Stroke and depression in very old age

Carl Hörnsten
“What can be asserted without evidence can be dismissed without evidence.” Christopher Hitchens, 2003
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Abstract

**Background** The prevalence and incidence of stroke are known to increase with age, which, combined with demographic change, means that very old patients with stroke are a growing patient group. Risk factors for incident stroke among very old people have not been widely investigated. The impact of depression on mortality in very old people who have had a stroke also remains unclear.

The aim of this thesis was to investigate the risk factors for incident stroke, the epidemiology of stroke and depression, and the consequences of having had a stroke regarding the risk of depression and mortality among very old people.

**Methods** A randomly selected half of 85-, all 90-, and all ≥95-year-olds in certain municipalities in Västerbotten County, Sweden, and Pohjanmaa County, Finland were targeted in a population-based cohort study from 2000-2012. The 65-, 70-, 75-, and 80-year-olds in all the rural and random samples from the urban municipalities in the same counties were furthermore targeted in a survey in 2010.

In the cohort study patients were assessed in their homes, by means of the 15-item Geriatric Depression Scale (GDS-15) and other assessment scales, as well as blood pressure measurements, several physical tests, and a review of medical diagnoses appearing in the medical charts. Incident stroke data were collected from medical charts guided by hospital registry records, cause of death records, and reassessments after 5 years. Depression was defined as a GDS-15 score ≥5. A clinical definition of all depressive disorders, based on assessment scale scores and review of medical charts was also used. A specialist in geriatric medicine evaluated the diagnoses. The survey included yes/no questions about stroke and depression status, and the 4-item Geriatric Depression Scale. Associations with mortality and incident stroke were tested using Cox proportional-hazard models.

**Results** In the ≥85-year-olds examined in 2005-2007 (n=601), the stroke prevalence was 21.5%, the prevalence of all depressive disorders was 37.8% and stroke was independently associated with depressive disorders (odds ratio 1.644, p=0.038). The prevalence of depression according to GDS-15 scores was 43.2% in people with stroke compared with 25.0% in people without stroke (p=0.001). However, in ≥85-year-olds examined in Sweden from 2000-2012 (n=955), from all past data collections in the study, depression was not independently associated with incident stroke.
In ≥65-year-olds who responded to a survey in 2010 (n=6098), the stroke prevalence rose with age from 4.7% among the 65- to 11.6% among the 80-year-olds (p<0.001). The prevalence of depression rose from 11.0% among the 65- to 18.1% among the 80-year-olds (p<0.001). In the group with stroke, depression was independently associated with dependence in personal activities of daily living and having a life crisis the preceding year, while in the non-stroke group, depression was independently associated with several additional demographic, social and health factors.

In ≥85-year-olds examined in 2005-2007 with valid GDS-15 tests (n=452), having had a stroke was associated with increased 5-year mortality [hazard ratio (HR) 1.53, 95% confidence interval (CI) 1.15-2.03]. Having had a stroke and depression was associated with increased 5-year mortality compared with having only stroke (HR 1.90, 95% CI 1.15-3.13), having only depression (HR 1.59, 95% CI 1.03-2.45), and compared with having neither stroke nor depression (HR 2.50, 95% CI 1.69-3.69). Having only stroke without a depression did not increase mortality compared with having neither stroke nor depression.

In ≥85-year-olds examined in Sweden from 2000-2012 (n=955), from all past data collections in the study, the stroke incidence was 33.8/1000 person-years during a mean follow-up period of about three years. In a comprehensive multivariate model, atrial fibrillation (HR 1.85, 95% CI 1.07–3.19) and higher systolic blood pressure (SBP; HR 1.19, 95% CI 1.08–1.30 per 10-mmHg increase) were associated with incident stroke overall. In additional multivariate models, diastolic blood pressure (DBP) ≥90 mmHg (HR 2.45, 95% CI 1.47–4.08) and SBP ≥160 mmHg (v. <140 mmHg; HR 2.80, 95% CI 1.53–5.14) were associated with incident stroke.

**Conclusion** The prevalence of both stroke and depression increased with age, and rates were especially high among very old people. Having had a stroke was independently associated with a higher prevalence of depression among very old people, however, depression was not independently associated with a higher incidence of stroke. Having had a stroke was associated with increased all-cause mortality among very old people, but only among those who were also depressed. High SBP (≥160 mmHg), DBP (≥90 mmHg) and atrial fibrillation were the only consistent independent risk factors for incident stroke among very old people.
# Abbreviations

ADL – Activities of Daily Living  
BMI – Body Mass Index  
CHF – Congestive Heart Failure  
CI – Confidence Interval  
CPAP – Continuous Positive Airway Pressure  
DBP – Diastolic Blood Pressure  
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, 4th ed  
GDS-15 – Geriatric Depression Scale, 15-item version  
GDS-4 – Geriatric Depression Scale, 4-item version  
GERDA – GErontological Regional DAtabase  
HR – Hazard Ratio  
HYVET – HYpertension in the Very Elderly Trial  
MADRS – Montgomery-Åsberg Depression Rating Scale  
MAP – Mean Arterial Pressure  
MeSH – Medical Subject Headings  
MI – Myocardial Infarction  
MMSE – Mini-Mental State Examination  
MNA – Mini-Nutritional Assessment  
OBS – Organic Brain Syndrome  
OR – Odds Ratio  
OSAS – Obstructive Sleep Apnea Syndrome  
PGCMS – Philadelphia Geriatric Center Morale Scale  
PP – Pulse Pressure  
PR – Prevalence Ratio  
RCT – Randomized Controlled Trial  
SBP – Systolic Blood Pressure  
TIA – Transient Ischemic Attack  
WHO – World Health Organization
Svensk sammanfattning

I västvärlden inklusive Sverige så ökar gruppen av människor som uppnår åldern 80 år eller äldre. Människorna som uppnår denna mycket höga ålder har en hög förekomst av kardiovaskulära riskfaktorer, har ofta flera samtida sjukdomar och ofta funktionsnedsättningar. Medicinska behandlingsåtgärder är ofta mindre effektiva och förknippade med biverkningar i åldersgruppen.


Vetenskapliga studier om stroke har tidigare negligerat mycket gamla människor, vilket i takt med den pågående demografiska utvecklingen framställt som allt mer orimligt. Det är ej helt klart vilka riskfaktorer som leder till att insjukna med stroke i mycket hög ålder. Överdödligheten förknippad med depression efter stroke är också oklar i åldersgruppen. Det är också oklart vad som skiljer depression efter stroke från depression bland den övriga befolkningen av äldre människor.


Bland deltagarna i kohortstudien bestämdes förekomsten av tidigare stroke baserat på genomgång av journaluppgifter och uppgifter från hembesöken. Förekomsten av depression bestämdes baserat på poängsättning från en
validerad skattningsskala för depression, samt baserat på en
sammanvägning av journaluppgifter och skattningsskalor. En specialist i
geriatrik fattade det slutliga beslutet om diagnoser. Insjuknande i stroke
bestämdes baserat på journalgenomgång av individ med stroke-relaterade
diagnoskoder i sjukhusregistret, i dödsorsaksregistret eller uppgift om stroke
vid femårsuppföljningen i studien. Bland deltagarna i enkätstudien
bestämdes förekomsten av tidigare stroke baserat på självrapportering, och
förekomsten av depression bestämdes baserat på en sammanvägning av
självrapportering och en skattningsskala för depression.

Förekomsten av stroke i enkätstudien steg med ålder, från 4.7% bland 65-
åringar till 11.6% bland 80-åringar. Förekomsten av stroke var omkring 20%
bland 85-åringar, med minimal variation mellan 85-, 90- och 95-åringar.
Förekomsten av depression var högre bland dem med stroke jämfört med de
övriga deltagarna, både gällande den sammanvägda diagnosen och baserat
endast på poängsättning. Stroke och sömnpåverkan var oberoende
associerade med depression.

Bland ≥65-åringar i enkätstudien var funktionsnedsättning och
genomgången livskris associerade med depression hos dem med en tidigare
stroke. Bland deltagare utan stroke var ett antal ytterligare externa faktorer,
inklusive subjektiv upplevelse av dålig ekonomi och att inte ha någon att
anförts om sig, associerade med depression.

Både stroke och depression var associerade med ökad dödlighet bland ≥85-
åringar. De med stroke utan depression hade en dödlighet i linje med
normalbefolkningen utan stroke eller depression. Förekomsten av samtidig
stroke och depression var associerad med högre dödlighet än
normalbefolkningen, jämfört med dem med endast stroke eller endast
depression.

Högt systoliskt blodtryck (≥160 mmHg), högt diastoliskt blodtryck (≥90
mmHg) och förmaksflimmer var oberoende riskfaktorer för att insjukna i
stroke bland ≥85-åringarna. Sambandet mellan blodtryck och strokerisk
försvagades ej hos människor med kognitiv eller funktionell nedsättning.
Tidigare stroke, hjärtsvikt, kognitiv nedsättning, näringsbrist, depressiva
symtom och låg gångastighet var också associerade med att insjukna i
stroke, men ej oberoende av varandra.

Sammanfattningsvis så stiger förekomsten av stroke med åldern och är
särskilt hög bland mycket gamla människor. Depression är betydligt
vanligare hos mycket gamla människor med stroke, även justerat för
störningsfaktorer. Depression är främst associerat med funktions-
nedättning hos människor med stroke, men med ett större antal externa faktorer hos människor utan stroke. Mycket gamla människor med stroke har särskilt hög dödlighet om de samtidigt är deprimerade, men en dödlighet i linje med normalbefolkningen om de inte är deprimerade. Högt systoliskt och diastoliskt blodtryck samt förmåksflimmer är viktiga och behandlingsbara orsaker till att drabbas av stroke i mycket hög ålder.
Original papers


Background

**Demographic change**

The population of ≥60-year-olds has expanded rapidly over the last decades, and is projected to continue to increase. The expansion is largely attributed to increased life expectancy in countries experiencing technical, medical and economical development. The expansion has slowed down in developed countries, but is still rapid in developing countries.

In developed countries, the population of ≥80-year-olds is expanding at a higher rate than that of ≥60-year-olds. The number of ≥80-year-olds as a proportion of the total Swedish population increased notably between 1970, 1990 and 2010, as illustrated in Figure 1. Comparable increases have been observed in other developed countries.

**Figure 1.** Population pyramid of the proportion of ≥80-year-olds compared with the total population in Sweden in 1970 (black), 1990 (brown) and 2010 (green).
For scientific purposes the populations of ≥80-year-olds or ≥85-year-olds are commonly designated "very old people" or the "oldest old". The World Health Organization (WHO) commonly uses ≥80-year-olds to mark a demographic subdivision. There is a corresponding Medical Subject Heading (MeSH) term, "Aged, 80 and over", that is used to index research concerning very old people. For research on people between 65-79 years the MeSH term used is "Aged". In Swedish research, historically, ≥85-year-olds have been used as the most common demographic subdivision in the study of very old people. Deciding limits for age stratification categories is an inherently arbitrary process, although it is useful in facilitating data comparisons among different research projects.

Very old people differ from younger people in several respects. Among the very old, social isolation and loneliness increases and former social structures such as participation in the workforce are no longer in effect. Systolic Blood Pressure (SBP) levels increase, which may lead to cardiovascular disease, although there have been reports of decreasing SBP levels in the highest age ranges among very old people. The prevalence of dementia rises markedly, for example in Western Europe from 2.6% between the years 65-69, to 12.9% between the years 80-84 and 43.1% among ≥90-year-olds. Cognitive decline and reduced physical ability bring an increase in functional disability, leading to a loss of independence and need for assistance with daily living. The prevalence of depressive disorders appears to be high in very old people. Disease processes are generally more difficult to monitor due to increased multimorbidity from several simultaneous conditions, and medical treatment options are likely to cause side effects. Considering these distinguishing features, it is useful to consider very old people as separate group in research concerning epidemiological features, prevention and treatment options.

**Stroke**

Stroke is a disease caused by reduced blood flow to the brain, leading to damage of the brain tissue. Depending on the location of the damaged tissue, stroke can lead to symptoms ranging from minor loss of sensory function, to loss of consciousness in the most severe cases. Stroke was estimated to be the second most common cause of death, accounting for 11.1% of all deaths (after 13.3% for ischemic heart disease), in a large meta-analysis from 2010. Another meta-analysis estimated that there were about 25.7 million stroke survivors, and 6.5 million deaths from stroke globally in 2013.
**Definition of stroke**
After a series of meetings in the 1970s, a standard definition of stroke was specified by the WHO as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin”\(^{14}\). Temporary focal disturbances of cerebral function that are resolved within 24 hours have traditionally been classified as transient ischemic attacks (TIA)\(^{15}\). The WHO released several slightly altered definitions of stroke in the 1970s\(^{14-16}\), but the notion of stroke as a clinical diagnosis of disturbed cerebral function, with a symptom duration of more than 24 hours or leading to death before that point, and a cause of vascular origin, has been widely adopted in subsequent scientific work.

An emerging perspective in stroke diagnostics rejects the time-based and clinical stroke definition once proposed by the WHO, in favor of a definition rooted in pathophysiology. This new stroke definition emphasizes the detection of a central nervous system infarction, non-traumatic intracerebral hemorrhage, or non-traumatic subarachnoid hemorrhage based on technological, pathological or clinical analysis, while recognizing variants associated with symptoms of disturbed cerebral function as well as silent variants without any documented acute symptoms\(^{17}\). The inclusion of clinical analysis as grounds for a stroke diagnosis means that the main difference between the new definition and the traditional WHO definition is that silent strokes are also recognized as actual strokes.

**Stroke in old people**

*Epidemiology*
The prevalence of stroke rises markedly with age\(^{13}\), and is higher in men than in women\(^{18}\). Large epidemiological surveys have reported self-reported stroke prevalence rates of about 5% among ≥65-year-olds, and 10% among very old people\(^{19,20}\), with slightly lower rates if the numbers are restricted to cases confirmed by medical records\(^{19}\). Notably, one study specifically targeting 85-year-olds found a stroke prevalence of 18.8% based on multiple sources of information\(^{21}\). This discrepancy raises the possibility that the stroke prevalence in very old people may be underestimated when certain methods are used to collect diagnoses. It is probably important to combine multiple sources of information to produce an accurate measure of stroke prevalence and incidence in very old age groups.

The incidence of stroke also rises with age\(^{13,22}\), and is higher in men than in women\(^{18}\). Stroke incidence rates in general have decreased over recent
decades\textsuperscript{13,22}. While a study from southern Sweden between 1993-1995 and 2001-2002\textsuperscript{23} and a study in northern Sweden between the years 1985-1998\textsuperscript{24} found the stroke incidence unchanged, a more recent nationwide study between the years 1987-2010 found a decreasing stroke incidence\textsuperscript{25}. The decrease in the incidence seen in the United Kingdom was less pronounced among very old people\textsuperscript{22}. The stroke incidence among $\geq$85-year-olds was found to be 20.78/1000 person-years in a meta-analysis (95\% CI 16.74-23.78)\textsuperscript{26}. The stroke incidence in the same age group was 20.2/1000 person-years between 2000-2002 in southern Sweden\textsuperscript{23}, but another study specifically targeting 85-year-olds in western Sweden found a stroke incidence of 57.2/1000 person-years\textsuperscript{27}.

\textit{Complications}

Stroke can lead to various degrees of neurological deficit depending on the location of the cerebral infarction/hemorrhage. The neurological deficit can include loss of sensory function, motor function, motor control, cranial nerve function (including dysphagia, loss of vision, and loss of hearing), aphasia or even unconsciousness. It is common for pneumonias and venous thromboembolism to occur during the hospital stay after a stroke\textsuperscript{28}. Fatigue\textsuperscript{28,29}, depression\textsuperscript{28,30} and shoulder pain\textsuperscript{28,31} are also common after a stroke. In very old people, stroke is associated with higher mortality\textsuperscript{26,32,33} and reduced functional recovery\textsuperscript{26,32} compared with younger individuals.

\textit{High blood pressure as a preventable risk factor}

High blood pressure is an established risk factor for stroke in younger populations\textsuperscript{34,35}, however, there is a lack of relevant observational data from very old people. Hypertension did not appear to be a risk factor for incident stroke among very old people as reported in three population-based cohort studies\textsuperscript{36-38}, although another such study found that higher SBP was associated with incident stroke\textsuperscript{27}. Furthermore, according to a large meta-analysis, the association between hypertension and stroke mortality appears to be notably weaker among very old people in comparison with younger age groups\textsuperscript{39}.

Treatment of high blood pressure with antihypertensive medication is considered to reduce the risk of stroke in younger populations\textsuperscript{34}. There is less evidence from the very old age group, but one randomized controlled trial (RCT) of very old people found that antihypertensive treatment decreased the risk of stroke mortality\textsuperscript{40} and a meta-analysis of very old participants from several RCTs found that that antihypertensive treatment also reduced the risk of stroke\textsuperscript{41}. As the positive effects of antihypertensive treatment were seen in relatively healthy very old individuals, it is unclear whether the results apply on the population-level.
Other risk factors
Other established risk factors for stroke include genetic factors, physical inactivity, dyslipidemia, unhealthy diet, obesity, diabetes mellitus, cigarette smoking, atrial fibrillation, acute myocardial infarction, cardiomyopathy and carotid stenosis. Less established risk factors include Obstructive Sleep Apnea Syndrome (OSAS), chronic inflammation/infections and drug abuse. Psychosocial circumstances including depression have also been suggested as possibly increasing the risk of stroke.

There is a lack of population-based studies investigating risk factors for incident stroke among very old people, however, atrial fibrillation was a risk factor for incident stroke in a large population-based cohort study among very old people. Depression has also been associated with incident stroke in a population-based cohort study and according to a post-hoc analysis of data from a clinical trial cohort.

In addition to treatment of high blood pressure with antihypertensive medication, there are several preventative measures in use that are thought to reduce the risk of suffering a stroke. Daily or semi-daily treatment with acetylsalicylic acid reduces the risk of stroke, and is recommended for people with sufficiently elevated stroke risk and as secondary prevention after stroke. Anticoagulative drugs reduce the risk of stroke in people with atrial fibrillation. Lipid-lowering drugs reduce the risk of stroke in people with dyslipidemia. Treatment with Continuous Positive Airway Pressure (CPAP) has appeared to reduce the risk of stroke in several observation studies. It has also decreased the risk of suffering additional strokes in RCTs of stroke survivors, but no RCT has investigated CPAP as primary prevention against stroke.

Treatment
The established treatment for ischemic stroke in the acute phase is intravenous thrombolysis. This decreases mortality and improves the outcome after stroke if distributed within 6 hours, but the treatment effects are notably better if administered within 3 hours. The benefits and risks associated with treating very old individuals with intravenous thrombolysis were swathed in uncertainty for many years, but a fairly recent RCT, the third international stroke trial, found no diminished treatment effects among a substantial number of very old study participants.

Specialized stroke care in a stroke ward, including structured rehabilitation, efforts to mitigate stroke risk factors and prevention of post-stroke complications, improves patient outcomes, compared with usual care. It is unclear whether care in stroke wards is also the best option also in very old
people, but comparisons between very old and younger patients in observational studies indicate that the very old also benefit from care in stroke units.  

**Depression**  
Depression can be used in a broader sense to refer to symptoms of low mood, or can refer to a particular psychiatric diagnosis, such as major depression.

**Definition of depression**  
The use of the word “depression” in health-care settings without further specification usually refers to a diagnosis of ”major depressive disorder” according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The diagnosis is based on the presence of five or more out of nine described symptoms, for most of the day, almost every day, during a two-week period, representing a change from previous functioning. These nine symptoms may include significant change in weight/appetite, insomnia or hypsomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate, and recurrent thoughts about death or suicidal thoughts, but have to include either depressed mood or loss of interest or pleasure in most activities. In addition, the symptoms must cause clinically significant distress or impairment in important areas of functioning, may not be the direct physiological effects of a substance or a general medical condition, may not be better explained by bereavement (in the preceding 2 months), and may not include discrete periods of persistent manic mood.

In a broader sense, ”depression” may encompass several other diagnoses according to the DSM-IV that require varying degrees of similar depressive symptoms, but do not fulfil the criteria for ”major depressive disorder”, such as ”minor depressive disorder”, ”dysthymia”, ”depression due to a general medical condition”, ”depression due to drug side effects” and ”atypical depression”. All of these diagnoses are examples of a categorical perspective on psychiatric disease, where psychiatric symptoms are fitted to the most appropriate diagnosis. However, a psychiatric diagnosis such as depression can also be viewed from a dimensional perspective, such as scores on assessment scales.

**Depression in old people**  
Depression in old age is associated with several idiosyncrasies. Somatic symptoms appear to be more common among old people who suffer from
depression than among younger people\textsuperscript{54}. Treatment of depression with antidepressants appears to be more difficult in people aged $\geq 65$ years\textsuperscript{55}. Antidepressants also appear to be ineffective in people with depression and dementia\textsuperscript{56,57}.

**Depression assessment scales**

There are several depression assessment scales based on subjective assessment by an examiner of each of the nine core symptoms of depression with subscores, which are tallied to give a total score. While this approach is generally useful, there may be issues concerning communicating the severity of symptoms and assigning subjective scores in some groups of old people.

The Geriatric Depression Scale (GDS) is a depression rating scale that was developed to be suitable for administration in broad populations of old people by the use of easily understood yes-no question\textsuperscript{58}. In a study of geriatric stroke patients, the original GDS was one of the best self-rating scales regarding internal consistency and sensitivity and predictive value against a clinical depression diagnosis based on a psychiatric interview\textsuperscript{59}. The original version contained 30 items, but a subsequent version with 15 items (GDS-15) is quicker to administer but maintains excellent psychometric properties\textsuperscript{60}. In a recent meta-analysis, the GDS-15 had a pooled sensitivity of 0.89 and a specificity of 0.77 compared with a diagnosis of major depression\textsuperscript{61}. The GDS-15 is also useful in assessing depression in people with cognitive impairment\textsuperscript{62}.

**Epidemiology**

The weighted average prevalence of all depressive disorders was 13.5\% and the weighted average prevalence of major depression was 1.8\% in a review of studies of community-dwellers aged $\geq 55$ and older\textsuperscript{63}. The pooled prevalence of all depressive disorders was 17.1\% (95\% CI 9.7-26.1\%) and the pooled prevalence of major depression was 7.2\% (95\% CI 4.4-10.6\%) in a meta-analysis of $\geq 75$-year-olds\textsuperscript{8}. However, the prevalence of depression is highly dependent on the definition of depression that is being used, which is reflected in the highly variable results from individual studies\textsuperscript{8,63}. The prevalence of all depressive disorders appears to increase with age\textsuperscript{8}, although it is less clear whether major depression, defined categorically, increases with age. The incidence of depression increased from 17/1000 person-years during the years 70-79 to 44/1000 person-years during the years 79-85 in a long-term cohort study\textsuperscript{64}.
Risk factors for depression
Regarding old populations in general, depression has been consistently associated with bereavement, sleep disturbance, functional disability, prior depression and female sex\textsuperscript{65}.

Vascular risk factors\textsuperscript{66} and inflammatory activity\textsuperscript{67} are also associated with depression. A long-term cohort study in Sweden found that high blood pressure predicted depressive symptoms among 68-year-olds, but decreasing blood pressure over time and low blood pressure were associated with depressive symptoms in the same individuals followed up as 81-year-olds\textsuperscript{68}.

Stroke and depression in old people
Depression is broadly thought of as a possible complication after stroke. For research purposes this phenomenon is sometimes categorized as ”post-stroke depression”.

Association between stroke and depression
People who have had a stroke have a higher prevalence of depression than those who have not, both measured cross-sectionally\textsuperscript{69} and after a set interval after suffering a stroke\textsuperscript{70,71}. These associations also appear to be supported in very old populations\textsuperscript{70,71}. Investigations into the extent of post-stroke depression have found highly variable results. One review that investigated the prevalence of depressive disorders one month after stroke found figures ranging from 11 to 55\%\textsuperscript{72}. Additionally, a meta-analysis of prospectively recruited stroke patients subsequently tested for depression found a pooled depression frequency of 33\% (95\% CI 29 to 36\%)\textsuperscript{30}. An updated meta-analysis that however excluded studies with age limits, found a similar pooled depression frequency of 31\% (95\% CI 28 to 35\%)\textsuperscript{73}.

While it is an established notion that suffering a stroke can lead to depression, some studies have also investigated the possibility that depression may lead to a stroke. Depression has been found to increase the incidence of stroke\textsuperscript{74,75}, although mostly in populations below very old age. One study of 85-year-olds also found this association\textsuperscript{27}.

Vascular hypothesis concerning post-stroke depression
It has been proposed that brain tissue damage incurred after a stroke is an important causative factor for depression\textsuperscript{76}. This proposition is supported partly by the epidemiological association between stroke and depression\textsuperscript{70,71}, but more specifically by the association between brain lesions revealed in
radiological examinations and depressive symptoms\textsuperscript{77-79}. It is also possible that the social consequences of having a stroke may cause depression.

The theoretical mechanism behind the increased stroke risk from depression is less well-understood. It has been speculated that direct neuroendocrine activation or inflammatory activity associated with depression may play a role\textsuperscript{74}. Depression is also associated with life-style factors such as obesity and smoking status, that may increase the stroke risk by proxy\textsuperscript{74}.

**Predicting post-stroke depression**

In people with stroke, depression has been consistently associated with stroke severity, functional disability, cognitive impairment and a history of depression\textsuperscript{80,81}. High neuroticism, low social support and genetic factors may also be associated with post-stroke depression\textsuperscript{82}. These factors partly coincide with the risk factors for depression in old people in general\textsuperscript{65}. Few studies have concurrently investigated factors associated with depression in people with stroke and without stroke, using comparable samples and study methodologies.

**Risk of mortality**

Depression after stroke appears to be associated with mortality in younger populations\textsuperscript{83}, although very old people have not been widely investigated. In one study of \textgeq75-year-old stroke survivors, the GDS score was associated with increased all-cause mortality\textsuperscript{84}. Few studies have included stroke-free comparison groups, although one study including <75-year-olds found that stroke survivors with and without ongoing depression had increased mortality, and people with only depression had a marginally increased mortality, compared with people without depression or stroke\textsuperscript{85}. The difference between people with a history of stroke with and without ongoing depression was not statistically tested, but overall depression appeared to be a weak predictor of mortality compared with stroke status\textsuperscript{85}.

**Risk of other consequences**

Depression after stroke has also been associated with reduced physical functioning\textsuperscript{86,87}, cognitive impairment\textsuperscript{88} and reduced well-being\textsuperscript{89}.

**Treatment of post-stroke depression**

Several RCTs indicate that treatment with antidepressants reduces depressive symptoms in people with post-stroke depression\textsuperscript{82,90}. Preventative treatment with antidepressants also appears to decrease the incidence of post-stroke depression\textsuperscript{82}. However, treatment of depression appears to be a difficult task in people aged \textgeq65 years old\textsuperscript{55}. Antidepressants are not an effective treatment for depression in very old people with
dementia\textsuperscript{50,57}. Treatment of post-stroke depression with antidepressants has not been widely investigated in very old people, but the negative results in people with dementia and the negative results in a small RCT\textsuperscript{91} that targeted people with a very old mean age are discouraging. Furthermore, antidepressants are associated with serious side effects in old people, such as possibly fatal episodes of arrhythmia\textsuperscript{92}.

OSAS is common after stroke\textsuperscript{93,94} and associated with depressive symptoms\textsuperscript{94,95}. Treatment of OSAS with CPAP may be useful to reduce depressive symptoms\textsuperscript{95}, also in people with stroke\textsuperscript{96}.
Rationale

Very old people have been neglected in stroke research in the past, partly because of the methodological issues involved in conducting research on the age group. A demographic shift in developed countries has increased the number of very old patients with stroke, leading to calls for research targeting the very old demographic group.

The association between stroke and depression has been investigated previously in both very old and younger populations, but few studies among very old people have adjusted this association for comorbidities.

While the characteristics, diseases and functional abilities associated with depression have been investigated in multiple aged populations and stroke disease cohorts, few studies have investigated factors associated with depression among old people with and without stroke concurrently, using identical settings, procedures and study variables. While stroke appears to be associated with depression, there may be additional associated factors that could help explain the causes of depression in old people with stroke compared with old people without stroke.

Depression after stroke appears to increase mortality in younger populations, but little data is available from the very old age group. In addition, the association between depression and mortality in people with stroke has rarely been investigated using stroke-free comparison groups. Only one study has investigated the association between depression and mortality among people with stroke compared with stroke-free groups, and it did not include any participants who were very old.

Risk factors for stroke have been investigated widely in younger populations, but few studies have investigated the very old age group. Clearly, risk factors for stroke in younger populations cannot reasonably be assumed to apply to the very old, considering the physiological, pathological and social changes associated with aging. Surprisingly, three population-based studies have reported that hypertension is not a risk factor for incident stroke among very old people, while another such study reported that increased SBP elevated the stroke risk. There is a current need for large population-based cohort studies to investigate high blood pressure, and depression, together with multiple other relevant factors, as risk factors for incident stroke among very old people.
Aims

General aim

The aim of this thesis was to investigate the risk factors for incident stroke, the epidemiology of stroke and depression, and the consequences of having had a stroke regarding the risk of depression and mortality among very old people.

Specific aims

Paper I
The aim of this paper was to investigate the prevalence of stroke and the association between stroke and depression in a population-based sample of people aged 85 years and older.

Paper II
The aim of this paper was to describe the prevalence of stroke and depression in 65-, 70-, 75- and 80-year-olds in northern Sweden and western Finland, and to investigate factors associated with depression among old people who have had stroke compared with old people who have not.

Paper III
The aim of this paper was to investigate the association between depression and mortality among people who have had stroke compared with people without stroke using a population-based sample of people aged 85 years and older.

Paper IV
The aim of this paper was to investigate risk factors for incident stroke among people aged 85 years and older.
Materials and methods

The population-based GErontological Regional DAtabase (GERDA) study was started in 2000 to investigate the health/disease status of very old people, and factors leading to good aging in this population. The settings and methods in Papers I-IV are presented in Table 1.

Table 1. Settings and methods in Papers I-IV

<table>
<thead>
<tr>
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<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
</tr>
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<td>Swe, Fin</td>
<td>Swe, Fin</td>
<td>Swe</td>
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<td>Pop-based</td>
<td>Pop-based</td>
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<td>Cohort study</td>
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<td>Survey</td>
<td>Interview, tests, medical charts</td>
<td>Interview, tests, medical charts</td>
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<tr>
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<td>-</td>
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<td>Stroke, GDS-15</td>
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<td>Depression</td>
<td>Mortality</td>
<td>Inc. stroke</td>
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<td>955</td>
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<tr>
<td>Population (N)</td>
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<td>886</td>
<td>1379</td>
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<td>Log-binomial</td>
<td>Cox</td>
<td>Cox</td>
</tr>
<tr>
<td>Follow-up</td>
<td>-</td>
<td>-</td>
<td>5 years</td>
<td>2-5 years</td>
</tr>
</tbody>
</table>

Swe, Sweden; Fin, Finland; pop-based, population-based; GDS, Geriatric Depression Scale

Setting
A randomly selected half of 85-, all 90- and all ≥95-year-olds in one urban (Umeå) and five rural municipalities (Dorotea, Malå, Sorsele, Storuman, Vilhelmina) in Västerbotten County, Sweden, were targeted with a population-based cohort study in 2000 and 2002. The study was expanded to target the same age groups in two municipalities (Vaasa, Mustasaari) in Pohjanmaa County, Finland, in 2006. Past participants were reassessed and new participants were recruited five years after the previous data collection in Sweden in 2005/2007, and 2010/2012, and in Finland in 2011.
All 65-, 70-, 75- and 80-year-olds in all rural, and random samples from the urban municipalities, in Västerbotten County (15 municipalities), Sweden, and Pohjanmaa County (17 municipalities), Finland, were targeted with a survey in 2010.

**Participants**

Of the 962 ≥85-year-olds eligible for participation in the cohort study in Sweden and Finland in 2005-2007, 76 died before they could be contacted, 170 declined to participate, 7 were not included for other reasons and 108 agreed to participate only partially. The 601 people who participated fully in the study were used as the final sample to investigate the prevalence of stroke, depressive disorders, and the association between stroke and depressive disorders in ≥85-year-olds (Paper I). Of the participants in 2005-2007, the 452 people with valid GDS-15 assessments were used to investigate the association between stroke, depression and mortality (Paper III).

To investigate age trends in stroke and depression prevalence and factors associated with depression in people with and without stroke (Paper II), a survey was sent to 5425 people in Sweden and 5271 in Finland. The response rate was 3779 (69.7%) and 3059 (58.0%) respectively, resulting in an overall response rate of 6838 of 10696 (63.9%). Of those who responded, the 6098 (89.2%) who answered the questions about having had a stroke and being depressed or the four relevant questions from a depression assessment scale were selected for the final sample. The final sample included 2441 of the 3925 (62.2%) 65-year-olds, 1496 of the 2507 (59.7%) 70-year-olds, 1246 of the 2310 (53.9%) 75-year-olds and 915 of the 1954 (46.8%) 80-year-olds, to whom the survey was sent.

To investigate the incidence of stroke and risk factors for incident stroke in ≥85-year-olds (Paper IV), several rounds of data collections in the cohort study in Sweden were combined. Five hundred and twenty-seven individuals were eligible for participation in 2000/2002, 612 in 2005/2007, and 796 in 2010/2012. When the same individual was eligible in multiple data collection rounds, they were included only from their first examination that included a home visit. Of 1935 potential participants, 419 were excluded due to being eligible in multiple rounds of data collection and 137 died before they could be contacted. Of 1379 eligible individuals, 160 declined to participate, 8 were excluded for other reasons, and 256 declined a home visit, resulting in a final sample of 955 individuals.

In the ≥85-year-old participants from 2005-2007 in Sweden and Finland, there were slightly more men (29.5% v. 22.1%, chi-squared test, p=0.026), but a similar age distribution, compared with non-participants (excluding
those who died before contact). In the larger sample of all unique ≥85-year-old participants from 2000-2012 in Sweden, there was also slightly more men (34.1% v. 28.3%; chi-squared test, p=0.028), but a similar age distribution, compared with non-participants (excluding those who died before contact and duplicates). Among the participants in the 2010 survey, the distribution of sexes was similar, but the mean age was lower, compared with non-participants, reflecting an increasing rate of non-participation in the highest age groups (70.5 v. 73.5, Welch test, p<0.001).

**Ethical approval**

The Regional Ethical Review Board of Umeå/Sweden approved home-based interviews and physical tests of ≥85-year-olds, combined with a review of medical records and a follow-up investigation of mortality (99-326, 05-063M), a follow-up investigation of stroke incidence (2014-221-31M) and a survey of ≥65-year-olds (2010-220-32Ö).

**Procedure**

**Baseline assessments**

Eligible individuals were informed about the study by post, then contacted by telephone. Participants underwent assessments and physical tests during visits to residences and institutional care facilities. Medical charts were reviewed, and relatives and institutional care staff were contacted to obtain supporting information when needed. Oral consent to participation was obtained during telephone calls and home visits. When cognitive impairment was suspected, a relative was also asked to provide consent. Examiners were nurses, physical therapists, physicians and medical students. Before starting the assessments the examiners were educated about the assessment scales and trained to use them under supervision.

**Mortality data**

Time of death data was initially acquired from the Swedish National Tax Board or through digital medical records in Sweden, but later confirmed/complemented with data from the National Board of Health and Welfare. The corresponding data from Finland was acquired from the Population Register Center.

**Stroke incidence data**

The follow-up period was up to five years. Registry information was collected from the government-run health care provider responsible for all inpatient care in the county. Causes of death were collected from the National Board of Health and Welfare. Records of inpatient care after baseline assessment
using International Classification of Diseases (10th version; ICD-10)\textsuperscript{97} code prefixes I60, I61, I63, I64, and H34; causes of death registered with ICD-10 code prefixes I60, I61, I63, I64, H34, I67, and G45; and subsequent diagnoses of stroke or transient ischemic attack within the last 5 years among people who participated in multiple GERDA assessments were compiled for all participants. A physician comprehensively reviewed the digital medical charts of individuals identified in this manner. All discrete stroke events described in medical charts were recorded. Of the 94 individuals with one or more incident strokes, 71 were identified using registry information (29 uniquely), 50 by cause of death (19 uniquely), and 20 by repeat study assessment (3 uniquely).

**Survey data**
The survey was posted in October 2010 in Sweden and Finland. It comprised 75 items, including questions about demographics, interests, health, attitudes and about diseases. One reminder was sent to participants who did not respond.

**Assessments**
- The GDS-15\textsuperscript{60} was used to screen for depressive symptoms during the home-visits. Scores $\geq 5$ are considered to indicate depression.
- The 4-item Geriatric Depression Scale (GDS-4)\textsuperscript{98} was used to screen for depressive symptoms in the survey.
- The Montgomery Åsberg Depression Rating Scale (MADRS)\textsuperscript{99} was also used to screen for depressive symptoms in the subset of participants who were interviewed by a physician.
- The Philadelphia Geriatric Center Morale Scale (PGCMS)\textsuperscript{100} was used to assess well-being.
- The Mini-Mental State Examination (MMSE)\textsuperscript{101} was used to test for cognitive impairment. Scores range from 0 to 30, with higher scores indicating better cognitive function.
- The Barthel Activities of Daily Living (B-ADL) Index\textsuperscript{102} was used to assess dependence in ADL. The scale ranges from 0 to 20, with a score of 20 indicating independence in personal ADL.
- The Mini-Nutritional Assessment (MNA)\textsuperscript{103} was used to assess nutrition. Scores range from 0 to 30, with scores $< 17$ indicating malnutrition and $\geq 24$ indicating normal nutrition.
- The confusion subscale of the Organic Brain Syndrome (OBS) scale\textsuperscript{104} consists of 39 items that describe symptoms of OBS including various psychiatric symptoms.
- The Life Orientation Scale (LOS)\textsuperscript{105} consists of six items that describe personal values and positive life orientation.
Physical measurements

**Blood pressure**
SBP and diastolic blood pressure (DBP) were measured manually with a calibrated sphygmomanometer with the patient lying down after 5 minutes of supine rest. Pulse pressure (PP) was calculated as SBP – DBP. Mean arterial pressure (MAP) was calculated as SBP/3 + DBP/2.

**Other measurements**
- Weight was measured using calibrated digital scales. Height was measured with a measuring stick.
- Usual gait speed was measured over 2.4 meters. Participants were instructed to walk at their usual pace and were allowed to use mobility aids when necessary. A mean of two tests was calculated. Individuals who were unable to perform the test due to physical impairment were assigned an imputed value of 0.01 m/s.
- The chair stand test consisted of the individual being asked to get up and sit down three times from an initial sitting position without support.

Study definitions

**Previous stroke**
In the cohort study, a previous stroke was considered to be present if the medical charts included a stroke diagnosis or if the individual, a caregiver, or a relative reported the diagnosis and it was found to be credible based on supporting information from medical charts or other assessments. In the survey, a previous stroke was defined as answering “yes” to the question “Have you had a stroke?”.

**Incident stroke**
Individuals with current stroke diagnoses in their medical charts after inclusion into the study were considered to have experienced incident stroke. A current stroke diagnosis was understood as discrete onset of neurological deficit that was designated as a stroke, but not a TIA, by a treating physician. Stroke events were classified as ischemic, hemorrhagic or unclassified. Events judged to be traumatic intracerebral hemorrhage were not considered to be strokes.
Depression
In the cohort study, depression was defined as a score ≥5 on the GDS-15 (Papers III, IV). In addition, a clinical definition of all depressive disorders, based on assessment scale scores and review of medical charts was also used (Paper I). A specialist in geriatric medicine evaluated depression diagnoses, based on results from the GDS, MADRS, OBS, LOS and PGCMS. In the survey, depression was defined as answering “yes” to the question “Are you depressed?” or a GDS-4 score ≥2 (Paper II).

Other medical diagnoses
In the cohort study, all other diagnoses were based on assessments conducted during home visits and on records from hospitals, general practitioners and institutional care facilities. A specialist in geriatric medicine evaluated all diagnoses, ensuring that the same criteria were used in all cohorts, both in Sweden and Finland.

Statistics
The Predictive Analytics Software 17.0 (Paper I), R 2.15.2 (Paper III) and R 3.0.2 (Papers II, IV) were used for the statistical analyses. A p-value of <0.05 was considered statistically significant.

In the cohort study, univariate associations with stroke and depression were calculated using chi-squared tests for comparing proportions and Student’s t tests (Paper I) and Welch tests (Paper III) for comparing means. Multivariate associations with depression were calculated as odds ratios (OR) with logistic regression analyses (Paper I). Associations with mortality (Paper III) and incident strokes (Paper IV) were calculated with Cox proportional-hazards regression analyses. In the survey, associations with depression in people with stroke compared with people without stroke were calculated as prevalence ratios (PR) with log-binomial regression analyses (Paper II).

For the investigation of associations with depressive symptoms in ≥85-year-olds (Paper I), out of a larger set of variables thought to be relevant based on clinical experience, variables associated with stroke or depression in univariate analyses (p<0.150) were entered into a multivariate logistic regression analysis.

For the investigation of associations with mortality in ≥85-year-olds (Paper III), univariate cox regression models were complemented with multivariate models, where the variables sex, age, MMSE score, and Barthel ADL Index score were entered as covariates. Covariate selection was based on clinical
relevance, but only a small number of covariates could be included due to the small number of events in some groups. The MMSE score and Barthel ADL Index score were entered in separate models because of a strong correlation between the variables. The variable age appeared to break the assumption of proportional hazards, so it was time-transformed with a penalized spline function, and then entered as a time-dependent variable in the final models.

For the investigation of associations with stroke incidence in ≥85-year-olds (Paper IV), baseline variables thought to be associated with incident stroke based on previous research and clinical experience were tested using univariate models. All continuous variables were also tested with corresponding quadratic terms to examine possible non-linear associations. Variables significantly associated with incident stroke were entered into multivariate models. No multivariate model included time-dependent terms. Basic, intermediate and comprehensive models were used, with the progressive introduction of variables and drop-outs due to missing values. Dementia and delirium (in the preceding month) were not included in the main multivariate models because of strong correlations (≥0.5) with MMSE. Quadratic B-ADL Index was not included due to strong correlations with MNA and MMSE scores and gait speed. SBP, DBP, PP, and MAP were included in separate multivariate models.

For the investigation of stroke and depression prevalence and associations with depression in ≥65-year-olds (Paper II), the epidemiological results were weighted according to the proportion of participants compared with known population totals in demographic strata based on home municipality, sex and age, and adjusted for finite population correction. Differences in prevalence between age groups, men and women, and Swedish and Finnish participants were tested using chi-squared tests, and the PRs between stroke and depression were tested using log-binomial regression models. Factors associated with depression in subgroups of people with and without stroke were also tested using log-binomial regression models. These analyses were not adjusted for the composition of the underlying population. Out of 75 items in the survey, 18 that had been associated with depression in previous studies or were thought to be relevant based on clinical experience were entered into univariate models.
Results

Background characteristics (I-IV)

Background characteristics for the selected samples are presented in Table 2.

<table>
<thead>
<tr>
<th>Table 2. Background characteristics in selected samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I n=601</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Women</td>
</tr>
<tr>
<td>Swedish</td>
</tr>
<tr>
<td>Institutionalized</td>
</tr>
<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Barthel ADL</td>
</tr>
<tr>
<td>MMSE</td>
</tr>
<tr>
<td>GDS-15</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
</tbody>
</table>

Dichotomous variables are shown as n (%), and continuous variables are shown as mean ± standard deviation. ADL, activities of daily living; MMSE, Mini-Mental State Examination; GDS-15, 15-item Geriatric Depression Scale; SBP, systolic blood pressure; BMI, body mass index.

Prevalence of stroke (I,II)

In 6098 ≥65-year-olds who responded to a survey in 2010, the stroke prevalence rose with age from 4.7% among the 65-year-olds to 11.6% among the 80-year-olds (p<0.001), and was 7.0% overall. The stroke prevalence was higher among men, 8.4±0.5% compared with 5.7±0.4% for women (p<0.001)

In 601 ≥85-year-olds who were visited in their homes from 2005-2007, the stroke prevalence was 21.5%. In this age group, the stroke prevalence did not appear to increase with age (p=0.387), and was not higher among men than women (p=0.863). Stroke prevalence rates are presented in Table 3.
Table 3. Prevalence (percentages) of stroke and depression

<table>
<thead>
<tr>
<th>Age</th>
<th>Stroke</th>
<th>Depression</th>
<th>Stroke, depression</th>
<th>No stroke, depression</th>
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<tbody>
<tr>
<td>Overall</td>
<td>4.7</td>
<td>11.0</td>
<td>20.2</td>
<td>10.6</td>
</tr>
<tr>
<td>65</td>
<td>5.8</td>
<td>11.1</td>
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<td>8.5</td>
<td>13.5</td>
<td>22.8</td>
<td>12.7</td>
</tr>
<tr>
<td>70</td>
<td>11.6</td>
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<td>n=912</td>
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<td>n=218</td>
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<td>21.1</td>
<td>10.3</td>
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<td>22.8</td>
<td>23.6</td>
<td>17.4</td>
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</table>

Prevalence figures are shown as percentages. In the age interval 65 to 80, depression was defined as a score of ≥2 on the GDS-4 or self-reported depression, and stroke was self-reported. In ≥85-year-olds depression was defined as a score of ≥5 on the GDS-15, and stroke was a clinical diagnosis based on assessments during home visits and review of medical records.

Incidence of stroke (IV)
In 955 ≥85-year-olds in Sweden from 2000-2012, including all past data collections in the study, the stroke incidence was 33.8/1000 person-years during a mean follow-up period of 2.9 years. Furthermore, the stroke incidence was 34.4/1000 person-years among women, and 32.6/1000 person-years among men. The stroke incidence was not significantly different between women and men (p=0.838), or between various ages among the ≥85-year-olds (p=0.389).

Prevalence of depression (I-III)
In 6098 ≥65-year-olds who responded to a survey in 2010, the depression prevalence rose from 11.0% among the 65-year-olds to 18.1% among the 80-year-olds (p<0.001), and was 12.8% overall. The depression prevalence was 13.5% among women compared with 12.0% for men (p=0.074).

In 601 ≥85-year-olds from 2005-2007, the prevalence of all depressive disorders was 37.8%. The prevalence of depression according to GDS-15 scores was 28.5%. The prevalence of depression was similar in men compared with women, both when using the clinical variable (p=0.215) and GDS-15 (p=0.287). Depression prevalence rates are presented in Table 3.
Association between stroke and depression (I-IV)
In 6098 ≥65-year-olds who responded to a survey in 2010, depression was more common in people with stroke overall [PR 1.77, 95% confidence interval (CI) 1.48-2.12], in men, in women, in 65-year-olds, 70-year-olds and 75-year-olds, but the association was not significant in 80-year-olds.

In 601 ≥85-year-olds from 2005-2007, the prevalence of depressive disorders was 50.4% in people with stroke compared with 34.3% in people without stroke (p<0.001). In 452 ≥85-year-olds who had valid GDS-15 tests in 2005-2007, the prevalence of depression according to GDS-15 scores was 43.2% in people with stroke compared with 25.0% in people without stroke (p=0.001). Depression was also more common among people with stroke in the subgroup of women (p<0.001), but not among men (p=0.616). Stroke (OR 1.64, 95% CI 1.03-2.63, p=0.038) and sleep disorders (OR 2.25, 95% CI 1.54-3.31, p<0.001) were independently associated with depressive disorders in a comprehensive multivariate model (Table 4).

| Table 4. Factors independently associated with depressive disorders. |
|-----------------|-----------------|----------|
| Age             | 0.96 (0.91-1.00) | 0.073    |
| Female sex      | 0.97 (0.62-1.52) | 0.893    |
| Institutionalized| 1.28 (0.76-2.13) | 0.353    |
| Single          | 1.77 (0.99-3.19) | 0.056    |
| Barthel ADL index| 0.95 (0.90-1.01) | 0.086    |
| MMSE (score)    | 0.99 (0.95-1.02) | 0.491    |
| Impaired vision | 1.47 (0.88-2.46) | 0.139    |
| Stroke          | 1.64 (1.03-2.63) | 0.038    |
| Heart disease   | 1.29 (0.86-1.95) | 0.218    |
| Diabetes Mellitus| 0.63 (0.36-1.11) | 0.109    |
| Sleep disorder  | 2.25 (1.54-3.31) | <0.001   |
| Epilepsy        | 1.36 (0.30-6.14) | 0.686    |
| Constipation    | 1.22 (0.81-1.84) | 0.353    |
| Urinary incontinence | 1.04 (0.67-1.63) | 0.855    |

OR, odds ratio; CI, confidence interval; ADL, activities of daily living; MMSE, Mini-Mental State Examination. Logistic regression was used. Cox & Snell R² = 0.134, Nagelkerke R² = 0.183.
However, in 955 ≥85-year-olds in Sweden from 2000-2012, including all past data collections in the study, depression was not independently associated with incident stroke.

Factors associated with depression in people with and without stroke (II)
In 6098 ≥65-year-olds who responded to a survey in 2010, depression among people with stroke was associated with dependence in personal ADL, impaired vision, living alone, having no one to talk to, poor finances, having a pain problem and having a life crisis the preceding year. In the non-stroke group, depression was associated with urban dwelling, myocardial infarction, cancer, diabetes, dependence in personal and instrumental ADL, impaired vision and hearing, weight loss, living alone, having no one to talk to, poor finances, having a pain problem, having a life crisis the preceding year and age. Additionally, the univariate associations of depression with cancer (p=0.026), not having someone to talk to (p=0.013) and poor finances (p=0.029) were weaker in people who had had a stroke than in people who had not, according to interaction analyses of the whole sample (Table 5).

Depression among people with stroke was independently associated with dependence in personal ADL and having a life crisis the preceding year. In the non-stroke group, depression was independently associated with diabetes, dependence in instrumental ADL, living alone, not having someone to talk to, poor finances, pain problems and having a life crisis the preceding year (Table 5).
Table 5. Factors associated with depression in people with and without stroke.

<table>
<thead>
<tr>
<th></th>
<th>Non-stroke PR (95% CI)</th>
<th>Stroke PR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>1.07 (0.93-1.24)</td>
<td>1.29 (0.90-1.85)</td>
</tr>
<tr>
<td>Finnish</td>
<td>1.03 (0.89-1.19)</td>
<td>1.33 (0.92-1.90)</td>
</tr>
<tr>
<td>Urban</td>
<td>1.26 (1.08-1.46)</td>
<td>0.93 (0.61-1.37)</td>
</tr>
<tr>
<td>MI</td>
<td>1.44 (1.11-1.83)</td>
<td>1.17 (0.74-1.76)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.37 (1.12-1.65)</td>
<td>0.76 (0.43-1.23)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td><strong>1.59 (1.30-1.91)</strong></td>
<td>1.47 (0.92-2.23)</td>
</tr>
<tr>
<td>Dep. P-ADL</td>
<td>1.76 (1.37-2.22)</td>
<td><strong>2.35 (1.60-3.32)</strong></td>
</tr>
<tr>
<td>Dep. I-ADL</td>
<td>1.74 (1.50-2.01)</td>
<td>1.31 (0.91-1.94)</td>
</tr>
<tr>
<td>Imp. vision</td>
<td>1.93 (1.28-2.73)</td>
<td>2.00 (1.02-3.21)</td>
</tr>
<tr>
<td>Imp. hearing</td>
<td>1.71 (1.00-2.62)</td>
<td>0.56 (0.03-2.05)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1.48 (1.11-1.91)</td>
<td>1.17 (0.56-2.02)</td>
</tr>
<tr>
<td>Living alone</td>
<td><strong>1.95 (1.68-2.25)</strong></td>
<td>1.46 (1.01-2.08)</td>
</tr>
<tr>
<td>No one to talk to</td>
<td><strong>3.79 (3.02-4.64)</strong></td>
<td>2.01 (1.07-3.16)*</td>
</tr>
<tr>
<td>University ed.</td>
<td>0.87 (0.70-1.08)</td>
<td>1.01 (0.54-1.67)</td>
</tr>
<tr>
<td>Poor finances</td>
<td><strong>2.89 (2.38-3.46)</strong></td>
<td>1.74 (1.06-2.63)*</td>
</tr>
<tr>
<td>Pain problem</td>
<td><strong>1.71 (1.44-2.05)</strong></td>
<td>1.64 (1.04-2.75)</td>
</tr>
<tr>
<td>Life crisis</td>
<td><strong>2.33 (2.01-2.72)</strong></td>
<td><strong>1.64 (1.13-2.45)</strong></td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.02-1.04)</td>
<td>1.01 (0.98-1.04)</td>
</tr>
</tbody>
</table>

PR, prevalence ratio. CI, confidence interval. MI, myocardial infarction. Dep. P-ADL, dependence in personal activities of daily living. Dep. I-ADL, dependence in instrumental activities of daily living. Imp. vision, impaired vision. Imp. hearing, impaired hearing. University ed., University educated. Denominators for proportions may vary due to missing values. Associations were estimated as prevalence ratios, using univariate log-binomial regression analyses. Bold type denotes a significant association with depression in multivariate analyses. *Having had a stroke significantly affected the association between depression and the variable in an interaction analysis performed on the whole sample.
Association between stroke, depression and all-cause mortality (III)

In 452 ≥85-year-olds who had valid GDS-15 tests from 2005-2007, having had a stroke was associated with increased 5-year mortality [hazard ratio (HR) 1.53, 95% CI 1.15-2.03]. Having had both a stroke and depression was associated with increased 5-year mortality compared with only having a stroke (HR 1.90, 95% CI 1.15-3.13), and only having depression (HR 1.59, 95% CI 1.03-2.45), and compared with having neither stroke nor depression (HR 2.50, 95% CI 1.69-3.69). Having only stroke without depression did not increase mortality compared with having neither stroke nor depression. The group differences remained after adjusting for age and sex but were weakened after adjusting for scores on the MMSE or Barthel ADL Index. (Figure 2, Table 6)

**Figure 2.** Kaplan–Meier curves of 5-year mortality according to stroke and depression status. GDS, Geriatric Depression Scale-15.
Table 6. Cox regression models of group differences in five-year mortality.

<table>
<thead>
<tr>
<th>Group</th>
<th>Univariate HR (CI)</th>
<th>Basic model HR (CI)</th>
<th>Model w. MMSE HR (CI)</th>
<th>Model w. B-ADL HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 v. 1</td>
<td>1.57 (1.16-2.13)</td>
<td>1.46 (1.07-1.98)</td>
<td>1.27 (0.94-1.73)</td>
<td>1.26 (0.92-1.72)</td>
</tr>
<tr>
<td>3 v. 1</td>
<td>1.31 (0.89-1.94)</td>
<td>1.31 (0.88-1.94)</td>
<td>1.37 (0.92-2.03)</td>
<td>1.30 (0.88-1.93)</td>
</tr>
<tr>
<td>4 v. 1</td>
<td>2.50 (1.69-3.69)</td>
<td>2.56 (1.72-3.81)</td>
<td>2.12 (1.42-3.18)</td>
<td>1.87 (1.24-2.83)</td>
</tr>
<tr>
<td>3 v. 2</td>
<td>0.84 (0.54-1.29)</td>
<td>0.90 (0.58-1.39)</td>
<td>1.08 (0.69-1.68)</td>
<td>1.03 (0.66-1.61)</td>
</tr>
<tr>
<td>4 v. 2</td>
<td>1.59 (1.03-2.45)</td>
<td>1.75 (1.13-2.71)</td>
<td>1.67 (1.07-2.58)</td>
<td>1.49 (0.96-2.32)</td>
</tr>
<tr>
<td>4 v. 3</td>
<td>1.90 (1.15-3.13)</td>
<td>1.95 (1.17-3.25)</td>
<td>1.55 (0.92-2.60)</td>
<td>1.44 (0.85-2.44)</td>
</tr>
</tbody>
</table>

Group 1, No stroke and GDS<5.
Group 2, No stroke and GDS≥5.
Group 3, Stroke and GDS<5.
Group 4, Stroke and GDS≥5.
HR, hazard ratio; CI, confidence interval; MMSE, Mini-Mental State Examination; B-ADL, Barthel Activities of Daily Living Index; GDS, 15-item Geriatric Depression Scale. The basic model was adjusted for age and sex. The two additional models were adjusted for age, sex, and MMSE or B-ADL scores respectively.

Factors associated with incident stroke (IV)

In 955 ≥85-year-olds in Sweden from 2000-2012, including all past data collections in the study, incident stroke was associated with atrial fibrillation, higher SBP per mmHg-increase and DBP ≥90 mmHg (Table 7). However, SBPs ≥160 mmHg (p=0.051) and 140-159 mmHg compared with <140 mmHg and higher DBP per mmHg-increase were not significant factors (Table 7). Incident stroke was also associated with previous stroke, congestive heart failure, slower usual gait speed, lower MNA score, higher GDS-15 score, MMSE score <18 (v. ≥24), dementia and delirium (Table 7).

In a comprehensive multivariate model, incident stroke was associated overall with atrial fibrillation (HR 1.85, 95% CI 1.07–3.19) and higher SBP (HR 1.19, 95% CI 1.08–1.30 per 10-mmHg increase) (Table 8). However, higher SBP was not associated with incident stroke in participants with SBP <140 mmHg (HR 0.90, 95% CI 0.53–1.53 per 10-mmHg increase). In additional multivariate models, DBP ≥90 mmHg (HR 2.45, 95% CI 1.47–4.08) and SBP ≥160 mmHg (v. <140 mmHg; HR 2.80, 95% CI 1.53–5.14) were associated with incident stroke (Table 9). Univariate and multivariate associations with incident stroke are presented in Figure 3.

The associations of incident stroke with SBP and DBP were not affected by interactions related to sex, ADL dependence or cognitive impairment (all p>0.25).
Table 7. Baseline characteristics and univariate associations with incident stroke.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=955 (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>89.3±4.7</td>
<td>1.02 (0.97-1.07)</td>
</tr>
<tr>
<td>Women</td>
<td>629 (65.9)</td>
<td>1.05 (0.68-1.62)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>219 (22.9)</td>
<td>1.86 (1.21-2.85)</td>
</tr>
<tr>
<td>SBP (/10-mmHg increase)</td>
<td>146.2±23.0</td>
<td>1.10 (1.01-1.21)</td>
</tr>
<tr>
<td>SBP ≥160 mmHg (vs. &lt;140)</td>
<td>298 (32.7)</td>
<td>1.71 (1.00-2.92)</td>
</tr>
<tr>
<td>SBP 140–159 mmHg</td>
<td>292 (32.1)</td>
<td>1.51 (0.86-2.65)</td>
</tr>
<tr>
<td>DBP (/10-mmHg increase)</td>
<td>74.2±11.5</td>
<td>1.17 (0.97-1.40)</td>
</tr>
<tr>
<td>DBP ≥90</td>
<td>119 (13.1)</td>
<td>2.05 (1.26-3.34)</td>
</tr>
<tr>
<td>PP (/10-mmHg increase)</td>
<td>72.1±19.6</td>
<td>1.09 (0.98-1.21)</td>
</tr>
<tr>
<td>MAP (/10-mmHg increase)</td>
<td>85.8±11.8</td>
<td>1.22 (1.03-1.45)</td>
</tr>
<tr>
<td>Barthel ADL index (score)</td>
<td>16.4±5.5</td>
<td>0.99 (0.94-1.03)</td>
</tr>
<tr>
<td>Barthel ADL index &lt;20</td>
<td>526 (55.7)</td>
<td>1.43 (0.95-2.15)</td>
</tr>
<tr>
<td>Usual gait speed (m/s)</td>
<td>0.5±0.3</td>
<td>0.37 (0.16-0.83)</td>
</tr>
<tr>
<td>Chair stand, able to</td>
<td>567 (64.1)</td>
<td>0.74 (0.48-1.16)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2±4.4</td>
<td>0.97 (0.92-1.02)</td>
</tr>
<tr>
<td>BMI &lt;23 kg/m² (vs. 23–29)</td>
<td>291 (32.1)</td>
<td>0.91 (0.57-1.46)</td>
</tr>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>138 (15.2)</td>
<td>0.78 (0.43-1.44)</td>
</tr>
<tr>
<td>MNA (score)</td>
<td>23.6±4.3</td>
<td>0.95 (0.91-1.00)</td>
</tr>
<tr>
<td>MNA &lt;17 (vs. ≥24)</td>
<td>75 (8.3)</td>
<td>1.35 (0.54-3.38)</td>
</tr>
<tr>
<td>MNA 17–23</td>
<td>300 (33.0)</td>
<td>1.35 (0.87-2.10)</td>
</tr>
<tr>
<td>GDS (score)</td>
<td>3.6±2.5</td>
<td>1.10 (1.01-1.19)</td>
</tr>
<tr>
<td>GDS ≥5</td>
<td>232 (28.4)</td>
<td>1.44 (0.91-2.29)</td>
</tr>
<tr>
<td>Rheumatic disease</td>
<td>136 (14.2)</td>
<td>0.84 (0.45-1.57)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>209 (21.9)</td>
<td>2.02 (1.29-3.15)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>148 (15.5)</td>
<td>1.32 (0.78-2.24)</td>
</tr>
<tr>
<td>CHF</td>
<td>278 (29.2)</td>
<td>1.68 (1.09-2.58)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>32 (3.4)</td>
<td>1.52 (0.62-3.75)</td>
</tr>
<tr>
<td>Ever-smoker</td>
<td>330 (35.0)</td>
<td>0.92 (0.59-1.41)</td>
</tr>
<tr>
<td>MMSE (score)</td>
<td>21.2±7.6</td>
<td>0.98 (0.95-1.01)</td>
</tr>
<tr>
<td>MMSE &lt;18 (vs. ≥24)</td>
<td>225 (24.3)</td>
<td>1.96 (1.16-3.34)</td>
</tr>
<tr>
<td>MMSE 18–23</td>
<td>248 (26.7)</td>
<td>1.28 (0.79-2.07)</td>
</tr>
<tr>
<td>Dementia</td>
<td>321 (33.6)</td>
<td>1.74 (1.13-2.69)</td>
</tr>
<tr>
<td>Education ≥8 years</td>
<td>221 (24.2)</td>
<td>1.28 (0.82-2.01)</td>
</tr>
<tr>
<td>Delirium (last month)</td>
<td>206 (21.6)</td>
<td>1.70 (1.01-2.87)</td>
</tr>
</tbody>
</table>

*HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure; ADL, activities of daily living; BMI, body mass index; MNA, Mini-Nutritional Assessment; GDS, Geriatric Depression Scale; CHF, congestive heart failure; MMSE, Mini-Mental State Examination; Count denominators may change due to missing values. Univariate Cox proportional-hazards models were used.*
Figure 3. Forest plot comparing univariate and multivariate associations with incident stroke. SBP, Systolic Blood Pressure; DBP, diastolic blood pressure.
Table 8. Multivariate associations with incident stroke.

<table>
<thead>
<tr>
<th></th>
<th>Basic model n=909 (92 events) HR (95% CI)</th>
<th>Intermediate model n=869 (89 events) HR (95% CI)</th>
<th>Comprehensive model n=759 (82 events) HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (/10-mmHg)</td>
<td>1.16 (1.06–1.27)</td>
<td>1.19 (1.09–1.31)</td>
<td>1.19 (1.08–1.30)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.78 (1.09–2.93)</td>
<td>1.79 (1.08–2.99)</td>
<td>1.85 (1.07–3.19)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.77 (1.13–2.77)</td>
<td>1.61 (1.01–2.56)</td>
<td>1.60 (0.98–2.63)</td>
</tr>
<tr>
<td>CHF</td>
<td>1.50 (0.94–2.41)</td>
<td>1.56 (0.96–2.52)</td>
<td>1.37 (0.82–2.30)</td>
</tr>
<tr>
<td>MMSE &lt;18 (v. ≥24)</td>
<td>1.82 (0.95–3.50)</td>
<td>1.50 (0.72–3.12)</td>
<td></td>
</tr>
<tr>
<td>MMSE 18–23</td>
<td>1.42 (0.86–2.33)</td>
<td>1.36 (0.81–2.29)</td>
<td></td>
</tr>
<tr>
<td>MNA (score)</td>
<td>0.97 (0.92–1.03)</td>
<td>0.97 (0.91–1.04)</td>
<td></td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
<td></td>
<td>0.39 (0.13–1.16)</td>
<td></td>
</tr>
<tr>
<td>GDS (score)</td>
<td></td>
<td>1.04 (0.95–1.14)</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; CHF, congestive heart failure; MMSE, Mini-Mental State Examination; MNA, Mini-Nutritional Assessment; GDS, Geriatric Depression Scale. Multivariate Cox proportional-hazards models were used.

Table 9. Multivariate associations with incident stroke for additional blood pressure measures.

<table>
<thead>
<tr>
<th></th>
<th>Basic models HR (95% CI)</th>
<th>Intermediate models HR (95% CI)</th>
<th>Comprehensive models HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP ≥160 mmHg (v. &lt;140)</td>
<td>2.20 (1.27–3.84)</td>
<td>2.51 (1.43–4.42)</td>
<td>2.80 (1.53–5.14)</td>
</tr>
<tr>
<td>SBP 140–159 mmHg</td>
<td>1.63 (0.93–2.86)</td>
<td>1.60 (0.90–2.85)</td>
<td>1.80 (0.97–3.34)</td>
</tr>
<tr>
<td>DBP ≥90 mmHg</td>
<td>2.08 (1.28–3.41)</td>
<td>2.33 (1.41–3.85)</td>
<td>2.45 (1.47–4.08)</td>
</tr>
<tr>
<td>DBP (/10-mmHg increase)</td>
<td>1.21 (1.01–1.45)</td>
<td>1.24 (1.04–1.49)</td>
<td>1.26 (1.05–1.52)</td>
</tr>
<tr>
<td>PP (/10-mmHg increase)</td>
<td>1.14 (1.03–1.27)</td>
<td>1.18 (1.05–1.31)</td>
<td>1.17 (1.04–1.31)</td>
</tr>
<tr>
<td>MAP (/10-mmHg increase)</td>
<td>1.33 (1.11–1.58)</td>
<td>1.38 (1.16–1.65)</td>
<td>1.38 (1.16–1.65)</td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure. Multivariate Cox proportional-hazards models were used. Basic models included atrial fibrillation, previous stroke, and congestive heart failure. Intermediate models additionally included categorical Mini-Mental State Examination, and Mini-Nutritional Assessment score. Comprehensive models additionally included Geriatric Depression Scale score and usual gait speed.
Discussion

Main findings (I-IV)
The prevalence of both stroke and depression increased with age, and rates were especially high among very old people. Having had a stroke was independently associated with a higher depression prevalence among very old people, however, depression was not independently associated with a higher stroke incidence. Having had a stroke was associated with increased all-cause mortality among very old people, but only among those who were also depressed. High SBP (≥160 mmHg), DBP (≥90 mmHg), PP, MAP, and atrial fibrillation were the only consistent independent risk factors for incident stroke among very old people.

High prevalence and incidence of stroke (I,II,IV)
The prevalence of stroke appeared to increase with increasing age among the ≥65-year-olds who participated in the survey. Our estimated stroke prevalence figures are in line with previously published self-reported results\(^\text{19,20}\). The higher stroke prevalence found for men than for women is also in line with previous studies\(^\text{18-20}\).

Among the ≥85-year-olds in the cohort study, the prevalence of stroke was similar in 85-, 90- and ≥95-year-olds, and also similar in women and men. Thus, while the stroke prevalence among very old people was high, the trend of an increasing stroke prevalence with age did not continue within the group of ≥85-year-olds. The attenuation of a sex-based difference in stroke prevalence in ≥85-year-olds is in line with results from previous studies\(^\text{18,19}\). The prevalence for the whole group of ≥85-year-olds was similar to that found in the GERDA data collection in 2000-2002\(^\text{106}\). Other studies that present the age-specific prevalence among those aged 85 and above\(^\text{19,107-109}\) found it to be in the range of 9.3–12.1%. A study that investigated only 85-year-olds\(^\text{21}\) found a prevalence of 18.8%. The high prevalence found in the present study may be due to most past studies using a single source of information to determine the prevalence of stroke, a suggestion that has also been made by others\(^\text{21}\). The difference may however be partly explained by a relatively high stroke incidence regionally combined with low case fatality\(^\text{24}\).

The stroke incidence among very old people in the present study was higher than that in the Framingham study\(^\text{38}\) (18.0/1000 person-years, 1948–82), the Oxford Vascular Study\(^\text{22}\) (18.2/1000 person-years, 1981–84; 16.5/1000 person-years, 2000–04) and the results among ≥85-year-olds in a meta-analysis\(^\text{26}\) (20.78/1000 person-years), but lower than that in the H70 study\(^\text{27}\).
(57.2/1000 person-years, 1986–89). We found a similar stroke incidence among women and men. The attenuation of a sex-based difference in stroke incidence in ≥85-year-olds is in line with previous studies.\(^{18,22}\)

The incidence observed in the present study was high, despite the decreasing incidence of stroke in recent decades.\(^{13,22}\) However, the incidence of stroke did not appear to decrease among <75-year-olds in northern Sweden between the years 1985-1998.\(^{24}\)

**High prevalence of depression (I-III)**

The prevalence of depression appeared to increase with increasing age, which is in line with previous findings based on assessment scales.\(^{8}\) The estimated depression prevalence figures among all ≥65-year-olds from the survey are in line with the average prevalence of 13.5% for all depressive disorders found in a review of community-dwellers that accepted participants aged ≥55 or older\(^{63}\) and the pooled prevalence of 17.1% for all depressive disorders found in a meta-analysis of ≥75-year-olds.\(^{8}\) The prevalence of depression among ≥85-year-olds in the cohort study was especially high, which is also in line with previous studies.\(^{8}\) However, it should be pointed out that the results from individual studies of depression prevalence vary widely depending on methodological choices\(^{8,63}\).

The prevalence of depression did not differ between men and women in the ≥85-year-olds, and the trend of a different prevalence in the ≥65-year-olds from the survey was not significant. Previous studies have generally found the prevalence of depression to be higher in women than in men\(^ {8,63,110}\), and female sex is considered a risk factor for depression\(^ {65}\).

**The association between stroke and depression (I-IV)**

Depression was more common among people with a previous stroke between the ages 65 and 80 years. This remained true in all age, sex and country subgroups, but did not reach significance in 80-year-olds. It is possible that less statistical power due to fewer participants and a lower participation rate among the 80-year-olds contributed to the non-significant result, but on the other hand both the prevalence of stroke and depression were higher among 80-year-olds than other age groups. Depression was more common among people with a previous stroke also in ≥85-year-olds, both using a clinical definition of depression and using a cutoff score on the GDS-15 to define depression. The prevalence of depression among very old people with stroke in the present study was higher than the pooled frequency of 33% found in a meta-analysis that however did not provide age-specific data\(^ {30}\).
The finding of a higher prevalence of depression for people with stroke than a comparison group without stroke is in line with one hospital-based study with depression assessments 20 months post-stroke\(^71\) and one population-based study with depression assessments 6 months post-stroke\(^70\), both of which found similar results among both very old and younger individuals. Out of three additional studies that investigated the prevalence of depression post-stroke, but which did not present results for very old participants, two found a higher prevalence\(^111,112\) and one found a trend towards a higher prevalence\(^113\) among people with stroke compared with people without stroke. However, one study that investigated the cumulative incidence of depression\(^114\) and one study that investigated the 1-year incidence of depression\(^115\) found similar rates among people with stroke compared to people without stroke. The evidence suggests that depression is more common among people with stroke than among those without, and that very old people are no different in this regard.

According to the present study, stroke may independently increase the risk of depression among very old people, even when adjusting for several demographic variables, diseases and functional level. It is possible that the brain damage incurred after a stroke directly influences depression pathology or that this association is explained by the social consequences of the stroke. However, the logistic regression model controlled for differences in social conditions which might indicate that the brain damage in itself is of major importance. Sleep disorder was also independently associated with depression, which is logical considering that disturbed sleep is an important symptom of depression. An alternative explanation is that OSAS may lead to a higher depression prevalence in people with sleep disorders. OSAS is common after stroke\(^93\), is associated with depressive symptoms\(^95\), and treatment of OSAS with CPAP may be useful to reduce depressive symptoms\(^95\), also in people with stroke\(^96\). A systematic review of predictors for depression among people with stroke singled out stroke severity as a consistent risk factor\(^80\), which supports the notion that brain tissue damage is an important mechanism underlying the association between stroke and depression.

However, depression or depressive symptoms were not independently associated with incident stroke among very old people. This contradicts previous findings that point to depression as a possible risk factor for stroke in very old people\(^27\). Depression was also associated with incident stroke in a meta-analysis that did not specifically target very old people\(^74\). It is possible that the association between depression and incident stroke is less clear in the very old age group due to multimorbidity which makes it difficult to identify depression or depressive symptoms as independent risk factors. In
addition, it is theoretically possible that the psychological stress related to depression may be a less relevant contributing factor to cerebrovascular disease in very old people than in younger age groups.

**Stroke status mediating factors associated with depression (II)**

The association between dependence in personal ADL and depression found in people with stroke is in line with previously published results. The association between having a life crisis and depression in people with stroke has not been widely investigated, but social distress was found to be associated with depression in people with stroke in an earlier study. Regarding people without stroke, the association between impaired instrumental ADL and depression is in line with disability being associated with depression in a meta-analysis of community dwellers, although personal ADL was not independently associated with depression in people without stroke in the present study. A life crisis in the preceding year was also associated with depression in people without stroke, which is in line with previously reported associations between bereavement and depression among community-dwellers.

Depression was associated with a larger number of external factors in people without stroke, such as living alone, not having someone to talk to and poor finances, but also diabetes, and having problems with pain. The difference regarding external factors was further supported by interaction analyses of the whole sample, where having had a stroke appeared to weaken the associations between depression and not having someone to talk to, poor finances and cancer.

It is possible that among people with stroke, physical disability denoted by dependence in personal ADL is associated with depression, while external factors are less important. One possible explanation is that dependence in personal ADL is likely to be linked to the severity of the stroke, or the extent of the damage to the brain after stroke, which could be the underlying factor that causes depression. Stroke severity has been strongly associated with depression in previous studies. It is also possible that people with stroke may be particularly sensitive to the social consequences of loss of independence in personal ADL. In the already vulnerable state of having suffered a stroke, dependence in personal ADL may induce feelings of helplessness, reduce self-esteem and ultimately open the way to depression. Among people without stroke, external conditions such as their financial situation, living alone and not having anyone to confide in, appeared to be more important as factors associated with depression, according to our data.
Increased mortality in stroke survivors with depression (III)

A history of stroke increased mortality among very old people with ongoing depression, but not among those without depression, indicating that the increased mortality from stroke was strongly associated with depression. In a similar study among younger individuals\textsuperscript{85}, the increased mortality from stroke did not appear to be associated with depression. The finding that ongoing depression is associated with increased mortality among very old people who had had a stroke is in line with earlier results from stroke cohorts\textsuperscript{84,117,118}, including one study\textsuperscript{84} with a very old mean age among participants, although negative results have also been reported\textsuperscript{119}. A meta-analysis that mostly included participants below very old age found depression after stroke to be associated with increased mortality\textsuperscript{83}.

The increased mortality among very old people with a history of stroke was associated with depression as well as with functional dependence and cognitive impairment. When functional dependence or cognitive impairment was controlled for, the association between depression and mortality was weakened, indicating a clustering of factors associated with mortality. It is possible that among people with stroke, depression leads to cognitive impairment and functional dependence, in turn causing mortality, or that cognitive impairment and functional dependence lead to depression, in turn causing mortality.

Increased risk of stroke from high blood pressure and atrial fibrillation (IV)

The finding of independent associations between incident stroke and SBP \(\geq 160\) mmHg (v. \(< 140\) mmHg), DBP \(\geq 90\) mmHg, and higher SBP, DBP, PP, and MAP per mmHg-increase is not consistent with the results of most previous population-based cohort studies, which have found no association between hypertension and incident stroke among very old people\textsuperscript{36-38}. The results of the present study, however, agree with those of a population-based cohort study\textsuperscript{87} of 401 85-year-olds, which reported that SBP as a continuous measure was associated with incident stroke in analyses adjusted for sex and depression. In contrast to most observational studies, the randomized controlled HYpertension in the Very Elderly Trial (HYVET) found that antihypertensive therapy was associated with reduced stroke mortality and borderline associated with a lower stroke incidence\textsuperscript{40}. A meta-analysis that included HYVET data subsequently found that antihypertensive therapy reduced stroke incidence\textsuperscript{41}. 
Given the notable exclusion of people with cognitive and/or physical disability from the HYVET and other trials, and the mostly negative results from population-based cohort studies among very old people, it remains unclear whether hypertension truly increases stroke risk in representative populations of very old people. Our population-based data, from a sample that included many people with disabilities, indicate that high blood pressure is a risk factor for incident stroke among very old people. Furthermore, the association between blood pressure and incident stroke appeared to be similar in people with and without ADL dependence or cognitive impairment.

Stroke risk appeared to increase linearly overall with SBP values, but this finding does not indicate a clinically meaningful difference between high and low blood pressure in all intervals. For example, a linear increase in risk was observed for individuals with SBP ≥140 mmHg, but not for those with SBP <140 mmHg. From another perspective, the results of categorical models suggested that SBP ≥160 mmHg (v. <140) increased stroke risk, but the difference between SBPs of 140–159 and <140 mmHg had no clear effect on this risk.

In the present study, SBP ≥160 mmHg (v. <140 mmHg) was not associated with incident stroke in the univariate model, but this association was strong in the comprehensive multivariate model. In addition, associations of incident stroke with SBP 140–159 mmHg (v. <140 mmHg) and DBP ≥90 mmHg appeared to grow stronger in multivariate models. The difference between univariate and multivariate results suggests that confounding factors may obscure the association between high blood pressure and incident stroke. The negative results of some previous studies may be partly explained by modest adjustment for blood pressure confounders.

The finding of an independent association between atrial fibrillation and incident stroke among very old people is in line with the results of a large population-based study. In the present study, congestive heart failure, low MNA score, MMSE score <18, low gait speed, and high GDS-15 score were associated with incident stroke, but not independently of each other. Some of these factors may increase stroke risk, individually or collectively as a measure of geriatric multimorbidity, but we could not establish them as independent risk factors.
Methodological considerations

**Inclusion of participants**
Participants were recruited based on residence in the investigated areas and age according to population registers in Sweden and Finland. The samples from the cohort study included 51.0-69.3% (depending on the extent of missing values in central study variables) and the sample from the survey included 57.0% of the eligible participants in the population. The participation rate in the survey declined markedly with increasing age, from 62.2% among the 65-year-olds to 46.7% among the 80-year-olds. The participation rate in the cohort study did not appear to be affected overall by participant age to the same extent as in the survey, although the participation rate of individuals with valid GDS-15 scores was slightly lower among ≥95- (47.0%) compared with 90- (53.6%) and 85-year-olds (51.5%). While the overall participation rate for GDS-15 assessments may appear low, it should be considered that a non-negligible proportion of very old people have severe dementia and aphasia that make it difficult to answer the questions from the GDS-15.

Participation rates in epidemiological studies have declined over the last couple of decades. There are conflicting reports about whether older people are more or less likely to participate in epidemiological studies, but it is likely that there are particular difficulties associated with achieving a good participation rate in very old test subjects, who may have hearing impairment, vision impairment, aphasia, cognitive impairment and physical disability. Considering the sharply reduced participation rate with increasing age in the survey, it was probably an advantage to collect data about the very old participants in the cohort study through home visits.

Both the cohort study and the survey used partially random samples, but pure random sampling was not used in either. Associations should be considered statistically significant compared with a theoretical population that the participants are thought to represent, rather than compared with a population that they were randomly drawn from. However, design-based interference was used to estimate the prevalence of stroke and depression among 65- to 80-year-olds.

The sample of ≥85-year-olds included three age-groups that were representative of the population for each age-group, but not, strictly speaking, for ≥85-year-olds due to over-recruitment of participants in the highest age ranges. However, since the prevalence of stroke was similar in
85-, 90- and ≥95-year-olds, we considered the studied sample of the very old to be fairly representative of very old people who have had a stroke.

**Testing procedure**
For the baseline assessments of the cohort study, extensive information was collected concerning medical diagnoses, current medical treatment and demographics. Various assessment scales for depression, functional disability and cognitive impairment were included, as were physical tests such as blood pressure measurements and walking speed tests. However, some limitations concerning the baseline tests should still be pointed out. Blood tests were only taken for a small subset of participants in the first data collection of the study, meaning that we could not screen for clinically undetected diabetes, dyslipidemia or inflammatory activity, however clinical diagnoses of diabetes and systemic inflammatory diseases were registered based on reviewing of medical charts. Electrocardiography testing was not performed, which excluded screening for clinically undetected atrial fibrillation, but clinical diagnoses of atrial fibrillation were registered.

A general issue with the data collection procedure is that most baseline variables represent prevalent measures, with time of exposure not taken into account. This is a common design flaw with epidemiological studies, but also a logical feature of studies that select participants based on demographic residence. On the other hand, such selection mechanisms offer the opportunity to compare diseased populations with the rest of the individuals in a demographic cohort.

**Assessment of stroke**
Stroke assessments in research can be based on existing data such as diagnoses in medical charts, self-reported diagnoses and death certificates or they can be based on proactive testing of all participants according to a set protocol. While the latter is a widely used and a sound method for recruiting consecutive stroke patients to a hospital-based stroke cohort, it is arguably less efficient in population-based settings where a majority of participants are stroke-free and many of the people with a history of stroke were affected some time ago.

Stroke assessments in this thesis were based on existing data. Previous strokes were determined based on a review of medical charts and study assessments by a specialist in geriatric medicine in the cohort study, and self-reports through a yes/no question in the survey. Incident strokes were determined based on a review of medical charts guided by administrative registry data, death certificates and reassessment after five years in the study. Register data have been shown to be an accurate measure of
stroke, but we chose to review the medical charts of all individuals with potential strokes to increase the reliability of our incident stroke measure and to avoid including temporally misplaced stroke diagnoses.

Both the prevalence and incidence of stroke were high compared with previous age-stratified results from ≥85-year-olds. It is likely that some strokes were clinically undetected and therefore not included in the study, or that some TIAs were misclassified as strokes.

Ischemic, hemorrhagic and unclassified strokes were considered collectively in this thesis. While it would have been interesting to investigate ischemic and hemorrhagic strokes separately, the proportion of hemorrhagic strokes decreases with age, and it is unlikely that we would have been able to collect a sufficient number of participants to draw meaningful conclusions about hemorrhagic strokes alone. Additionally, due to the collection of existing stroke diagnoses in the medical records, a subset of the participants were not subject to computer aided tomography investigations, making it impossible to classify these strokes as either ischemic or hemorrhagic.

**Assessment of depression**

Depression assessments in research can be based on categorical diagnoses such as a diagnostic interview leading to a diagnosis according to the DSM-IV, or a dimensional diagnosis such as reaching a cut-off score on a depression assessment scale. Diagnoses based on a diagnostic interview are directly rooted in the definitions of different types of depression and are generally viewed as the golden standard for diagnosing depression. However, depression diagnoses in this thesis were mostly dimensional, using cut-off scores on the GDS-15. The major disadvantage of using an assessment scale to diagnose depression is that there are no guarantees that the criteria underpinning the definition of depression are actually met in individual patients. On the other hand, an assessment scale is an inherently more transparent and reproducible measure scientifically, and ease-of-use/efficiency is usually better than when a diagnostic interview is used, which may be a very important factor in large population-based studies.

In Paper I, however, the depression diagnoses were based on all available data, including GDS, MADRS, PGCMS, LOS and OBS as well as documentation from medical records.

**Measurement of blood pressure**

In the present study, blood pressure was measured while participants were supine. In other observational studies, it is generally measured while participants are seated. This difference raises the possibility of a systematic difference in blood pressure that may have affected our results.
with other studies. Measuring blood pressure in a supine position might have overestimated the blood pressure levels, which could theoretically have influenced the stroke risk associated with high blood pressure.

Blood pressure was also measured manually by multiple testers, which probably increased the variability of our results. This variability is unlikely to have resulted in structural bias due to its chaotic nature, however, it is possible that the association between high blood pressure and stroke risk would have been even stronger had the baseline assessments of blood pressure been more uniform.
Clinical implications

A large proportion of very old people have had a previous stroke. In addition, depression is very common among very old people who have had a stroke compared with stroke-free individuals, even when the figures are adjusted for confounders. The markedly high prevalence of both stroke and depression among very old people, means that clinicians need to be prepared to meet this age group with specialized knowledge about these conditions. The demographic shift in the western world makes it even more important to secure such information going forward.

The high prevalence and incidence of stroke and high prevalence of depression among old people in northern Sweden and western Finland, both on the same northern latitude, are in line with previous findings of a higher concentration of disease in these regions. For example, dementia\textsuperscript{123,124}, hip-fractures\textsuperscript{125} and poor oral health\textsuperscript{126,127} also appears to be more common in northern Sweden. Myocardial infarction was more common in northern Sweden historically, but incidence rates appear to have normalized over the last decades due to effective primary prevention\textsuperscript{128}. Clinicians in northern Sweden as well as politicians and hospital administrators should be aware of these regional patterns.

The risk factors for depression in old stroke survivors may differ somewhat from those in old people without stroke. Dependency in personal ADL was the most important associated factor in people with stroke, while other additional external factors were associated with depression in people without stroke. These results may indicate that different approaches are needed for prevention and treatment of depression among old people with and without a previous stroke.

Very old people who have had a stroke and who are depressed have a markedly high mortality rate, compared with those who have had a stroke but no depression, and compared with stroke-free individuals without depression. While we were unable to establish the causality firmly between depression and mortality, our findings support the view that depression is a serious condition. There is a need for treatment options to reduce the high mortality rate in very old stroke survivors who are depressed.

High SBP, DBP, and atrial fibrillation increase the risk of stroke among very old people and should be appropriately managed. Blood pressure levels below 160 mmhg systolic and 90 mmhg diastolic are desirable to minimize
stroke risk. The association between blood pressure levels and stroke risk does not appear to differ in the important subgroups among very old people of those with cognitive impairment and ADL dependency. While additional RCTs of the effect of antihypertensive treatment in these sub-groups are indicated, our observational results indicate that antihypertensive treatment is also appropriate for people with cognitive impairment and ADL dependency.

**Implications for further research**

Continuous efforts are needed in investigating the burden of stroke, including current prevalence and incidence measures. Combining information from multiple sources is key to accurate measurement of stroke prevalence and incidence.

Future observational studies of risk factors for stroke in very old people should make an effort to temporally separate potential risk factors, to possibly bring clarity to the risk exposure of individuals for whom multiple concurrent factors exist. There is a need for new RCTs to investigate the impact of several preventive measures to reduce the risk of stroke, including physical activity, weight reduction and diet. Such studies should make an effort to recruit participants representative of very old populations, including individuals with ADL dependency and cognitive impairment. A further significant goal is to attempt to investigate risk factors for radiological outcome measures of brain infarctions and brain hemorrhage, although this may be difficult in very old people for logistical and ethical reasons.

Considering its great impact on mortality and wellbeing, and the sparsity of evidence-based treatment options, there is an urgent need to find effective treatments of post-stroke depression in very old people. The support for medical treatment with antidepressant drugs is weak in the very old age group. Both prevention of depression after an incident stroke and treatment of those with depression need to be investigated in this age group.

The established theory of a vascular etiology for depression offers an interesting pathway to possibly prevent depression in general populations of old people as well. If brain lesions are casually linked with subsequent depressive symptoms, it follows that prevention directed at cardiovascular risk factors may prevent depression as well. Such preventive effects would be difficult to investigate in very old people due to multimorbidity, but it would be interesting to investigate if for example treatment of high blood pressure with antihypertensive medication could prevent depression in very old people.
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