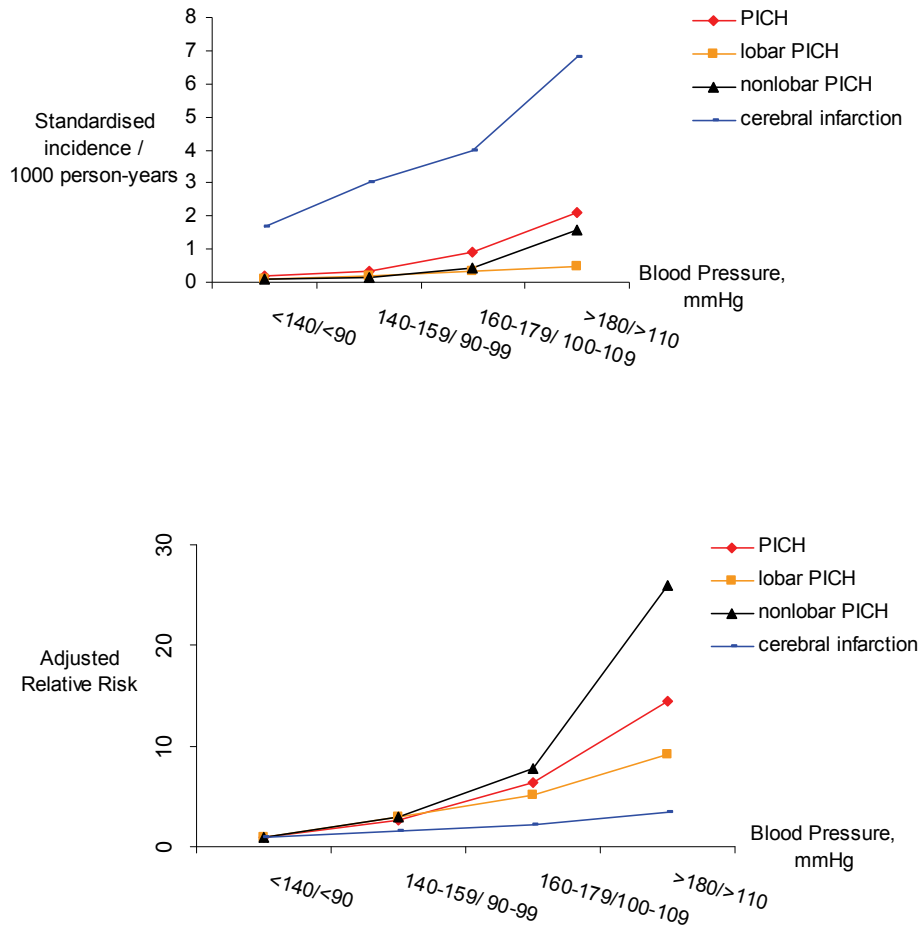
The incidence of stroke and stroke and different types of stroke in Malmö, varies between immigrants from different birth countries. There are no reliable data on stroke subtype frequencies in former Soviet, but the higher incidence of ICH among immigrants from East Asia is in agreement with the previously reported higher frequencies of this type of stroke in this region. However, the extent to which genetics and environmental risk factors affect overall stroke incidence, remains to be explored.

## Incidence of stroke subtypes in relation to blood pressure

In total 27 702 out of 28 449 participants from the Malmö Diet and Cancer Study were included in this study (paper II). 38.7 % were men, and mean age at screening was  $58 \pm 8$  years. During the follow-up period 701 of the subjects suffered a stroke (613 cerebral infarction and 88 PICH).

The incidence of all stroke subtypes increased progressively with the degree of hypertension, as can be seen in figure 1. The crude and standardised incidence was highest for cerebral infarction in all blood pressure groups. The relative risk of suffering a PICH with hypertension grade 3 (BP  $\geq 180/\geq 110$  mmHg) was 14.4 (95% CI, 6.4-32) as compared with BP  $<140/<90$  mmHg. The corresponding relative risk of suffering a cerebral infarction was 3.4 (CI 2.6-4.5). The relative risk was highest for nonlobar PICH (figure 1). The proportion of PICH of all stroke cases, increased from 7% in the normotensive group to 19.5% in the group with hypertension grade 3.





**Figure 1.** The standardised (age, sex) incidence respectively the adjusted relative risk of stroke subtype, in relation to blood pressure

In this study, beside elevated blood pressure, age, male sex, BMI, smoking, diabetes and alcohol consumption were independently associated with cerebral infarction. Age and male sex were also associated with PICH. Male sex and diabetes were related to nonlobar PICH, whereas age was associated with lobar PICH. The relative risk of lobar PICH for smokers was 1.97 (95% CI 0.99-3.9).

In a sub-analysis of this material (not in paper), we excluded two PICH cases with oral anticoagulation treatment at the time of stroke event. The results remained unchanged apart from for male sex which was no longer statistically significant.

## Conclusion

The incidence of PICH and cerebral infarction increased progressively with increased blood pressure. Although hypertension was associated with substantially higher incidence rates and absolute numbers of cerebral infarction, which is most important in public health perspective, the relationship with PICH, especially with nonlobar location, was strongest in terms of relative risks.

## Risk factors for PICH and PICH with lobar and nonlobar location

This study (paper III) was conducted with data from the Malmö Preventive Project. Risk factors in all cases of PICH during the follow-up period, in total 147 cases, were compared to 1 029 stroke-free controls (7 controls matched for age, sex and screening-year for each PICH case). 82 % were men and mean age at screening was  $62 \pm 7$  years.

### *Risk factors for PICH*

Compared with their respective controls, PICH patients had higher blood pressure, higher triglyceride levels and BMIs and were shorter in stature. They also had a history of diabetes, psychiatric and/or alcohol problems significantly more often, and more of them were living alone (table 2, paper III). The results from the final step in the backward conditional logistic regression analysis are given in Table 1.

	OR, last step
Systolic blood pressure (per 10 mmHg)	1.2 (1.2-1.5)
Diabetes (yes vs. no)	2.4 (1.1-5.5)
Log triglycerides	1.5 (1.04-2.1)
BMI	
Height, cm	0.97(0.95-0.998)
Alcohol abuse (yes vs. no)	
Psychiatric morbidity (yes vs. no)	1.6 (1.002-2.7)
Living alone (yes vs. no)	1.5 (0.99-2.2)

**Table 1.** Multivariate adjusted odds ratios (95% CI) for risk factors associated with PICH

### *Risk factors for lobar and nonlobar PICH*

Hypertension, diabetes, high levels of triglycerides and BMI and history of psychiatric morbidity were more common in patients with non-lobar PICH than in the matched controls. Hypertension and high levels of triglycerides were more common in lobar PICH patients than in controls.

Systolic blood pressure (OR per 10 mm Hg 1.5, CI 1.3-1.7), diabetes (OR 3.5, CI 1.5-8.6) and psychiatric morbidity (OR 3.0, CI 1.6-5.6) were independently associated

with nonlobar PICH, whereas systolic blood pressure (OR per 100 mmHg 1.3, CI 1.1-1.5) and smoking (OR 2.0, CI 1.1-3.9) were associated with lobar PICH. When lobar and nonlobar cases were directly compared, no statistically significant differences were found in risk factors

### *Conclusion*

Beside high blood pressure also diabetes, high triglyceride levels, and psychiatric morbidity were associated with PICH. In addition to high blood pressure, diabetes and psychiatric morbidity were associated with nonlobar PICH, whereas smoking was associated with lobar PICH.

## Survival and Stroke Recurrence rates in patients with PICH

Prognosis and prognostic factors were established in all cases of PICH registered in STROMA between 1993 and 2000.

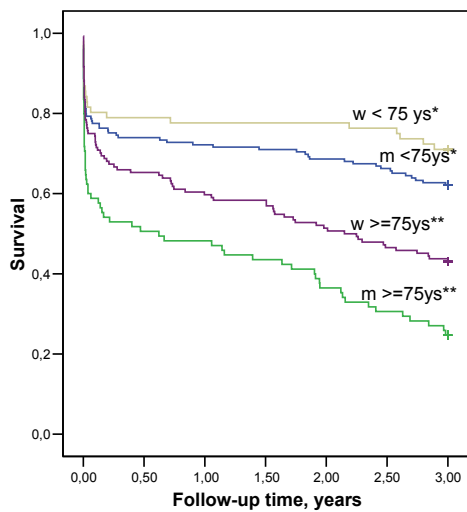
The mean age was 73 years, 29 % of the patients were  $\geq 80$  years, and 46 % were female. Beside older age in women, there were no differences in the baseline characteristics between men and women. The 28-day CFR for all PICH patients was 26 %, and the 3-year mortality rate was 49 %. In patients less than 75 years old, 20 % of the women and 23 % of the men died within 28 days ( $p=0.38$ ). The corresponding figures for patients aged 75 years or older, were 26 % and 41% respectively ( $p=0.02$ ).

Male sex was found to be an independent risk factor for both 28-day and 3-year mortality rates. Other independent predictors of death were age  $> 65$  years, central and brainstem haemorrhage site, intraventricular haemorrhage, increased volume of bleeding and decreased level of consciousness.

Twelve percent of the patients had a recurrent stroke event and the stroke recurrence rate was 5.1 % per person-year. Recurrent cerebral infarction and ICH occurred at approximately the same rate. Only age  $> 65$  years was related to recurrent stroke.

### *Conclusion*

Women had better survival rates than men after PICH. The difference is largely explained by higher 28-day mortality in male patients older than 75 years (figure 2). However, the underlying reasons have yet to be explored



**Figure 2.** Survival after PICH in men (m) and women (w) above and below 75 years. \*  $p=0.2$ , women vs men < 75 years. \*\*  $p<0.003$ , women vs men  $\geq$  75 years.

# METHOLOGICAL CONSIDERATIONS

A proposal of criteria for an ‘ideal epidemiologic stroke study’ was first made in 1987<sup>192</sup> and has then been revised, lately in 2004<sup>58</sup> (table 2).

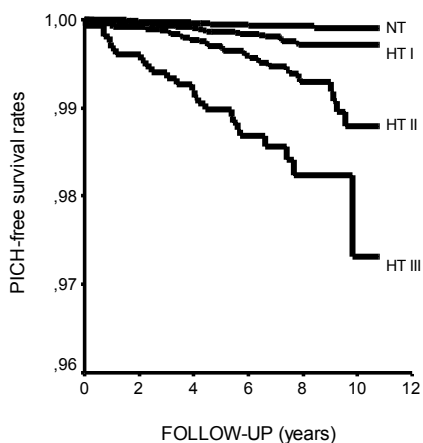
Domains	Core Criteria	Supplimentary Criteria
Standard definitions	<p>World Health Organisation definition of stroke</p> <p>At least 80% CT/MRI verification of the diagnosis of ischemic stroke, intracerebral hemorrhage, and subarachnoidal hemorrhage</p> <p>First-ever-in-lifetime stroke</p>	<p>Classification of ischemic stroke into subtypes (eg, large artery disease, cardioembolic, small artery disease, other)</p> <p>Recurrent stroke</p>
Standard methods	<p>Complete, population-based case ascertainment, based on multiple overlapping sources of information (hospitals, outpatient clinics, general practitioners, death certificates)</p> <p>Prospective study design</p> <p>Large, well-defined, and stable population, allowing at least 100 000 person-years of observation</p> <p>Follow-up of patients’ vital status for at least 1 month</p> <p>Reliable method for estimating denominator (census data <math>\leq</math> 5 years old)</p>	<p>Ascertainment of patients with TIA, recurrent strokes and those referred for brain, carotid, or cerebrola vascular imaging</p> <p>“Hot pursuit” of cases</p> <p>Direct assessment of under-ascertainment by regular checking of general practitioners’ databases and hospital admissions for acute vascular problems and cerebrovascular imaging studies and/or interventions</p>
Standard data presentation	<p>Complete calendar years of data; <math>\leq</math>5 years data averaged together</p> <p>Men and women presented separately</p> <p>Mid-decade age bands (eg 55 to 64 years) used in publications, including oldest age group (<math>\geq</math> 85 years)</p> <p>95% confidence interval around dates</p>	<p>Unpublished 5-years age bands available for comparison with other studies</p>

**Table 2.** Gold standard for a stroke incidence study, according to Feigin et Carter, 2004.

### Study design

In paper I-III, the information of risk factors was collected before the stroke event or death. Due to the prospective design, assessment of risk factors was not influenced by stroke event. However, we do not know whether some risk factors have changed on the individual level during the long follow-up period, in particular in the MPP cohort (paper III), but also in the MDC (paper II). As participants with detected vascular risk factor at baseline examination were referred for further evaluation and treatment, it is plausible that these individuals have a reduced risk for stroke during the follow-up time. However, we lack information on the proportion of participants in the cohorts that received treatment after referral. If anything, it should be expected that the relationship in our studies would be even stronger in a population which have not received interventions.

In addition, a change of exposure over time would have diluted the observed associations. Instead, in paper II, the differences between the blood pressure groups increased continuously over the entire follow-up period (Fig 3).



**Figure 3.** Crude incidence of PICH in relation blood pressure category (NT <140/90 mmHg; HT I, 140-159/90-99 mmHg; HT II, 160-179/100-109 mmHg and HT III,  $\geq 180/\geq 110$  mmHg)

In Göteborg, Sweden, the frequency of hypertension, smoking and hypercholesterolemia was found to decrease in men and women between 1987 and 2006, whereas diabetes and BMI increased in men.<sup>193</sup> We can thus not exclude the possibility that participants included in the cohort studies later were healthier with regard to vascular diseases than those who were recruited early in the study. To avoid that variations in the characteristics of populations over time influence the results, a nested case-control design was used in the third study (Paper III, MPP cohort). The PICH cases were matched with controls of the same age, sex and screening year. However, this prevented the effects of age and sex on the incidence of PICH from being studied. In the MDC the screening period was five years, and a prospective cohort design was used in paper II. Paper IV describes a prospective observational

study. Information on haemorrhagic characteristics, clinical data and vascular risk factors were assessed without knowledge of the patients' outcome.

### *Representativity of the study population*

The attendance rate in the MPP study was 71%, but only 41% in the MDC. Similar decline in attendance rates during the last decades is observed by others.<sup>194, 195</sup> Generally, non-participants (i.e. invited to participate, but for various reasons did not) in health screening programs have less favourable health and/or socioeconomic situation.<sup>194, 196-198</sup> This is reflected in the MPP<sup>199</sup> and in the MDC<sup>179</sup> cohorts by a higher total mortality in non-participants as compared to participants. With respect to the general population, there might be an under-estimation of the associations we found in paper II and III. However, non-invited birth cohorts of men who were compared to those invited in the MPP, did not differ with respect to overall and cardiovascular mortality.<sup>199</sup>

### *Quality of stroke ascertainment*

Cases with stroke diagnosis were achieved from three different sources; STROMA (paper I-IV), The Swedish hospital discharge register and The Swedish cause of death register (paper II-III).

In STROMA, the CT frequency increased from 64.3 % to 98.3 % between 1989 and 2001, with the largest increase between 1991 and 1992. This threshold is the reason for the chosen time period in paper IV (1993-2000). The reduced proportion of unspecified stroke corresponded closely to an increased proportion of cerebral infarctions. This suggests that most unspecified stroke were due to cerebral infarction. Overall, few cases of ICH seems to be hidden in the category unspecified stroke, irrespectively of the source of case ascertainment, as indicated in table 3.

Source	ICH (ICD 431/I61.0-9)	UND (ICD 436/I64.0-9)	PICH
STROMA	78 (73*)	12 (0)	73
Cause of Death Register**	11 (11)	7 (1)	12
National Patient Register**	8 (3)	54 (0)	3
Total	97	73	88

**Table 3.** Number of identified ICH and stroke UND in different sources of case ascertainment procedure in paper II. ( ) indicate the number of verified PICH. \* = 5 cases were secondary ICH. \*\* = cases outside Malmö.

The screening process applied to the STROMA database includes a daily broad search among patients admitted to the hospital. The hospitalisation rate of stroke patients in Malmö between 1993 and 1998 was 95 %.<sup>200</sup> The additional 5 % either died at the emergency ward (0.3 %) or were treated as outpatients (4.7 %). The case ascertainment, however, does not include screening in the primary care databases. In other stroke registers 1.6 %<sup>201</sup> respectively 3.7 %<sup>202</sup> of identified stroke patients were

found by such supplementary searching. These patients were not examined at the hospital, and in Lund, Sweden,<sup>202</sup> 86 % were living in nursing homes. Up until 1995 a systematic active search for stroke cases in nursing homes was included in the case-identification process in STROMA. It was found that all cases of suspected stroke had been referred for CT examination and hence included through the case-identification process at the hospital. Anyhow, some non-hospitalised patients might have been missed, and we can not exclude that there were changes in referral praxis between 1996 and 2001. Stroke severity is higher in ICH as compared to cerebral infarction,<sup>203</sup> and it is likely that a majority of the non-hospitalised stroke cases suffered a cerebral infarction.

It can not be ruled out that some patients died as a result of stroke before reaching the hospital. Others reported a pre-hospital PICH mortality of 6%<sup>130</sup> respectively 7%.<sup>129</sup> However, a review of all autopsy records of out-of-hospital deaths in Malmö, in 1989 and 1990, revealed only 7 missed cases in STROMA (0.6% of all stroke events) during these two years.<sup>200</sup> Cases with identified cerebral infarction in paper I and II were for practical reasons (large number and clinical diagnosis) not scrutinised in the case ascertainment procedure as cases with suspected ICH and undefined stroke. We can not rule out that some cases with ICH were miscoded as cerebral infarction.

### *Haemorrhage characteristics*

We used the ABC/2-formula in estimation of the bleeding volume. The formula ABC/3 was recently recommended, in cases of irregularly and separately shaped bleedings, which is often the case in OAT-induced bleedings.<sup>204</sup> However, calculating the volume as ABC/2 formula tends to overestimate the volume,<sup>204</sup> so this probably does not explain why the volumes calculated in this work were in the lower range compared with other studies, in particular in OAT-induced bleedings.<sup>153, 205</sup> It has been estimated that in approximately a quarter of the cases, the haemorrhage volume expands during the first hours.<sup>148, 206</sup> The smaller bleeding volumes reported in our study may partly be due to early hospital-admission and thus early CT examinations in our centre. However, we lack information on time from stroke onset to the time of CT-scanning, as well as a second CT examination (to evaluate haemorrhage growth), and no further conclusions can be made.

### *Risk factors*

The associations between the vascular risk factors (as blood pressure, smoking, lipids) and incidence of stroke and cardiovascular disease have been verified in many previous studies from MPP and MDC.<sup>207-210</sup>

In the MDC (paper II), we lacked values of blood glucose and lipids. However, the percentage of diabetes in PICH and the association with nonlobar PICH, is in line with the results from the MPP cohort (paper III), where diabetes diagnosis was assessed by blood glucose level as well as self reported diabetes.

The percentage of smokers was lower in the MDC as compared to the MPP. There are several possible explanations for this difference. First, there was a decline of smoking



in the general population during this time period.<sup>193</sup> Then, smoking<sup>195</sup> could be more common among non-responders, and the rate of non-responders was higher in MDC compared with MPP. Nevertheless, smoking was an independent risk factor for lobar PICH in the MDC, and in the MPP smokers had a relative risk for lobar PICH of 1.97 (95 % CI: 0.99-3.9). A limitation with prospective cohort studies is that the risk factor arsenal is restricted to what was of most interest and reasonable achievable at the time of the initial study design. As a consequence in our studies, we lack information of for example cholesterol fractions, hemostatic parameters, antitrombotic medication and genetic factors.

### *Missing value*

In Malmö 1990 cohort (paper I), 0.04 % participants lacked information of birth country and in the MDC (paper II), 1.5 % out of 28 449 participants had missing information of one or more risk factors. These participants were not included in the studies, and we can not rule out that exclusion of these participants might have influenced the results. In the MPP (paper III), only a computer based questionnaire was used. The participants could choose between a 'yes' or 'no' answer. For technical limitations at the time, a 'non-answer' was coded as 'no', so we cannot differentiate between these two answers, or estimate the actual rates of missing values, which is a limitation. In the prognosis study (paper IV), information on vascular risk factors was obtained from medical records and the frequency of missing data on vascular risk factors was considerable (hypertension n=79 (16.7 %), smoking n=191 (40.3 %), ischemic heart disease n=77 (16.2 %) and diabetes n=83 (17.5 %). Information on the level of consciousness at admission and intraventricular haemorrhage was missing in 5 and 9 cases respectively. In order not to loose power in the multivariate analysis, missing values were coded as a separate category.

# GENERAL DISCUSSION

The main purposes of this thesis were to evaluate risk factors and prognosis of PICH. In epidemiological studies, a risk factor indicates that the persons which are exposed to the risk factor have higher risk to develop the disease as compare to the unexposed, an information that might have implications in preventive work for example.

It has been claimed that 'attempts to infer the underlying disease by analysis of clinical risk factors...is at best an approximation of what would be learned by microscopy',<sup>211</sup> however, it must be borne in mind that the incidence of PICH is low, and the post-mortem examinations may not always be carried out for various reasons, including ethical concerns. Therefore, the amount of information available from such studies is limited. The results of epidemiological studies do not prove what causes a particular disease in terms of cellular pathology, but the information obtained may help us to understand the development of the disease, i.e. the aetiology.

Accurate prognoses are important for several reasons. Apart from providing the patient and relatives with information on the expected outcome, prognoses can be used in the design of research projects and the assessment of care facilities. Only twelve community-based studies on prognosis following PICH had been carried out up until 2000, and the number of participants included did not exceed 122.<sup>212</sup> The increasing interest in this rare stroke subtype during the past decade is mirrored by the increasing number of community-based publications on prognosis.<sup>18, 53, 128-130</sup> In order to obtain reliable information on the risk factors and prognosis concerning less common diseases, large cohorts are required. In addition, reliable case ascertainment and diagnosis are crucial. Few individual study centres can fulfil these requirements, and the majority of previous studies on prognosis are multicentre studies.<sup>53, 128-130</sup>

In prospective large-cohort studies, stroke diagnosis is often obtained from hospital and/or national discharge registers.<sup>72, 74, 80, 83</sup> In this work, information was obtained from a local stroke register, employing a broad case-retrieval procedure, in addition to national registers, which improve the case finding possibilities.<sup>213</sup> The next step is to verify the stroke diagnosis. For practical reasons it is seldom possible to verify each potential stroke case in large epidemiological studies, especially as the diagnosis of cerebral infarction is mainly based on clinical information. PICH diagnosis, on the other hand, is based on characteristics seen in CT and/or MRI examinations. In this work the same emphasis was placed on diagnosis verification regardless of the source of information on cases.

## *Relation between country of birth and intracerebral haemorrhage*

Previous studies have shown differences in the incidence of stroke between individuals of different ethnic origin living in the same country,<sup>59-61, 66</sup> although such studies are not common. The assignment of ethnicity may vary, and self-reported ethnicity has been suggested to be the optimal method.<sup>214</sup> By using ethnicity as a marker, the

heterogeneity of the cohort will be increased by second- and third-generation immigrants who have adopted the lifestyle of their new country and are exposed to its environment. On the other hand, self-reporting of country of birth, as used in the present work, may lead to erroneous classification of ethnicity. For example, second-generation immigrants would give their country of birth as Sweden, although they belong to a different ethnic group. In spite of the small numbers in the groups of people born in another country, we observed a higher risk of ICH in immigrants from China/Vietnam and the former Soviet Union than in participants born in Sweden. This is in accordance with the high rates of ICH reported in Asia,<sup>54, 64, 74, 215, 216</sup> and the higher rate of ICH among Chinese immigrants compared with Whites in New York (USA).<sup>217</sup>

According to the results of the MONICA project (Monitoring of Trends and Determinants in Cardiovascular Disease, by the World Health Organization), the overall stroke rate in Moscow and Novosibirsk, Russia, was high.<sup>218</sup> According to another study published by the WHO, the highest stroke mortality rates were observed in Eastern Europe and the countries of the former Soviet Union.<sup>219</sup> There are no reliable incidence data on different stroke subtypes in the Soviet Union<sup>7</sup>, but a high rate of ICH has been reported in Georgia.<sup>220</sup>

The elevated stroke burden in East Asia and the former Soviet Union could be explained by high rates of hypertension<sup>221</sup> and diabetes.<sup>222</sup> High alcohol consumption in the former Soviet Union<sup>223</sup> probably also influences the risk of stroke. Even 20 years after migration from China to the USA, hypertension was still the most important risk factor for stroke among Chinese stroke patients<sup>224</sup> and more prevalent as compared with stroke patients with other ethnicities.<sup>217</sup> The overall stroke mortality rate was found not to differ between Chinese immigrants and Whites, and was significantly lower than the mortality rate among Chinese in China during the same period,<sup>225</sup> indicating that genetic factors had less influence than environmental factors.

Previous studies on the population in Malmö have shown higher incidences of stroke in areas with low socioeconomic conditions and a large proportion of immigrants.<sup>124</sup> Low income and living alone influence health care costs in Malmö, in contrast to country of birth.<sup>226</sup> However, the extent to which the continued high risk of ICH among immigrants from East Asia and the former Soviet Union seen in the present work can be attributed to genetic factors, rather than lifestyle, vascular risk factors or lower use of health care services has yet to be explored.

### *Blood pressure and stroke*

In prospective studies, risks are often expressed in terms of relative risks for the sake of convenience. However, in order to assess the clinical and public health implications, relative risks must be translated into the number of incidences during a specified period of time. Few studies have compared the incidence of stroke subtypes, in terms of absolute and relative risks, in relation to hypertension. In this work it was found that elevated blood pressure is associated with a higher risk of PICH in terms of relative risk. However, in terms of the number of cases, i.e. the standardised incidence during a

defined period of time, elevated blood pressure is associated with a greater number of cases of cerebral infarction. The standardised incidence of cerebral infarction, classified according to age and sex, increased with higher blood pressure (hypertension grade 3), from 1.7 to 6.8 per 1000, while the corresponding incidences of PICH increased from 0.2 to 2.1 per 1000. These figures reflect the numbers of patients expected to suffer a stroke, and thus the importance of hypertension on stroke incidence from a public health perspective.

As reported in a previous publication by our group, uncontrolled hypertension, despite pharmacological treatment, is highly prevalent.<sup>208</sup> We lack information on treatment compliance, but an Australian case-control study showed a nearly five-fold elevated risk of PICH when medication for hypertension was not taken.<sup>227</sup> Others have estimated that the treatment of patients with hypertension could prevent 17 to 28% of haemorrhagic strokes (including subarachnoidal haemorrhages).<sup>228</sup> They did not report blood pressure levels, but in our cohort the mean blood pressure levels were higher than recommended<sup>186</sup> in all treated groups. This further indicates the importance of blood pressure control in preventing PICH.

Relative risks depend entirely on the risk of the reference group. PICH, as compared to cerebral infarction, is unusual in normotensive individuals, which could explain why the gradient of the RR associated with blood pressure is steeper for PICH than for cerebral infarction. However, it also underlines the strong relationship between elevated blood pressure and PICH, while other risk factors (e.g. smoking, diabetes, alcohol and BMI) are also important for the incidence of cerebral infarction.

#### *Risk factors for lobar and nonlobar PICH*

The first prospective large-cohort studies on risk factors for stroke did not differentiate between ischaemic and haemorrhagic stroke.<sup>80, 229</sup> Knowledge of the differences in stroke aetiology and the introduction of CT imaging in the diagnostic procedure have later contributed to separate analysis of these two subtypes.<sup>72, 78, 83, 108</sup> In the present work it was found that subdivision according to the site of haemorrhage in PICH enhanced the possibility of identifying predictive factors for PICH. For instance, diabetes was independently related to non-lobar PICH and smoking to lobar PICH.

A higher prevalence of diabetes in patients with non-lobar PICH as compared to those with lobar PICH was reported in a case-control study,<sup>107</sup> and is in line with the present results. Diabetes is strongly associated with increased severity of extracranial atherosclerosis assessed by means of carotid intima-media thickness,<sup>230</sup> autopsy-verified coronary artery disease<sup>231</sup> and angiography-verified peripheral artery disease.<sup>232</sup> Although diabetes is correlated to both small- and large-vessel-related cerebral infarctions,<sup>233</sup> the association with specific intracranial vasculopathy is less clear<sup>234</sup>. In fatal stroke, diabetes is independently related to the prevalence of intracranial atherosclerotic plaque.<sup>235</sup>

Smoking is also related to a range of atherosclerotic manifestations,<sup>232, 236</sup> but biological evidence of an association with specific cerebral vascular pathologies is less

clear.<sup>10, 234</sup> Autopsy of the circle of Willis and its major branches, performed on samples in a prospective study (the Honolulu Heart Study), showed an association with smoking and atherosclerosis in the larger, but not the smaller branches.<sup>237</sup> A positive relation has been observed between smoking and ICH with increasing age in men.<sup>238</sup>

Smoking is linked to the formation of aneurysms.<sup>239</sup> We can not exclude that some cases with vascular malformations were missed in the lobar PICH groups.<sup>240, 241</sup> The diagnostic procedure to identify vascular malformations as the cause of the haemorrhage involves catheter angiography, an investigation with relatively high risks, and is only performed in certain cases.<sup>163</sup> No data are available on the use of angiography in patients with intracerebral haemorrhage at our hospital. The decision to perform angiography is often made in collaboration with colleagues from the neurosurgery and neuroradiology departments. Although speculative, smoking-induced microaneurysms might explain the relation to lobar PICH.<sup>242</sup>

The results obtained in this work suggest that elevated blood pressure is related to both non-lobar and lobar PICH, but in particular to non-lobar. It has been postulated that an acute increase in blood pressure or cerebral blood flow may cause rupture of perforating arteries by inducing fibrinoid necrosis (the acute form of arteriolosclerosis) in vessels with or without former vasculopathy.<sup>40, 243</sup> Physiologically, the arterioles serve as resistance vessels, responsible for the autoregulation of the cerebral blood flow. The capacity of these vessels to dilate and contract as the result of various stimuli is crucial for their autoregulatory function.<sup>244, 245</sup> It has been suggested that impaired autoregulation due to arteriolosclerosis makes the most distal and smaller arterioles more sensitive to the influence of elevated blood pressure, with secondary smooth muscle damage and possible rupture as a consequence.<sup>44</sup> However, CAA, also leads to impaired vessel elasticity and the variation in pulse pressure was proposed to explain the distribution of CAA and arteriolosclerosis. The pulse pressure within the cerebral vessel tree is higher in the deep parts of the brain, i.e. close to the feeding vessels of the brain, which makes the non-lobar arterioles more susceptible to increased blood pressure, as compared with the lobar located arterioles. On the other hand, the high pulse-pressure may protect the non-lobar vessels from amyloid deposition.<sup>246</sup>

Symptoms of depression are related to increased risk of cerebral infarction.<sup>116-119</sup> It is interesting to note that, although we used a rather unspecific definition of psychiatric morbidity, participants who ‘had received treatment or care for nervous or psychiatric problems at some time’ had a clearly increased risk of suffering PICH, in particular non-lobar PICH, an average of fourteen years later. One explanation of this could be a less healthy lifestyle and poor compliance with treatment (for example not taking antihypertensive medication) among those with psychiatric disorders.<sup>120, 247</sup> The strong association to non-lobar PICH remains to be evaluated. The questionnaire did not differentiate between psychiatric diagnoses and lacked information on the time of mental illness. Patients with depression have decreased cerebrovascular reactivity, independently of classical vascular risk factors.<sup>122</sup> Decreased cerebrovascular reactivity is a sign of impaired elasticity of the arteriolar vessels, and is observed in

arteriosclerosis-related diseases such as lacunar infarction.<sup>248</sup> Interestingly, APOE ε2, which is associated with lobar PICH, is not related to depressive disorders.<sup>249</sup>

### *Prognosis*

It was established that of the patients admitted to Malmö University Hospital between 1993 and 2000 with first-ever PICH, approximately a quarter died within one month, and half within three years. These low fatality rates, compared with other studies, could reflect low PICH severity (small bleeding volume) as well as more efficient patterns of care, but may also be explained by a combination of differences in study sample and study design. For example, we included only patients with first-ever PICH, which means lower comorbidity in terms of previous brain lesions. Other differences include admission rates of various centres and ethnicity, which could influence PICH and stroke mortality.<sup>135, 250</sup>

The better survival in women could largely be explained by better survival in female patients aged over 75 years. This is in accordance with previous studies on stroke patients,<sup>138, 251</sup> but to our knowledge this has not been demonstrated specifically for PICH. In the general population, men are at higher risk of cardiovascular disease,<sup>252</sup> and a similar relationship has been reported in stroke patients<sup>138, 139</sup>. This is reflected by the lower age of men at the time of their first PICH event. In the present work, no significant differences were found between men and women in cardiovascular comorbidity, except for smoking, which was more frequent among men, but a high percentage of data was missing. Differences in mortality could also be explained by differences in management. In Sweden, women with ischaemic stroke due to atrial fibrillation received anticoagulant treatment less often than men.<sup>141</sup> However, a recent study in Denmark showed no sex-related differences in acute hospital care among stroke patients, including early admission to the stroke unit, early CT, and treatment with antiplatelet or anticoagulant therapy.<sup>253</sup>

In clinical practice, early prognosis is often desired by both care-givers and relatives of the patient. Although scores can be calculated based on information from the acute phase, including haemorrhagic characteristics and level of consciousness,<sup>145, 146</sup> prognosis is a complicated task. In fact, in a single-centre study, it was found that the physicians tended to be pessimistic in early prognosis after ICH, with self-fulfilling prophesy of poor outcome as a consequence.<sup>254</sup> The level of consciousness often has considerable influence on the decision to give early “do not resuscitate” orders.<sup>255</sup> However, few studies have presented survival rates in unselected PICH patients who were unconscious on admission to the hospital.<sup>54, 130</sup> In the current work, 25% of the unconscious patients survived four weeks and 6 patients out of 19 could return to their own homes or to rehabilitation ward, although with major neurological deficits. Future studies on outcome should perhaps consider predictive factors in the sub-acute state as baseline as well.

## FURTHER RESEARCH

In the present thesis the value of separate analysis of PICH subtypes was highlighted. As a consequence of the development of new diagnostic tools, the possibilities of detecting secondary causes of ICH, and hence the potential to study well-defined subtypes of primary intracerebral haemorrhage, have been improved since the performance of the present studies.

Large haemorrhage volume is the single most important predictor of bad outcome. Ongoing expansion may be detected by radiological evaluation. Little is known, however, about which factors are associated with haemorrhage volume and volume expansion. Basically, the factors that were found to be associated with increased risk of PICH in our studies might as well be associated with haemorrhage volume by their effects on endothelial level.

Atherosclerosis is an inflammatory process in the vessel wall. A number of inflammatory markers have been found to be associated with increased risk of cerebral infarction. Although small vessel disease, an atherosclerosis related process, seems to underly nonlobar PICH, previous studies did not find a relation between inflammatory markers and PICH. Studies on this topic, with specific analysis on PICH subtypes might be of value.

In addition, manifestations that might be related to PICH, as for example cerebral microbleeds, are detected by newer MRI methods. Histopathological analysis and population-based data on apolipoprotein E genotype support that the distribution of microbleeds might be related to specific underlying vasculopathologies. The predictive value of cerebral microbleeds in people with and without former stroke, as well as the correlations to classical and new vascular risk factors are subjects for further evaluation. These results could have implications for our understanding of the underlying mechanisms and thus for stroke prevention.

# CONCLUSIONS

In the city of Malmö, southern Sweden, the incidence of stroke and stroke subtypes varies between immigrants from different countries. An increased incidence of ICH among immigrants from China/Vietnam and the former Soviet Union, as compared to the incidence among citizens born in Sweden, was observed. This reflects the higher rate of stroke in these countries as well as the higher rate of ICH in Asia. The extent to which this results are caused by genetic, vascular, environmental and/or socioeconomic factors remains to be evaluated.

The incidence of primary ICH (PICH) and cerebral infarction increased with increasing blood pressure. Although hypertension was associated with substantially higher incidence rates and absolute numbers of cerebral infarction, which is most important in the public health perspective, the relationship of PICH to hypertension, especially with non-lobar location, was strongest in terms of relative risk.

Increasing age and male sex were associated with PICH. Besides high blood pressure, diabetes, high triglyceride levels and psychiatric morbidity were modifiable risk factors for PICH.

Diabetes and psychiatric morbidity were independent risk factors for non-lobar PICH, whereas smoking and high age were associated with lobar PICH.

Approximately a quarter of the patients admitted for first-ever PICH died within one month, and half died within three years. Besides haemorrhage volume, intraventricular haemorrhage, higher age and brainstem or central haemorrhage site were also associated with early fatality.

Women exhibited better survival than men after PICH. The difference is largely explained by higher 28-day mortality in male patients aged over 75 years. However, the underlying reasons are yet to be explored

Twelve percent of the patients had a recurrent stroke event and the stroke recurrence rate was 5.1 % per person-year. Recurrent cerebral infarction and ICH occurred at approximately the same rate. Only age > 65 years was related to recurrent stroke.



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# REFERENCES

1. Riks-stroke, The Swedish Stroke Register *Årsrapport*. 2007;www.riks-stroke.org/content/analyser/Rapport07.pdf
2. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: Predictors for death, dependency, and recurrent stroke within the first year. *Stroke*. 2003;34:122-126
3. Hallstrom B, Jonsson AC, Nerbrand C, Norrving B, Lindgren A. Stroke incidence and survival in the beginning of the 21st century in Southern Sweden: Comparisons with the late 20th century and projections into the future. *Stroke*. 2008;39:10-15
4. Terent A. Trends in stroke incidence and 10-year survival in Soderhamn, Sweden, 1975-2001. *Stroke*. 2003;34:1353-1358
5. Stegmayr B, Asplund K, Kuulasmaa K, Rajakangas AM, Thorvaldsen P, Tuomilehto J. Stroke incidence and mortality correlated to stroke risk factors in the WHO MONICA project. An ecological study of 18 populations. *Stroke*. 1997;28:1367-1374
6. Sudlow CL, Warlow CP. Comparing stroke incidence worldwide: What makes studies comparable? *Stroke*. 1996;27:550-558
7. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: A systematic review. *Lancet Neurol*. 2009
8. The World Health Organization MONICA project (monitoring trends and determinants in cardiovascular disease): A major international collaboration. WHO MONICA project principal investigators. *J Clin Epidemiol*. 1988;41:105-114
9. Goldstein LB, Jones MR, Matchar DB, Edwards LJ, Hoff J, Chilukuri V, Armstrong SB, Horner RD. Improving the reliability of stroke subgroup classification using the trial of org 10172 in acute stroke treatment (TOAST) criteria. *Stroke*. 2001;32:1091-1098
10. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: Importance of population-based studies. *Stroke*. 2003;34:2050-2059
11. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. *Lancet*. 2003;362:1211-1224
12. van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: Diagnosis, causes and management. *Brain*. 2001;124:249-278
13. Broderick JP, Brott T, Tomsick T, Miller R, Huster G. Intracerebral hemorrhage more than twice as common as subarachnoid hemorrhage. *J Neurosurg*. 1993;78:188-191
14. Nilsson OG, Lindgren A, Stahl N, Brandt L, Saveland H. Incidence of intracerebral and subarachnoid haemorrhage in Southern Sweden. *J Neurol Neurosurg Psychiatry*. 2000;69:601-607
15. Juvela S. Prevalence of risk factors in spontaneous intracerebral hemorrhage and aneurysmal subarachnoid hemorrhage. *Arch Neurol*. 1996;53:734-740
16. 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*. 1997;28:491-499
17. Appelros P, Nydevik I, Seiger A, Terent A. High incidence rates of stroke in Örebro, Sweden: Further support for regional incidence differences within Scandinavia. *Cerebrovasc Dis*. 2002;14:161-168
18. Hallstrom B, Norrving B, Lindgren A. Stroke in lund-orup, sweden: Improved long-term survival among elderly stroke patients. *Stroke*. 2002;33:1624-1629

19. Khan FA, Engstrom G, Jerntorp I, Pessah-Rasmussen H, Janzon L. Seasonal patterns of incidence and case fatality of stroke in Malmo, Sweden: The stroma study. *Neuroepidemiology*. 2005;24:26-31
20. Lauria G, et al. Incidence and prognosis of stroke in the Belluno province, Italy. *Stroke*. 1995;26:1787-1793
21. 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*. 2001;32:1732-1738
22. Kolominsky-Rabas PL, Sarti C, Heuschmann PU, Graf C, Siemonsen S, Neundoerfer B, Katalinic A, Lang E, Gassmann KG, von Stockert TR. A prospective community-based study of stroke in Germany--the Erlangen stroke project (ESPRO): Incidence and case fatality at 1, 3, and 12 months. *Stroke*. 1998;29:2501-2506
23. Lovelock CE, Molyneux AJ, Rothwell PM. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: A population-based study. *Lancet Neurol*. 2007;6:487-493
24. Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. *Lancet*. 2008;371:1612-1623
25. Tissue plasminogen activator for acute ischemic stroke. The National Institute of neurological disorders and stroke rt-PA stroke study group. *N Engl J Med*. 1995;333:1581-1587
26. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, Lutsep HL, Nesbit GM, Grobelny T, Rymer MM, Silverman IE, Higashida RT, Budzik RF, Marks MP. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial. *Stroke*. 2005;36:1432-1438
27. Dorland's illustrated medical dictionary. *W.B. Saunders company*. 2007;31st edition
28. Gilbert JJ, Vinters HV. Cerebral amyloid angiopathy: Incidence and complications in the aging brain. I. Cerebral hemorrhage. *Stroke*. 1983;14:915-923
29. Vinters HV, Gilbert JJ. Cerebral amyloid angiopathy: Incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. *Stroke*. 1983;14:924-928
30. Attems J, Lauda F, Jellinger KA. Unexpectedly low prevalence of intracerebral hemorrhages in sporadic cerebral amyloid angiopathy: An autopsy study. *J Neurol*. 2008;255:70-76
31. Masuda J, Tanaka K, Ueda K, Omae T. Autopsy study of incidence and distribution of cerebral amyloid angiopathy in Hisayama, Japan. *Stroke*. 1988;19:205-210
32. Neumann MA. Combined amyloid vascular changes and argyrophilic plaques in the central nervous system. *J Neuropathol Exp Neurol*. 1960;19:370-382
33. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein e epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. *Ann Neurol*. 1995;38:254-259
34. Ritter MA, Droste DW, Hegedus K, Szepesi R, Nabavi DG, Csiba L, Ringelstein EB. Role of cerebral amyloid angiopathy in intracerebral hemorrhage in hypertensive patients. *Neurology*. 2005;64:1233-1237
35. Itoh Y, Yamada M, Hayakawa M, Otomo E, Miyatake T. Cerebral amyloid angiopathy: A significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly. *J Neurol Sci*. 1993;116:135-141
36. Nicoll JA, Burnett C, Love S, Graham DI, Dewar D, Ironside JW, Stewart J, Vinters HV. High frequency of apolipoprotein e epsilon 2 allele in hemorrhage due to cerebral amyloid angiopathy. *Ann Neurol*. 1997;41:716-721

37. Seifert T, Lechner A, Flooh E, Schmidt H, Schmidt R, Fazekas F. Lack of association of lobar intracerebral hemorrhage with apolipoprotein e genotype in an unselected population. *Cerebrovasc Dis.* 2006;21:266-270
38. Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, Kase CS, Pessin MS. Apolipoprotein e epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. *Stroke.* 1996;27:1333-1337
39. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: Validation of the Boston criteria. *Neurology.* 2001;56:537-539
40. Lammie GA. Pathology of small vessel stroke. *Br Med Bull.* 2000;56:296-306
41. Bousser MG, Biousse V. Small vessel vasculopathies affecting the central nervous system. *J Neuroophthalmol.* 2004;24:56-61
42. Takebayashi S, Kaneko M. Electron microscopic studies of ruptured arteries in hypertensive intracerebral hemorrhage. *Stroke.* 1983;14:28-36
43. Lammie GA. Hypertensive cerebral small vessel disease and stroke. *Brain Pathol.* 2002;12:358-370
44. Fisher CM. The arterial lesion underlying lacunes. *Acta neuropath (Berlin).* 1969;12:1-15
45. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. *JNeuropathExpNeurol.* 1971;30:536-550
46. Feigin I, Prose P. Hypertensive fibrinoid arteritis of the brain and gross cerebral hemorrhage: A form of "Hyalinosis". *Arch Neurol.* 1959;1:98-110
47. Ooneda G, Yoshida Y, Suzuki K, Sekiguchi T. Morphogenesis of plasmatic arterionecrosis as the cause of hypertensive intracerebral hemorrhage. *Virchows Arch A Pathol Pathol Anat.* 1973;361:31-38
48. Rosenblum WI. The importance of fibrinoid necrosis as the cause of cerebral hemorrhage in hypertension. Commentary. *J of Neuropathology and Experimental Neurology.* 1993;52 no.1:11-13
49. Lammie GA, Brannan F, Slattery J, Warlow C. Nonhypertensive cerebral small-vessel disease. An autopsy study. *Stroke.* 1997;28:2222-2229
50. Amano S. Vascular changes in the brain of spontaneously hypertensive rats: Hyaline and fibroid degeneration. *JPath.* 1976;121:119-128
51. Furuta A, Ishii N, Nishihara Y, Horie A. Medullary arteries in aging and dementia. *Stroke.* 1991;22:442-446
52. Vonsattel JP MR, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: A comparative histological study. *Ann Neurol.* 1991;30:637-649
53. Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. *Stroke.* 2009;40:394-399
54. Inagawa T, Ohbayashi N, Takechi A, Shibukawa M, Yahara K. Primary intracerebral hemorrhage in izumo city, japan: Incidence rates and outcome in relation to the site of hemorrhage. *Neurosurgery.* 2003;53:1283-1297; discussion 1297-1288
55. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: A systematic review. *Stroke.* 2003;34:2060-2065
56. Benatru I, Rouaud O, Durier J, Contegal F, Couvreur G, Bejot Y, Osseby GV, Ben Salem D, Ricolfi F, Moreau T, Giroud M. Stable stroke incidence rates but improved case-fatality in Dijon, France, from 1985 to 2004. *Stroke.* 2006;37:1674-1679
57. Islam MS, Anderson CS, Hankey GJ, Hardie K, Carter K, Broadhurst R, Jamrozik K. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: The Perth community stroke study. *Stroke.* 2008;39:776-782

58. Feigin VL, Carter K. Editorial comment--stroke incidence studies one step closer to the elusive gold standard? *Stroke*. 2004;35:2045-2047
59. Flaherty ML, Woo D, Haverbusch M, Sekar P, Khoury J, Sauerbeck L, Moomaw CJ, Schneider A, Kissela B, Kleindorfer D, Broderick JP. Racial variations in location and risk of intracerebral hemorrhage. *Stroke*. 2005;36:934-937
60. Qureshi AI, Giles WH, Croft JB. Racial differences in the incidence of intracerebral hemorrhage: Effects of blood pressure and education. *Neurology*. 1999;52:1617-1621
61. Feigin V, Carter K, Hackett M, Barber PA, McNaughton H, Dyall L, Chen MH, Anderson C. Ethnic disparities in incidence of stroke subtypes: Auckland regional community stroke study, 2002-2003. *Lancet Neurol*. 2006;5:130-139
62. Kay R, Woo J, Kreel L, Wong HY, Teoh R, Nicholls MG. Stroke subtypes among chinese living in Hong Kong: The Shatin stroke registry. *Neurology*. 1992;42:985-987
63. Keong Wai JK, George John, Chong Tin, Biard Alison, Donnan G A. A comparative study of stroke subtypes between Asians and Caucasians in two hospital-based stroke registries. *Neurol J Southeast Asia*. 1998;3:19-21
64. Kitamura A, Nakagawa Y, Sato M, Iso H, Sato S, Imano H, Kiyama M, Okada T, Okada H, Iida M, Shimamoto T. Proportions of stroke subtypes among men and women  $\geq 40$  years of age in an urban Japanese city in 1992, 1997, and 2002. *Stroke*. 2006;37:1374-1378
65. Connor MD, Modi G, Warlow CP. Differences in the nature of stroke in a multiethnic urban South African population: The Johannesburg hospital stroke register. *Stroke*. 2009;40:355-362
66. Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, Paik MC, Hauser WA. Stroke incidence among White, Black, and Hispanic residents of an urban community: The Northern Manhattan stroke study. *Am J Epidemiol*. 1998;147:259-268
67. Wolfe CD, Rudd AG, Howard R, Coshall C, Stewart J, Lawrence E, Hajat C, Hillen T. Incidence and case fatality rates of stroke subtypes in a multiethnic population: The South London stroke register. *J Neurol Neurosurg Psychiatry*. 2002;72:211-216
68. Markus HS, Khan U, Birns J, Evans A, Kalra L, Rudd AG, Wolfe CD, Jerrard-Dunne P. Differences in stroke subtypes between black and white patients with stroke: The South London ethnicity and stroke study. *Circulation*. 2007;116:2157-2164
69. Saposnik G, Caplan LR, Gonzalez LA, Baird A, Dashe J, Luraschi A, Llinas R, Lepera S, Linfante I, Chaves C, Kanis K, Sica RE, Rey RC. Differences in stroke subtypes among natives and Caucasians in Boston and Buenos Aires. *Stroke*. 2000;31:2385-2389
70. Saposnik G, Del Brutto OH. Stroke in South America: A systematic review of incidence, prevalence, and stroke subtypes. *Stroke*. 2003;34:2103-2107
71. Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL. The incidence of deep and lobar intracerebral hemorrhage in Whites, Blacks, and Hispanics. *Neurology*. 2005;65:518-522
72. Rodriguez BL, D'Agostino R, Abbott RD, Kagan A, Burchfiel CM, Yano K, Ross GW, Silbershatz H, Higgins MW, Popper J, Wolf PA, Curb JD. Risk of hospitalized stroke in men enrolled in the Honolulu heart program and the Framingham study: A comparison of incidence and risk factor effects. *Stroke*. 2002;33:230-236
73. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. 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;335:765-774

74. Song YM, Sung J, Lawlor DA, Davey Smith G, Shin Y, Ebrahim S. Blood pressure, haemorrhagic stroke, and ischaemic stroke: The Korean national prospective occupational cohort study. *Bmj*. 2004;328:324-325
75. Broderick J, Brott T, Tomsick T, Leach A. Lobar hemorrhage in the elderly. The undiminishing importance of hypertension. *Stroke*. 1993;24:49-51
76. Jackson CA, Sudlow CL. Is hypertension a more frequent risk factor for deep than for lobar supratentorial intracerebral haemorrhage? *J Neurol Neurosurg Psychiatry*. 2006;77:1244-1252
77. Rautio A, Eliasson M, Stegmayr B. Favorable trends in the incidence and outcome in stroke in nondiabetic and diabetic subjects: Findings from the Northern Sweden MONICA stroke registry in 1985 to 2003. *Stroke*. 2008;39:3137-3144
78. Folsom AR, Rasmussen ML, Chambless LE, Howard G, Cooper LS, Schmidt MI, Heiss G. Prospective associations of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. The atherosclerosis risk in communities (ARIC) study investigators. *Diabetes care*. 1999;22:1077-1083
79. Hyvarinen M, Tuomilehto J, Mahonen M, Stehouwer CD, Pyorala K, Zethelius B, Qiao Q. Hyperglycemia and incidence of ischemic and hemorrhagic stroke-comparison between fasting and 2-hour glucose criteria. *Stroke*. 2009;40:1633-1637
80. Boysen G, Nyboe J, Appleyard M, Sorensen PS, Boas J, Somnier F, Jensen G, Schnohr P. Stroke incidence and risk factors for stroke in Copenhagen, Denmark. *Stroke*. 1988;19:1345-1353
81. Feldmann E, Broderick JP, Kernan WN, Viscoli CM, Brass LM, Brott T, Morgenstern LB, Wilterdink JL, Horwitz RI. Major risk factors for intracerebral hemorrhage in the young are modifiable. *Stroke*. 2005;36:1881-1885
82. Lukovits TG, Mazzone TM, Gorelick TM. Diabetes mellitus and cerebrovascular disease. *Neuroepidemiology*. 1999;18:1-14
83. Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: Association of blood pressure, cholesterol, and antioxidants. *Stroke*. 1999;30:2535-2540
84. Levi F, Lucchini F, Negri E, La Vecchia C. Trends in mortality from cardiovascular and cerebrovascular diseases in Europe and other areas of the world. *Heart*. 2002;88:119-124
85. Lindstrom E, Boysen G, Nyboe J. Influence of total cholesterol, high density lipoprotein cholesterol, and triglycerides on risk of cerebrovascular disease: The Copenhagen City Heart Study. *Bmj*. 1994;309:11-15
86. Benfante R, Yano K, Hwang LJ, Curb JD, Kagan A, Ross W. Elevated serum cholesterol is a risk factor for both coronary heart disease and thromboembolic stroke in hawaiian japanese men. Implications of shared risk. *Stroke*. 1994;25:814-820
87. Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT, Jr., Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. *Neurology*. 2004;63:1868-1875
88. Ebrahim S, Sung J, Song YM, Ferrer RL, Lawlor DA, Davey Smith G. Serum cholesterol, haemorrhagic stroke, ischaemic stroke, and myocardial infarction: Korean national health system prospective cohort study. *Bmj*. 2006;333:22
89. Engstrom G, Lind P, Hedblad B, Stavenow L, Janzon L, Lindgarde F. Effects of cholesterol and inflammation-sensitive plasma proteins on incidence of myocardial infarction and stroke in men. *Circulation*. 2002;105:2632-2637
90. Segal AZ, Chiu RI, Eggleston-Sexton PM, Beiser A, Greenberg SM. Low cholesterol as a risk factor for primary intracerebral hemorrhage: A case-control study. *Neuroepidemiology*. 1999;18:185-193

91. Tanaka H, Ueda Y, Hayashi M, Date C, Baba T, Yamashita H, Shoji H, Tanaka Y, Owada K, Detels R. Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. *Stroke*. 1982;13:62-73
92. Inagawa T. Risk factors for primary intracerebral hemorrhage in patients in Izumo city, Japan. *Neurosurg Rev*. 2007;30:225-234; discussion 234
93. Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea medical insurance corporation study. *Lancet*. 2001;357:922-925
94. Iribarren C, Jacobs DR, Sadler M, Claxton AJ, Sidney S. Low total serum cholesterol and intracerebral hemorrhagic stroke: Is the association confined to elderly men? The Kaiser permanente medical care program. *Stroke*. 1996;27:1993-1998
95. Tandon N, Harmon JT, Rodbard D, Jamieson GA. Thrombin receptors define responsiveness of cholesterol-modified platelets. *J Biol Chem*. 1983;258:11840-11845
96. Kroes J, Ostwald R. Erythrocyte membranes--effect of increased cholesterol content on permeability. *Biochim Biophys Acta*. 1971;249:647-650
97. Heiner AL, Gibbons E, Fairbourn JL, Gonzalez LJ, McLemore CO, Brueseke TJ, Judd AM, Bell JD. Effects of cholesterol on physical properties of human erythrocyte membranes: Impact on susceptibility to hydrolysis by secretory phospholipase a2. *Biophys J*. 2008;94:3084-3093
98. Iribarren C, Reed DM, Chen R, Yano K, Dwyer JH. Low serum cholesterol and mortality. Which is the cause and which is the effect? *Circulation*. 1995;92:2396-2403
99. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. *Jama*. 2008;300:2142-2152
100. Jood K, Jern C, Wilhelmsen L, Rosengren A. Body mass index in mid-life is associated with a first stroke in men: A prospective population study over 28 years. *Stroke*. 2004;35:2764-2769
101. Kurth T, Gaziano JM, Berger K, Kase CS, Rexrode KM, Cook NR, Buring JE, Manson JE. Body mass index and the risk of stroke in men. *Arch Intern Med*. 2002;162:2557-2562
102. Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE. Prospective study of body mass index and risk of stroke in apparently healthy women. *Circulation*. 2005;111:1992-1998
103. Song YM, Sung J, Davey Smith G, Ebrahim S. Body mass index and ischemic and hemorrhagic stroke: A prospective study in Korean men. *Stroke*. 2004;35:831-836
104. Sturgeon JD, Folsom AR, Longstreth WT, Jr., Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. *Stroke*. 2007;38:2718-2725
105. Fogelholm R, Murros K. Cigarette smoking and risk of primary intracerebral haemorrhage. A population-based case-control study. *Acta Neurol Scand*. 1993;87:367-370
106. Thrift AG, McNeil JJ, Donnan GA. The risk of intracerebral haemorrhage with smoking. The Melbourne risk factor study group. *Cerebrovasc Dis*. 1999;9:34-39
107. Woo D, Sauerbeck LR, Kissela BM, Khoury JC, Szaflarski JP, Gebel J, Shukla R, Pancioli AM, Jauch EC, Menon AG, Deka R, Carrozzella JA, Moomaw CJ, Fontaine RN, Broderick JP. Genetic and environmental risk factors for intracerebral hemorrhage: Preliminary results of a population-based study. *Stroke*. 2002;33:1190-1195



108. Lund Haheim L, Holme I, Hjermmann I, Tonstad S. Risk-factor profile for the incidence of subarachnoid and intracerebral haemorrhage, cerebral infarction, and unspecified stroke during 21 years' follow-up in men. *Scand J Public Health*. 2006;34:589-597
109. Kurth T, Kase CS, Berger K, Gaziano JM, Cook NR, Buring JE. Smoking and risk of hemorrhagic stroke in women. *Stroke*. 2003;34:2792-2795
110. Kurth T, Kase CS, Berger K, Schaeffner ES, Buring JE, Gaziano JM. Smoking and the risk of hemorrhagic stroke in men. *Stroke*. 2003;34:1151-1155
111. Juvela S, Hillbom M, Palomaki H. Risk factors for spontaneous intracerebral hemorrhage. *Stroke*. 1995;26:1558-1564
112. Thrift AG, Donnan GA, McNeil JJ. Heavy drinking, but not moderate or intermediate drinking, increases the risk of intracerebral hemorrhage. *Epidemiology*. 1999;10:307-312
113. Hillbom M, Numminen H. Alcohol and stroke: Pathophysiologic mechanisms. *Neuroepidemiology*. 1998;17:281-287
114. Paul SL, Dewey HM, Sturm JW, Macdonell RA, Thrift AG. Prevalence of depression and use of antidepressant medication at 5-years poststroke in the North East Melbourne stroke incidence study. *Stroke*. 2006;37:2854-2855
115. Steffens DC KK, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. *Stroke*. 2002;Jun;33:1636-1644.
116. Jonas BS, Mussolino ME. Symptoms of depression as a prospective risk factor for stroke. *Psychosom Med*. 2000;62:463-471
117. May M, McCarron P, Stansfeld S, Ben-Shlomo Y, Gallacher J, Yarnell J, Davey Smith G, Elwood P, Ebrahim S. Does psychological distress predict the risk of ischemic stroke and transient ischemic attack? The Caerphilly study. *Stroke*. 2002;33:7-12
118. Nilsson FM, Kessing LV. Increased risk of developing stroke for patients with major affective disorder a registry study. *Eur Arch Psychiatry Clin Neurosci*. 2004;254:387-391
119. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Psychological distress, major depressive disorder, and risk of stroke. *Neurology*. 2008;70:788-794
120. Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking. A national perspective. *Jama*. 1990;264:1541-1545
121. Hamer M, Molloy GJ, Stamatakis E. Psychological distress as a risk factor for cardiovascular events: Pathophysiological and behavioral mechanisms. *J Am Coll Cardiol*. 2008;52:2156-2162
122. de Castro AG, Bajbouj M, Schlattmann P, Lemke H, Heuser I, Neu P. Cerebrovascular reactivity in depressed patients without vascular risk factors. *J Psychiatr Res*. 2008;42:78-82
123. Thrift AG, Dewey HM, Sturm JW, Paul SL, Gilligan AK, Srikanth VK, Macdonell RA, McNeil JJ, Macleod MR, Donnan GA. Greater incidence of both fatal and nonfatal strokes in disadvantaged areas: The Northeast Melbourne stroke incidence study. *Stroke*. 2006;37:877-882
124. Engstrom G, Jerntorp I, Pessah-Rasmussen H, Hedblad B, Berglund G, Janzon L. Geographic distribution of stroke incidence within an urban population: Relations to socioeconomic circumstances and prevalence of cardiovascular risk factors. *Stroke*. 2001;32:1098-1103

125. McFadden E, Luben R, Wareham N, Bingham S, Khaw KT. Social class, risk factors, and stroke incidence in men and women. A prospective study in the European prospective investigation into cancer in Norfolk cohort. *Stroke*. 2009
126. Kuper H, Adami HO, Theorell T, Weiderpass E. The socioeconomic gradient in the incidence of stroke: A prospective study in middle-aged women in Sweden. *Stroke*. 2007;38:27-33
127. Jakovljevic D, Sarti C, Sivenius J, Torppa J, Mahonen M, Immonen-Raiha P, Kaarsalo E, Alhainen K, Tuomilehto J, Puska P, Salomaa V. Socioeconomic differences in the incidence, mortality and prognosis of intracerebral hemorrhage in finnish adult population. The FINMONICA stroke register. *Neuroepidemiology*. 2001;20:85-90
128. Flaherty ML, Haverbusch M, Sekar P, Kissela B, Kleindorfer D, Moomaw CJ, Sauerbeck L, Schneider A, Broderick JP, Woo D. Long-term mortality after intracerebral hemorrhage. *Neurology*. 2006;66:1182-1186
129. Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term survival after primary intracerebral haemorrhage: A retrospective population based study. *J Neurol Neurosurg Psychiatry*. 2005;76:1534-1538
130. Nilsson OG, Lindgren A, Brandt L, Saveland H. Prediction of death in patients with primary intracerebral hemorrhage: A prospective study of a defined population. *J Neurosurg*. 2002;97:531-536
131. Tatu L. Primary intracerebral hemorrhages in the Besancon stroke registry. *European Neurology*. 2000;43:209-214
132. Ovary C, Suzuki K, Nagy Z. Regional differences in incidence rates, outcome predictors and survival of stroke. *Neuroepidemiology*. 2004;23:240-246
133. McGuire AJ, Raikou M, Whittle I, Christensen MC. Long-term mortality, morbidity and hospital care following intracerebral hemorrhage: An 11-year cohort study. *Cerebrovasc Dis*. 2007;23:221-228
134. van Beijnum J, Lovelock CE, Cordonnier C, Rothwell PM, Klijn CJ, Al-Shahi Salman R. Outcome after spontaneous and arteriovenous malformation-related intracerebral haemorrhage: Population-based studies. *Brain*. 2009;132:537-543
135. Saposnik G, Baibergenova A, O'Donnell M, Hill MD, Kapral MK, Hachinski V. Hospital volume and stroke outcome: Does it matter? *Neurology*. 2007;69:1142-1151
136. Dennis MS. Outcome after brain haemorrhage. *Cerebrovasc Dis*. 2003;16 Suppl 1:9-13
137. Appelros P, Stegmayr B, Terent A. Sex differences in stroke epidemiology: A systematic review. *Stroke*. 2009;40:1082-1090
138. Holroyd-Leduc JM, Kapral MK, Austin PC, Tu JV. Sex differences and similarities in the management and outcome of stroke patients. *Stroke*. 2000;31:1833-1837
139. Olsen TS, Dehlendorff C, Andersen KK. The female stroke survival advantage: Relation to age. *Neuroepidemiology*. 2009;32:47-52
140. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: Secular trends in Rochester, Minnesota, through 1989. *Stroke*. 1996;27:373-380
141. Glader EL, Stegmayr B, Norrving B, Terent A, Hulter-Asberg K, Wester PO, Asplund K. Sex differences in management and outcome after stroke: A Swedish national perspective. *Stroke*. 2003;34:1970-1975
142. Hosomi N, Naya T, Ohkita H, Mukai M, Nakamura T, Ueno M, Dobashi H, Murao K, Masugata H, Miki T, Kohno M, Kobayashi S, Koziol JA. Predictors of intracerebral hemorrhage severity and its outcome in Japanese stroke patients. *Cerebrovasc Dis*. 2008;27:67-74

143. Tuhim S, Dambrosia JM, Price TR, Mohr JP, Wolf PA, Hier DB, Kase CS. Intracerebral hemorrhage: External validation and extension of a model for prediction of 30-day survival. *Ann Neurol*. 1991;29:658-663
144. Tuhim S, Dambrosia JM, Price TR, Mohr JP, Wolf PA, Heyman A, Kase CS. Prediction of intracerebral hemorrhage survival. *Ann Neurol*. 1988;24:258-263
145. Ruiz-Sandoval JL, Chiquete E, Romero-Vargas S, Padilla-Martinez JJ, Gonzalez-Cornejo S. Grading scale for prediction of outcome in primary intracerebral hemorrhages. *Stroke*. 2007;38:1641-1644
146. Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ich score: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke*. 2001;32:891-897
147. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987-993
148. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1-5
149. Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. Incidence and time course. *Stroke*. 1996;27:1783-1787
150. Broderick JP, Diringer MN, Hill MD, Brun NC, Mayer SA, Steiner T, Skolnick BE, Davis SM. Determinants of intracerebral hemorrhage growth: An exploratory analysis. *Stroke*. 2007;38:1072-1075
151. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology*. 2006;66:1175-1181
152. Sjalander A, Engstrom G, Berntorp E, Svensson P. Risk of haemorrhagic stroke in patients with oral anticoagulation compared with the general population. *J Intern Med*. 2003;254:434-438
153. Sjoblom L, Hardemark HG, Lindgren A, Norrving B, Fahlen M, Samuelsson M, Stigendal L, Stockelberg D, Taghavi A, Wallrup L, Wallvik J. Management and prognostic features of intracerebral hemorrhage during anticoagulant therapy: A swedish multicenter study. *Stroke*. 2001;32:2567-2574
154. Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke*. 2008;39:2993-2996
155. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. *Neurology*. 2004;63:1059-1064
156. Kazui S, Minematsu K, Yamamoto H, Sawada T, Yamaguchi T. Predisposing factors to enlargement of spontaneous intracerebral hematoma. *Stroke*. 1997;28:2370-2375
157. Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A. Blood pressure management in acute intracerebral hemorrhage: Relationship between elevated blood pressure and hematoma enlargement. *Stroke*. 2004;35:1364-1367
158. Tetri S, Juvela S, Saloheimo P, Pyhtinen J, Hillbom M. Hypertension and diabetes as predictors of early death after spontaneous intracerebral hemorrhage. *J Neurosurg*. 2009;110:411-417
159. Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein HM, Divani AA, Reddi AS. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med*. 2007;25:32-38
160. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, Heeley E, Skulina C, Parsons MW, Kim JS, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y,

- Heritier S, Morgenstern LB, Chalmers J. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): A randomised pilot trial. *Lancet Neurol.* 2008;7:391-399
161. Fogelholm R, Murros K, Rissanen A, Avikainen S. Admission blood glucose and short term survival in primary intracerebral haemorrhage: A population based study. *J Neurol Neurosurg Psychiatry.* 2005;76:349-353
  162. Christensen H, Fogh Christensen A, Boysen G. Abnormalities on ECG and telemetry predict stroke outcome at 3 months. *J Neurol Sci.* 2005;234:99-103
  163. Broderick J, Connolly S, Feldmann E, Hanley D, Kase C, Krieger D, Mayberg M, Morgenstern L, Ogilvy CS, Vespa P, Zuccarello M. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: A guideline from the american heart association/american stroke association stroke council, high blood pressure research council, and the quality of care and outcomes in research interdisciplinary working group. *Circulation.* 2007;116:e391-413
  164. Kalra L, Langhorne P. Facilitating recovery: Evidence for organized stroke care. *J Rehabil Med.* 2007;39:97-102
  165. Ronning OM, Guldvog B, Stavem K. The benefit of an acute stroke unit in patients with intracranial haemorrhage: A controlled trial. *J Neurol Neurosurg Psychiatry.* 2001;70:631-634
  166. Sarker SJ, Heuschmann PU, Burger I, Wolfe CD, Rudd AG, Smeeton NC, Toschke AM. Predictors of survival after haemorrhagic stroke in a multi-ethnic population: The South London Stroke Register (SLSR). *J Neurol Neurosurg Psychiatry.* 2008;79:260-265
  167. Gujjar AR, Deibert E, Manno EM, Duff S, Diringner MN. Mechanical ventilation for ischemic stroke and intracerebral hemorrhage: Indications, timing, and outcome. *Neurology.* 1998;51:447-451
  168. Hemphill JC, 3rd, Newman J, Zhao S, Johnston SC. Hospital usage of early do-not-resuscitate orders and outcome after intracerebral hemorrhage. *Stroke.* 2004;35:1130-1134
  169. Bailey RD, Hart RG, Benavente O, Pearce LA. Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. *Neurology.* 2001;56:773-777
  170. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, Ikeda D, Greenberg SM. Apolipoprotein e genotype and the risk of recurrent lobar intracerebral hemorrhage. *N Engl J Med.* 2000;342:240-245
  171. Inagawa T. Recurrent primary intracerebral hemorrhage in Izumo city, Japan. *Surg Neurol.* 2005;64:28-35; discussion 35-26
  172. Bae H, Jeong D, Doh J, Lee K, Yun I, Byun B. Recurrence of bleeding in patients with hypertensive intracerebral hemorrhage. *Cerebrovasc Dis.* 1999;9:102-108
  173. Passero S, Burgalassi L, D'Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. *Stroke.* 1995;26:1189-1192
  174. Gonzalez-Duarte A, Cantu C, Ruiz-Sandoval JL, Barinagarrementeria F. Recurrent primary cerebral hemorrhage: Frequency, mechanisms, and prognosis. *Stroke.* 1998;29:1802-1805
  175. Neau JP, Ingrand P, Couderq C, Rosier MP, Bailbe M, Dumas P, Vandermarcq P, Gil R. Recurrent intracerebral hemorrhage. *Neurology.* 1997;49:106-113
  176. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet.* 2001;358:1033-1041

177. Population and housing census 1990. Stockholm, statistics Sweden. ISBN 91-618-0406-1.
178. Berglund G, Elmstahl S, Janzon L, Larsson SA. The Malmo Diet and Cancer study. Design and feasibility. *J Intern Med.* 1993;233:45-51
179. Manjer J, Carlsson S, Elmstahl S, Gullberg B, Janzon L, Lindstrom M, Mattisson I, Berglund G. The Malmo Diet and Cancer study: Representativity, cancer incidence and mortality in participants and non-participants. *Eur J Cancer Prev.* 2001;10:489-499
180. Trelle E. Community-based preventive medical department for individual risk factor assessment and intervention in an urban population. *Prev Med.* 1983;12:397-402
181. Jerntorp P, Berglund G. Stroke registry in Malmo, Sweden. *Stroke.* 1992;23:357-361
182. World health organization. International classification of diseases. 10th revision. [www.who.int/classifications/apps/icd/icd10online/](http://www.who.int/classifications/apps/icd/icd10online/). 2007
183. Socialstyrelsen. The national patient register.
184. The national register of cause of death. Stockholm, Sweden; centre for epidemiology, the national board of health and welfare; 2002.
185. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J. The abcs of measuring intracerebral hemorrhage volumes. *Stroke.* 1996;27:1304-1305
186. 2003 European society of hypertension-European society of cardiology guidelines for the management of arterial hypertension. *J Hypertens.* 2003;21:1011-1053
187. Wallstrom P, Wirfalt E, Lahmann PH, Gullberg B, Janzon L, Berglund G. Serum concentrations of beta-carotene and alpha-tocopherol are associated with diet, smoking, and general and central adiposity. *Am J Clin Nutr.* 2001;73:777-785
188. World health organization. WHO expert committee on diabetes mellitus:Second report. *Technical Report.* 1980;Series 646:1-80
189. Peterson B, Trelle E, Kristenson H. Comparison of gamma-glutamyltransferase and questionnaire test as alcohol indicators in different risk groups. *Drug Alcohol Depend.* 1983;11:279-286
190. Riks-stroke, the Swedish stroke register. *Acute forms.* 2004; [www.riks-stroke.org/content/forms/english/acute.pdf](http://www.riks-stroke.org/content/forms/english/acute.pdf)
191. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* 1974;2:81-84
192. Malmgren R, Warlow C, Bamford J, Sandercock P. Geographical and secular trends in stroke incidence. *Lancet.* 1987;2:1196-1200
193. Harmsen P, Wilhelmsen L, Jacobsson A. Stroke incidence and mortality rates 1987 to 2006 related to secular trends of cardiovascular risk factors in Gothenburg, Sweden. *Stroke.* 2009
194. Sogaard AJ, Selmer R, Bjertness E, Thelle D. The Oslo health study: The impact of self-selection in a large, population-based survey. *Int J Equity Health.* 2004;3:3
195. Van Loon AJ, Tjshuis M, Picavet HS, Surtees PG, Ormel J. Survey non-response in the Netherlands: Effects on prevalence estimates and associations. *Ann Epidemiol.* 2003;13:105-110
196. Janzon L, Hanson BS, Isacson SO, Lindell SE, Steen B. Factors influencing participation in health surveys. Results from prospective population study 'men born in 1914' in Malmo, Sweden. *J Epidemiol Community Health.* 1986;40:174-177
197. O'Byrne AM, Kavanagh AM, Ugoni A, Diver F. Predictors of non-attendance for second round mammography in an Australian mammographic screening programme. *J Med Screen.* 2000;7:190-194

198. Kjoller M, Thoning H. Characteristics of non-response in the Danish health interview surveys, 1987-1994. *Eur J Public Health*. 2005;15:528-535
199. Berglund G, Nilsson P, Eriksson KF, Nilsson JA, Hedblad B, Kristenson H, Lindgarde F. Long-term outcome of the malmo preventive project: Mortality and cardiovascular morbidity. *J Intern Med*. 2000;247:19-29
200. Pessah-Rasmussen H, Engstrom G, Jerntorp I, Janzon L. Increasing stroke incidence and decreasing case fatality, 1989-1998: A study from the stroke register in Malmo, Sweden. *Stroke*. 2003;34:913-918
201. Coull AJ, Silver LE, Bull LM, Giles MF, Rothwell PM. Direct assessment of completeness of ascertainment in a stroke incidence study. *Stroke*. 2004;35:2041-2045
202. Hallstrom B, Jonsson AC, Nerbrand C, Petersen B, Norrving B, Lindgren A. Lund stroke register: Hospitalization pattern and yield of different screening methods for first-ever stroke. *Acta Neurol Scand*. 2007;115:49-54
203. Andersen KK, Olsen TS, Dehlendorff C, Kammersgaard LP. Hemorrhagic and ischemic strokes compared: Stroke severity, mortality, and risk factors. *Stroke*. 2009;40:2068-2072
204. Huttner HB, Steiner T, Hartmann M, Kohrmann M, Juettler E, Mueller S, Wikner J, Meyding-Lamade U, Schramm P, Schwab S, Schellinger PD. Comparison of abc/2 estimation technique to computer-assisted planimetric analysis in warfarin-related intracerebral parenchymal hemorrhage. *Stroke*. 2006;37:404-408
205. Tatu L, Moulin T, El Mohamad R, Vuillier F, Rumbach L, Czorny A. Primary intracerebral hemorrhages in the Besancon stroke registry. Initial clinical and CT findings, early course and 30-day outcome in 350 patients. *Eur Neurol*. 2000;43:209-214
206. Leira R, Davalos A, Silva Y, Gil-Peralta A, Tejada J, Garcia M, Castillo J. Early neurologic deterioration in intracerebral hemorrhage: Predictors and associated factors. *Neurology*. 2004;63:461-467
207. Engstrom G, Stavenow L, Hedblad B, Lind P, Eriksson KF, Janzon L, Lindgarde F. Inflammation-sensitive plasma proteins, diabetes, and mortality and incidence of myocardial infarction and stroke: A population-based study. *Diabetes*. 2003;52:442-447
208. Li C, Engstrom G, Hedblad B, Berglund G, Janzon L. Blood pressure control and risk of stroke: A population-based prospective cohort study. *Stroke*. 2005;36:725-730
209. Li C, Engstrom G, Hedblad B, Berglund G, Janzon L. Risk factors for stroke in subjects with normal blood pressure: A prospective cohort study. *Stroke*. 2005;36:234-238
210. Lind P, Engstrom G, Stavenow L, Janzon L, Lindgarde F, Hedblad B. Risk of myocardial infarction and stroke in smokers is related to plasma levels of inflammation-sensitive proteins. *Arterioscler Thromb Vasc Biol*. 2004;24:577-582
211. Mohr JP (1995) The pathogenesis of single penetrator infarcts. in Lacunar and other subcortical infarctions DG, Norrving B, Bamford J, Bogousslavsky J (eds), pp29-31, Oxford University Press: Oxford.
212. Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: The Oxfordshire community stroke project. *Stroke*. 1993;24:796-800
213. Stegmayr B, Asplund K. Measuring stroke in the population: Quality of routine statistics in comparison with a population-based stroke registry. *Neuroepidemiology*. 1992;11:204-213
214. Kaplan JB, Bennett T. Use of race and ethnicity in biomedical publication. *JAMA*. 2003;289:2709-2716

215. Liu M, Wu B, Wang WZ, Lee LM, Zhang SH, Kong LZ. Stroke in China: Epidemiology, prevention, and management strategies. *Lancet Neurol.* 2007;6:456-464
216. Zhang LF, Yang J, Hong Z, Yuan GG, Zhou BF, Zhao LC, Huang YN, Chen J, Wu YF. Proportion of different subtypes of stroke in China. *Stroke.* 2003;34:2091-2096
217. Fang J, Foo SH, Jeng JS, Yip PK, Alderman MH. Clinical characteristics of stroke among Chinese in New York city. *Ethn Dis.* 2004;14:378-383
218. Tolonen H, Mahonen M, Asplund K, Rastenyte D, Kuulasmaa K, Vanuzzo D, Tuomilehto J. Do trends in population levels of blood pressure and other cardiovascular risk factors explain trends in stroke event rates? Comparisons of 15 populations in 9 countries within the WHO MONICA stroke project. World Health Organization monitoring of trends and determinants in cardiovascular disease. *Stroke.* 2002;33:2367-2375
219. Sarti C, Rastenyte D, Cepaitis Z, Tuomilehto J. International trends in mortality from stroke, 1968 to 1994. *Stroke.* 2000;31:1588-1601
220. Tsiskaridze A, Djibuti M, van Melle G, Lomidze G, Apridonidze S, Gaurashvili I, Piechowski-Jozwiak B, Shakarishvili R, Bogousslavsky J. Stroke incidence and 30-day case-fatality in a suburb of Tbilisi: Results of the first prospective population-based study in georgia. *Stroke.* 2004;35:2523-2528
221. Wolf HK, Tuomilehto J, Kuulasmaa K, Domarkiene S, Cepaitis Z, Molarius A, Sans S, Dobson A, Keil U, Rywik S. Blood pressure levels in the 41 populations of the WHO MONICA project. *J Hum Hypertens.* 1997;11:733-742
222. Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: Estimates and projections to the year 2010. *Diabet Med.* 1997;14 Suppl 5:S1-85
223. Pomerleau J, McKee M, Rose R, Haerper CW, Rotman D, Tumanov S. Hazardous alcohol drinking in the former soviet union: A cross-sectional study of eight countries. *Alcohol Alcohol.* 2008;43:351-359
224. Fang J, Foo SH, Fung C, Wylie-Rosett J, Alderman MH. Stroke risk among Chinese immigrants in New York city. *J Immigr Minor Health.* 2006;8:387-393
225. Fang J, Madhavan S, Alderman MH. Cardiovascular mortality of Chinese in New York city. *J Urban Health.* 1999;76:51-61
226. Beckman A, Merlo J, Lynch JW, Gerdtham UG, Lindstrom M, Lithman T. Country of birth, socioeconomic position, and healthcare expenditure: A multilevel analysis of Malmö, Sweden. *J Epidemiol Community Health.* 2004;58:145-149
227. Thrift AG, McNeil JJ, Forbes A, Donnan GA. Three important subgroups of hypertensive persons at greater risk of intracerebral hemorrhage. Melbourne risk factor study group. *Hypertension.* 1998;31:1223-1229
228. Woo D, Haverbusch M, Sekar P, Kissela B, Khoury J, Schneider A, Kleindorfer D, Szaflarski J, Pancioli A, Jauch E, Moomaw C, Sauerbeck L, Gebel J, Broderick J. Effect of untreated hypertension on hemorrhagic stroke. *Stroke.* 2004;35:1703-1708
229. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke. The Framingham study. *JAMA.* 1981;245:1225-1229
230. Sigurdardottir V, Fagerberg B, Hulthe J. Preclinical atherosclerosis and inflammation in 61-year-old men with newly diagnosed diabetes and established diabetes. *Diabetes care.* 2004;27:880-884
231. Goraya TY, Leibson CL, Palumbo PJ, Weston SA, Killian JM, Pfeifer EA, Jacobsen SJ, Frye RL, Roger VL. Coronary atherosclerosis in diabetes mellitus: A population-based autopsy study. *J Am Coll Cardiol.* 2002;40:946-953

232. Diehm N, Shang A, Silvestro A, Do DD, Dick F, Schmidli J, Mahler F, Baumgartner I. Association of cardiovascular risk factors with pattern of lower limb atherosclerosis in 2659 patients undergoing angioplasty. *Eur J Vasc Endovasc Surg.* 2006;31:59-63
233. Rincon F, Sacco RL, Kranwinkel G, Xu Q, Paik MC, Boden-Albala B, Elkind MS. Incidence and risk factors of intracranial atherosclerotic stroke: The Northern Manhattan stroke study. *Cerebrovasc Dis.* 2009;28:65-71
234. Aboyans V, Lacroix P, Criqui MH. Large and small vessels atherosclerosis: Similarities and differences. *Prog Cardiovasc Dis.* 2007;50:112-125
235. Mazighi M, Labreuche J, Gongora-Rivera F, Duyckaerts C, Hauw JJ, Amarenco P. Autopsy prevalence of intracranial atherosclerosis in patients with fatal stroke. *Stroke.* 2008;39:1142-1147
236. Howard G, DrPH; Lynne E. Wagenknecht, DrPH; Gregory L. Burke, MD, MS; Ana Diez-Roux, PhD; Gregory W. Evans, MS; Paul McGovern, PhD; F. Javier Nieto, MD, PhD; Grethe S. Tell, PhD; for the ARIC Investigators. Cigarette smoking and progression of atherosclerosis. *JAMA.* 1998;279:119-124
237. Reed DM, Resch JA, Hayashi T, MacLean C, Yano K. A prospective study of cerebral artery atherosclerosis. *Stroke.* 1988;19:820-825
238. Abbott RD, Curb JD, Rodriguez BL, Masaki KH, Yano K, Schatz IJ, Ross GW, Petrovitch H. Age-related changes in risk factor effects on the incidence of coronary heart disease. *Ann Epidemiol.* 2002;12:173-181
239. Juvola S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: A long-term follow-up study. *Stroke.* 2001;32:485-491
240. Hino A FM, Yamaki T, Iwamoto Y, Katsumori T. Value of repeat angiography in patients with spontaneous subcortical hemorrhage. *Stroke* 1998 Dec;29(12):2517-21. 1998;29:2517-2521
241. Wakai S KN, Nagai M. Lobar intracerebral hemorrhage. A clinical, radiographic, and pathological study of 29 consecutive operated cases with negative angiography. *J Neurosurg.* 1992;76:231-238
242. Cole FM, Yates P. Intracerebral microaneurysms and small cerebrovascular lesions. *Brain.* 1967;90:759-768
243. Caplan L. Intracerebral hemorrhage revisited. *Neurology.* 1988;38:624-627
244. Rudzinski W, Swiat M, Tomaszewski M, Krejza J. Cerebral hemodynamics and investigations of cerebral blood flow regulation. *Nucl Med Rev Cent East Eur.* 2007;10:29-42
245. Paulson OB, Waldemar G, Schmidt JF, Strandgaard S. Cerebral circulation under normal and pathologic conditions. *Am J Cardiol.* 1989;63:2C-5C
246. Auer RN, Sutherland GR. Primary intracerebral hemorrhage: Pathophysiology. *Can J Neurol Sci.* 2005;32 Suppl 2:S3-12
247. McCreadie RG. Diet, smoking and cardiovascular risk in people with schizophrenia: Descriptive study. *Br J Psychiatry.* 2003;183:534-539
248. Molina ea. Impaired cerebrovascular reactivity as a risk marker for first-ever lacunar infarction. *Stroke.* 1999;30:2296-2301
249. Surtees PG, Wainwright NW, Bowman R, Luben RN, Wareham NJ, Khaw KT, Bingham SA. No association between APOE and major depressive disorder in a community sample of 17,507 adults. *J Psychiatr Res.* 2009
250. Ayala C, Greenlund KJ, Croft JB, Keenan NL, Donehoo RS, Giles WH, Kittner SJ, Marks JS. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995-1998. *Am J Epidemiol.* 2001;154:1057-1063



251. Eriksson SE, Olsson JE. Survival and recurrent strokes in patients with different subtypes of stroke: A fourteen-year follow-up study. *Cerebrovasc Dis*. 2001;12:171-180
252. Barrett-Connor E. Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys lecture. *Circulation*. 1997;95:252-264
253. Palnum KD, Andersen G, Ingeman A, Krog BR, Bartels P, Johnsen SP. Sex-related differences in quality of care and short-term mortality among patients with acute stroke in Denmark: A nationwide follow-up study. *Stroke*. 2009;40:1134-1139
254. Becker KJ, Baxter AB, Cohen WA, Bybee HM, Tirschwell DL, Newell DW, Winn HR, Longstreth WT, Jr. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. *Neurology*. 2001;56:766-772
255. Alexandrov AV, Bladin CF, Meslin EM, Norris JW. Do-not-resuscitate orders in acute stroke. *Neurology*. 1995;45:634-640



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