Blood pressure in advanced age
- with focus on epidemiology, cognitive impairment and mortality

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To my grandmother, in memoriam
- tätä minä tiedän, ystävä.

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ABSTRACT

The general conception is that blood pressure increases with age, but that diastolic blood pressure (DBP) starts decreasing in the elderly. There are, however, indications that systolic blood pressure (SBP) might also decline in advanced age, but further studies are needed to establish whether this is true. Midlife hypertension is an acknowledged risk factor for mortality and dementia. Some research has, however, suggested more complicated associations between blood pressure and these outcomes in old age, as *low* blood pressure has been linked to both increased mortality and increased risk of dementia. Research on this subject, especially in very old people (≥85 years of age), is still limited. The purpose of the present thesis was to investigate blood pressure epidemiology in old age and associations between blood pressure and mortality and cognition in very old people.

Subjects were mainly derived from the Umeå 85+/GERDA (GErontological Regional DAtabase) study, a study on individuals aged 85 years, 90 years or ≥95 years carried out in northern Sweden and Finland in 2000-2007. For analysis of blood pressure change with age, data from this study were combined with data from the U70 study that was carried out in the city of Umeå, Sweden between 1981-1990 and included individuals aged 70-88 years. Investigations were performed during a home visit in the Umeå 85+/GERDA study and at a geriatric centre in the U70 study. SBP and DBP were measured in the supine position in both studies and pulse pressure (PP) was calculated as SBP-DBP. Main outcome variables were 4-year mortality, Mini-Mental State Examination (MMSE) scores, dementia and blood pressure change with age and over the years. Treatment with antihypertensive drugs was also considered.

Blood pressure changes with age and time were investigated using 1133 blood pressure measurements from 705 individuals aged ≥70 years performed between 1981 and 2005. DBP continually decreased with increasing age, whereas SBP and PP increased up to age 74.5 and 80.6 years, respectively, to then start decreasing. Mean SBP and DBP also decreased over the years. The prevalence of treatment with antihypertensive drugs increased during the same period and is probably one explanation for the decrease in blood pressure with time. Blood pressure also decreased in longitudinal analyses of those individuals who participated in more than one data collection. Women had higher SBP and PP than men.

The association between blood pressure and 4-year mortality was investigated in a sample of 348 individuals aged ≥85 years. Results indicated a non-linear association between SBP and mortality, i.e. both lower and higher SBP were associated with increased mortality. The lowest mortality risk was associated with an SBP of 164 mmHg (95% confidence interval 154-184 mmHg). The analyses were adjusted for a number of diseases and health factors and

thus suggest a negative effect of low SBP on survival, independent of health status. There was no association between DBP or PP and 4-year mortality.

The impact of blood pressure on MMSE scores and dementia was investigated both in a cross-section of 575 individuals and longitudinally in two samples including 102 and 205 individuals, respectively, all ≥85 years old. Cross-sectional analysis demonstrated nonlinear associations between SBP and PP and MMSE scores, indicating poorer cognitive function with both low and high blood pressure. The association between DBP and MMSE scores was linear, higher DBP being associated with higher scores. Individuals with dementia had lower blood pressure than those without dementia. Longitudinally, over five years, no association between baseline blood pressure and incident dementia or change in MMSE scores could be demonstrated. Mean blood pressure declined over this time period, and this decline was greater in individuals who developed dementia than in those who remained dementia free. A greater decline in blood pressure was associated with a greater decline in MMSE scores.

In conclusion, this study has shown a decrease in both SBP and DBP in advanced age and also that low blood pressure is associated with both increased mortality and poor cognitive function in very old people. These associations might not be fully explained by underlying disease or poor health status; the underlying mechanisms are so far mostly speculative. Very high blood pressure might also remain a risk factor for the mentioned outcomes even in very old age, at least in some people. No association between baseline blood pressure and cognitive decline or incident dementia could be demonstrated, but blood pressure decline was associated with cognitive decline and incident dementia. The direction of this association remains to be determined. Blood pressure also decreased over the years from 1981 to 2005, probably partly due to an increasing prevalence of treatment with antihypertensive drugs.

SVENSK SAMMANFATTNING
(SUMMARY IN SWEDISH)

Den finns en allmän uppfattning att blodtrycket stiger med åldern. Detta stämmer dock bara delvis, då man har visat att det *diastoliska* blodtrycket sjunker hos äldre. Dessutom finns det en del studier som har föreslagit att även det *systoliska* blodtrycket sjunker i mycket hög ålder, men det behövs fortfarande mer forskning inom ämnet.

Högt blodtryck, hypertoni, är en välkänd riskfaktor för hjärt-kärlsjukdom och ökad dödlighet. Dessutom har hypertoni visats vara en riskfaktor för demens. Dessa samband är dock främst fastslagna för medelålders och yngre äldre personer och det finns forskning som tyder på att sambanden mellan blodtryck och dödlighet och demens i hög ålder kan vara annorlunda, då man påvisat att *lågt* blodtryck kan vara kopplat till ökad dödlighet och ökad risk för demens hos de allra äldsta. Det rådande forskningsunderlaget inom detta område är dock begränsat, speciellt vad gäller mycket gamla individer (≥85 år gamla). Syftet med denna avhandling var därför dels att kartlägga blodtryckets epidemiologi i hög ålder och dels att studera sambanden mellan blodtryck och dödlighet respektive kognitiv förmåga hos mycket gamla individer.

Denna avhandling baseras huvudsakligen på uppgifter från den så kallade Umeå 85+/GERDA (GErontologisk Regional DAtabas) studien, en studie som omfattar individer som är 85, 90 och ≥95 år gamla och som genomförts i norra Sverige (Västerbotten) och Finland (Österbotten) år 2000-2007. För att studera blodtrycksförändringar med åldern kombinerades denna studie med material från den så kallade U70-studien som genomfördes i Umeå mellan åren 1981 och 1990 och som omfattade individer som var 70-88 år gamla.

Datainsamlingen gjordes i form av hembesök i Umeå 85+/GERDA-studien, medan man i U70-studien undersökte deltagarna på en geriatrisk mottagning. Blodtrycket mättes i liggande i båda studierna och dessutom uppskattades *pulstrycket* genom att räkna ut skillnaden mellan systoliskt och diastoliskt blodtryck. Man samlade även in uppgifter om bland annat läkemedelsan-vändning och personerna testades med Mini-Mental Test (MMT, en skala som mäter kognitiv förmåga).

Totalt fanns 1133 blodtrycksmätningar från 705 unika individer som var 70 år eller äldre registrerade. Statistiska analyser visade att på populationsnivå sjönk det diastoliska blodtrycket med stigande ålder, medan det systoliska blodtrycket och pulstrycket steg upp till 74,5 respektive 80,6 års ålder, varefter de började sjunka. Medelblodtrycket i befolkningen sjönk också över åren från 1981-2005. Andelen som behandlades med blodtryckssänkande läkemedel steg under samma period och detta kan vara en förklaring till varför medelblod-trycket sjönk. Kvinnor hade högre blodtryck än män.

Sambandet mellan blodtryck och dödlighet undersöktes i en population som bestod av 348 individer som var 85 år eller äldre och som följdes i fyra år. Ett

icke-linjärt samband mellan systoliskt blodtryck och ökad dödlighet noterades, eller med andra ord, dödligheten var större hos både de som hade lägst och de som hade högst utgångsblodtryck. Man kunde räkna ut att 164 mmHg var den blodtrycksnivå som medförde lägst dödlighet, rent matematiskt. Resultaten justerades statistiskt för förekomst av en rad sjukdomar och hälsofaktorer och då man trots detta kunde notera det ovanstående sambandet tyder det på att lågt systoliskt blodtryck har en effekt på dödlighet som är oberoende av underliggande dålig hälsa eller sjukdom. Inget samband mellan diastoliskt blodtryck eller pulstryck och dödlighet kunde noteras.

Blodtryckets påverkan på kognitiv förmåga och demens hos individer 85 år och äldre undersöktes både i ett tvärsnitt av 575 individer och även longitudinellt i två separata urval som bestod av 102 respektive 205 individer. I tvärsnitt observerades ett icke-linjärt samband mellan systoliskt blodtryck respektive pulstryck och poäng på MMT. Det vill säga, både lågt och högt blodtryck var associerat med sämre resultat på ett kognitivt test som utfördes samma dag. Det fanns även ett linjärt samband mellan diastoliskt blodtryck och MMT poäng, d.v.s. högre diastoliskt tryck var kopplat till bättre resultat på MMT. Det noterades även att individer med demens hade lägre medelblodtryck än de utan demens.

I de longitudinella urvalen, som sträckte sig över fem år, kunde inget samband mellan utgångsblodtrycket och risken att insjukna i demens ses. Det fanns heller inget samband mellan blodtryck och förändring i kognitiv förmåga enligt MMT. Medelblodtrycket sjönk dock över åren, och denna blodtryckssänkning var mer uttalad hos de som utvecklade demens under uppföljningsperioden än hos de som inte gjorde det. En större blodtryckssänkning var även kopplat till en större försämring i resultat på MMT, även om man inte kan fastslå vilken riktning detta samband hade, d.v.s. om blodtrycket eller den kognitiva förmågan sjönk först.

Sammanfattningsvis har denna studie påvisat att blodtrycket sjunker i hög ålder samt att lågt blodtryck är associerat med både ökad dödlighet och sämre kognitiv funktion/demens hos mycket gamla människor. Underliggande sjukdomar eller dålig hälsa verkar inte helt kunna förklara dessa samband utan det kan även vara så att det låga blodtrycket i sig innebär en ökad risk. Det är dock ännu oklart om lågt blodtryck föregår demenssjukdomen eller om demenssjukdomen ger lågt blodtryck. Det förefaller också som att mycket högt blodtryck kvarstår som en riskfaktor även hos de mycket gamla, i alla fall hos vissa individer. Medelblodtrycket i populationen sjönk med åren från 1981 till 2005, vilket sannolikt delvis beror på en ökande förekomst av blodtryckssänkande behandling, men det kan även finnas andra orsaker.

TIIVISTELMÄ SUOMEKSI
(SUMMARY IN FINNISH)

On yleinen käsitys, että verenpaine nousee iän myötä. Tämä on kuitenkin vain osittain totta, sillä on osoitettu, että *diastolinen* verenpaine laskee vanhemmiten. Lisäksi jotkin tutkimukset ovat viitanneet siihen, että myös *systolinen* verenpaine laskee erittäin vanhalla iällä, mutta tästä aiheesta tarvitaan vielä lisää tutkimuksia.

Korkea verenpaine, verenpainetauti, on tunnettu sydän- ja verisuonitautien sekä lisääntyneen kuolleisuuden riskitekijä. Verenpainetaudin on osoitettu olevan myös dementian riskitekijä. Nämä yhteydet on kuitenkin pääasiassa todettu keski-ikäisillä ja nuorehkoilla vanhuksilla. Lisäksi joidenkin tutkimusten mukaan näiden riippuvuus voi olla toisenlainen, sillä on osoitettu, että *alhainen* verenpaine voi olla kytköksissä sekä lisääntyneeseen kuolleisuuteen että lisääntyneeseen dementian riskiin erittäin vanhoilla ihmisillä. Tästä aiheesta on varsinkin erittäin vanhojen ihmisten ($\geq$ 85 vuotta) osalta edelleen hyvin vähän tutkimustietoa. Tämän väitöskirjan tarkoituksena olikin tutkia vanhan iän verenpaineen epidemiologiaa, sekä myös tutkia verenpaineen yhteyttä kuolleisuuteen ja kognitioon erittäin vanhoilla ihmisillä.

Tämä väitöskirja perustuu pääasiassa nk. Umeå 85+/GERDA-tutkimukseen, jossa tutkittiin 85-, 90- ja $\geq$95-vuotiaita henkilöitä Pohjois-Ruotsissa (Västerbotten) ja Suomessa (Pohjanmaa) vuosina 2000–2007. Verenpaineessa iän myötä tapahtuvien muutosten tutkimiseksi yhdistettiin mainitun tutkimuksen tiedot U70-tutkimuksen tietoihin. U70-tutkimus toteutettiin Umeåssa, Ruotsissa vuosina 1981–1990 ja siihen osallistui 70–88-vuotiaita henkilöitä. Tutkimukset suoritettiin Umeå 85+/GERDA -tutkimuksessa kotikäynneillä ja U70-tutkimuksessa geriatriatrisella klinikalla. Systolinen ja diastolinen verenpaine mitattiin molemmissa tutkimuksissa makuuasennossa ja *pulssipaine* määritettiin laskemalla systolisen ja diastolisen verenpaineen ero. Tutkimuksessa kerättiin myös tietoa muun muassa lääkkeiden käytöstä ja henkilöt testattiin käyttäen Mini-Mental State Examination -testiä (MMSE, kognitiivisia toimintoja mittaava asteikko).

Verenpainemittauksia oli kokonaisuudessaan 1133 kappaletta yhteensä 705 henkilöltä, iältään $\geq$70 vuotta. Tilastollinen analyysi osoitti, että väestön tasolla, diastolinen verenpaine laski iän myötä, kun taas systolinen verenpaine ja pulssipaine nousivat 74,5 ja 80,6 vuoden ikään asti, vastaavasti, minkä jälkeen ne alkoivat laskea. Väestön keskimääräinen verenpaine väheni myös vuosina 1981–2005. Verenpainetta alentavilla lääkkeillä hoidettujen henkilöiden osuus kasvoi samana aikana ja tämä on luultavasti yksi selitys verenpaineen keskimääräiseen laskuun ajan myötä. Naisilla oli korkeampi verenpaine kuin miehillä.

Verenpaineen ja kuolleisuuden välistä yhteyttä tutkittiin otoksesta, joka koostui 348 henkilöstä, iältään 85 vuotta tai enemmän, ja joita seurattiin neljän

vuoden ajan. Epälineaarinen yhteys lähtötilanteen systolisen verenpaineen ja kuolleisuuden välillä löytyi, tai toisin sanoen, kuolleisuus oli suurin sekä niillä, joilla oli alhainen, että niillä, joilla oli korkea systolinen verenpaine. Matemaattisesti laskien 164 mmHg:n systoliseen verenpaineeseen liittyi alhaisin kuolleisuusriski. Tilastollisessa analyysissä otettiin huomioon lukuisat erilaiset sairaudet ja terveyteen vaikuttavat seikat, ja koska edellä mainittu yhteys oli silti havaittavissa, tämä osoittaa, että alhaisella systolisella verenpaineella on vaikutusta kuolleisuuteen huonosta terveydentilasta tai sairaudesta riippumatta. Diastolisen verenpaineen tai pulssipaineen ja kuolleisuuden välillä ei havaittu yhteyttä.

Verenpaineen vaikutusta kognitiiviseen toimintakykyyn ja dementiaan ≥85-vuotiailla henkilöillä tutkittiin sekä 575 henkilön poikittaistutkimuksena että pitkittäistutkimuksena kahdessa otoksessa, joissa oli 102 ja 205 henkilöä. Poikittaistutkimuksessa osoitettiin sekä systolisen verenpaineen että pulssipaineen, kunkin erikseen, epälineaarinen yhteys MMSE-arvoihin. Toisin sanoen sekä alhainen että korkea verenpaine olivat yhteydessä kognitiivisessa testissä samana päivänä saatuihin huonoihin tuloksiin. Diastolisen verenpaineen ja MMSE-arvojen välillä oli lineaarinen yhteys, toisin sanoen korkeampi diastolinen verenpaine yhdistyi parempiin MMSE-tuloksiin. Voitiin myös todeta, että dementiaa sairastavilla henkilöillä oli alhaisempi verenpaine kuin dementiaa sairastamattomilla.

Yli viiden vuoden ulottuneessa pitkittäistutkimuksessa ei voitu nähdä yhteyttä lähtötilanteen verenpaineen ja dementiaan sairastumisen riskin välillä. Lähtötilanteen verenpaine ei myöskään ollut yhteydessä MMSE:llä todettuun kognitiivisten toimintojen heikkenemiseen. Keskimääräinen verenpaine aleni kuitenkin tämän ajanjakson aikana, ja tämä aleneminen oli suurempaa niillä henkilöillä, jotka seuranta-aikana sairastuivat dementiaan. Suurempi verenpaineen aleneminen yhdistyi myös huonompiin MMSE-tuloksiin, tosin ei voitu määritellä aleniko verenpaine ennen kognitiivisen toiminnan heikkenemistä vai sen jälkeen.

Yhteenvetona voidaan todeta tutkimuksen osoittaneen, että verenpaine alenee iäkkäillä ja että alhainen verenpaine erittäin vanhoilla henkilöillä on yhteydessä sekä lisääntyneeseen kuolleisuuteen että huonompaan kognitiiviseen toimintakykyyn/dementiaan. Näyttää siltä, että olemassa olevat sairaudet tai heikko terveydentila eivät täysin selitä näitä yhteyksiä, vaan että alhainen verenpaine itsessään voisi lisätä riskejä. On kuitenkin vielä epäselvää, lisääkö alhainen verenpaine dementian riskiä vai aiheuttaako dementia itsessään verenpaineen alenemisen. Lisäksi näyttää myös siltä, että erittäin korkea verenpaine on edelleen riskitekijä erittäin vanhoille henkilöille, ainakin joillekin yksilöille. Väestön keskimääräinen verenpaine on laskenut vuodesta 1981 vuoteen 2005, osittain lisääntyneen verenpainetta alentavan lääkehoidon takia, mutta tähän voi olla myös muita syitä.

ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ADL	Activities of Daily Living
ADRDA	Alzheimer's Disease and Related Disorders Association
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutical Chemical (classification system)
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
DBP	Diastolic Blood Pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GDS-15	Geriatric Depression Scale, 15-item version
GERDA	GErontological Regional DAtabase
HR	Hazard Ratio
JNC 7	7th report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure
mmHg	Millimeter of Mercury
MADRS	Montgomery-Åsberg Depression Rating scale
MMSE	Mini-Mental State Examination
MNA	Mini Nutritional Assessment
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NNT	Numbers Needed to Treat
OBS	Organic Brain Syndrome (scale)
PGCMS	Philadelphia Geriatric Center Morale Scale
PP	Pulse Pressure
RR	Risk Ratio
SBP	Systolic Blood Pressure
SD	Standard Deviation
WHO	World Health Organization

ORIGINAL PAPERS

I.   Molander L, Lövheim H, Norman T, Nordström P, Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. Journal of the American Geriatric Society. 2008; 56(10): 1853-9.

II.   Molander L, Gustafson Y, Lövheim H. Low blood pressure is associated with cognitive impairment in very old people. Dementia and Geriatric Cognitive Disorders. 2010; 29(4): 335-41.

III.   Molander L, Gustafson Y, Lövheim H. Longitudinal associations between blood pressure and dementia in the very old. Dementia and Geriatric Cognitive Disorders. 2010; 30(3): 269-276.

IV.   Molander L, Lövheim H. Blood pressure change and antihypertensive treatment in old and very old people – evidence of age and cohort effects. In manuscript.

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INTRODUCTION

Growing older is inevitable. The aging process is one of the most natural aspects of human life and no one expects to avoid it. However, just *how* and *how quickly* we age is open to discussion and manipulation. Our individual journeys towards old age begin at birth and the influence of such aspects as genetics, lifestyle and environmental factors and disease serve to shape the unique old person we will eventually become. It has become increasingly possible to influence some of these factors, not least due to advances in medical diagnosis and treatment and as a result, the focus on prevention and treatment of risk factors has increased, even in old age. Previous research within these areas has mainly focused on young and middle-aged populations, but with the growing number of individuals reaching advanced age, this practice is no longer justified. Aging affects a wide array of bodily systems and the physiology of the old person is not directly comparable to that of the young. Furthermore, heterogeneity is a major characteristic of the old population, including as it does a diversity of individuals with varying health statuses and life stories. Consequently, risk factor profiles should not be directly extrapolated either from young to old individuals or from one old individual to another without scientific support. This is also true for hypertension, which is a very common and frequently treated risk factor for cardiovascular disease. The oldest individuals are commonly underrepresented in studies of blood pressure epidemiology and clinical trials of antihypertensive treatments. However, a growing body of evidence suggests that the impact of hypertension could be modified by age and that in very old age, the relation between blood pressure and health-related outcomes could be different.

The very old - very many and very different

The term *very old* (previously 'oldest old') most commonly refers to individuals aged 80 years or over [1], although in the current thesis the term will be used primarily for samples ≥85 years of age. The number of individuals in this age group has increased dramatically over the last few decades, most notably so in more developed countries. In Sweden, only 1.5% of the population was 80 years or older in the year of 1950 but in 2010 this proportion had risen to 5.3% [2]. Corresponding numbers for the whole world are 0.6% and 1.5%, the latter representing 105 637 000 individuals [2]. This rise is projected to continue. With this in mind, it becomes clear that the very old represent an age group that can no longer be considered negligible, either in society or in research. Their exceptional survival and unique attribute of having lived long lives and hence been subject to a wide array of environmental and other factors further warrant a deserved specific focus on them in research and in the design of health strategies, both in order to improve care of their health-related problems but also because they are role models for successful aging.

Aging affects most organs and physiological functions in the body and many diseases also become more common with age. As a consequence, individuals of advanced age often suffer from several concurrent physical impairments and diseases, leading to heavy health care expenditure and often to polypharmacy. Nevertheless, the very old are heterogeneous; there are great variations in health and functional status within this age group [3], meaning that each individual's circumstances must always be considered.

Blood pressure

Physiology

Blood pressure is an entity defined by scientists but created by nature and is an important variable in upholding the homeostasis of the human body. A brief description of the concept of blood pressure and its physiology will be presented below.

The vascular system has two main functions. First, to enable delivery of blood from the heart to the rest of the body and second, to cushion the pulsations caused by the intermittent contractions of the heart, keeping capillary blood flow steady [4]. Blood pressure is the pressure that the blood exerts on the vessel wall but blood pressure can also be considered a marker of the force that keeps the blood circulating. Two main determinants of blood pressure are *cardiac output* and *peripheral (vessel) resistance* [5, 6].

Blood pressure is not the same throughout the vascular system. The mean blood pressure is high in the aorta but decreases gradually from the large arteries to the arterioles, to the capillaries, to the venules, to the veins and as the blood re-enters the heart through the venae cavae, the pressure is down to 0 [6]. Hence, blood pressure measured in one of the arms is not the same as that in, for example, small arteries in the foot. When *blood pressure* is spoken of in the clinic, it is usually *arterial pressure* that is referred to and, given the common way of measurement (see below), more specifically the arterial pressure in the arm.

There are also several regulatory mechanisms that affect blood pressure; the most important are presented below. The fastest regulation is mediated by the *sympathetic nervous system*, that can raise blood pressure and subsequently blood flow in seconds in response to, for example, muscle exercise or emotional arousal [6]. Further, *baroreceptors* in vessel walls at certain locations in the body react to increased or decreased stretch of the vessel wall and can initiate blood pressure change via nerve stimulation and *chemoreceptors* respond to chemical alterations associated with low blood pressure and raise blood pressure via similar nervous paths [6]. The *renin-angiotensin-aldosterone system* (RAAS) serves to ensure adequate blood flow through the kidneys by increasing blood pressure in a stepwise process involving the three mediating substances renin, angiotensin and aldosterone. Activation of the RAAS leads to vessel const-

riction and reabsorption of sodium and water in the kidney and ultimately, to a higher blood pressure [6]. To counteract the strain induced by too high blood pressure, the heart can release *natriuretic peptides* in response to stretch of the myocardium. These peptides reduce heart rate and blood pressure for example through inhibition of the RAAS and sympathetic nervous system [7]. The brain has its own system for maintaining an adequate blood supply; thanks to the process of *autoregulation*, cerebral blood flow can be sustained through a wide range of blood pressures [6, 8].

Blood pressure is commonly subdivided into two main entities – *systolic blood pressure* (SBP) and *diastolic blood pressure* (DBP). SBP is the pressure observed during systole, the period when the heart contracts, and DBP represents diastole, the period when the heart rests and is refilled with blood [6]. *Pulse pressure* (PP) is defined as the difference between SBP and DBP and hence represents the additional pressure exerted on the vessel wall during systole. Pulse pressure is considered to be an indirect marker of large artery stiffness [9].

Epidemiology

Blood pressure and aging

It is a common and mainly justifiable argument that blood pressure rises with age. Epidemiological studies have indeed demonstrated that mean blood pressure increases with age [10-15], not only in old age but also in young adults [16]. Blood pressure might not increase in *all* people but increasing pressure in a subgroup of individuals leads to an increase in mean blood pressure in the population [16]. However, blood pressure does not seem to increase indefinitely. DBP has been shown to decrease in old age whereas SBP continues to rise [10, 11, 13-15, 17, 18], leading to an increasing prevalence of isolated systolic hypertension and an increasing PP.

Whereas the rise in blood pressure in younger ages is mainly caused by increased vascular resistance in *peripheral* blood vessels [9, 19], the blood pressure changes in old age can be attributed to stiffening of large, *central*, arteries [19], encompassing vessel wall changes such as increased amounts of collagen, decreased content and increased destruction of the elastic protein elastin, calcification and possibly also to alterations in vascular smooth muscle tone [9]. The reduction in elasticity leads to diminished arterial compliance, and subsequently to an enhanced pulse wave velocity [5] and higher blood pressure during systole and lower blood pressure during diastole. This process is more pronounced in individuals with hypertension, as the high blood pressure puts extra strain on the elastin components of the vessel walls [20]. The increase in arterial stiffness also leads to an altered reflection of the pulse wave. In younger people, the pulse wave is *reflected* during diastole, thereby increasing DBP and augmenting blood flow through the coronary vessels during diastole, increasing the blood supply to the heart itself. In older people with stiff arteries,

however, this pulse wave reflection occurs earlier, in the end of systole. This causes an increase in SBP and subsequently a decrease in DBP [4]. This mechanism has, however, been questioned in a review demonstrating that even in younger age, the pulse wave is reflected primarily during systole [21]. The reduction in DBP with aging nonetheless attenuates the perfusion of the heart during diastole, which predisposes to ischemia, at the same time as a high SBP increases the strain on the heart, causing hypertrophy of the myocardium and an increased demand for coronary perfusion [20], resulting in an unfavorable situation for the aging heart. Other underlying mechanisms for the increase in blood pressure with age include age-related reductions in blood volume and cardiac output [5], alterations in the function of and response to the sympathetic nervous system [22] and a reduced baroreceptor sensitivity [5, 22], the latter leading to increased blood pressure variability [5]. Further, some secondary causes of hypertension (discussed below), such as sleep apnoea, become increasingly prevalent with high age, contributing to rising blood pressure levels.

However, contradicting the aforementioned results, some studies have also demonstrated an age-related fall in SBP [12, 23-25]. These seemingly contrasting results might be a consequence of differences in the age range of the studied individuals. Studies that demonstrate a continuous increase in SBP have mostly not included very old people, and it may be that SBP does not decrease until individuals reach a very advanced age. The characteristics and causes of this decline have yet to be determined.

Sex differences in blood pressure

Men are generally considered to have higher blood pressure than women, but this seems to only be true in younger ages. In older populations, higher blood pressure in women than in men has been demonstrated [18, 26] and studies covering a large age range have shown that the trend towards higher blood pressure in men is reversed [10, 11, 27] or the difference between sexes is at least narrowed [17, 28] in higher age. As a consequence, sex is an important factor to consider in research into blood pressure in both young and old age.

Time trends in blood pressure

Apart from the blood pressure changes that come with age, mean blood pressure has also been shown to decrease over the previous decades [18, 25, 29, 30], indicating cohort effects on blood pressure. The awareness of hypertension has increased over the same period and thus a rising prevalence of antihypertensive treatment at least partly explains this decline, although there might also be other underlying factors. This topic will be elaborated further in the Discussion section of this thesis.

Blood pressure measurement

History

The history of blood pressure starts in the middle of the 18th century, when Stephen Hales began studying the concept and performed the first blood pressure measurements on animals, but it was not until a century later that the *mercury manometer* was invented by John Leonard Marie Poisseuille [31-33], marking the advent of more reliable blood pressure estimations and introducing *millimeter of mercury* (mmHg) as the unit of choice [33]. The early measurement techniques involved invasive manipulation of arteries, which prevented their use in clinical practice, but in 1855 Karl von Vierordt devised the principle of estimating blood pressure by recording the externally applied pressure needed to obliterate the pulse, and during the subsequent decades, this principle was put into practice [31-33]. In the 1880s, Samuel Siegfried Karl Ritter von Basch suggested the use of an inflatable bag, connected to a manometer, to apply pressure on the artery and the *sphygmomanometer* was born, although then applied on the radial artery at the wrist. A decade later, Scipione Riva-Rocci presented his method of using a wrap-around compression cuff applied to the upper arm to compress the brachial artery, the technique still used today. Henrich von Recklinghausen improved this technique by initiating the use of a wider cuff, reducing the risk of falsely high SBP values. Palpation of the radial artery was employed to determine SBP, but estimation of DBP was not possible. At the beginning of the 20th century, Nikolai Korotkoff, a Russian physician, invented the *auscultatory* method of determining blood pressure when he noted that by placing a stethoscope over the brachial artery at the elbow, below the pressure cuff, one could hear distinct sounds produced by the blood flow at different degrees of pressure application. Using the Korotkoff sounds, not only SBP but also DBP could be reliably determined [31-33].

Current guidelines

Today, blood pressure measurement is one of the most commonly performed clinical investigations. According to the 7th report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) [34], the recommended method for estimating blood pressure in the clinic is auscultatory, and requires a stethoscope and a sphygmomanometer with a cuff of a size appropriate for the subject's upper arm, i.e. the combination of Riva-Rocci's and Korotkoff's methods. The subject should be seated in a chair with both feet placed on the floor and the arm at heart level and have had at least five minutes of seated rest. At least two blood pressure measurements should be performed and the average value calculated. Similar recommendations are also made in guidelines from the World Health Organization (WHO) [35] and the European societies of Hypertension (ESH) and Cardiology (ESC) [36], among others. If indicated, e.g. in the case of suspected postural

hypotension, blood pressure should also be measured standing up [34]. Previously, in Sweden, blood pressure was commonly measured in a supine position, although in most other countries it was measured while seated. In the last few decades, this practice has changed also in Sweden. Especially in old individuals, supine blood pressure measurement results in values that are some mmHg higher than in the seated position [37, 38]. This effect has been shown to be more pronounced in individuals aged 80 years or above (mean±standard deviation (SD) 5.3±7.9 mmHg for SBP) [38]. Apart from body position, the accuracy of blood pressure measurement can be affected by a number of other factors such as positioning of the subject's arm, inadequate cuff size, insufficient rest, activities such as concurrent talking, too rapid deflation of the cuff, investigator bias [39], the white coat effect (see below), instrumental malfunction (e.g. poorly calibrated equipment) and the auscultatory gap phenomenon [40], emphasizing the importance of standardized blood pressure measurements.

Blood pressure also varies greatly in the same individual and blood pressure variability can be even more pronounced in old people due to a decrease in baroreceptor sensitivity [5]. If several blood pressure measurements are made on the same subject, the first value is often some mmHg higher than the second [41, 42] and it has been shown that using a single blood pressure value may result in falsely high values which may lead to incorrect hypertension diagnoses [42, 43]. Repeated blood pressure measurements thus improve the reliability of the blood pressure estimation [40, 44]. Blood pressure measured on several separate occasions results in even better reliability and also has a higher predictive value for cardiovascular disease [44].

The blood pressure measured at one point in time in the clinic should be distinguished from the individual's "true" blood pressure, which might more correctly be defined as average blood pressure over a prolonged period, where diurnal variations etc. are taken into account. It is, however, almost impossible to reliably determine or define this "true" blood pressure, although ambulatory blood pressure measurements performed repeatedly over, for example, 24 hours using automated devices provide some additional information [39, 45].

Hypertension

Hypertension represents a situation when blood pressure has become patho-logical. The concept of hypertension has been defined based on studies showing that too high blood pressure can imply a negative impact on the hemodynamic system and on cardiovascular health. It is important to emphasize that hyper-tension is not primarily a *disease*, but an asymptomatic risk factor.

Definition and prevalence

The definition of hypertension has varied over the years. Before studies examining the relations between different blood pressure levels and the risk of

cardiovascular disease had emerged, blood pressure was considered to rise naturally with age with an SBP of *100 plus age* being deemed normal and the diagnosis of hypertension was often made based on symptoms [46]. A number of limits had, however, been postulated by various researchers, but with little scientific support [47]. At the beginning of the 20th century, SBP was the focus of attention in determining the presence of hypertension [48] but by the middle of the century, interest had shifted towards DBP as the best marker for cardio-vascular risk, hence treatment was initiated principally based on high DBP levels [47-50]. The scientific support for this view was, however, weak. In sub-sequent decades, several large studies, such as the Framingham study [51], again suggested SBP was the prime marker of an increased risk of cardiovascular illness and focus once again shifted towards SBP [34, 48]. The first guidelines for treatment of hypertension were published in 1973 by the Task Force for the National High Blood Pressure Education Program [52], followed by the first report of the JNC (JNC I) in 1977 [53].

At present, hypertension is most commonly diagnosed during routine check-ups and before any symptoms are manifested. Many international and national task forces and committees have published guidelines on the mana-gement and treatment of hypertension and the current general recommendation is that a sustained blood pressure of SBP ≥140 mmHg and/or DBP ≥90 mmHg should be regarded as hypertension [34, 54-57]. Commonly used limits for the definition of hypertension, adopted from the JNC 7 report [34] are presented in Table 1. Some guidelines suggest additional subdivision of blood pressure ≥140/90 into hypertension Grades 1-3 [55, 56].

TABLE 1. Guidelines for the definition of hypertension.

	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Stage 1 hypertension	140-159	or	90-99
Stage 2 hypertension	≥160	or	≥100

Note: Adopted from JNC 7, 2003 [34].

Hypertension can be subdivided into *secondary hypertension* and *essential hypertension*. Secondary hypertension represents a minor part of all cases and refers to hypertension caused by an underlying disease, such as renal paren-chymal disease, renovascular stenosis, Cushing's syndrome, phaeochromo-cytoma, hyperaldosteronism or obstructive sleep apnoea and hypertension induced by drugs [36]. Essential hypertension, on the other hand, has no known underlying cause, although there could be predisposing factors, such as obesity [5], that increase the risk of hypertension.

The prevalence of hypertension increases with age, which is not surprising considering the previously discussed rise in blood pressure with age, but

absolute prevalence numbers vary greatly among studies. In a report from the Swedish Council on Technology Assessment in Health care, an overview of some studies of hypertension prevalence indicate prevalence numbers from 9-27% at age 30-39 to 28-52% at age 50-59, 53-83% at age 70-79 and 65-84% in individuals aged 80 years and older [58].

White-coat hypertension

The term *white-coat effect* refers to the phenomenon of higher blood pressure values being obtained in clinical settings than at home, due to an alerting reaction to the environment and the doctor or nurse. *White-coat hypertension*, or *isolated office/clinic hypertension* is the presence of clinical hypertension in a subject who is normotensive outside the clinic [36, 59]. Guidelines from ESH/ESC define white-coat hypertension as repeated blood pressure measurements in the clinic of ≥140/90 combined with measurements taken at home of <135/85 [36]. In two studies on individuals referred to hypertension clinics for blood pressure evaluation, the prevalence of white-coat hypertension was 15.4% [60] and 28.1% [61], using the definition above. The white-coat effect seems to increase with age and to be higher in women [61] and it has been shown to be smaller if the assessor is a nurse instead of a doctor [62]. The role of white-coat hypertension as a risk factor for cardiovascular morbidity and mortality is unclear but it is probably not a totally innocuous condition and an increased mortality among white-coat hypertensives compared to clinical normotensives has been demonstrated [63].

Blood pressure as a risk factor

With the development of increasingly accurate methods for measuring it, the interest in blood pressure as a factor potentially associated with disease increased. In 1913, Janeway published results from the first large epidemiological study of blood pressure and its relation to different causes of death in which he introduced the term *hypertensive cardiovascular disease* [64, 65]. Today, hypertension is a well-known risk factor for a number of medical conditions, most of them associated with dysfunction in the cardiovascular system. Higher blood pressure is a risk factor for vessel disease as it increases the risk of arterial stiffness and atherosclerosis [66]. Other risk factors often occur simultaneously with hypertension in the same individual, further increasing the risk for cardiovascular events. Examples of such risk factors are smoking, dyslipidemia, impaired glucose tolerance, obesity and heredity for cardiovascular disease [5, 36]. Figure 1 presents an overview of the added cardiovascular risk from different combinations of blood pressure and other risk factors, directly adopted from the 2007 ESH/ESC guidelines for hypertension [36]. For a full description of the risk factors and signs of subclinical organ damage considered, please see the ESH/ESC report [36].

FIGURE 1. Combined cardiovascular risk estimate based on blood pressure and other risk factors.

	Blood pressure (mmHg)				
	Normal SBP 120-129 or DBP 80-84	**High normal** SBP 130-139 or DBP 85-89	**Grade 1 HT** SBP 140-159 or DBP 90-99	**Grade 2 HT** SBP 160-179 or DBP 100-109	**Grade 3 HT** SBP ≥180 or DBP ≥110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
≥3 risk factors, metabolic syndrome, subclinical organ damage or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Adopted from the 2007 ESH/ESC guidelines [36]. 10-year risk for a fatal or non-fatal cardiovascular (CV) event, 'added' meaning the additional risk above average risk. HT=Hypertension.

Cardiovascular disease and mortality

Hypertension is a well-documented risk factor for cardiovascular diseases such as ischemic heart disease, heart failure and stroke [34, 55, 58, 66], which lead to an increased risk of cardiovascular mortality [66]. In fact, the role of hypertension as a risk factor for mortality is often taken for granted, and the awareness of its detrimental effects is also widespread within the community. However, in contrast a number of studies have suggested a correlation between *low* blood pressure and increased mortality in elderly populations [67-77], although the mechanism behind this association remains undetermined. Several studies have suggested that underlying disease or poor health status explain the paradoxical relation [67, 72, 74], but other studies have suggested that low blood pressure on its own is a predictor of death, regardless of health status, at least in the very old [68, 71, 76, 77]. To complicate matters even more, some studies have demonstrated J- or rather U-shaped relationships between blood pressure and mortality in the old, i.e. increased mortality with both low *and* high blood pressure values [26, 68, 71, 78, 79], and some have suggested that low blood pressure and mortality are only associated in the short term [72].

To summarize, hypertension is a reliably established risk factor for cardiovascular disease and mortality, at least in midlife and younger old ages, but there are indications of more complicated associations between blood pressure and mortality in older populations, and perhaps especially in the very old. Because of the variability of results from different studies, additional research is needed.

Hypotension and postural hypotension

Hypotension can be defined as abnormally low blood pressure. Sudden falls in blood pressure as a reaction to acute illness or hypovolemia might quickly

compromise the circulation, but whether *chronic hypotension* should be considered a disease remains unclear, even though hypotension has over the years been ascribed a number of symptoms such as dizziness, tiredness and fatigue, and low blood pressure has been treated in some countries [80]. There are no established blood pressure limits for this kind of hypotension, although limits of approximately 90-110/50-60 mmHg have been suggested by some [80, 81]. According to guidelines for hypertension, any blood pressure <120/80 mmHg is considered normal or even optimal (Table 1) [34, 36, 56], although it is obvious that there must be a minimum blood pressure level beyond which circulation is compromised. Just when this level is reached probably varies substantially among individuals.

Postural, or orthostatic, hypotension is present when an individual experiences a significant blood pressure decline in connection with a postural shift from the supine to the standing position, and is more common in the elderly due to autonomic dysfunction and other physiological effects of aging [82]. The JNC 7 defines a decrease of >20 mmHg in SBP or >10 mmHg in DBP as postural hypotension [34]. Common causes of postural hypotension are hypovolemia, baroreflex or autonomic dysfunction and venodilating medications, and common symptoms include unsteadiness or dizziness on standing [34].

A short history of antihypertensive drug treatment

As hypertension emerged as a risk factor for morbidity and mortality, interest was aroused in ways of treating this condition. The first chemical compound for lowering blood pressure was *sodium thiocyanate*, developed at the beginning of the 20th century after recognition of the role of sodium in blood pressure elevation. Early treatment of high blood pressure was otherwise limited to measures such as sodium restriction, rest and subsequently surgery in the form of sympathectomy, employed until the mid-20th century when the advent of new drug treatments reduced the interest in surgery [64]. *Hydralazine* and *reserpine* were released in the 1950s and were both effective in reducing blood pressure, but they produced severe side effects, like many of the other early antihypertensive drugs [58, 64]. The end of the same decade saw the release of *thiazide diuretics*, initially intended for treating fluid retention [58].

The first randomized controlled trial of antihypertensive treatment, the Veterans Administration Study, was carried out in the 1960s and investigated the effects of a combination therapy of hydrochlorothiazide, reserpine and hydralazine. A great reduction was shown in fatal and non-fatal events with treatment [83-85]. Knowledge concerning the regulatory mechanisms behind blood pressure steadily increased. The unveiling of the role of norepinephrine in sympathetic signaling and the discovery of the RAAS system set the stage for new drugs. In the 1960s, *beta-blockers* and *calcium antagonists* emerged [58, 64]. The first *angiotensin converting enzyme (ACE) inhibitor* was developed in the late 1970s but the first *angiotensin receptor blocker* was not released until 1995 [64].

Treatment recommendations in old age

The benefits of reducing high blood pressure by means of antihypertensive treatment in terms of reduced mortality and morbidity from cardiovascular diseases in those aged 60-80 years have been clearly demonstrated in meta-analyses [86, 87]. However, according to both meta-analysis of intervention studies [86, 88, 89] and current clinical guidelines [36, 55, 56], the benefits of treatment in even older age have been unclear, with some indications that it might even be harmful. Nevertheless, guidelines have recommended that ongoing antihypertensive treatment should not be cancelled when an individual reaches very old age [36, 55, 56]. To bridge this gap in knowledge over, an interventional study exclusively designed for those aged 80 or over called The Hypertension in the Very Elderly Trial (HYVET) was initiated. This study had to be terminated prematurely as the effect of treatment in reducing mortality was so great that it was unethical to continue the study. The HYVET study showed positive effects of antihypertensive treatment in terms of reduced risks for heart failure, all-cause mortality, death from stroke and a reduction in the rate of any cardio-vascular event [90]. The HYVET study, however, had several limitations and these will be addressed further in the Discussion part of this thesis.

Dementia and cognitive impairment

Dementia

Dementia is mainly a late-life disease. The prevalence of dementia increases substantially with age and varies among geographical areas. The prevalence of dementia in ≥85-year-olds is approximately 20-25% in Europe [91, 92], with somewhat higher prevalence numbers in the Americas and the lowest in Africa [92]. Even within the very old group, dementia prevalence increases with age, although perhaps not exponentially [93].

Although there are several different dementia disorders with partly differing symptoms, all feature multiple cognitive deficits, including memory impairment and one or more of the following: aphasia, apraxia, agnosia, or impairment of executive functioning [94]. In order to fulfill the criteria for dementia, the patient must have symptoms severe enough to impair social or occupational functioning and the current state should represent a decline from a previously higher cognitive level [94].

Dementia can be either a *primary degenerative* or a *secondary* disorder, in the latter case caused by organic disease or substances. Combinations of different etiologies are also common and lead to various forms of mixed dementias. Generally, secondary causes of dementia should be ruled out before a primary diagnosis, such as *Alzheimer's disease* is made [94]. Alzheimer's disease is the most common form of primary degenerative dementia, pathologically characterized by deposits of amyloid protein both diffusely in the brain parenchyma but also specifically in neuritic plaques and intraneuronal neurofibrillary tangles [95].

Genetic factors may influence the risk of developing the disease, especially the young-onset type, although mutations in the apolipoprotein E genes may influence Alzheimer's disease in the elderly [95]. *Vascular dementia* is the second most common type of dementia and results from vascular lesions in the brain [96]; evidence of cerebrovascular disease is required for a diagnosis [94]. Other types of dementia include: frontotemporal dementia, Lewy body disease, substance- or trauma-induced dementia and dementia due to diseases such as Parkinson's, Pick's, Huntington's and Creutzfeldt-Jakob or dementia due to other general medical conditions or infectious diseases [94, 97].

Criteria for dementia disorders can, for example, be found in the Diagnostic and Statistical Manual of Mental Disorders, currently in its 4th edition (DSM IV) [94, 98]. The NINCDS-ADRDA (National Institute of Neurological and Comm-unicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association) criteria are also widely used in diagnosing Alzheimer's disease [99].

Cognitive impairment

The term *cognitive impairment* is used in the present thesis to describe a broad range of cognitive failure of varying degrees. Cognitive level is often evaluated using various assessment scales, possibly the best known being the Mini-Mental State Examination (MMSE) scale, developed by Folstein, Folstein and McHugh in the 1970s [100]. This scale is widely used and useful both as a screening tool for cognitive impairment and as a means of following the progress of cognitive dysfunction over time [101] and will be described in more detail in the method-ology section of this thesis. There are also several other cognitive assessment scales [102].

Blood pressure and cognitive impairment/dementia

Hypertension has been shown to imply an additional risk of developing cognitive impairment and dementia. It seems rather clear from longitudinal studies that higher blood pressure in midlife and in younger old age increases the risk of later cognitive decline and clinical dementia [103-110]. Not only vascular dementia [103, 105] but also Alzheimer's disease [103-105] have been shown to be asso-ciated with earlier hypertension. Correlations between higher blood pressure and concurrent cognitive impairment have also been demonstrated in cross-sectional studies [108, 111].

However, despite the large body of evidence in support of this association, opposing results from other studies complicate the conclusions regarding blood pressure and cognitive functioning. In both cross-sectional [112-116] and long-itudinal studies [115, 117-120], a connection between *low* blood pressure and impaired cognition and dementia has been suggested, and yet other studies have demonstrated nonlinear associations [105, 121, 122]. These conflicting findings could partly be attributed to differences in age among the participants. Studies dem-

onstrating that hypertension is a risk factor for dementia have mainly included individuals aged up to 70 years at baseline. Higher blood pressure at ages 70 and 75 was also associated with later dementia in a Swedish study [103]. Associations with low blood pressure, however, have mainly been demonstrated in even older populations [112, 115-117, 119, 120]. However, the existing research base is not conclusive and only a few studies have examined the full age span of very old individuals. Taken also that the prevalence of dementia in this age group is very high [92], this warrants further research.

As a reduction in blood pressure has been noted in individuals with incident or prevalent dementia [103, 118], it also remains unclear whether low blood pressure precedes or follows dementia disease and longitudinal studies are needed to answer this question.

The benefits of reducing blood pressure levels in hypertension to prevent cognitive impairment and dementia in old age are less clear than those regarding cardiovascular outcomes. In a systematic review of four randomized, double-blind, placebo-controlled trials including participants aged 60-89 years of age, no effect of active treatment on dementia incidence could be seen [123].

RATIONALE FOR THIS THESIS

High blood pressure has been thoroughly studied and acknowledged as a risk factor and marker for disease, and as a result, hypertension is a very common and often treated medical condition. It is vital to understand the natural history of blood pressure in order to correctly interpret its importance as a risk factor or marker for disease while at the same time taking into account its important function as an upholder of a normal homeostasis. The epidemiology of blood pressure in advanced age, however, remains uncertain and there is a need for studies that investigate this topic in the very oldest. To correctly interpret blood pressure changes it is also important to consider how the mean blood pressure in the population might have changed over the years.

It is generally accepted that the burden of hypertension increases with age, but this notion has been challenged as studies suggesting inverse or nonlinear associations between blood pressure and morbidity and mortality in old age have emerged. The results differ widely and a larger body of evidence is needed before any final conclusions can be drawn regarding how hypertension in the elderly should be handled. Mortality and dementia/cognitive impairment are important examples of outcomes that are associated with midlife hypertension but where the association with blood pressure in old age could be more complex. It is essential to further study these areas in old and very old individuals, not least given the high rates of hypertension, antihypertensive treatment and dementia in this age group.

The impact of blood pressure has never before been studied in very old individuals in northern Sweden. Very old individuals have long been neglected in research but with the growing number of individuals reaching high ages, this practice is no longer justifiable.

AIMS OF THIS THESIS

The overall aim of this thesis was to investigate the epidemiology of blood pressure in old age, to study blood pressure changes and antihypertensive drug use over the last few decades and further to investigate the association between blood pressure and mortality and cognitive impairment in very old people.

Specific aims

Paper I
To examine the relationship between blood pressure levels and all-cause mortality in a sample of very old people.

Paper II
To investigate the cross-sectional association between blood pressure and cognitive impairment in a very old population.

Paper III
To investigate the longitudinal association between blood pressure and incident dementia and cognitive decline over five years in the very old.

Paper IV
To study blood pressure changes with age in old and very old people and to investigate how mean blood pressure and antihypertensive drug use has changed over the years from 1981 to 2005.

METHODS

This thesis is based on data from two population-based cohort studies carried out in the county of Västerbotten in northern Sweden – The Umeå 85+/GERDA (GErontological Regional DAtabase) study (Papers I-IV) and the Umeå Longitudinal study (U70) (Paper IV). The former encompasses individuals aged 85 years and older and was started in the year of 2000 with two data collections performed so far, whereas the latter consists of four investigations carried out in the years of 1981, 1984, 1987 and 1990 and includes subjects aged 70-88 years. Both studies include both cross-sectional and longitudinal samples. Figure 2 gives a summary of all the data collections in both studies and Table 2 offers an overview of the samples and variables studied in the separate papers. The methodologies of these two studies will be presented separately. A substantial amount of data was collected in both studies, but only those variables relevant to this thesis are presented here.

FIGURE 2. Overview of all the data collections in the U70 and Umeå 85+/GERDA studies, according to age groups.
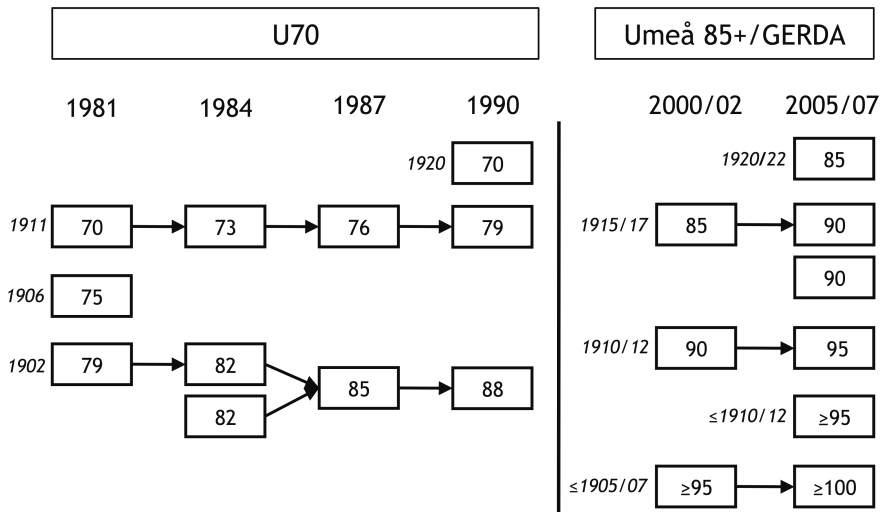
Numbers in boxes represent age in years, year of birth is given in italics. Arrows connect cohort samples.

TABLE 2. Overview of Papers I-IV.

	Paper I (Sample I)	Paper II (Sample II)	Paper III (Sample IIIa+b)	Paper IV (Sample IV)
Sample size (n)	348	575	102 / 205	1133
Age span (baseline), years	85-103	85-103	85-99/85-103	70-103
Study design	Longitudinal	Cross-sectional	Longitudinal	Cross-sectional /Longitudinal
Geographical area	Umeå/ Rural area	Umeå/Rural area /Finland	Umeå/ Rural area	Umeå
Included data collections				
Umeå 85+/GERDA 2000/02	X			
Umeå 85+/GERDA 2005/07		X		
Umeå 85+/GERDA longitudinal			X	
U70				X
Main outcomes				
Blood pressure change			X	X
Time trends in blood pressure				X
Antihypertensive drug use				X
4-year mortality	X	X		
MMSE scores			X	
Incident dementia			X	

The Umeå 85+/GERDA study

Settings and participants

The Umeå 85+ study was started in the year of 2000 with the purpose of investigating the general health and prerequisites for good aging in individuals aged 85 years and older. The first data collection included participants from the urban municipality of Umeå and from five small rural municipalities (Dorotea, Malå, Storuman, Sorsele and Vilhelmina), all in the county of Västerbotten in Sweden. Data collection was performed in 2000-2001 in Umeå and 2002 in the rural municipalities. For the second investigation carried out in 2005-2006/2007 (urban/rural) the project was expanded into the dual-centre GERDA study, that also included participants from two municipalities in Pohjanmaa, Finland (Mustasaari and Vaasa), investigated in 2005-2007. The Finnish municipalities are inhabited both by Swedish-speaking and Finnish-speaking individuals. Collaborators in the Umeå 85+/GERDA study include the units for Geriatric Medicine, Physiotherapy and Occupational Therapy within the Department of Community Medicine and Rehabilitation, the Departments of Nursing and Social Work, all at Umeå University, Novia University of Applied Sciences, the University of Vaasa and Åbo Akademi University. Figure 3 gives an overview of the data collections in the Umeå 85+/GERDA study and also shows the third data collection, which is currently (2010) in progress.

FIGURE 3. Overview of the data collections in the Umeå 85+/GERDA study.
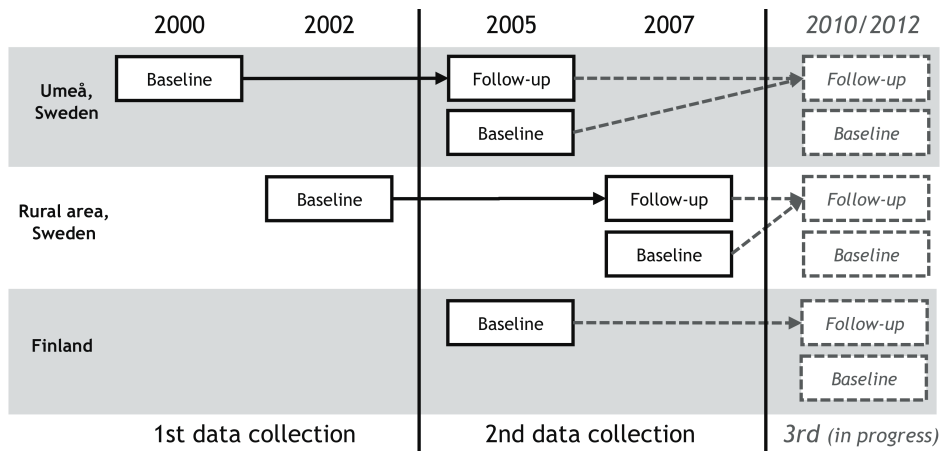
Potential participants were drawn from population records of the Swedish National Tax Board or the Finnish Population Register Centre and divided into age groups based on year of birth. Due to the relatively large number of individuals aged 85 years, every second individual on the list of 85-year-olds was included and it was decided by lots whether odd or even numbers should

be selected. Consequently, half of all 85-year-olds, all 90-year-olds and all those aged 95 years or above (based on year of birth) and living in the designated geographical area on the 1st of January in the respective year of investigation (2000/02 and 2005/07), were eligible for participation in each data collection. All those who were eligible for the 2000/02 investigation and were alive five years later, including non-responders, were invited to participate in 2005/07.

Procedure

Potential participants were first sent a letter with information about the study and then received a telephone call from an investigator, during which informed consent was acquired and an appointment for the interview was made. Informed consent from the next of kin was also obtained if the subject was found to be cognitively impaired. For those in institutional care, the telephone call was usually placed to a member of the staff who could evaluate the person's cognitive state and contact was then made with either the participant or a next of kin.

The data collection took place during home visits. If a person refused a home visit, they were asked whether the investigators could examine medical records and/or talk to relatives and caregivers. A structured interview and physical examinations were performed during one or more visits to the participant in their home. If the individual was in institutional care a member of the staff was also interviewed, with the participant's approval. If applicable, relatives were also interviewed. The interview protocol included general questions on life and medical history and also several assessment scales and was delivered in the participant's native tongue, Swedish or Finnish. Permission to access medical records was requested during the interview.

Investigations in Umeå were carried out over the whole year and some examinations took place in to the subsequent year (2001 and 2006, respectively), whereas investigations in the rural municipalities were carried out in the summers (May-September) of 2002 and 2007. The data collection in Finland took place from late 2005 throughout 2006. The oldest participants were investigated first.

Sociodemographics

Education was defined as number of years in school based on the subject's self-report or information from relatives. In some cases, only the achieved educational level was known and the number of years was then estimated based on knowledge of the schooling system.

The participant was considered to be in *their own/ordinary housing* if they lived independently in their own apartment or house with or without home-help services. Civil status was recorded in several possible categories but in the present thesis, the variable was collapsed into *single* or *not single*, called *living with spouse* or not in Paper I. Data on *smoking* and *alcohol consumption* were

collected but only current use is presented in this thesis due to limited information about the extent of previous consumption.

Assessment scales

The *Mini-Mental State Examination (MMSE)* [100, 101] was used as a global cognitive measure. This scale has a possible score of 0-30, where lower values indicate poorer cognitive performance. Areas covered include orientation, registration, attention and calculation, word recall and language (including naming, reading, following instructions, writing and copying) [100]. A score of 23 or less is often considered to indicate cognitive impairment [101], but this cutoff was not used in the present study.

The confusion subscale of the *Organic Brain Syndrome (OBS) scale* [124] was used to evaluate general psychopathology and symptoms of delirium, dementia, depression and psychosis. Evaluation was performed through observation of the participant and interview with relatives and caregivers.

The 15-item version of the *Geriatric Depression Scale (GDS-15)* [125] was used to screen for depressive symptoms. The scale has a maximum score of 15, with higher scores indicating increasing severity of the depressive state. The *Montgomery-Åsberg Depression Rating Scale (MADRS)* [126] was used to further evaluate depressive status but was only used when the investigator was a physician or a medical student with knowledge of psychiatric symptoms. In the 2000/02 data collection, a specialist in geriatric medicine re-visited all participants with a GDS-15 score ≥5 to perform the MADRS.

The *Barthel Activities of Daily Living (ADL) Index* [127] was used to evaluate degree of dependency in personal ADL (p-ADL) and the possible score ranges from 0-20 points where 20 indicates total independence in p-ADL. The *Mini Nutritional Assessment (MNA)* [128] was used to estimate nutritional status. The scale gives scores from 0-30 points, where 17-23.5 points are indicative of risk of malnutrition and scores below 17 of manifest malnutrition.

Blood pressure measurement

Blood pressure was determined manually using a sphygmomanometer cuff and stethoscope and was measured once in a supine position after five minutes of rest. SBP and DBP were noted at Korotkoff phases I and V, respectively. PP was calculated as SBP-DBP. In a small number of cases, blood pressure values were derived from medical records from recent routine check-ups at the primary healthcare center or institutional care facility. Blood pressure was measured in a seated position in some participants who could or would not lie down. Missing values for the blood pressure variable, in individuals who did consent to a home visit, were caused mainly by interruption of the interview by the participant or such severe cognitive impairment that blood pressure measurement could not be performed. In a small number of cases, instrumental malfunction or failure to hear the Korotkoff sounds also resulted in missing values.

Standing blood pressure was also measured but will not be analyzed in the current thesis.

Physical examinations

Pulse frequency was counted by palpation of the radial artery with the subject lying down. *Weight* and *height* were measured using a standard bathroom scale and a tape measure and *Body Mass Index (BMI)* was calculated as kg/m^2.

Medical diagnoses

Earlier and current medical diagnoses were derived from self-report, caregivers and relatives and from inpatient and primary care medical records. In 2005/07, diagnoses were classified as "currently present", "present in the last five years" and "present >5 years earlier". Some conditions could naturally belong to more than one of these categories.

Dementia was diagnosed if the participant had a previous diagnosis according to medical records and/or using questions asked or assessments performed during the home visit. A specialist in geriatric medicine reviewed all interview protocols and, based on information from the interviews and medical records and on results on the MMSE and OBS scales, a dementia diagnosis was established. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) [98] criteria for subtypes of dementia were used as a basis for diagnosis. In the first data collection, a small number of participants were also further evaluated at the Geriatric Clinic at Umeå University Hospital. For Paper III, some dementia diagnoses were derived from the death certificates and medical records of individuals who died during the follow-up. Swedish death certificates include information about cause of death and often also underlying conditions, such as dementia. Medical records were scrutinized to further evaluate whether or not there were indications of dementia development prior to death. A junior physician performed the primary investigation of medical records, and in uncertain cases and all cases where dementia was suspected, a specialist in geriatric medicine was consulted. If there was any degree of uncertainty, dementia status was considered to be "unknown" at time of death.

Depression was diagnosed based on information about diagnosis and ongoing treatment from medical records or using assessments from the home visit, such as GDS-15, OBS and MADRS. The DSM IV [98] criteria for depressive disorders were used. Individuals who had a depression diagnosis and were being treated with antidepressants were considered to have depression, whether or not they had any current depressive symptoms.

Hypertension was similarly diagnosed, based on previous diagnosis with ongoing antihypertensive treatment or a blood pressure of ≥160/95 mmHg on examination. This limit was used to avoid exaggerating the prevalence of hypertension due to the single blood pressure measurement.

A variable entitled *heart disease* was defined based on a history of: arrhythmia, heart failure, myocardial infarction, angina pectoris, heart surgery, valvular disease, endo- or myocarditis or cardiac conduction abnormalities. The most common heart diseases were heart failure, atrial fibrillation and angina pectoris.

Mortality

Mortality data were collected from the official registers of the National Tax Board or retrieved from medical records for the participants in the 2000/02 data collection and extended to four years from inclusion for each participant. Death certificates were also used to retrieve dementia diagnoses in some cases (see above).

The U70 study

Settings and participants

The U70 study was started for the purpose of studying medical and social conditions among older people in northern Sweden and was carried out in the municipality of Umeå. The study design, including selected age groups, was intended to resemble the H70 study carried out in Gothenburg, Sweden [129]. Four data collections were performed at three-year intervals between 1981 and 1990. An overview of the data collections is presented in Figure 2.

The first data collection in 1981 included a representative sample of people aged 70, 75 and 79 years. However, due to limited resources, the 75-year-old cohort was dropped in the next round in 1984 and instead all those aged 82 years and living in the municipality were included (i.e. an expansion of the original 79-year-old cohort). Further follow-ups were performed in 1987 and in 1990. In 1990, a new group of 70-year-olds was also included. Non-responders were not excluded from participation in subsequent rounds. Participants were acquired from official population records, and age groups were defined based on year of birth. All subsamples were stratified according to sex and sorted according to date of birth, and a similar number of men and women were then systematically selected, for example by including every other man and every third woman, depending on the sex distribution of the samples.

Procedure

All eligible individuals were contacted first by letter and then by telephone and were asked to give their informed consent. In cases of severe cognitive impairment the next of kin were also contacted to give their consent. Investigations took place at a geriatric centre, lasted one day and included: a medical interview concerning symptoms, disorders and pharmacological drug use; a review of medical records; the taking of blood samples and an electrocardiogram; a physical and dental examination; a social interview; anthropometric

measurements; neuropsychological tests and an assessment of dietary intake. Home visits were made to some people who could not or were unwilling to come to the geriatric centre. Investigations were carried out from February through May in each respective year.

Blood pressure measurement

Similarly to the Umeå 85+/GERDA study, *blood pressure* was determined manually using a mercury manometer or sphygmomanometer with cuff and stethoscope and was measured once in a supine position after five minutes of rest. Systolic and diastolic blood pressure were noted at Korotkoff phases I and V, respectively. PP was calculated as SBP-DBP.

Assessment scales and physical examinations

The *MMSE* [100], described above, was performed in 1984, 1987 and 1990. *Pulse frequency* was counted by palpation of the radial artery with the subject lying down. *Weight* and *height* were measured and *BMI* calculated as kg/m^2.

Pharmacological treatment

In both studies, data on pharmacological drug use were collected by asking the participant to verbally report or show the investigator lists of medications or actual containers for all prescription and non-prescription drugs they were taking. The information was also validated against medical records.

Drugs were classified according to the Anatomical Therapeutical Chemical (ATC) classification system [130]. Drugs belonging to ATC classes C02 ('antihypertensives'), C03 ('diuretics'), C07 ('beta blocking agents'), C08 ('calcium-channel blockers') and C09 ('agents acting on the renin-angiotensin system') were considered to be antihypertensive drugs. For Paper IV, diuretics were further classified into thiazides (including all low-ceiling diuretics, C03A+B), loop (high-ceiling diuretics, C03C) and potassium-sparing (C03D). Combination drugs were subdivided into each of the corresponding classes. Each drug use was coded as "used" or "not used" and specific doses or indications for treatment were not taken into consideration. Drugs taken irregularly on a "when needed" indication (pro re nata, PRN) were considered to be "not used" with the exception of short-acting nitroglycerine, which was included although it is principally taken on a PRN basis.

Ethics

Both Swedish data collections in the Umeå 85+/GERDA study (§99-326, §05-063M) and all in the U70 study (1981-03-03 §9, 1984-02-07 §1, 1987-02-03 §3, 1989-12-12 §213/89) were approved by the Regional Ethical Review Board in Umeå. The Finnish data collection in the GERDA study was approved by the Ethics Committee of Vaasa Central Hospital (05-87). Informed consent was

acquired from all participants, and also from the next of kin for individuals with severe cognitive impairment and dementia. The participants could discontinue their participation at any point without a stated reason and without detriment.

Sample descriptions

The various samples used in this thesis are presented below. The small discordance in the number of dropouts is due to differences regarding required data for inclusion in the respective samples. Sample I-IV corresponds to the samples used in Papers I-IV, respectively.

Sample I - Umeå 85+/GERDA 2000/02

In the first Swedish Umeå 85+/GERDA data collection, there were 527 eligible participants. Forty-four (8.3%) died before contact was made. These did not differ in sex or age from those remaining. Fifty-two people declined participation and 83 were excluded, as their blood pressure was not measured. These 135 people did not differ regarding sex, age or 4-year mortality from the final sample, which included 348 people, 72.0% of those asked to participate (Figure 4). Characteristics of this sample are presented in Table 3.

Sample II - Umeå 85+/GERDA 2005/07

In the 2005/07 Umeå 85+/GERDA investigation, 963 individuals were eligible for participation. Seventy-three (7.6%) died before contact was made. They did not differ in sex or age from those remaining. In addition, 181 declined to participate and blood pressure values or MMSE scores were missing in 134 subjects. These 315 people were more likely to be women (p=0.012) but did not differ regarding age or nationality from the final sample of 575 people, 64.6% of those asked to participate (Figure 4). Characteristics of this sample are presented in Table 4.

FIGURE 4. Depiction of Samples I and II.


```
                    ┌─────────────────────┐
                    │ Eligible participants│
                    │      2000/02        │
                    │      N=527          │
                    └─────────────────────┘
                              │
                              ├──────────► Died before contact, n=44
                              │
                    ┌─────────────────────┐
                    │     Contacted       │
                    │      2000/02        │
                    │      N=483          │
                    └─────────────────────┘
                              │
                              ├──────────►  ┌─────────────────────┐
                              │             │    Participants     │
                              │   Declined, n=52     2000/02      │
                              │   Missing BP, n=83   N=348        │
                              │             └─────────────────────┘
                              │                        Sample I
   Died during follow-up, n=302
   Moved from the area, n=2
                              │
        ┌─────────────────────┐     ┌─────────────────────────┐
        │     Available       │     │ New eligible participants│
        │      2005/07        │     │        2005/07          │
        │      N=179          │     │        N=784            │
        └─────────────────────┘     └─────────────────────────┘
                    │                           │
                    └──────►┌─────────────────────┐◄──────┘
                            │ Eligible participants│
                            │      2005/07        │
                            │      N=963          │
                            └─────────────────────┘
                                      │
   Died before contact, n=73          │
   Declined, n=181                     │
   Missing BP or MMSE, n=134           │
                            ┌─────────────────────┐
                            │ Cross-sectional sample│
                            │      2005/07        │
                            │      N=575          │
                            └─────────────────────┘
                                     Sample II
```

TABLE 3. Characteristics of the participants in Sample I.

Age, years	MEN			WOMEN		
	85 (n=47)	90 (n=37)	≥95 (n=14)	85 (n=92)	90 (n=91)	≥95 (n=67)
	Mean±SD (95% CI)	Mean±SD (95% CI)	Mean±SD (95% CI)	Mean±SD (95% CI)	Mean±SD (95% CI)	Mean±SD (95% CI)
SBP, mmHg	155.3±23.0 (148.5-160.0)	143.5±21.9 (136.2-150.8)	133.4±18.7 (122.6-144.1)	156.4±23.0 (151.7-161.2)	146.0±24.6 (140.9-151.1)	138.2±22.7 (132.6-143.7)
DBP, mmHg	78.7±12.3 (75.1-82.3)	74.1±10.0 (70.8-77.5)	72.1±8.7 (67.1-77.2)	78.6±10.1 (76.5-80.7)	73.4±10.7 (71.2-75.6)	73.2±11.3 (70.4-75.9)
PP, mmHg	76.6±19.1 (71.0-82.1)	69.4±17.1 (63.7-75.1)	61.2±18.3 (50.6-71.8)	77.8±20.7 (73.5-82.1)	72.7±21.3 (68.2-77.1)	65.0±18.4 (60.5-69.5)
Barthel ADL Index	18.8±3.3	17.8±4.4	17.4±4.0	18.2±4.3	15.5±5.7	10.4±7.5
BMI, kg/m^2	25.7±4.0	25.6±3.8	24.2±3.2	25.4±4.4	25.0±5.4	22.7±4.5
MMSE	24.4±5.4	23.7±4.9	21.5±7.9	24.3±5.5	21.0±8.2	15.9±10.0
MNA	25.1±2.9	24.7±3.4	25.1±2.3	24.5±3.5	22.1±4.9	19.3±5.6
Education, years	6.1±1.4	6.1±1.5	5.3±1.8	6.3±2.0	6.4±2.0	6.0±2.1
No of medications	5.1±3.9	5.2±4.3	6.1±4.6	6.1±3.9	8.0±5.2	7.1±4.2
	%	%	%	%	%	%
Living with spouse	53.2	29.7	21.4	5.4	2.2	4.5
Own housing	87.2	59.5	42.9	77.2	52.7	25.4
Diagnoses						
Atrial fibrillation	12.8	16.2	35.7	13.0	23.1	20.9
Dementia	19.1	16.2	21.4	19.6	27.5	53.7
Depression	21.3	13.5	14.3	25.0	40.9	36.1
Diabetes Mellitus	14.9	10.8	21.4	10.9	16.5	9.0
Heart failure	25.5	16.2	35.7	16.3	35.2	30.3
History of stroke	21.3	16.2	14.3	19.6	25.3	16.4
Hypertension	70.2	48.6	21.4	77.2	56.0	31.3
Malignancy last 5y	23.9	24.3	21.4	3.3	4.4	3.0
Medications						
ACE inhibitors	12.8	8.3	14.3	6.5	17.6	7.6
Analgesics	48.9	50.0	28.6	60.9	68.1	77.3
Antidepressants	10.6	8.3	7.1	19.6	25.3	16.7
Beta-blockers	29.8	22.2	14.3	27.2	22.0	10.6
Calcium blockers	12.7	8.3	7.1	14.1	11.0	3.0
Diuretics	38.3	50.0	50.0	45.7	62.6	48.5

Individual variables could include a smaller *n* due to missing values.

TABLE 4. Characteristics of the participants in Sample II.

Age, years	85 (n=207)	90 (n=210)	≥95 (n=158)
	Mean±SD (95% CI)	Mean±SD (95% CI)	Mean±SD (95% CI)
SBP, mmHg	149.8±22.8 (146.7-152.9)	144.9±23.5 (141.7-148.1)	139.1±22.5 (135.6-142.6)
DBP, mmHg	75.2±10.0 (73.8-76.6)	75.2±12.8 (73.5-76.9)	71.7±12.3 (69.8-73.7)
PP, mmHg	74.6±20.4 (71.8-77.4)	69.7±19.6 (67.0-72.3)	67.4±19.7 (64.3-70.5)
Education, years	7.1±2.0	7.1±2.7	6.9±2.6
Barthel ADL Index	17.6±4.7	16.1±5.7	13.1±6.7
BMI, kg/m^2	26.2±4.2	25.1±4.1	24.8±4.3
MMSE	23.0±6.2	19.7±7.8	16.4±8.1
	%	%	%
Women	66.7	67.6	77.2
Single	70.0	84.1	95.5
Swedish	60.4	66.2	58.2
Own housing	75.8	64.1	35.3
Alcohol users	37.1	32.4	24.2
Current smoker	2.9	4.3	2.5
Dementia	26.1	42.9	56.3
Depression	32.4	39.5	38.0
Diabetes Mellitus	17.4	14.8	10.1
Heart failure	23.7	29.5	42.4
History of stroke	22.2	20.5	22.2
Current hypertension	70.0	70.0	50.0
Hypertension >5y earlier	46.4	48.6	32.3
Heart disease	59.9	71.4	69.6
Antihypertensive drugs°	71.8	70.5	76.6

Individual variables could include a smaller *n* due to missing values.
° Indication for treatment not considered.

Sample III - Umeå 85+/GERDA longitudinal sample

Sample III constitutes the longitudinal sample from the Umeå 85+/GERDA study, which only includes individuals from Sweden. Two samples (IIIa and IIIb) were used and they are presented in Figure 5. Of the 527 eligible participants in 2000/02, 44 died before contact was made and 130 declined a home visit, leaving 353 participants at baseline. During the five years of follow-up, 216 individuals died, leaving 137 available for follow-up. Those who died were older, had lower blood pressure, lower MMSE and Barthel ADL Index scores and were more likely to live in institutions or suffer from dementia, depression or heart disease but there was no difference in sex distribution, education or history of stroke between these and the remaining sample. Thirty-five individuals declined a home visit at follow-up and these did not differ from the remaining 102 people for any of the mentioned parameters. Sample IIIa consists of these 102 people, who were investigated twice.

Sample IIIb was included to increase the sample size for analyses of baseline blood pressure and incident dementia. This sample comprises all those who were visited at baseline and who could be evaluated for incident dementia (including individuals who died during follow-up) and had baseline blood pressure values; a total of 205 individuals, which includes 92 individuals from Sample IIIa. Characteristics of these samples are presented in Table 5.
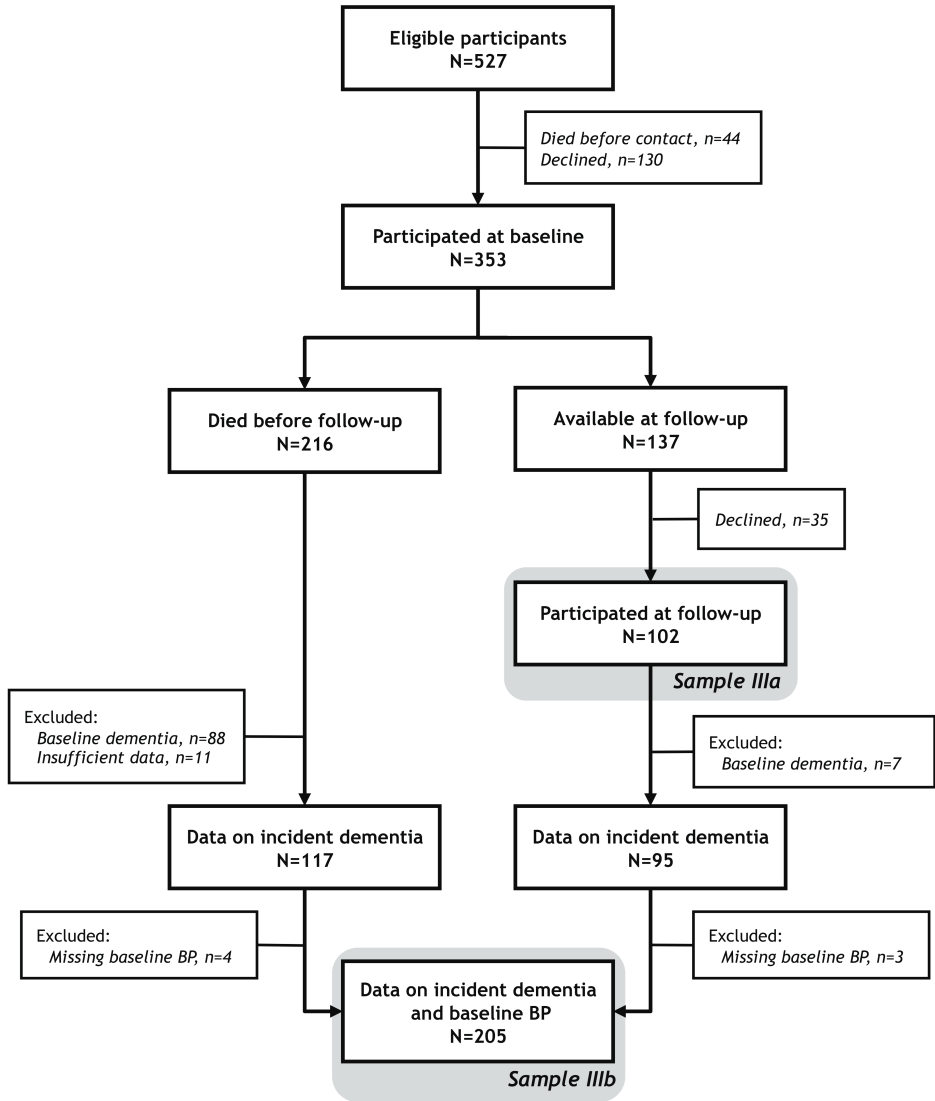
Sample IV - U70 and Umeå 85+/GERDA

Paper IV includes all data collections performed in the municipality of Umeå within both the Umeå 85+/GERDA and U70 studies. Each data collection is considered separately, meaning a person partaking in several data collections could contribute several measurements, hence, each potential measurement will be called a *case*. There were 699 eligible cases in the Umeå 85+/GERDA study and 840 in the U70 study. The number of lost cases (i.e. missing cases due to refused participation or missing data) was 218 (31.2%) in the Umeå 85+/ GERDA study and 150 (17.9%) in the U70 study (p<0.001).

There was no age difference between the dropouts and the remaining cases in either study but in the U70 study, the proportion of women among the dropouts was higher (p=0.004). Blood pressure was not measured in 38 of the remaining 1171 cases. Consequently, the final sample included 1133 blood pressure measurements from 705 unique individuals, of whom 247 were investigated twice or more. Characteristics of this sample are presented in Table 6.

FIGURE 5. Depiction of Samples IIIa and IIIb.


```
                    ┌─────────────────────┐
                    │ Eligible participants│
                    │       N=527          │
                    └─────────────────────┘
                              │
                              │    ┌──────────────────────────────┐
                              ├────│ Died before contact, n=44    │
                              │    │ Declined, n=130              │
                              │    └──────────────────────────────┘
                    ┌─────────────────────┐
                    │ Participated at baseline │
                    │       N=353          │
                    └─────────────────────┘
```

Eligible participants
N=527

Died before contact, n=44
Declined, n=130

Participated at baseline
N=353

Died before follow-up
N=216

Available at follow-up
N=137

Declined, n=35

Participated at follow-up
N=102

Sample IIIa

Excluded:
 Baseline dementia, n=88
 Insufficient data, n=11

Excluded:
 Baseline dementia, n=7

Data on incident dementia
N=117

Data on incident dementia
N=95

Excluded:
 Missing baseline BP, n=4

Excluded:
 Missing baseline BP, n=3

Data on incident dementia
and baseline BP
N=205

Sample IIIb

TABLE 5. Characteristics of the participants in Samples IIIa+b.

	Sample IIIa N=102			Sample IIIb N=205
	Baseline	Follow-up		Baseline
	Mean±SD	Mean±SD	p	Mean±SD
Mean age	87.3±3.4	92.0±3.4	-	88.8±4.1
SBP, mmHg	154.8±21.6	141.0±20.5	<0.001	150.3±23.5
DBP, mmHg	77.0±10.4	72.1±12.8	0.001	76.0±10.6
PP, mmHg	78.2±19.2	69.1±17.7	<0.001	74.2±20.7
Barthel ADL Index	19.1±2.7	15.7±5.8	<0.001	18.5±3.3
BMI, kg/m^2	25.1±4.0	24.2±4.0	0.002	25.3±4.5
GDS-15	3.2±2.2	3.8±2.8	0.03	3.7±2.6
MMSE	26.1±3.2	19.5±7.0	<0.001	25.7±3.2
MNA	25.0±3.4	23.4±4.2	<0.001	24.6±3.5
Education, years	6.2±2.1	-	-	6.1±2.0
No of medications	4.5±3.3	6.3±3.9	<0.001	5.9±4.5
	%	%	p	%
Women	75.5	-	-	67.3
Own housing	85.3	57.8	<0.001	75.1
Atrial fibrillation	7.8	10.8	<0.001	17.1
Dementia	6.9	41.2	<0.001	#
Depression	17.6	40.2	<0.001	23.9
Diabetes Mellitus	5.9	9.8	0.34	12.2
Heart failure	9.8	31.4	<0.001	21.5
History of stroke	15.7	26.5	0.003	18.5
Antihypertensive drugs°	53.5	67.6	0.01	63.7
Dementia drugs	4.9	8.8	0.13	4.3

Individual variables could include a smaller *n* due to missing values.
° Indication for treatment not considered.
Individuals with dementia at baseline were excluded

TABLE 6. Characteristics of the participants in Sample IV.

| | U70 | | | | Umeå 85+/GERDA | |
	1981 n=187	1984 n=180	1987 n=139	1990 n=174	2000 n=224	2005 n=229
SBP, mmHg	Mean (95% CI) 167.0 (163.1-170.9)	Mean (95% CI) 153.0 (149.2-156.9)	Mean (95% CI) 157.5 (153.0-161.9)	Mean (95% CI) 150.8 (147.2-154.4)	Mean (95% CI) 147.8 (144.8-150.8)	Mean (95% CI) 142.9 (140.0-145.8)
DBP, mmHg	87.6 (85.6-89.7)	80.6 (78.8-82.4)	80.8 (78.6-83.1)	81.7 (80.0-83.4)	74.9 (73.4-76.3)	71.7 (70.3-73.1)
PP, mmHg	79.7 (76.2-83.2)	72.3 (69.1-75.5)	77.0 (73.2-80.7)	69.3 (66.4-72.3)	73.0 (70.3-75.6)	71.2 (68.8-73.7)
Women	n (%) 90 (48.1)	n (%) 109 (60.6)	n (%) 86 (61.9)	n (%) 102 (58.6)	n (%) 168 (75.0)	n (%) 162 (70.7)
Age	Mean±SD 74.7±3.7	Mean±SD 79.1±4.2	Mean±SD 81.8±4.3	Mean±SD 79.5±7.8	Mean±SD 89.6±4.6	Mean±SD 90.2±4.1
Pulse, beats/min	77.7±14.0	76.1±12.2	76.2±13.3	72.5±11.2	68.3±9.8	70.0±10.8
MMSE	#	26.7±5.3	25.1±6.7	25.1±8.0	21.4±8.4	21.1±6.6
BMI, kg/m2	25.2±4.0	24.7±3.7	24.3±3.7	24.5±3.8	24.3±4.7	24.5±4.1

Individual variables could include a smaller n due to missing values. #There was no MMSE in 1981.

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Statistical analyses

All statistical analyses were two-tailed and p-values <0.05 were considered significant. Versions 11, 13 and 16 of the Statistical Package for Social Sciences (SPSS®), the Predictive Analytics Software (PASW®) Statistics 17.0 (both from SPSS Inc., Chicago, IL) and SYSTAT 5.2 (Systat Software Inc., Chicago, IL) were used for handling data and performing statistical analyses.

Blood pressure epidemiology

Umeå 85+/GERDA (Papers I-III)

Differences in blood pressure levels between age groups and sexes were investigated in both cross-sectional and longitudinal samples from the Umeå 85+/GERDA study (Samples I-III). Analysis of variance (ANOVA) with Bonferroni post hoc test was used when studying differences between the three age groups, and Student's t-test was used for comparing mean values between the sexes. In longitudinal analyses, Paired samples t-test was used to investigate changes in blood pressure. If distributions were skewed, the Wilcoxon signed ranks test was used instead.

U70 and Umeå 85+/GERDA (Paper IV)

Blood pressure epidemiology was further investigated in the combined sample from the U70 and Umeå 85+/GERDA studies (Sample IV). A multiple linear regression model was constructed to estimate the individual effects of age, sex and investigation year on SBP, DBP and PP. Curvilinear (quadratic) associations between age and blood pressure were controlled for by including age squared in the regression models, and the maximum points of these curves were calculated based on the 2nd degree functions obtained from the regression coefficients. Longitudinal blood pressure change was investigated using Paired samples t-test in those individuals who had two or more blood pressure measurements. Absolute blood pressure change was calculated by subtracting the first value from the last value and linear regression models were used to analyze the impact of age, sex and initial blood pressure on absolute blood pressure change. Follow-up time was also adjusted for.

Additional analyses

Differences in blood pressure between Finnish and Swedish as well as urban and rural areas were investigated in Sample II using linear regression. Models were adjusted for age and sex. Antihypertensive drug use in the various groups was compared using Student's t-test and the Pearson chi-square or Fisher exact tests.

Mean blood pressure in individuals in Sample IV who were of the same age but examined in different years was compared using Student's t-test.

Time trends in antihypertensive drug use (Paper IV)

Time trends in antihypertensive drug use were studied in Sample IV. Multiple linear regression, adjusted for age and sex, was used to examine whether year of investigation had any influence on the number of antihypertensive drugs taken.

Blood pressure and mortality (Paper I)

The association between blood pressure and 4-year mortality was investigated in Sample I. The sample was stratified into four categories based on SBP: ≤120 mmHg, 121 to 140 mmHg, 141 to 160 mmHg and >160 mmHg. Ranges were based on commonly used cutoffs for hypertension that were modified somewhat to obtain groups of sufficient size. Similarly, the sample was stratified based on DBP: ≤70 mmHg, 71 to 89 mmHg and ≥90 mmHg, and on PP: <60 mmHg, 60-71 mmHg, 72-89 mmHg and ≥90 mmHg. ANOVA with Bonferroni post hoc test was used when studying differences in continuous variables and the Pearson chi-square or Fisher exact tests were used to compare proportions, pairwise, between these blood pressure groups.

A number of variables were investigated regarding their association with mortality, using Student's t-test for continuous variables and the Pearson chi-square or Fisher exact tests for dichotomous variables. Variables found to be related to mortality ($p<0.15$) were entered into Cox proportional hazards regression models with four-year mortality as the dependent variable. A stepwise method based on Likelihood Ratio was used to determine the final model. Results were presented in terms of hazard ratios (HR) with confidence intervals (CIs). To investigate the presence of curvilinear (quadratic) associations, the Cox model was performed including SBP and SBP squared. From this analysis, an equation of the second degree was formulated for the survival curve. This equation was differentiated with respect to SBP, and then used to calculate the SBP value at which the mortality was lowest. This Cox regression risk function of SBP was visualized in a graph, where the risk associated with SBP 140 mmHg was given the index value of 100.

Blood pressure and cognition - cross-sectional (Paper II)

Multiple linear regression was used to investigate the association between blood pressure parameters and MMSE score in Sample II. The models were adjusted for BMI, age, sex, nationality, education in years, number of prescribed antihypertensive drugs, current depression, hypertension present more than five years earlier, history of stroke and heart disease. To evaluate the possibility of curvilinear (quadratic), associations, squared blood pressure was included in the models. Other continuous variables included in the regression models were also evaluated with regard to curvilinear associations with MMSE score. The relationships between blood pressure variables and MMSE scores were plotted

at mean of covariates based on coefficients from the multiple linear regression models.

Additionally, Student t-test was used to compare means between groups and ANOVA with Bonferroni post hoc test was used when studying differences in continuous variables between the three age groups.

Blood pressure and cognition – longitudinal (Paper III)

Longitudinal associations between blood pressure and dementia and MMSE scores were investigated in Sample III. Paired samples t-test was used to investigate changes in continuous variables and Student t-test to compare means between groups. If distributions were skewed, the Wilcoxon signed ranks test and the Mann-Whitney u-test were used. McNemar's test was used to compare proportions between baseline and follow-up. Logistic and linear regression models, adjusted for age and sex and, when applicable, baseline blood pressure, were used to investigate associations between blood pressure, blood pressure change and dementia and MMSE scores, respectively. Absolute change in blood pressure and MMSE scores was calculated as the difference between the baseline and the follow-up value.

RESULTS

Blood pressure epidemiology

Age and sex differences

Cross-sectional results from Umeå 85+/GERDA (Papers I+II)

Table 3 shows mean blood pressure values in 2000/02, presented according to sex and age. SBP and PP were significantly lower in the ≥95-year-olds than in the 85-year-olds in both men (SBP: p=0.005, PP: p=0.021) and women (SBP: p<0.001, PP: p<0.001). In women, SBP was also lower in the 90-year-olds than in the 85-year-olds (p<0.001) and DBP was higher in the 85-year-olds compared with both the 90-year-olds (p=0.003) and the ≥95-year-olds (p=0.005). Mean SBP was 147.7 mmHg in both men and women (95% CI 143.0-152.4 mmHg for men, 144.7-150.8 mmHg for women) and mean DBP was 76.1 and 75.3 mmHg (95% CI 73.8-78.3 and 73.9-76.6 mmHg) in men and women, respectively. There were no significant differences in blood pressure between the sexes (data not shown).

Table 4 shows mean blood pressures according to age group in the 2005/07 data collection. SBP (p<0.001), DBP (p=0.015) and PP (p=0.002) were all lower in those aged ≥95 years than in the 85-year-olds. DBP (p=0.016) was also lower in the oldest age group compared with the 90-year-olds, and PP was lower in the 90-year-olds than in the 85-year-olds (p=0.037). Women had a higher mean PP (71.9 vs. 68.2 mmHg, p=0.042) but there were no other differences in blood pressure between sexes.

**Cross-sectional results from U70 and Umeå 85+/GERDA (Paper IV)**

Mean blood pressure in the different years is presented in Table 6 and Figure 6 illustrates mean SBP and DBP in the different samples and at different ages. A trend towards decreasing blood pressure with higher ages can be seen, as well as higher blood pressure in earlier samples.

Multiple linear regressions were performed to investigate the relative impact of age and sex on blood pressure (Table 7). The models were also adjusted for BMI and year of investigation and the age squared was included to check for curvilinear relationships, which were found for SBP and PP, but not for DBP (p=0.90 for squared variable). DBP decreased by 0.35 mmHg for each year of increasing age (p<0.001). The age at which SBP and PP reached their maximum values was found to be 74.5 years for SBP and 80.6 years for PP. Based on the second-degree equation, the expected absolute decline in SBP from 75 to 80 years of age was 0.93 mmHg, from 80 to 85 years 2.5 mmHg, from 85 to 90 years 4.1 mmHg and from 90 to 95 years 5.6 mmHg.

Women had a higher mean SBP and PP than men (6.30 and 5.92 mmHg higher respectively, p<0.001) but no sex difference for DBP was detected (p=0.80). Blood pressure variation with age in men and women separately can be seen in Figure 7 (this figure is not included in Paper IV).

FIGURE 6. Mean SBP and DBP according to age and year.
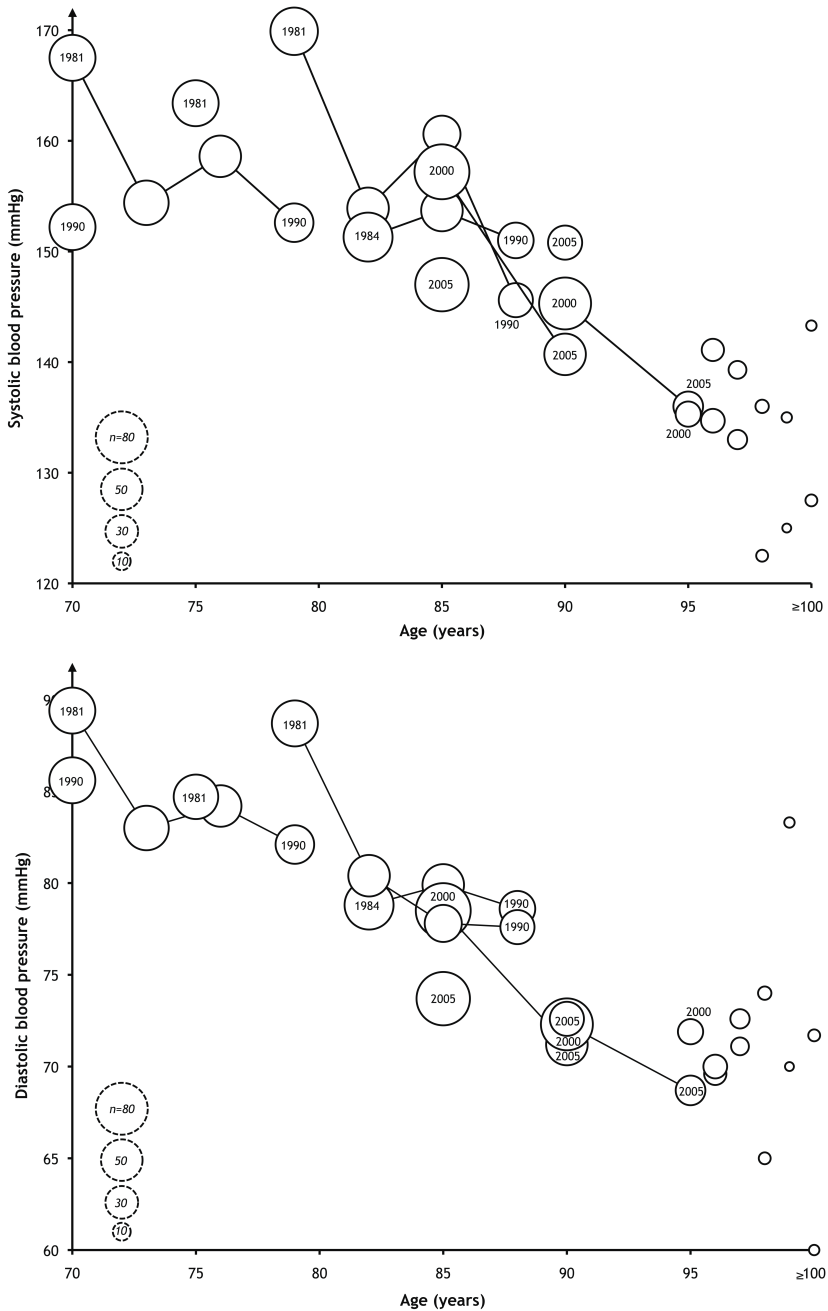
Note: Each circle represents one cross-sectional sample (people of the same age, investigated in the same year) and the area of the circles represents the relative size of the samples. Bold lines connect cohort samples. The center of each circle corresponds to the mean value.

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TABLE 7. Multiple linear regressions of blood pressure.

	Unstandardized β (95% CI)	Standardized β	p
Systolic blood pressure			
Year of investigation	-0.44 (-0.69 to -0.19)	-0.16	<0.001
Age	4.66 (1.00 to 8.3)	1.39	0.013
Age squared	-0.03 (-0.05 to -0.01)	-1.55	0.006
Male sex	-6.30 (-9.42 to -3.19)	-0.12	<0.001
BMI	0.78 (0.40 to 1.15)	0.12	<0.001
Diastolic blood pressure			
Year of investigation	-0.34 (-0.46 to -0.22)	-0.24	<0.001
Age	-0.35 (-0.49 to -0.21)	-0.21	<0.001
Male sex	-0.20 (-1.68 to 1.29)	-0.007	0.80
BMI	0.44 (0.26 to 0.62)	0.14	<0.001
Pulse pressure			
Year of investigation	-0.13 (-0.34 to 0.10)	-0.05	0.26
Age	5.38 (2.22 to 8.55)	1.95	<0.001
Age squared	-0.03 (-0.05 to -0.01)	-2.01	<0.001
Male sex	-5.92 (-8.62 to -3.23)	-0.13	<0.001
BMI	0.31 (-0.02 to 0.63)	0.06	0.064

SBP model: R^2 0.11, *p*-value <0.001. DBP model: R^2 0.18, *p*-value <0.001.
PP model: R^2 0.04, *p*-value <0.001. β = regression coefficient
Year of investigation was entered in four digits, and age in years.

FIGURE 7. SBP and DBP according to age and sex.

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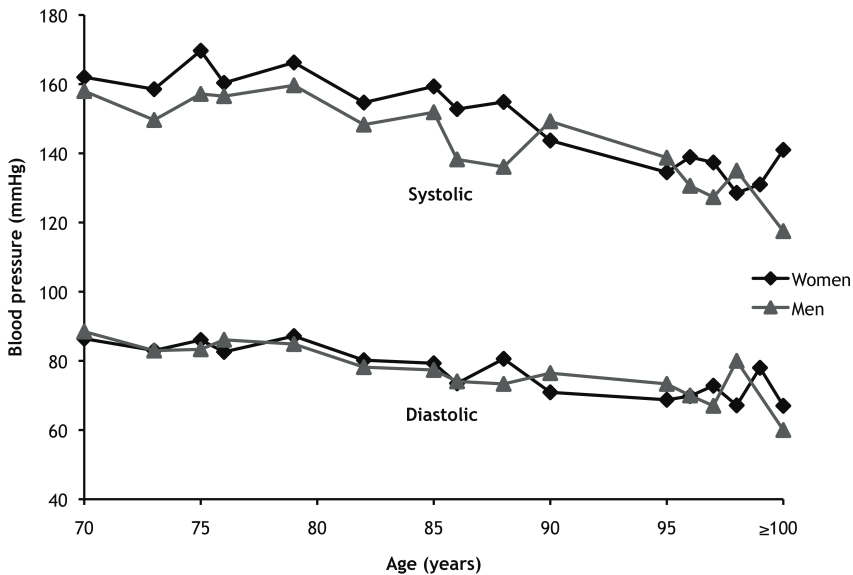
Longitudinal results from Umeå 85+/GERDA (Paper III)

There was a significant decline in mean SBP, DBP and PP (Table 5) in Sample IIIa. Over the five years, SBP decreased in 68.7%, DBP in 57.4% and PP in 63.8% of the participants (by 5 mmHg or more). Sex and age differences were not investigated because of the small sample.

Longitudinal results from U70 and Umeå 85+/GERDA (Paper IV)

Blood pressure change was investigated longitudinally in those who participated in more than one examination (range 2-4). The first and last available blood pressure values for each person were compared. Mean SBP, DBP and PP at follow-up were significantly lower than at baseline (Table 8). SBP declined in 64.8%, DBP in 58.3% and PP in 56.3% of the participants (by ≥5 mmHg).

TABLE 8. Mean blood pressure at baseline and follow-up in longitudinal analyses.

	Baseline	Follow-up	p
	Mean±SD	Mean±SD	
SBP, mmHg (n=247)	160.8±24.8	147.3±24.0	<0.001
DBP, mmHg (n=240)	82.3±12.9	76.5±12.6	<0.001
PP, mmHg (n=240)	78.7±22.0	70.9±20.3	<0.001

Absolute blood pressure decline was investigated in linear regression models (Table 9) adjusted for age, sex, time from first to last examination (in whole years, range 3-9) and baseline SBP, DBP and PP, respectively.

TABLE 9. Multiple linear regressions of longitudinal blood pressure change.

	Unstandardized β (95% CI)	Standardized β	p
SBP change			
Age at baseline	-0.46 (-0.84 to -0.08)	-0.13	0.018
Male sex	-9.99 (-15.88 to -4.1)	-0.17	<0.001
Baseline SBP	-0.70 (-0.81 to -0.59)	-0.61	<0.001
Follow-up time, years	0.10 (-1.38 to 1.58)	0.01	0.89
DBP change			
Age at baseline	-0.10 (-0.30 to -0.10)	-0.06	0.33
Male sex	-1.10 (-4.19 to -1.99)	-0.04	0.48
Baseline DBP	-0.60 (-0.72 to -0.48)	-0.57	<0.001
Follow-up time, years	0.24 (-0.55 to 1.03)	0.04	0.54
PP change			
Age at baseline	-0.39 (-0.72 to -0.06)	-0.13	0.02
Male sex	-8.90 (-14.0 to -3.80)	-0.17	<0.001
Baseline PP	-0.73 (-0.84 to -0.62)	-0.65	<0.001
Follow-up time, years	-0.35 (-1.64 to 0.94)	-0.03	0.59

SBP model: R^2 0.40, *p*-value <0.001. DBP model: R^2 0.31 *p*-value <0.001.
PP model: R^2 0.44, *p*-value <0.001. β = regression coefficient

Baseline blood pressure was a strong predictor of blood pressure decline and higher age and male sex predicted larger declines in SBP and PP, but not DBP. At baseline, 40.5% of these individuals were treated with antihypertensive drugs, compared to 51.8% at follow-up. The mean number of antihypertensive drugs received at baseline was 0.55 and 0.78 at follow-up.

Time trends in blood pressure

Results from U70 and Umeå 85+/GERDA (Paper IV)

For each subsequent year the investigation was performed, mean SBP decreased by 0.44 mmHg (p<0.001) and DBP decreased by 0.34 mmHg (p<0.001). PP had no significant relation to year of investigation (Table 7). Analyses were adjusted for age, sex and BMI.

Blood pressure difference between the years in certain age groups

Blood pressure change over the years was further investigated by comparing individuals of the same age but examined in different years. Analyses were performed on Sample IV. Mean blood pressure values are presented in Table 10. Individuals aged 70 years in 1981 had significantly higher SBP (p<0.001) and PP (p=0.003) than those aged 70 years in 1990. There was also a trend towards higher DBP (p=0.053). Similarly, those aged 79 years in 1981 had higher SBP (p<0.001), DBP (p=0.009) and PP (p=0.005) than 79-year-olds in 1990. However, there was no difference in blood pressure between individuals aged 85 years in 1987 and in 2000, whereas 85-year-olds in 2005 had lower SBP (p=0.012) and DBP (p=0.007) than 85-year-olds in 1987 and also had lower SBP (p=0.003) and DBP (p=0.003) than 85-year-olds in 2000.

TABLE 10. Mean blood pressure for different ages over the years.

	1981	1987	1990	2000	2005
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Age 70					
SBP, mmHg	167.5±22.4		152.2±22.5		
DBP, mmHg	89.4±12.0		85.6±8.8		
PP, mmHg	78.2±21.4		67.3±17.9		
Age 79					
SBP, mmHg	169.9±27.2		152.6±19.7		
DBP, mmHg	88.7±13.7		82.1±10.5		
PP, mmHg	82.8±24.1		70.5±17.2		
Age 85 #					
SBP, mmHg		156.8±29.0		157.2±22.7	147.0±20.9
DBP, mmHg		78.9±14.6		78.5±10.9	73.7±9.9
PP, mmHg		78.4±24.1		78.7±21.1	73.3±18.4

Also includes some individuals aged 86 years in 2000 and 2005.

Geographical differences

These analyses were performed on the Umeå 85+/GERDA samples. There were no differences in SBP, DBP or PP between the urban and rural areas in 2000/02 (Sample I), in analyses adjusted for age and sex (data not shown). In 2005/07 (Sample II), however, both SBP (148.4 vs. 143.4 mmHg, p=0.034) and DBP (78.2 vs. 71.2 mmHg, p<0.001) were higher in the rural areas but there was no difference in PP (p=0.63). There were no differences between the 2005/07 urban and rural populations with regards to the proportion of participants receiving antihypertensive drugs, nor in the average number of antihypertensive drugs taken per person (data not shown). Also in 2005/07, there were no differences in SBP, DBP or PP between the Swedish and Finnish subsamples (p=0.83/0.72/0.64) in analyses adjusted for age and sex.

Time trends in antihypertensive drug use

Results from U70 and Umeå 85+/GERDA (Paper IV)

Pharmacological drug use is presented in Table 11. In 1981, 39.0% of the participants were treated with antihypertensive drugs, and those treated received on average 1.26 types of drugs. In 2005, the proportion of participants on antihypertensive drugs had increased to 69.4%, and they received a mean number of 1.76 types of drugs. For the entire sample, the mean number of antihypertensive drugs per individual increased from 0.49 in 1981 to 1.22 in 2005. Women received more antihypertensive drugs than men (0.86 vs. 0.61, p<0.001).

In linear regression adjusted for age, sex and investigation year, it was found that for each subsequent year, the mean number of antihypertensive drugs received per individual increased by 0.033 (95% CI 0.025 to 0.042, p<0.001). Age had no significant effect on antihypertensive drug use (B=-0.01, p=0.09), but women received 0.18 more antihypertensive drugs than men (95% CI 0.074 to 0.279, p=0.002).

TABLE 11. Cardiovascular drug use in different years.

Drug class	ATC-code	U70				Umeå 85+/GERDA	
		1981 n=187	1984 n=180	1987 n=139	1990 n=174	2000 n=224	2005 n=229
		%	%	%	%	%	%
Warfarine	B01AA03	1.6	1.7	0.7	1.7	4.5	3.1
Acetylsalicylic acid	B01AC06	9.1	13.9	14.4	21.8	41.5	42.4
Digitalis	C01AA	20.3	17.2	19.4	13.2	19.6	10.0
Nitroglycerine #	C01DA	13.9	16.7	18.0	24.1	26.3	29.3
Lipid lowering drugs	C10	0	0	0	0.6	0	4.8
Diuretics	C03	30.5	38.9	37.4	31.0	51.8	47.6
Thiazides		18.7	21.1	15.1	6.9	8.9	11.4
Loop		8.0	15.0	19.4	22.4	40.6	36.2
Potassium-sparing		7.5	7.2	17.3	10.9	12.5	8.7
Beta-blockers	C07	13.4	11.1	14.4	13.2	18.8	38.4
Calcium-channel blockers	C08	1.6	2.8	7.9	6.9	10.3	14.0
RAAS-blockers	C09	0	0	0.7	1.7	11.2	21.8
Other antihypertensives	C02	3.7	4.4	1.4	4.0	1.3	0.4
Any antihypertensive drug		39.0	45.0	44.6	42.5	63.8	69.4
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
No of antihypertensive drugs		0.49±0.67	0.57±0.72	0.62±0.79	0.57±0.76	0.95±0.86	1.22±1.1
No of antihypertensive drugs among treated		1.26±0.44 (n=73)	1.27±0.52 (n=81)	1.39±0.58 (n=62)	1.34±0.58 (n=74)	1.48±0.60 (n=143)	1.76±0.80 (n=159)

All medications are presented regardless of treatment indication. # Represents both short- and long-acting preparations.

Blood pressure and mortality

Results from Umeå 85+/GERDA 2000/02 (Paper I)

The 4-year mortality rate was 56.9%, constituting 198 individuals. SBP (p<0.001), DBP (p=0.043) and PP (p<0.001) were all inversely and significantly associated with mortality. Characteristics of the four SBP categories are presented in Table 12.

TABLE 12. Characteristics of SBP groups, Sample I.

SBP, mmHg	≤120 n=59	121-140 n=97	141-160 n=103	>160 n=89
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Age	91.5±4.6	90.9±4.6	88.7±4.4 ***	87.7±3.6 ***
Barthel ADL Index	12.3±7.3	15.2±6.3	16.9±5.5 ***	18.2±4.2 ***
MMSE	18.4±8.8	19.8±8.5	22.9±7.5 **	24.7±5.0 ***
MNA	20.0±5.2	22.2±4.6 *	23.7±4.2 ***	25.0±4.2 ***
	%	%	%	%
Women	76.3	67.0	73.8	71.9
Atrial fibrillation	30.5	16.5 *	21.4	9.0 ***
Dementia	42.4	35.1	24.3*	14.6 ***
Depression	42.9	32.3	26.5	19.3
Diabetes Mellitus	16.9	12.4	9.7	14.6
Heart failure	49.2	30.2 *	14.6 ***	19.1 ***
Hypertension	32.2	25.8	62.1 ***	100.0 ***
ACE inhibitors	18.6	8.3	11.8	7.9 *
Beta blockers	20.3	19.8	24.5	22.5
Calcium blockers	6.8	6.3	12.7	13.5
Diuretics	67.8	50.0 *	49.0 *	40.4 **
4-year mortality	81.4	61.9 *	46.6 ***	47.2 ***

Stars represent significance of comparisons with those in the ≤120 mmHg group. *p<0.05 **p<0.01 ***p<0.001. Individual variables could include a smaller *n* due to missing values.

Factors associated with mortality, including age and sex, were entered into stepwise Cox regression analyses together with SBP as a categorical variable. Seven factors, significantly associated with increased mortality, remained in the final model, presented in Table 13: SBP (see below), higher age, male sex, lower Barthel ADL Index scores, lower MMSE scores, atrial fibrillation and diabetes mellitus. Factors excluded during the stepwise procedure were: treatment with diuretics or ACE inhibitors, heart failure, malignancy in the last five years, chronic lung disease, depression, BMI, malnutrition in terms of low MNA scores and cardiovascular diseases such as history of stroke and recent myocardial infarction. Dementia was replaced by MMSE, as MMSE was a stronger predictor (data not shown). Figure 8 represents survival in the various SBP categories. Those with the lowest SBP (≤120 mmHg) showed a substantially and significantly increased mortality compared with the others. Those with the highest SBP (>160 mmHg) had the second highest hazard ratio, suggesting a U-

shaped mortality curve. This hypothesis was confirmed by substituting the SBP categories for SBP and SBP squared in the adjusted Cox model. Both SBP (p<0.001) and SBP squared (p=0.001) were significantly associated with mortality, supporting the presence of a U-shaped association (Figure 9). The SBP associated with the lowest mortality was 164.2 mmHg (95% CI 154.1-183.8 mmHg). Excluding deaths within the first year did not alter the findings (data not shown). The presence of any antihypertensive medication at baseline was controlled for in an additional model but did not alter the findings (data not shown).

TABLE 13. Non-adjusted and adjusted Cox regression of variables associated with 4-year mortality.

	Non-adjusted HR (95% CI)	Adjusted HR (95% CI)
SBP	***	***
SBP ≤120 mmHg#	1	1
SBP 121-140 mmHg	0.50 (0.34-0.72) ***	0.44 (0.29-0.68) ***
SBP 141-160 mmHg	0.32 (0.21-0.48) ***	0.44 (0.29-0.68) ***
SBP >160 mmHg	0.33 (0.22-0.51) ***	0.60 (0.37-0.96) *
Female sex		0.61 (0.43-0.85) **
Age		1.05 (1.02-1.09) *
Barthel ADL Index		0.96 (0.92-1.00) *
MMSE		0.96 (0.93-0.98) **
Atrial fibrillation		1.94 (1.38-2.74) ***
Diabetes mellitus		1.52 (1.02-2.27) *

Reference group. *p<0.05 **p<0.01 ***p<0.001.

Additional results from Umeå 85+/GERDA 2000/02

These analyses were performed on Sample I. DBP and PP were entered into Cox regression models as categorical variables together with the same variables as described above for SBP. A stepwise method of removal was employed and neither DBP nor PP remained in the final models, implying their lack of association with 4-year mortality in adjusted analyses (data not shown).
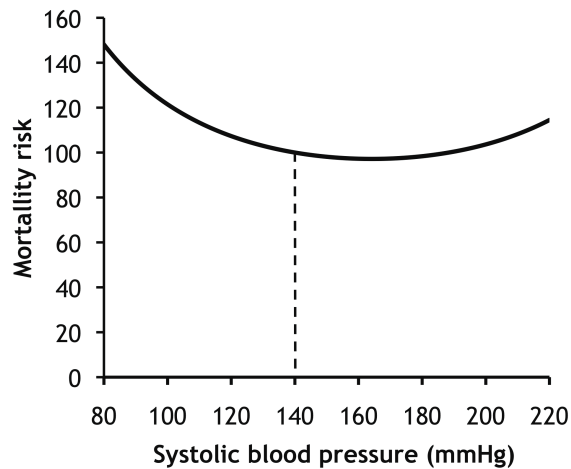
FIGURE 8. Survival in different categories of SBP based on multiple Cox regression.
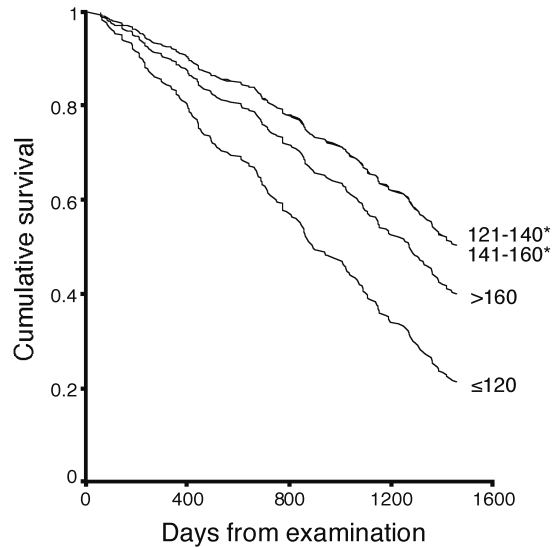
P-values of comparison with the ≤120 mmHg group: 121-140 mmHg p<0.001; 141-160 mmHg p<0.001; >160 mmHg p=0.032. *Note that the curves for these two groups overlap.

FIGURE 9. Mortality risk associated with different levels of SBP.

Adjusted for sex, age, MMSE score, Barthel ADL Index score, atrial fibrillation and diabetes mellitus. Risk associated with SBP 140 mmHg is used as index (=100).
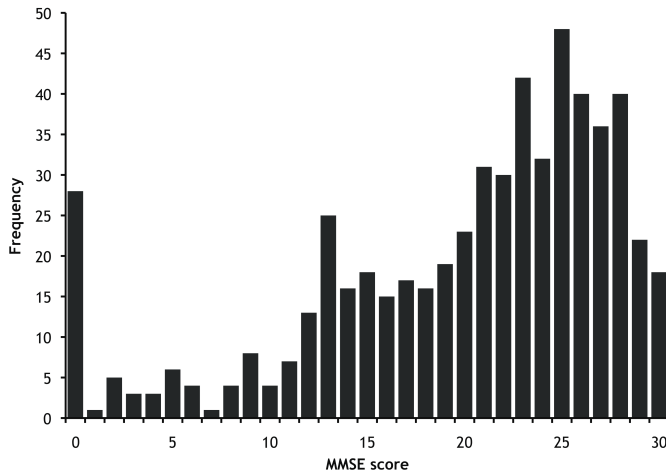
Blood pressure and cognitive impairment/dementia

Cross-sectional results

Results from Umeå 85+/GERDA 2005/07 (Paper II)

Characteristics of the participants are shown in Table 4. The distribution of MMSE scores in the sample is shown in Figure 10 (not included in Paper II).

FIGURE 10. Distribution of MMSE scores in Sample II.

Mean scores on the MMSE differed significantly among all age groups, with the highest score in the youngest age group and the lowest in the oldest (p-values <0.001). Mean MMSE score was lower among women than men (19.4 vs. 21.3 points, p=0.003) and women had a slightly higher mean age (90.4 vs. 89.4 years, p=0.009), due to a high proportion of women in the oldest age group. Use of antihypertensive drugs was associated with higher MMSE scores (20.4 vs. 18.7, p=0.049). Participants with dementia had lower mean SBP, DBP and PP than those without dementia (Table 14).

TABLE 14. Blood pressure in individuals with and without dementia.

	Dementia n=233	No dementia n=342	p
	Mean±SD	Mean±SD	
SBP, mmHg	136.5±21.7	150.9±22.6	<0.001
DBP, mmHg	72.2±12.4	75.7±11.2	<0.001
PP, mmHg	64.3±17.7	75.2±20.4	<0.001

The association between blood pressure and MMSE score was investigated using multiple linear regression (Table 15). In addition to blood pressure, BMI and BMI squared, age, sex, nationality, education in years, number of pre-

scribed antihypertensive drugs (range 0-4), current depression, hypertension present >5 years earlier, history of stroke and heart disease were controlled for.

According to these models, SBP and PP, but not DBP, were significantly associated with MMSE score (Table 15). The association between PP and MMSE score was linear and positive, whereas a nonlinear association between SBP and MMSE score was found. Both low and high SBP were associated with lower scores on the MMSE. There was also a nonlinear association between BMI and MMSE scores, both low and high BMI predicted lower scores on the MMSE (data not shown). Figure 11 presents MMSE scores as a function of SBP and PP, adjusted for the above-mentioned variables. DBP is not included due to its lack of significance.

A lower mean blood pressure was seen among those where blood pressure had been measured while seated. However, excluding these subjects as well as subjects for whom blood pressure was acquired from medical records did not alter the observed associations between blood pressure and MMSE scores (data not shown).

Another model was performed for DBP and PP, where SBP and SBP squared were adjusted for. Neither of the two other blood pressure parameters was significant, whereas SBP was significant in both the PP and DBP models (data not shown). Further, 98 participants were not included in the multiple regression models, principally due to missing values for the education variable. To evaluate whether this could have affected the results, education was removed from the models. All blood pressure parameters were significantly associated with MMSE scores in these models and nonlinear associations were found for SBP and DBP (data not shown).

TABLE 15. Multiple linear regression of blood pressure and MMSE score.

	SBP model n=477 B	DBP model n=476 B	PP model n=476 B	p
SBP	0.28			0.004
SBP squared	-0.001			0.027
DBP		0.35		0.099
DBP squared		-0.002		0.149
PP			0.07	<0.001
R^2 for model	0.28	0.24	0.27	
P for model	<0.001	<0.001	<0.001	

Adjusted for age, sex, nationality, education in years, BMI, BMI squared, number of antihypertensive drugs (0-4), current depression, hypertension >5 years earlier, history of stroke and heart disease.
B=Regression coefficient (unstandardized).

FIGURE 11. Graphs of MMSE score related to blood pressure.
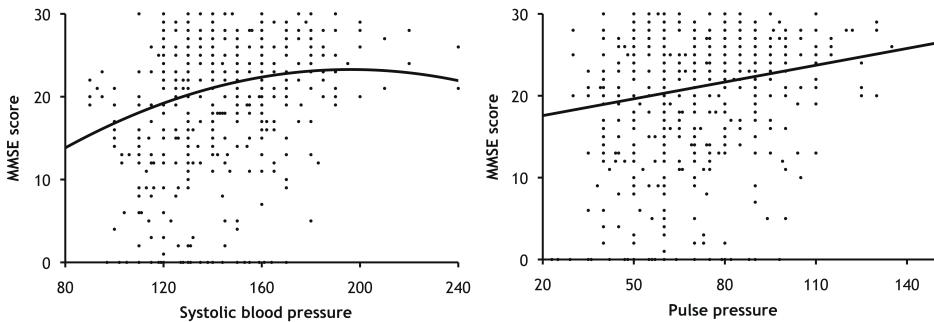
Adjusted for age, sex, nationality, education in years, number of antihypertensive drugs (0-4), BMI, BMI squared, current depression, hypertension >5 years earlier, history of stroke and heart disease. Dots represent one or several individual cases.

Longitudinal results

Results from Umeå 85+/GERDA (Paper III)

The following results were obtained from analyses on Sample IIIa (Table 5). Mean decline in MMSE scores over the five years was 6.6 points (SD±5.9, range -6 to 26). In linear regression models adjusted for age and sex, SBP (p=0.72), DBP (p=0.32) or PP (p=0.88) at baseline were not associated with change in MMSE scores. Quadratic nonlinear associations were tested for by including squared blood pressure variables, but no association between baseline blood pressure and change in MMSE scores could be found in these analyses either (data not shown). Baseline MMSE score was also not associated with change in SBP (p=0.27), DBP (p=0.87) or PP (p=0.19) over the five years in linear regressions adjusted for sex and age. However, decline in SBP (β=0.074, p=0.008), but not DBP (p=0.10) or PP (p=0.07), predicted decline in MMSE scores according to linear regressions adjusted for age, sex and baseline blood pressure.

Among the 205 individuals in Sample IIIb (Table 5) there were 69 incident dementia cases. In logistic regressions adjusted for age, sex and follow-up time, baseline blood pressure did not predict the development of dementia (Table 16). Similar analyses, adjusted for age and sex, were performed on Sample IIIa and could not demonstrate any association between baseline blood pressure and incident dementia either (Table 16).

In Sample IIIa, those who developed dementia exhibited a greater decline in SBP and PP than those who remained dementia free, according to linear regressions adjusted for age, sex and baseline blood pressure (Table 17). Further, incident dementia cases had significantly lower SBP (134.2 vs. 145.9 mmHg, p=0.01) and PP (64.0 vs. 72.2 mmHg, p<0.041) at follow-up than dementia-free subjects, but there was no difference in DBP (70.3 vs. 73.6 mmHg, p=0.27). Analyses of blood pressure in individuals with and without dementia

at baseline were not possible due to the small number of individuals with baseline dementia available at follow-up.

TABLE 16. Mean blood pressure according to dementia status and results of logistic regressions of baseline blood pressure and incident dementia.

	Incident dementia	No dementia	Odds ratio	p
	Mean±SD	Mean±SD		
Sample IIIa #	(n=35)	(n=60)		
SBP, mmHg	153.9±26.2	156.2±18.4	1.000	0.73
DBP, mmHg	77.4±11.1	77.3±10.1	1.002	0.91
PP, mmHg	76.6±19.8	78.9±19.3	0.995	0.66
Sample IIIb †	(n=69)	(n=136)		
SBP, mmHg	149.2±24.7	150.8±23.0	0.993	0.30
DBP, mmHg	75.3±10.7	76.4±10.5	0.985	0.30
PP, mmHg	73.9±20.2	74.4±21.0	0.995	0.54

\# Adjusted for age and sex. † Adjusted for age, sex and follow-up time.

TABLE 17. Mean blood pressure decline and results of linear regressions of blood pressure change according to dementia status.

	Incident dementia n=35	No dementia n=60	B	p
	Mean±SD	Mean±SD		
SBP decline, mmHg	18.8±28.9	10.8±23.1	10.0	0.02
DBP decline, mmHg	6.2±15.6	4.1±14.0	2.0	0.49
PP decline, mmHg	13.8±24.1	6.7±21.4	8.0	0.04

Adjusted for age, sex and baseline SBP, DBP and PP, respectively.
B = regression coefficient (unstandardized).

DISCUSSION

Main findings

Blood pressure change with age was investigated in individuals aged 70 years and older. In general, blood pressure decreased with increasing age but more specifically, SBP and PP increased up to the ages of 74.5 and 80.6 years, respectively, and then started decreasing. Longitudinally, over 3-9 years, SBP declined in 64.8%, DBP in 58.3% and PP in 56.3% of the participants. Mean blood pressure also decreased over the years, indicating that there might be cohort effects on blood pressure. The prevalence of treatment with antihypertensive drugs increased over time, and those treated received an increasing number of drugs. Women had higher blood pressure than men in individuals ≥70 years of age. Few sex differences in blood pressure were, however, seen among those ≥85 years of age specifically.

A nonlinear association between SBP and 4-year mortality in people aged 85 years and over was demonstrated, where both lower and higher SBP were associated with increased mortality. The highest mortality was observed in those with an SBP ≤120 mmHg in categorical analyses, and the lowest mortality risk was associated with an SBP of 164.2 mmHg (95% CI 154.1-183.8 mmHg), according to calculations. The analyses were adjusted for a number of diseases and health factors. There was no association between DBP or PP and 4-year mortality.

Nonlinear associations between SBP and MMSE scores were demonstrated in cross-sectional analysis of individuals aged ≥85 years, indicating poorer cognitive function with both low and high SBP. Similar nonlinear associations were found for PP, whereas the association between DBP and MMSE scores was linear; higher DBP was associated with higher MMSE scores. In longitudinal analysis over five years, no association, either linear or nonlinear, between baseline blood pressure and incident dementia could be demonstrated. However, mean blood pressure declined over this time period, and this decline was greater in individuals with incident dementia than in those who remained dementia free. There was a correlation between decline in blood pressure and decline in MMSE scores.

Blood pressure epidemiology

Blood pressure decline in old age

The findings from the present study agree with previous reports of blood pressure decline in old age. Some studies have shown that only DBP decreases, while SBP continually increases [10, 11, 17], but others have also demonstrated an age-related fall in SBP [12, 23-25, 131], as in the present study. One explanation for the disagreement between results could be that studies which have not demonstrated a decline in SBP included younger old participants and thus failed to

capture the SBP decline that seems to occur in very high age, such as in the current subjects aged ≥85 years. In the current study, SBP and PP increased with age until 74.5 and 80.6 years of age, respectively, and then started decreasing, whereas DBP decreased linearly, implying that DBP reaches its peak value at a younger age. In some studies SBP did not decline in individuals ≥80 years of age [15, 18, 132]. However, in all of these studies all who were 80 years or older were considered jointly and thus it is uncertain whether these results were really valid for the full age span of very old people.

Either way, it is likely that the age when blood pressure starts declining varies widely among individuals. Also, as illustrated in the present results, blood pressure decline should probably not be expected to occur in everyone. Differences in underlying characteristics, such as the presence of disease or treatment with drugs that lower blood pressure, could explain this individual variation. In a sample of healthy individuals free from diseases or medications that could affect blood pressure, SBP and DBP increased from middle age and reached a plateau, without declining, in older women, but continued to increase in men, implying that the epidemiology of blood pressure might be different in healthy individuals [28]. However, the number of individuals aged 80 years or older in that study was limited. Adjustment for potential underlying health factors was not performed in the present study due to possible differences in diagnostic criteria in the two included studies, but would be important in future research in order to identify individuals who could be prone to experience a decline in blood pressure. These individuals could potentially benefit from expanded follow-up of blood pressure and antihypertensive treatment.

Potential mechanisms behind blood pressure decline in advanced age

As previously described, the increase in SBP and decrease in DBP with age, also indicated in the present study, can be attributed to the stiffening of large arteries. However, reduction in arterial stiffness is not a likely explanation for the eventual SBP decline observed in the present study as this condition is, essentially, irreversible [20], although it can be influenced by antihypertensive treatment [133].

Perhaps SBP decline in very old age is an effect of organ failure as, for example, cardiac and kidney functions diminish with age and disease and the ability to sustain a higher blood pressure could thus be reduced. In the Leiden 85-plus study, low SBP was found to correlate with a lower cardiac output and smaller stroke volume in a sample of 90-year-olds [134]. The reduction in blood pressure could be a part of the 'normal' aging process, involving deterioration in many bodily functions. A long life with increasing arterial stiffness, in many cases augmented by hypertension, also increases the risk of developing left ventricular hypertrophy and subsequent congestive heart failure [135], which might lead to blood pressure decline [24]. Diseases such as dementia may also lead to a lower blood pressure, as both earlier and current results suggest, and a

potentially increasing prevalence of treatment with blood-pressure lowering drugs with age (whether they are prescribed for hypertension, heart failure or other conditions) could naturally also reduce mean blood pressure levels. The more sedentary lifestyle in advanced age might also lead to a smaller demand for oxygen and other substances throughout the body, and cerebral atrophy due to aging could diminish the metabolic demands of the brain [136], leading to a reduced demand for blood flow and a lower blood pressure.

A higher BMI was associated with higher SBP and DBP in the present study (Table 7), indicting that poorer nutritional status or low body weight might predispose an individual to a decline in blood pressure, as also suggested by others [24]. A survival bias due to increased mortality in individuals with hypertension could also contribute; but this would be contradicted by the fact that low blood pressure, rather than hypertension, seems to be associated with an increased mortality rate in the very old (see below). Selective mortality might affect results from studies on repeated cross-sectional samples but should not explain results from longitudinal analyses of individual subjects, such as those presented in the present thesis. Longitudinal declines in blood pressure can, on the other hand, be influenced by cohort effects, as discussed below.

Sex- and geographical differences

In the combined results from the U70 and Umeå 85+/GERDA studies, comprising individuals aged 70 years and older, women had higher SBP and PP than men. Similar findings have been observed in studies of other older populations [10, 11, 15, 17, 18, 26]. It has previously been shown that men have higher blood pressure in younger ages but that in older populations the association is reversed [10, 11, 27] or the difference at least narrowed [17, 28]. However, in the Umeå 85+/GERDA study, the only significant difference in blood pressure between men and women was that women seemed to have a higher PP in 2005/07. In the H70 study from Gothenburg, Sweden, women had higher SBP than men up to 82 years of age, but in even older individuals there was no difference [23]. These results could suggest that the sex difference shifts in old age but disappears in very old age.

Possible explanations could be that men with high blood pressure die younger or that hypertension in old age is treated more vigorously in men, although this is contradicted by the observation that women received more antihypertensive drugs than men in the present study. Another possibility is that some difference in underlying factors such as cardiac function or other morbidities causes a greater blood pressure decline in men than women. Male sex did constitute a predisposition to a larger blood pressure decline in the longitudinal results from the present study. It has also been postulated that women might experience an accelerated rise in blood pressure in relation to menopause [137], hence "catching up" with male counterparts. In addition, if women indeed experience a later blood pressure increase, their exposure to

hypertension at a given age has been shorter and they might survive to a higher age even with hypertensive disease.

Regarding geographical differences, blood pressure and the prevalence of hypertension has been shown to be higher in Finland than in Sweden, at least in younger old individuals [13, 138], but there were no differences in blood pressure between Swedish and Finnish participants in the present study.

People from rural areas had higher SBP and DBP than those from the urban municipality in 2005/07, but not in 2000/02. The difference observed in the former investigation does not seem to be attributable to differences in treatment with antihypertensive drugs and could possibly instead be the result of, for example, differences in lifestyle. That although there was no difference in antihypertensive drug treatment there was still a difference in blood pressure might reflect less aggressive treatment of hypertension in the rural areas. Whether this difference in blood pressure could lead to differences in mortality rates between the urban and rural areas remains to be determined.

Time trends in blood pressure

There was not only an age-related, but also a time-related decline in blood pressure in the present study, which was also apparent when blood pressure in individuals of the same age but investigated in different years was compared, indicating cohort effects on blood pressure. During the study period, the prevalence of treatment with antihypertensive drugs increased, which may serve as part of the explanation for the observed decline. The increase in treatment is probably a result of increased awareness of hypertension as a risk factor and changes in guidelines regarding blood pressure levels at which treatment should be initiated [34, 53]. In the early 1980s, treatment decisions were also made principally based on DBP levels [49, 50] but this focus has shifted during the last few decades and now both high SBP and DBP are indications for treatment. Given the high prevalence of isolated systolic hypertension in old age, it seems likely that this could have increased the prevalence of treatment.

There are several earlier reports of blood pressure decline in the recent decades. Glynn et al demonstrated a similar decline in mean blood pressure in the 1980s, which was only partly explained by the increasing prevalence of antihypertensive treatment in the same period [25]. The H70 study, started in 1971, also noted how blood pressure declined between their subsequent 70-year-old cohorts [30]. Their comparisons were based exclusively on individuals who were not on treatment with antihypertensive drugs. Declining blood pressure over the years was also demonstrated in a prospective American study carried out between 1960-1991 [139], a Finnish study covering the time period of 1982-1997 [140], and a Danish study performed between 1964 and 1991[29]. Although the prevalence of antihypertensive treatment also increased over the years in the Danish study, the number of untreated people with normal blood pressure

at screening also increased, implying that the increase in treatment was not the sole cause of the observed blood pressure decline.

The WHO MONICA (World Health Organization, multinational MONI-toring of trends and determinants in CArdiovascular disease) project is an international collaborative study of trends in and risk factors for cardiovascular disease that was performed between the mid-1980s and the mid-1990s in indi-viduals aged 35-64 (25-64 in some samples) years. In a summary of the trends in blood pressure in 38 MONICA populations from 21 different countries, blood pressure declined in most populations, but not in all, over these years [138]. This change was combined with a decreasing prevalence of hypertension that was seen in most populations [141]. Increases in both awareness and treatment of hypertension were also widely noted.

Surprisingly, the Northern Swedish MONICA project indicated only small changes in mean blood pressure in individuals aged 25-64 years from 1986-1999; mean SBP seemed to have increased a little in men and DBP decreased somewhat in women [142]. In the GOT-MONICA study, performed in Goth-enburg, Sweden, from 1985-1995, mean SBP and DBP increased with time [143]. No increase in the prevalence of antihypertensive drug use was seen in either of these Swedish studies [142, 143]. These results from Swedish populations are surprising and disagree with the present results, which demonstrated both blood pressure decline and increases in treatment during a similar time period. However, the present study covered a wider time span and an older age group than the MONICA studies, which might help explain the disparity in the findings. Further, the GOT-MONICA study reported an increase in alcohol consumption and in the proportion of overweight or obese subjects and these changes might have led to increased blood pressure levels in that study [143]. Body composition has probably not affected the results from the present study, as there was little variation in BMI between the different data collections (Table 6) and adjustment for BMI in the regression models did not cancel out the effect of investigation year.

Apart from increases in antihypertensive drug treatment, other possible explanations could lie behind the decline in blood pressure over the years. Improved treatment of conditions that could lower blood pressure, such as heart failure and dementia, has led to better survival among those affected and possibly increased the proportion of individuals with low blood pressure. Due to differences in diagnostic methods and criteria in the U70 and Umeå 85+/ GERDA studies, the prevalence of different medical conditions over the years were not compared. Further, even though it might not have had a great infl-uence on the present study population, increased awareness of the detrimental effects of lifestyle factors associated with hypertension, such as obesity and physical inactivity, and improved management of these problems may have had an impact on mean blood pressure levels. The pharmacological treatment of dyslipidemia has increased over the years and cholesterol levels seem to

have decreased [142], which has probably led to a reduction in atherosclerotic disease and as a result reduced the risk of developing hypertension. Treatment with lipid-lowering drugs was, however, in principal non-existent in the present samples (Table 11). It should also be stressed that there are non-pharmacological means of treating hypertension; such as weight loss, reduction in intake of salt and fat, limited alcohol consumption and physical exercise [5, 34], that might have become more common over the years, not least due to more public awareness of hypertension and its risks. A greater prevalence of treatment with other drugs that might be blood-pressure-lowering, such as selective serotonin reuptake inhibitors [144, 145], could also influence mean blood pressure levels, as could general changes in diet such as reduction in the intake of salt. There could also be more long-term explanations for the cohort effects, such as differences in the environment, nutritional status and health-promoting behavior during adolescence and younger age among different cohorts, but this is difficult to evaluate.

Blood pressure and mortality

The present results are in accordance with previous studies that have shown an association between low blood pressure and increased mortality in the old [67-77, 146]. Several studies have suggested that this is a consequence of concurrent frailty or poor health status [67, 72, 74, 146], whereas others have demonstrated that the impact of low blood pressure on mortality remains even after adjustment for functional status and diseases [68, 71, 76, 77]. Those with the lowest SBP in the present study had lower MMSE and ADL scores and a higher prevalence of heart failure and dementia, implying that these individuals had a poorer health status. However, when these and a number of other risk factors were considered together with SBP in regression analyses, the correlation between low SBP and mortality remained. This implies a partly independent correlation between low SBP and increased 4-year all-cause mortality.

More correctly, not only low but also very high blood pressure was associated with poorer survival, as illustrated by the nonlinear associations. Some earlier studies have suggested similar J- or rather U-shaped relationships between blood pressure and mortality in the old [26, 68, 78, 79]. In results from the Framingham study, there were U-shaped associations between low SBP and mortality, but only in participants with prior cardiovascular disease. In those free of cardiovascular disease the mortality risk increased with higher pressures, with low blood pressure having no impact, implying that low blood pressure might be a marker for cardiovascular disease or, alternatively, that individuals with cardiovascular disease are more sensitive to hypotension [79].

The Framingham study also demonstrated an increased risk of cardiovascular events with increasingly severe hypertension even in individuals ≥80 years, although not all differences were statistically significant [132]. It seems that

hypertension, or at least not severe hypertension, cannot be ruled out as a risk factor for mortality in the very old. The SBP value associated with the lowest mortality in the present study was 164.2 mmHg (95% CI 154.1-183.8 mmHg). The confidence interval for this result was wide but the result nonetheless suggests an optimal SBP level higher than expected. In a previous study it was concluded that for men above 85 years of age, the SBP associated with the lowest mortality was 182 ± 2.2 mmHg, compared with 134 ± 3.3 mmHg (±SD) in those aged 65-84 years [68]. These results suggest an optimal SBP for individuals aged 85 or older that could be well above the present recommendation of ≤140 mmHg.

The categorical analyses indicated that those with an SBP ≤120 mmHg had the highest mortality rate. This should not be interpreted as an absolute limit but the result is interesting considering that an SBP <120 mmHg is considered optimal according to guidelines [34, 36, 56]. The limit for when, and if, hypotension becomes dangerous probably varies among individuals due to different underlying physiological and health-related circumstances.

It has been demonstrated that a blood pressure *decline* is more strongly associated with mortality than low blood pressure in itself [26]. A Swedish study of individuals aged 75 to 90 years demonstrated that the timing of the decline in blood pressure, especially SBP, was associated with mortality, where those who exhibited an earlier decline in SBP died at a younger age and those in whom SBP started declining a few years later survived to a somewhat higher age [23]. Blood pressure decline was also associated with increased mortality in a study of individuals ≥65 years of age and poorer health in individuals who experienced a fall in blood pressure seemed to explain this association [147].

It seems possible that low blood pressure, or perhaps predominantly blood pressure *decline*, could be a result of weakening due to disease, malnutrition [146], the aging process etc., and associated with a decline in health that will eventually lead to death; low blood pressure should perhaps not be seen as a *risk factor* for mortality but rather a *marker* of an increased mortality risk. However, an independent effect of the low blood pressure itself on mortality cannot yet be excluded, as is also suggested by the present results. If blood pressure falls below a certain critical point, regardless of the reason, blood flow to essential areas such as the cardiac or cerebral circulation may perhaps be so impaired that normal metabolism fails, with an immediate or gradual effect on survival. Low DBP could lead to impaired perfusion of the coronary arteries of the heart, but DBP was not associated with mortality in the present study, at least not after adjustment for other factors. Low DBP has, however, been associated with a higher mortality in other studies [74]. If low blood pressure is a risk factor for increased mortality in advanced age, it would be very important to determine whether treatment with blood-pressure-lowering drugs could accelerate this process. Antihypertensive treatment in old age is discussed further below.

Low blood pressure might also increase the risk of orthostatic hypotension and falls, which in turn increase the risk of injuries, fractures, physical impairment and subsequent death. This argumentation suggests that low blood pressure could be a more immediate risk factor for mortality than hypertension. Indeed, the effect of hypertension on cardiovascular risk is most often a rather slow process, with pathology that accumulates over several years before the actual cardiovascular disease or death occurs. It is likely that the association between high blood pressure and mortality observed in the present results reflects a hypertensive disease that has been present for several years preceding the current investigation. Glynn et al demonstrated an association between low blood pressure and increased mortality in individuals aged ≥65 years, that was only valid for the three first years of follow-up. After three years, higher blood pressure at baseline predicted increases in mortality [72]. However, in the present study, the nonlinear association between SBP and increased mortality remained even when deaths during the first year were excluded and in another study, the inverse relation between blood pressure and mortality remained after deaths during the first two years of follow-up had been excluded [71]. Perhaps low blood pressure is indeed a risk factor, or risk marker, primarily in the short term, but the short term is up to a few years, whereas from a longer time perspective, high blood pressure increases the mortality risk even in the old population.

Blood pressure and cognition

In cross-sectional results from the present study, both lower and higher SBP and lower PP were associated with poorer performance on the MMSE, and individuals with dementia had lower blood pressure. As there were few people with very high blood pressure, the association with high blood pressure is uncertain, but similar nonlinear associations between blood pressure and cognitive test scores have been reported in previous cross-sectional studies [121, 122, 148] and several others have demonstrated associations between low blood pressure and an increased prevalence of dementia and cognitive impairment [112-116].

Cross-sectional results are important in indicating associations, but cannot be used to determine causality. Previous longitudinal studies in individuals of advanced age have also suggested an association between low blood pressure and incident dementia [117, 118] or cognitive impairment [115, 119], but this could not be confirmed in the present study; nor was there any association between *high* blood pressure at baseline and incident dementia or cognitive decline. Quadratic nonlinear associations were also tested for but could not be demonstrated, although such associations have been indicated in other longitudinal samples [105, 121, 149]. Several other studies, of individuals aged 75 years or older and with 3 to 10-year follow-ups, have similarly failed to demonstrate any association between baseline blood pressure and incident dementia or cognitive decline [150-153]. Two of the studies mentioned indicated that blood pressure

decline was associated with cognitive decline [150, 153], as was also demonstrated in the present study.

Hypertension in *midlife* has clearly been shown to increase the risk for cognitive decline and dementia in older age [103-109] but in contrast, associations between low blood pressure and cognitive impairment have mainly, but not only [105], been suggested in cross-sectional [112-116] and longitudinal studies [115, 117-120] of *late-life* populations. Thus, there may be a transition from hypertension to hypotension as the strongest predictor for cognitive impairment that is dependent on age, and differences in age among studied populations could consequently explain some of the discrepancies between studies. This transition was demonstrated in a study of individuals aged 55-85 years, where baseline blood pressure was not associated with cognitive function at follow-up in those aged <65 years, was negatively associated with cognitive function in those aged 65-74 years and seemed to be positively associated with cognitive function in those aged ≥75 years, particularly in a subgroup aged 85 years [120]. In one study in the very old, earlier hypertension increased the likelihood of dementia and cognitive impairment at baseline, whereas higher blood pressure at baseline corresponded to better cognitive functioning prospectively [119], also illustrating that high and low blood pressure might both be associated with cognitive impairment, but at different stages in life. Although research indicates that this transition seems to take place around 80 years of age, it seems unlikely that mere chronological age should be the determining factor. Instead, there are probably some underlying mechanisms that are more common in very old age, such as a large disease burden or age-related physiological changes that explain the associations. However, it remains undetermined whether low blood pressure increases the risk or is a result of cognitive impairment, as will be discussed under the next heading.

The length of follow-up also seems to have an impact on results from longitudinal studies of blood pressure and dementia. Skoog et al investigated the association between blood pressure and dementia over 15 years in a sample aged 70 years at baseline. Higher SBP and DBP at baseline was associated with the development of dementia at ages 79-85 years, but there were no associations with prior blood pressure values in those who developed dementia before the age of 79 [103]. In the same study, blood pressure declined before dementia onset. These results imply that the time between blood pressure measurement and diagnosis could be of importance and the follow-up time in the present study may have been too short to demonstrate an association between baseline blood pressure and dementia, but it was sufficient to capture a decline in blood pressure possibly associated with dementia, as discussed below.

Temporal associations and postulated mechanisms

Incident dementia and cognitive decline were associated with lower blood pressure at follow-up in the present study, which could suggest that the reduc-

tion in blood pressure is an effect of dementia and cognitive impairment. However, it is difficult to evaluate exactly the temporal association as information concerning blood pressure values and cognitive performance were only available at two points in time, at baseline and after five years. This wide time span, and the lack of intermittent blood pressure measurements, make it impossible to know how blood pressure decline and cognitive decline are linked in time. Blood pressure change according to dementia status at baseline could not be investigated in the present thesis due to the small sample size, but MMSE scores at baseline had no impact on blood pressure decline over five years. However, the sample was relatively healthy at baseline and had high scores on the MMSE (range 17-30), which might explain why no association could be demonstrated.

Other studies have indeed indicated that the decline in blood pressure in advanced age is more pronounced in individuals with prevalent or incident dementia [103, 118, 151]. It has been suggested that the pathological processes of dementia, at least Alzheimer's disease, could affect brain areas responsible for blood pressure regulation leading to a lower blood pressure [154, 155]. In addition, elderly individuals with dementia are more likely to have poor nutritional status and lower body mass [156] and this might have negative effects on their blood pressure. People with heart failure also seem to have a higher risk of developing cognitive impairment [157-159] and some studies have shown that an association between low blood pressure and cognitive impairment is confined to individuals with heart failure [158], implying that heart failure might influence the associations found.

Low blood pressure could, however, also be a risk factor for dementia. A decline in blood pressure *before* the onset of dementia has been demonstrated [103, 131, 151, 160] and although this could be a marker of preclinical pathology, low blood pressure, caused by high age, deterioration in health or other mechanisms, could also in itself increase the risk of dementia and cognitive deterioration. Potentially, low blood pressure could result in hypoperfusion of the brain, increasing the risk of dysfunction in oxygen-deprived nerve cells. Associations between reduced cerebral blood flow and cognitive impairment have indeed been demonstrated [136, 161]. A reduced metabolic demand due to underlying brain atrophy could explain the observed reduction in cerebral blood flow [136] but, conversely, insufficient cerebral perfusion could contribute to brain atrophy. A connection between low blood pressure and brain atrophy has been demonstrated in very old individuals with and without dementia [162].

The brain has its own autoregulatory system for sustaining an adequate blood pressure even if the systemic blood pressure varies, but with very low blood pressure, this mechanism fails and hypoperfusion could be the result [6]. Cerebral autoregulation might be impaired by Alzheimer pathology, rendering the brain more sensitive to blood pressure changes, although this has been demonstrated mostly in studies on mice [163]. Chronic hypertension also affects

cerebral autoregulation, leading to poorer tolerance of lower blood pressure [22]. As a result, if blood pressure decreases in a previously hypertensive individual, cerebral blood flow might be endangered. Alzheimer's disease is also associated with changes in neurotransmitter systems [95], which could potentially influence blood pressure regulation.

It seems that the connections between blood pressure, brain pathology and cognitive function could be multidirectional, and the temporal association between low blood pressure and dementia is unclear and potentially complex. Perhaps low blood pressure could increase the risk of developing dementia, but dementia also causes reductions in blood pressure. One problem with studying temporal associations is that dementia disease does not appear abruptly; rather it develops successively and its severity also varies considerably between individuals at the time of diagnosis. It can therefore be difficult to ascertain, for example, whether or not low blood pressure was present before the cognitive decline began.

Antihypertensive treatment in the very old

As previously stated, the benefits of reducing blood pressure in very old people are uncertain. The HYVET study [90] was therefore a great leap forward in understanding the role of antihypertensive treatment in the very old. However, the HYVET study had some important limitations: the majority (73%) of the participants were 80-84 years old and even older individuals were underrepresented; the target blood pressure was 150/80 mmHg and only those with a sustained SBP above 160 mmHg were included in the study, which is not in accordance with current clinical guidelines. Exclusion criteria such as dementia, recent stroke and heart failure that required treatment resulted in the participants in the HYVET study being healthier than the general very old population and the results of the study might not be applicable to frail very old individuals. For example, only 12% of the participants had a cardiovascular disease and only 2.9% had heart failure [90]. Compare this with the much higher prevalence numbers from the present, population-based, study (Tables 3 and 4), and it becomes clear that HYVET only represents a subgroup of the very old. Ongoing treatment with antihypertensive drugs was cancelled for a large number of participants in the placebo group, and it is difficult to say whether this massive withdrawal of treatment could have affected the poorer outcomes in the placebo group. Further, as the study was terminated after only 1.8 years, due to the major positive effect of treatment, the effect of longer-term treatment remains unknown.

In a recent updated review of antihypertensive treatment in the elderly, results from HYVET were combined with those from other studies including individuals aged 80 years or older [87]. The results showed that treatment had no effect on mortality in general (risk ratio (RR) 0.98, 95% CI 0.87-1.1) or on cardi-

ovascular or cerebrovascular mortality specifically but had a positive effect on cardiovascular mortality and morbidity combined (RR 0.75, 95% CI 0.65-0.87). The benefit of antihypertensive treatment in very old people thus remains unclear.

The effect of antihypertensive treatment on cognition in old age also remains undetermined, as results from different interventional studies point in different directions [164]. In a systematic review of four randomized, double-blind, placebo-controlled studies, including individuals with a mean age of 75.4 years (range 60-89 years) with no prior cerebrovascular disease, no positive effect of treatment versus placebo on reducing the risk of incident dementia could be found [123]. A meta-analysis of sixteen studies measuring the effect of treatment on cognitive function demonstrated improvement in MMSE scores with treatment, but where other cognitive performance scales had been used, there were indications that treatment had different effects on different cognitive areas [165].

Regarding the very old specifically, the HYVET study included a substudy called the HYVET cognitive function assessment (HYVET-COG) study but no beneficial effect of treatment on incident dementia could be demonstrated in this study, although there was a trend towards beneficial effects on MMSE scores (p=0.08) [166]. The follow-up period was, however, limited (mean 2.2 years) and the above mentioned limitations of the HYVET study naturally also apply to this substudy.

A common problem in these trials, as well as other trials on antihypertensive treatment, is that individuals on placebo are often started on antihypertensive drugs when they pass a certain limit in blood pressure beyond which it is not considered ethical for them to abstain from treatment. A further problem is that compliance in taking the drugs is poorer in cognitively impaired individuals, which could influence treatment effects. In many studies, cognitive outcomes have only been secondary end points and the cognitive assessments have varied [164], implying the need for further studies that focus on the cognitive effects of antihypertensive treatment.

In the current study, use of antihypertensive medication was associated with higher MMSE scores. This could indicate a protective effect of treatment but treatment with antihypertensive drugs could also be a marker of previously high blood pressure, which in itself could be protective. A further possible explanation is that antihypertensive treatment is cancelled more often in individuals with dementia and hence low MMSE scores.

One important aspect of antihypertensive treatment in the very old is the potentially higher risk of adverse drug reactions due to the physiological effects of aging and the high prevalence of disease [167]. Antihypertensive treatment may predispose elderly people to postural hypotension, syncope and falls [168]. Drug interactions are also more common in this age group due to polypharmacy. One can argue that in these old individuals, quality of life might be prioritized above a small reduction in risk, and treatment should perhaps be cancelled more libe-

rally on account of side effects. Perhaps lower Numbers Needed to Treat (NNT) should be required to initiate treatments in older age, given their already limited expected survival and sensitivity to adverse drug effects. In the HYVET study, there were only a few serious adverse events that could be attributed to the trial medication [90], but the prevalence of less serious side effects was not presented.

The prevalence of hypertension was high in the very old people in this study (Table 3), although the prevalence decreased from the youngest to the oldest; unsurprising considering the decreasing blood pressure with age. The present hypertension diagnoses were partly based on a single blood pressure measurement of ≥160/95 mmHg, which should be taken into consideration. Similarly high prevalence numbers have, however, been demonstrated in other studies [58]. A substantial number of those with an SBP of ≤120 mmHg had hypertension diagnoses and were taking antihypertensive drugs (Table 12). This could partly be explained by the high prevalence of heart failure in this group, which is a treatment indication for some of the antihypertensive medications, but could also represent excessive treatment and/or poor follow-up of previously hypertensive patients, whose blood pressure had declined with no accompanying reduction in their medication.

The duration of hypertension is likely to affect the risk associated with the condition. As blood pressure, at least SBP, increases well into old age, many of the oldest individuals may not have been subject to hypertension for a very long time and this could explain why hypertension does not seem to be such a great risk factor despite its high prevalence. Given the relatively short expected survival in *all* very old individuals, treating this "late-life hypertension" to prevent adverse events in the longer term might be of less value, especially when considering the risk of side effects from the treatment.

A recent reappraisal of the European guidelines on hypertension management [54], concludes that there is much evidence to confirm that individuals >65 years of age benefit from antihypertensive treatment as much as younger patients, and that the HYVET study indicates that there are also benefits in patients ≥80 years of age. They recommend that blood pressure-lowering treatment should not be discontinued in the very old. However, they emphasize that the HYVET study population were generally healthy and that it remains uncertain whether the results can be extrapolated to frail very old individuals. Furthermore, they emphasize the need for trials in the elderly that aim at reducing blood pressure to below the recommended SBP of 140 mmHg and that individual consideration and careful monitoring is important when treating the elderly [54].

Reversed epidemiology?

The term *reversed epidemiology* refers to paradoxical observations of inverse relations between common cardiovascular risk factors and outcomes [146], such as in the present thesis where low blood pressure, rather than high, was associated with increased mortality and poorer cognitive performance. There are also other indications of reversed epidemiological associations in old age, for example concerning BMI. In the present results, BMI was associated with MMSE scores in a nonlinear fashion; both low and high BMI values were associated with a lower score on the MMSE. A high BMI in midlife has been shown to be associated with an increased risk of dementia [169] but, in contrast, a higher BMI has been linked to a lower risk of dementia in the old [170, 171]. The studies mentioned were longitudinal and it is possible that the cross-sectional design of the present study influenced the results. In line with the current results, low BMI has previously been associated with poorer results on the MMSE [172]. Including BMI in the present analyses did not invalidate the associations found between blood pressure and MMSE scores. A higher BMI has also been linked to better survival [146] and being underweight according to BMI to poorer survival [170, 173] and changes in body mass have been associated with blood pressure decline [24].

The presence of the metabolic syndrome (the definition of which varies some-what, but includes the presence of several cardiovascular risk factors such as hypertension, dyslipidemia, impaired glucose metabolism and obesity) has been associated with better cognitive function in the very old [174]. A "reversed metabolic syndrome" has also been suggested as a risk factor for mortality in old age in one study [175], something the authors attributed to malnutrition and/or other chronic disorders. Some of the influence of risk factors might, however, be indiscernible in studies of very old populations, as the general rates of morbidity and mortality are so high that they might disguise the effect of a specific risk factor.

The underlying reasons behind the observed paradoxical associations are probably manifold but, nonetheless, these results in a wider perspective imply that traditional cardiovascular risk *markers* might not be as valid in high age as in the young. In some cases, even risk *factor* profiles might be inverted. Perhaps our preconceived notions regarding factors associated with poorer outcomes – hypertension, overweight, metabolic syndrome – are not as valid in high age.

Ethical considerations

Ethical approval was acquired for all the separate data collections in both the U70 and Umeå 85+/GERDA studies. All participants were informed they could discontinue their participation at any point without stating the reason and if there were signs of discomfort on the participant's side, the interview was terminated or continued in another session. All investigators had a medical education and experience of working with old people, and were able to address respectfully concerns or emotions evoked in the participants by, for example, questions that could potentially cause emotional distress. In many cases, the Umeå 85+/GERDA home visits resulted not only in data collection but also in social conversations and the investigators were often invited to stay behind for a chat or a cup of coffee. In the U70 study, the participants were offered food and drinks during their day at the clinic.

Including individuals with cognitive impairment and dementia in research studies entails an ethical dilemma. On the one hand, it can be difficult to ascertain their understanding of the circumstances surrounding participation and the preservation of autonomy, on the other they represent a group that is often underrepresented in medical research and it is vital that they be included in studies in order to improve the knowledge and management of their diseases. These difficulties were addressed by taking careful consideration of the reactions from participants with dementia and termination of the interview if any discomfort, whether verbal or physical, was noted. Approval from the next of kin was always obtained.

Another ethical concern is how to handle the unveiling of unknown medical conditions in study participants. It might be unethical to ignore suspected illnesses in study subjects but at the same time, this kind of screening could result in unnecessary testing and treatment. In the first Umeå 85+/GERDA data collection, individuals with suspected illnesses were referred to their general practitioners for follow-up, but this practice was dropped in the second data collection due to the large amount of work it caused for the receiving doctors. In 2005/07 many subjects were instead advised by the investigator to seek medical attention if there were signs of serious illnesses. In the U70 study, participants with previously unknown medical conditions were often referred to primary care or specialist doctors.

Methodological considerations

Study design

Umeå 85+/GERDA

The Umeå 85+/GERDA study covers a relatively large number of very old individuals from a geographical area where this age group has not been studied previously, making it unique. The study is population-based, which increases its external validity and the transferability of results to other similar populat-

ions. All investigators had received training in the examination procedure and the included scales. The study design, however, has some limitations that should be mentioned.

Home visits often lasted several hours and a relatively large number of subjects were to be examined. Consequently, each data collection in Umeå took more than twelve months, meaning that all participants were not examined during the same period of the year. The oldest individuals where investigated first, which led to some participants in the 85-year-old group turning 86 before they were examined. The data collection in Finland also lasted about one year and could not be started until the end of 2005, meaning some individuals were one year older than at inclusion. The exact age in years was always used in the analyses, but age groups were defined based on age on inclusion. Due to limited resources, not all individuals ≥85 years could be included in the study but instead of using a random sample of individuals ≥85 years of age, three separate age groups were selected. This practice was employed to assure that the whole age span was represented in sufficient numbers – a random sample would probably have resulted in a bias towards younger individuals, given their higher numbers, and disrupted the purpose of the study, which was to investigate the full span of very old individuals.

The Umeå 85+/GERDA study includes individuals from both urban and more rural areas and also samples from both Sweden and Finland. This geographical variation might complicate the reproducibility of results from this study. However, the Finnish sample was only used in one of the current papers and in that sample, there were no differences in blood pressure between Swedish and Finnish participants.

The combination of U70 and Umeå 85+/GERDA

The combination of the U70 and Umeå 85+/GERDA studies rendered a large sample that covered both a wide age range and time period and made possible analyses of both cohort and age effects on blood pressure. The combination of different cohort studies does, however, raise some methodological concerns.

The two studies were performed in the same geographical area, and the investigation procedure was similar regarding the main variables used, namely blood pressure and pharmacological drug use. However, blood pressure was measured by a nurse in a hospital environment in the U70 study and in the participants' homes in the Umeå 85+/GERDA study and a white coat effect could have led to higher blood pressure values in the U70 study. The magnitude of the white coat effect is difficult to determine. In a sample with a mean age of 51 years, the mean white coat effect was 9±16 mmHg for SBP and 7±12 mmHg for DBP and increased with age [61] but it is impossible to assess the impact of the white coat effect in the present study. The white coat effect is not, however, universal and should only affect part of the research sample.

The inclusion process was somewhat different for the two studies, for example regarding the distribution of the two sexes. In the U70 study equal numbers of men and women were consciously included, whereas in Umeå 85+/GERDA women were overrepresented, resulting in a lower proportion of women in the U70 samples (Table 6). Also, the sex distribution of the U70 study was distorted by the inclusion of all individuals aged 82 years in 1984. These matters were addressed by always adjusting for sex in the regression analyses.

The ages of participants varied between the two studies, although there was some age overlap, and the full age span was not represented in all data collections. Adjusting for age and year of investigation in multiple regression models might not fully compensate for this weakness. Additionally, a time span of ten years (1990-2000) is not represented, which disrupts the continuity of the study. It is difficult to evaluate whether this would have affected the results.

There was a larger dropout rate in the Umeå 85+/GERDA study, which could be explained by the higher age of the subjects in this study and the higher prevalence of severe illness or cognitive impairment that might lead an individual or their next of kin to decline participation.

Missing values

Given the high age of the included subjects, a large dropout rate due to mortality is to be expected and was also apparent in the longitudinal sample from the Umeå 85+/GERDA study. Those who died during the follow-up were frailer and had lower blood pressure and a high prevalence of dementia, meaning that the remaining sample represented those individuals who were healthiest at baseline, which could have biased the results. This problem was addressed by including in some analyses participants who had died but could be evaluated for dementia. The dropout rates for the other samples used were acceptable, ranging from 17.9-31.2% of those who were contacted.

One weakness of this and similar studies is the potential bias caused by missing values in subjects with cognitive impairment, caused both by their reduced ability to respond to questions and instructions and the possibly increased prevalence of undiagnosed conditions in individuals with dementia [176]. However, the reliability o the main variables used in the present study – blood pressure, dementia, MMSE and pharmacological drug use – should not be greatly affected by cognitive status.

Reliability of outcome measures

Blood pressure

Blood pressure was measured in the same way in all participants in both studies, though with some exceptions, as discussed below. Each participant had a quiet rest for at least five minutes before they were examined. However, blood pressure was measured by different assessors using different cuffs, which is lik-

ely to have affected the reliability of blood pressure measurements somewhat. Furthermore, blood pressure measurement was performed only once, and while the subject was lying down, which is not in accordance with current guidelines. At the time the U70 study was started, blood pressure was often measured lying down in Sweden and even when the Umeå 85+/GERDA study was initiated, this practice was common in the clinical setting. Supine blood pressure values have been shown to be some mmHg higher than values measured while seated [37, 38], and using a single value instead of the average of repeated measurements may also lead to higher values [41, 42], facts which should be remembered when comparing blood pressure values from the present thesis with other studies. However, as the same bias should apply to all blood pressure measurements, it is less likely to have affected the directions of the observed associations. The difference between supine and sitting values was most pronounced in individuals aged 80 years or above in one study [38] and hence it is possible that the blood pressures measured in the Umeå 85+/ GERDA study are systematically somewhat higher. However, taking this effect into consideration, the present results would only have been even clearer, as blood pressures were still lower in the older individuals in Umeå 85+/GERDA.

In the Umeå 85+/GERDA study, some blood pressure values were taken in the sitting position in individuals who could not or were unwilling to lie down, and some values were taken from medical records. In the 2000/02 data collection, less than 20 values were acquired in these ways and it is unlikely that this would have affected the results. In the total 2005/07 sample, however, this number was approximately 100, mainly representing seated values. As stated above, seated blood pressure values are often higher than supine and this could affect the results. In Paper II, where the 2005/07 material was used, separate analyses were performed where values taken seated or from medical records were excluded and the results remained unchanged. In Paper IV, the manner of measurement was not taken into consideration. However, given that seated measurements result in higher values, removal of these values should, if anything, lead to lower blood pressure values in the ≥85-year-olds in 2005/07 and hence the findings of lower blood pressure in higher age and at later investigation year would only be clearer.

Mortality data

Swedish regulations regarding registration of deaths are strict. When an individual has died, a doctor is required to report this to a national registry immediately and very few deaths are lost to this follow-up. In the current thesis, data on mortality was collected from these official records and from computerized medical records, where information about deaths is automatically updated from the national register on a regular basis. Consequently, the mortality data used in this thesis can be considered very reliable.

Assessment of cognitive impairment

The MMSE has been shown to have good inter-rater and test-retest reliability, at least in the shorter term, good criterion and construct validity, moderate to high specificity and a high sensitivity for dementia, although the sensitivity is lower regarding detection of mild cognitive impairment [101, 177]. The internal consistency is less impressive, but this is not surprising as the scale was intentionally designed to represent different cognitive aspects [101]. However, the MMSE has limitations. It is dependent on focused participation on the part of the subject and sufficient hearing and eyesight to complete all tasks. Results may be affected by factors such as education, which was adjusted for in some, but not all of the present analyses. The MMSE also suffers from potential ceiling and floor effects [177], where the maximum score of 30 might underestimate individuals with well-preserved cognitive function and a score of 0 represents a spectrum of people with varying levels of severe cognitive failure. In the current study, at least in Sample II, there seemed to be a relatively large floor effect, whereas the ceiling effect was less apparent (Figure 10). As can be seen from the figure, relatively few individuals had scores from 1-11 points, especially compared to the numerous scores of 0. This might indicate that the MMSE is not completely linear; a cognitive deterioration in an individual already at the lower end of the scale might lead to the loss of several points at once, whereas a cognitive decline of the same magnitude in an individual with high scores might only result in the loss of a few points. This could be a problem when comparing declines in MMSE scores among individuals.

A further problem with the MMSE is that its use is not fully standardized, and there is variation in how some of the items are delivered and the answers interpreted in different studies and settings, making it difficult to compare values between studies. To the author's knowledge, there are also no published studies that have tested the reliability of the Swedish translation of the MMSE. In the Umeå 85+/GERDA study, the investigators received similar instructions on how to deliver the MMSE and often discussed among themselves how answers should be interpreted. The same version of the MMSE was used both in 2000/02 and 2005/07, except that a Finnish translation was used for Finnish-speaking participants in 2005. Hence, the use of the MMSE within this study was relatively standardized. This version was, however, somewhat different from that used in the U70 study, but the MMSE scores from the U70 study were only used as a background variable.

Dementia diagnoses

Dementia diagnoses were made based on information from the interview protocol and medical records. A specialist in geriatric medicine reviewed the available material and made the diagnoses but did not examine the subjects in person (except in those cases when he performed the home visit himself), which is a limitation.

Only medical records and death certificates were used to diagnose dementia in those who died between the two Umeå 85+/GERDA data collections, which reduces the amount of available data. All these diagnoses were, however, reviewed by a specialist in geriatric medicine and cases where there was any degree of uncertainty were excluded. Analyses excluding these diagnoses were also performed, and the same results were obtained. Further, it should be noted that secondary causes of dementia, such as disease or substance use, could not be excluded due to lack of access to blood samples and other requisite data.

Antihypertensive drugs

The collection of pharmacological drug data is reliable; participants were interviewed regarding the drugs they used and this information was cross-checked in digital medical records, which are automatically updated after prescription. The individuals' compliance with drug treatment is, however, unknown. Information about treatment indications and doses was unavailable and drugs considered antihypertensive could have been prescribed as a result of other indications. However, regardless of the reason for treatment, these drugs can be considered to lower blood pressure and are thus still relevant for the present study, which primarily focuses on blood pressure in itself and very little on the actual effects of treatment of hypertension.

Statistics

One important weakness of the sample used in Paper III is the limited number of subjects, primarily the result of a high mortality rate. The majority of participants with dementia and many with low blood pressure were unavailable for follow-up. However, when individuals who died but could nevertheless be evaluated for incident dementia were included, the number of participants with low blood pressure at baseline increased. As cross-sectional studies, such as the present Paper II, are of little value in establishing the direction of any demonstrated associations, longitudinal studies are of great importance. Longitudinal studies on very old individuals, however, are troublesome as they are subject to a high risk of bias because of the high mortality rate, and healthier subjects are more prone to be alive at follow-up. This was also the case in the present longitudinal analyses.

Clinical implications

The findings concerning declining blood pressure in advanced age, combined with the high prevalence of antihypertensive treatment in old people, and the observation that many individuals with low blood pressure were being treated with antihypertensive drugs, motivate improved monitoring of blood pressure and improved follow-up of the effects and side-effects of treatment in this age group. Unnecessary treatment of old individuals should be avoided, especially considering their sensitivity to adverse drug reactions. With more frequent follow-ups of blood pressure levels and symptoms, there is a greater chance of identifying any adverse effects of treatment.

It seems likely that some decline in blood pressure is to be expected as a part of the *normal aging process*, and it is important to consider this effect in relation to the possible existence of pathological causes for low blood pressure, which could be treated or prevented.

Blood pressure levels affect a number of outcomes, but not all of them have been considered in this thesis. When making clinical decisions, however, it is necessary to consider all these outcomes. Consequently, implications arising from this study have to be combined with results from other studies that have investigated more carefully, for example, the associations between blood pressure and stroke or heart failure in old age. The combined risk factor profile of each person also has to be considered together with the blood pressure levels, especially in old people who are often influenced by several risk factors and diseases simultaneously (see Figure 1 for reference), while taking into consideration that the role of other risk factors too might be altered in old age. In addition, many old individuals are treated as a matter of *secondary prevention* after a cardiovascular event has occurred, which already puts them at higher risk than middle-aged hypertensives who receive treatment primarily as a primary preventive measure.

Very old samples are overrepresented among the studies which have shown that low blood pressure is a risk factor for increased mortality and cognitive impairment or dementia. This implies that age probably influences the association. However, it seems unlikely that it is the actual chronological age that is the foundation of this influence, but rather 'biological age', perhaps in terms of frailty, disease and vessel changes etc. Thus, it would be misleading to suggest an age cut-off after which low blood pressure might become a risk factor for poorer outcomes, although high age might be an indicator of the increased probability of such associations.

Nonlinear associations illustrate the heterogeneity of very old individuals, as associations between both low and high blood pressure are present within the same age group. This emphasizes the importance of individual decisions and careful consideration of each elderly person's unique circumstances in the clinical setting. Perhaps there are two groups of very old people: one that includes

individuals who are healthier, and biologically younger than their age, who then have risks associated with hypertension similar to those of the younger old individuals and who benefit from a lower blood pressure; and one that includes those who are frailer due to disease or marked age-related physical and physiological changes, in whom low blood pressure is a risk factor or risk marker. The effects of antihypertensive treatment in this, postulated, second group are yet to be determined and as a result, one cannot rely on current guidelines for treatment of hypertension when it comes to frail very old individuals.

Generally, it is probably a mistake to apply the limits for hypertension strictly in the very old as optimal blood pressure levels possibly vary both with age and among people. Old individuals might require a somewhat higher blood pressure to sustain an adequate circulation and to avoid, for example, cerebral hypoperfusion. Treatment guidelines *cannot* be applied to very old individuals uncritically or routinely and the pros and cons of treatment, including the expected benefit of treatment based on NNT values or other measures, should be carefully evaluated in combination with the patient's own wishes. In patients with a short expected survival time, prevention of risk factors might be of little value and this should be considered.

No matter whether low blood pressure is a risk factor or a risk marker for mortality, and no matter whether low blood pressure precedes or follows a dementia disease, it can still be an important warning sign to the clinician that the individual is at greater risk of suffering several poor outcomes. It remains to be determined whether treatment of the hypotension per se would benefit these patients, but careful investigation and treatment of potential underlying disorders could possibly reduce their risk of adverse events.

Implications for further research

There are now quite a number of studies that have demonstrated associations between low blood pressure and mortality and cognitive impairment in old age, but the mechanisms behind these associations remain unclear. Future studies should focus on trying to more effectively identify factors that might explain these associations and that might be possible targets for treatment and prevention. Heart failure and cardiac arrhythmias are conditions that could mediate some of the effects of low blood pressure on poor outcomes, and should as such be considered in epidemiological studies. Careful diagnosis of these conditions is essential in these cases.

Many previous studies have not considered the presence of nonlinear associations with blood pressure, and it is possible that relations between low blood pressure and outcomes such as those investigated in this thesis could have been missed. It is important that future studies consider the possibility of such associations, not only regarding blood pressure but also other risk factors, such as BMI, where the existence of nonlinear trends has been implied.

Given the relatively large research base that indicates deviant associations with blood pressure, and other risk factors, and outcomes in very old individuals, it is important that this age group is included in epidemiological, and interventional, studies. It now seems apparent that knowledge derived from younger old populations cannot be directly applied to individuals of advanced age. Further, the very old represent quite a wide age range and what applies to the 85-year-olds might not be applicable to 95- or 100-year-olds. As a result, subgroup analyses based on age or age intervals should also be performed on the very old.

There are still gaps in the research regarding antihypertensive treatment in the very old, especially concerning frail very old individuals where there is no clear evidence. To better understand the benefits or hazards of treatment in these individuals, it would be of value to study the effects of treatment in different predefined subgroups of the very old population.

There is also a lack of intervention studies with long follow-up periods. Future interventional studies should also consider dementia or cognitive failure as important outcomes, and carefully investigate the presence of adverse effects from the studied drugs, including the impact on quality of life. Interventional studies of healthy very old populations might, however, be difficult to motivate ethically now that there is evidence of the positive effects of treatment in this group. Epidemiological studies investigating previous and current use of antihypertensive drugs might thus also be of value.

There are few effective treatments for *hypotension*, but interventional studies aimed at *raising* blood pressure in individuals with low blood pressure, by pharmacological or other means, and studying the influence of outcomes such as mortality and dementia should be considered.

One problem with performing longitudinal studies on very old individuals is the high mortality rate that not only reduces the size of samples but also potentially biases the samples towards the healthier individuals. Future longitudinal studies on the very old should address this by performing repeated follow-up investigations at shorter time intervals than in the present study, to increase the number of individuals participating in follow-ups. Studies with larger samples, longer follow-ups and studies covering large age spans of old people would be of value. Repeated follow-ups could also provide better information on the course of blood pressure as a risk factor and provide data on how blood pressure *change* influences the risk of mortality and morbidity.

Regarding cognitive outcomes specifically, more sensitive cognitive testing that can discover early signs of cognitive failure is important in trying to determine whether low blood pressure precedes or follows the cognitive impairment. A dementia diagnosis is a blunt instrument in this sense.

CONCLUSIONS

The present results, cross-sectional and longitudinal, suggest that mean blood pressure, both SBP and DBP, decreases in advanced age in the majority of the population, implying that blood pressure should not be expected to increase throughout life. Blood pressure also seems to have decreased with time from 1981 to 2005, indicating a cohort effect. Increased use of antihypertensive drugs might be one reason for the observed cohort effect, although there may also be other mechanisms such as changes in lifestyle factors and more effective treatment of other diseases associated with blood pressure.

A U-shaped association between SBP and mortality was demonstrated, which confirms results from previous studies that have shown both U-shaped associations and selective associations between low blood pressure and increased mortality, mostly in very old individuals. The optimal SBP for this age group could be above 140 mmHg on a population level.

This study further demonstrated a cross-sectional association between low blood pressure and cognitive impairment and dementia in the very old but longitudinal analyses indicated no relation between baseline blood pressure and cognitive decline or incident dementia. However, incident dementia and cognitive decline were associated with a greater blood pressure decline and lower blood pressure at follow-up. These findings to some extent imply that low blood pressure is an effect rather than a cause of dementia in the very old but this needs to be confirmed in further studies. Hypertension might not be a risk factor for dementia in this age group, at least not from a short-term perspective.

Taken together, the present study has demonstrated a number of somewhat paradoxical findings regarding blood pressure in advanced age compared to what has previously been shown for blood pressure in younger old age. The underlying causes of these inverted associations are largely undetermined, although there are several possible mechanisms. Underlying age- or disease-related physiological effects might at least partly explain these findings, and low blood pressure could primarily be a risk marker, rather than a risk factor. However, an independent effect of low blood pressure in itself cannot be excluded, as has also been demonstrated in the present study, and might even be considered likely in terms of poor blood circulation to vital parts of the body. The proper management of blood pressure, both high and low, in advanced age is still under debate but it can be concluded that careful monitoring of blood pressure levels and antihypertensive treatment is of utmost importance and cannot be neglected in the very oldest. Clinical decisions must be based on available evidence from very old individuals while also considering each unique individual's circumstances and total risk profile.

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Dedication

This thesis is dedicated to my late grandmother, *Kaarina Mikkola*, whose goodness and kindness will always motivate me to take good care of our elderly – because they deserve it.

The Finnish phrase at the beginning of this thesis – *tätä minä tiedän, ystävä* – translates to "this I know, friend" and is a reference to a game my grandmother and I used to play when I was little.

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