Blood Pressure in Very Old Age
Determinants, Adverse Outcomes, and Heterogeneity

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"Men dagen skrider mot nattens blund och brasan sjunker och mattas. Snart är försvunnen den korta stund, då ingen fattas."

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Abstract

**Background:** High blood pressure (BP) is the leading risk factor for disease and mortality worldwide. However, risks associated with high BP in very old age (≥ 80 or ≥ 85 years) are not entirely understood, as the majority of scientific studies have been performed with younger populations and existing scientific knowledge about very old individuals is sometimes contradictory. Results of previous studies of very old individuals suggest that the associations of BP with mortality and stroke differ with levels of physical and cognitive function. More studies that are representative of very old individuals, including individuals with multimorbidity, that are of adequate size, involve proper adjustment, and investigate non-linear associations, are needed to investigate these issues.

Systolic blood pressure (SBP) decline is common among very old individuals and has been shown to precede adverse events. Previous studies have shown that SBP change is associated with baseline SBP, age, and health-related factors, but determinants of SBP change have not been investigated using comprehensive, multivariate models.

The three main aims of this thesis were to investigate, in a sample of individuals aged ≥ 85 years, 1) determinants of SBP change, 2) the association of BP with mortality risk and whether this association differs with respect to gait speed and/or Mini-Mental State Examination (MMSE) score, and 3) the association of BP with stroke risk and whether this association differs with respect to the Barthel Activities of Daily Living (ADL) index and/or MMSE score.

**Methods:** The studies conducted for this thesis were based on data from the population-based Umeå 85+/Gerontological regional database study, which provided cross-sectional and longitudinal data on socioeconomic factors, medical conditions, drug prescriptions, and health-related assessments from 2000 to 2015. Participants were aged 85, 90, and ≥ 95 years, and lived in Västerbotten, Sweden, and Österbotten/Pohjanmaa, Finland. Follow-up assessments were conducted after 5 years. Mortality data were collected after 2 and 5 years, and stroke data were collected after 5 years, from death certificates, medical records, population registers, and the inpatient diagnosis register. Comprehensive multivariate models were developed to investigate determinants of SBP change using multiple linear regression, and to investigate associations of mortality and stroke risks with BP using Cox proportional-hazard regression models.

**Results:** Average (± standard deviation) baseline SBP was 146 ± 23 mm Hg, and average diastolic blood pressure (DBP) was 74 ± 11 mm Hg. Within 5 years, 61% of participants had died and 10% had had incident strokes.
Among participants followed for 5 years, the average annual SBP decline was 2.6 ± 5.4 mm Hg.

In a multivariate model, SBP decline was associated with later investigation year \((p = .009)\), higher baseline SBP \((p < .001)\), baseline antidepressant drug use \((p = .011)\), incident acute myocardial infarction during follow-up \((p = .003)\), use of a new diuretic drug during follow-up \((p = .044)\), and declining Barthel ADL index scores during follow-up \((p < .001)\).

In an age- and sex-adjusted analysis of the total sample, mortality risk was decreased in higher (vs. lower) BP categories \((SBP ≥ 165 vs. ≤ 125 mm Hg: hazard ratio [HR] \(0.50, p < .001\); DBP 70–74 vs. 75–80 mm Hg: HR 1.32, \(p = .031\)) \). In a comprehensively adjusted analysis of the total sample, SBP was not associated significantly with mortality risk. The associations of SBP with mortality in the gait speed < .5 m/s subcohort corresponded with those found in the total sample. In comprehensively adjusted analyses in the gait speed ≥ .5 m/s subcohort, mortality risk increased independently with higher (vs. lower) BP \((SBP ≥ 165 vs. 126–139 mm Hg: HR 2.13, p = .048; DBP > 80 vs. 75–80 mm Hg: HR 1.76, p = .026)\). In comprehensively adjusted analyses in the MMSE score subcohorts, SBP was associated significantly with mortality risk only in the 0–10 MMSE score subcohort; high and low SBP categories were associated independently with increased mortality risk, compared with an intermediary SBP category \((SBP ≥ 165 vs. 126–139 mm Hg; HR 4.54, p = .007; SBP ≤ 125 vs. 126–139 mm Hg: HR 2.23, p = .023)\). Higher BP was associated significantly with increased stroke risk in multivariate models \((SBP per 10 mm Hg increment: HR 1.19, p < .001; DBP per 10 mm Hg increment: HR 1.26, p = .013)\). SBP was not associated with stroke risk in participants with SBP < 140 mm Hg.

Interaction effects on the association with mortality were significant between SBP and gait speed (age- and sex-adjusted model: \(p = .031\)) but not between SBP and MMSE score. No interaction in the association with stroke was found between any BP measure and Barthel ADL index or MMSE score.

**Conclusion:** The decline in BP in very old age may be explained by health-related factors. Low BP may be a risk marker for short life expectancy, due to morbidity, in the general very old population and among very old individuals with low gait speeds. High BP seems to be an independent risk factor for mortality only in certain groups, which may be distinguished by high gait speed or very severe cognitive impairment. High SBP and DBP seem to increase stroke risk in very old age. These findings may contribute to a better understanding of the risks of adverse outcomes in very old individuals with different BP levels, the importance of comorbidity for these risks, and the etiology of SBP change.
Populärvetenskaplig sammanfattning

**Bakgrund:** Högt blodtryck är den största bidragande orsaken till sjukdom och död i världen. Man har ännu inte fastslagit om högt blodtryck ökar risken för sjukdom och död även i mycket hög ålder, vilket kan definieras som 80 år och äldre. Detta beror bland annat på att endast en liten andel av forskningen hittills har fokuserat på den här åldersgruppen. Mycket gamla människor skiljer sig från yngre på olika sätt som skulle kunna påverka riskerna med högt blodtryck. Till exempel är det vanligare med sjukdomar och att ha många samtidiga sjukdomstillstånd bland mycket gamla människor än i yngre åldersgrupper. Då andelen mycket gamla människor i befolkningen ökar kraftigt får dessa frågor allt större betydelse.

Det är vanligt med sjunkande blodtryck i mycket hög ålder, något som verkar föregå sjukdom och död. Tidigare studier har funnit att sjunkande blodtryck skulle kunna bero på ökande sjuklighet, högre ålder och högre begynnelseblodtryck. Man vet ännu inte vilka enskilda faktorer som bäst förklarar blodtrycksförändringen i mycket hög ålder, oberoende av andra faktorer.

Tidigare studier har visat att lägre blodtryck kan vara förenat med en ökad risk för tidig död bland mycket gamla människor. Det är oklart om risken för tidig död bättre kan förklaras av andra faktorer, s.k. störfaktorer. Störfaktorer kan till exempel vara sjukdomar som både påverkar blodtrycket och risken.

Fynd från tidigare studier av personer som är minst 65 år tyder på att sambandet mellan blodtryck och död kan skilja sig mellan grupper med hög eller låg gång hastighet, vilket används som ett ungefärligt mått på hälsotillståndet. Detta skulle även kunna ha betydelse för mycket gamla människor eftersom deras hälsotillstånd kan skilja sig mycket mellan individer. Man har också utrett huruvida sambandet mellan blodtryck och död skiljer sig mellan grupper med och utan kognitiv svikt, som till exempel kan bero på demenssjukdom, men inte kommit fram till entydiga resultat.

Ett fåtal studier har utrett strokerisken med högt blodtryck i mycket hög ålder. På grund av motsägelsefulla resultat är det ännu oklart om högt blodtryck ökar risken för stroke bland mycket gamla människor. Man har sett tecken på att sambandet mellan blodtryck och strokerisk skulle kunna skilja sig mellan grupper av mycket gamla människor med och utan kognitiv svikt, samt mellan grupper med och utan hjälpbehov i dagliga aktiviteter. Dagliga aktiviteter innefattar bland annat att tvätta sig, klä sig, gå på toaletten, äta och resa sig från en stol.

**Frågeställningar:** I den här avhandlingen undersöktes huvudsakligen tre frågeställningar. Den första var vilka faktorer som påverkar hur blodtrycks-
nivåerna förändras över tid i mycket hög ålder. Den andra frågeställningen var om olika blodtrycksnivåer är förenade med ökad risk för tidig död i mycket hög ålder och huruvida risken skiljer sig mellan grupper av mycket gamla människor med olika gånghastighet eller olika grader av kognitiv svikt. Den tredje frågeställningen var om olika blodtrycksnivåer är förenade med ökad risk för stroke i mycket hög ålder och om risken skiljer sig mellan grupper av mycket gamla människor med och utan kognitiv svikt eller hjälpbehov i dagliga aktiviteter. Även skillnader mellan gånghastighetsgrupper testades.

**Metod:** Avhandlingen bygger på befolkningsmaterialet Umeå85+/Gerontologisk regional databas (GERDA). Umeå85+/GERDA innehåller information från individer i åldrarna 85, 90 och 95 år och äldre, boende i Västerbotten, Sverige och Österbotten/Pohjanmaa, Finland. Informationen är insamlad vart femte år under perioden 2000-2015.

Umeå85+/GERDA innehåller information om socioekonomiska faktorer, sjukdomar och läkemedel. Informationen inhämtades med hjälp av ett standardiserat frågeformulär som deltagarna besvarade under ett hembesök, samt med hjälp av journaler, boendepersonal och anhöriga. Det gjordes även hälsorelaterade mätningar och tester under hembesöken, bl.a. av blodtryck och gånghastighet i vanlig takt. Skattningsskalorna Mini-Mental State Examination (MMSE) och Barthel Activities in daily living (ADL) index användes för att skatta kognitiv funktion respektive hjälpbehov i dagliga aktiviteter.

Deltagarna delades in i två gånghastighetsgrupper. Personer med högre gånghastighet (minst 0,5 m/s) utgjorde en grupp. I den andra gruppen var personer med lägre gånghastighet (under 0,5 m/s) och de som inte klarade av att genomföra testet på grund av bestående begränsningar av gångfunktionen.

Deltagarna grupperades också med avseende på olika grader av kognitiv svikt. Gruppindelningen baserades på MMSE-poäng; mycket svår kognitiv svikt (0-10 poäng), svår kognitiv svikt (11-17 poäng) och mild kognitiv svikt (18-23 poäng). Deltagare utan kognitiv svikt utgjorde en egen grupp (24-30 poäng).

Deltagarna delades även in i grupper med och utan hjälpbehov i dagliga aktiviteter, baserat på Barthel ADL index (under 20 respektive 20).

Blodtrycksförändring observerades över tiden mellan två Umeå85+/GERDA-insamlingar, vilket var 5 år. Dödsdatum och datum för stroke inhämtades från dödsbevis, befolkningsregister, journaler och sjukvårdens diagnoskodsregister i upp till 5 år.

Frågeställningarna utreddes med hjälp av statistiska metoder, baserat på materialet från Umeå85+/GERDA. Sambanden prövades med avseende på störfaktorer och skillnader mellan grupper.
Resultat: Förändringar av det systoliska blodtrycket undersöktes bland 297 deltagare. I genomsnitt sjönk blodtrycket med 2,6 mm Hg per år. För nästan två tredjedelar (62%) av deltagarna sjönk blodtrycket med minst 5 mm Hg på 5 år. Ungefär en fjärde del (26%) hade minst 5 mm Hg stigande blodtryck på 5 år.

Ett antal faktorer var förenade med förändring av det systoliska blodtrycket över 5 år, oberoende av varandra. Sjunkande systoliskt blodtryck var förenat med ett högre begynnelsesblodtryck, senare undersökningsår, att ha antidepressiv behandling, att få en hjärtinfarkt, att påbörja läkemedelsbehandling med diuretika eller få ökat hjälpbehov i dagliga aktiviteter. Man vet ännu inte vad som är orsak och verkan i dessa samband.

Frågeställningen om olika blodtrycksnivåer är förenade med ökad risk för tidig död undersöktes i ett urval av 806 deltagare. Inom 5 år avled nästan två tredjedelar (61%) av deltagarna. Risken för tidig död var mindre bland deltagare med högre blodtryck, jämfört med dem som hade lägre blodtryck. Största skillnaden uppmättes mellan deltagare med minst 165 mm Hg i systoliskt blodtryck, där risken var halverad, jämfört med dem som hade 125 mm Hg eller lägre. Detta samband verkar bero på störfaktorer, främst sjukdomar, som både orsakar lågt blodtryck och den ökade risken för tidig död.

Gånghastighetsgrupperna utgjordes av 312 deltagare med högre gångastighet och 433 med lägre gångastighet, varav 136 inte kunde genomföra mätningen på grund av bestående begränsning av gångfunktionen.

Sambandet mellan blodtryck och risken att dö inom 5 år verkade skilja sig mellan gångastighetsgrupperna. Gruppen med lägre gångastighet uppvisade samma samband som hela urvalet och hade ökad risk för tidig död med lägre blodtryck. Även här verkade sambandet förklaras av störfaktorer.

Personer med högre gångastighet uppvisade ett annat samband, där högre systoliskt blodtryck på minst 165 mm Hg var förenat med en fördubblad risk för tidig död, jämfört med 126-139 mm Hg. Högre diastoliskt blodtryck på över 80 mm Hg var också förenat med ökad risk för tidig död, jämfört med 75-80 mm Hg. Sambandet berodde inte på störfaktorer.


Särskilt gruppen med mycket svår kognitiv svikt uppvisade ett annorlunda samband mellan systoliskt blodtryck och risken för tidig död, jämfört med övriga deltagare. Bland dessa deltagare var risken för tidig död mer än fyrdubblad med höga blodtryck på minst 165 mm Hg, jämfört med 126-139
mm Hg. De med blodtryck 125 mm Hg eller lägre hade dubbelt så hög risk för tidig död, jämfört med 126-139 mm Hg. Dessa samband var oberoende av störfaktorer.

Frågeställningen om strokerisk med högt blodtryck utreddes i ett urval av 955 deltagare. Inom 5 år fick 94 deltagare en stroke, vilket motsvarar en av tio. Högre blodtryck var förenat med ökad risk för stroke, jämfört med lägre blodtryck. Risken att få en stroke inom 5 år var fördubblad bland deltagare med högt systolisk blodtryck på minst 160 mm Hg, jämfört med under 140 mm Hg, eller med höga diastoliska blodtryck på minst 90 mm Hg, jämfört med under 90 mm Hg. Sambanden var oberoende av en mängd andra riskfaktorer. Strokerisken med högt blodtryck verkade inte påverkas av gånghastigheten, den kognitiva nivån, eller hjälpbehovet i dagliga aktiviteter.

**Slutsatser:** Blodtrycket verkar sjunka hos de flesta i mycket hög ålder. Sjunkande systoliskt blodtryck kan till stor del förklaras av högre begynnelsesblodtryck, senare undersökningssår, att ha antidepressiv läkemedelsbehandling, att få en hjärtinfarkt, att påbörja läkemedelsbehandling med diuretika eller få ökat hjälpbehov i dagliga aktiviteter.

Lågt blodtryck verkar i mycket hög ålder vara ett tecken på olika underliggande sjukdomsprocesser, som ökar risken att dö inom 5 år. Detta samband verkar särskilt gälla personer med lägre gånghastighet, vilket kan vara ett tecken på sämre hälsa.

Högt blodtryck verkar endast vara förenat med ökad risk för tidig död i särskilda grupper, som kan utmärkas av högre gånghastighet eller mycket svår kognitiv svikt. Även lågt systoliskt blodtryck kan vara förenat med ökad risk för tidig död bland personer med mycket svår kognitiv svikt. I dessa grupper kan sambandet vara oberoende av störfaktorer.

Högre blodtryck verkar vara förenat med ökad risk för stroke i mycket hög ålder, oberoende av en mängd andra sjukdomstillstånd. Det finns sannolikt en gräns för hur lågt blodtryck som är gynnsamt med avseende på strokerisken, men det är ännu inte klarlagt var den gränsen går. Sambandet mellan högt blodtryck och strokerisk verkar inte skilja sig mellan grupper med olika hög gånghastighet, kognitiv nivå, eller hjälpbehov i dagliga aktiviteter.

Dessa fynd kan bidra till en bättre förståelse för blodtrycksförändring, risken med högt och lågt blodtryck i mycket hög ålder samt hälsotillståndets betydelse för dessa risker.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CALIBER</td>
<td>Cardiovascular Research using Linked Bespoke Studies and Electronic Health Records</td>
</tr>
<tr>
<td>CHS</td>
<td>Cardiovascular Health Study</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>EPESE</td>
<td>Established Populations for Epidemiological Studies of the Elderly</td>
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<td>GDS</td>
<td>Geriatric Depression Scale</td>
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<tr>
<td>GERDA</td>
<td>Gerontological Regional Database</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HYVET</td>
<td>Hypertension in the Very Elderly Trial</td>
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<tr>
<td>LASA</td>
<td>Longitudinal Ageing Study Amsterdam</td>
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<td>MAP</td>
<td>Mean arterial pressure</td>
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<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<tr>
<td>MNA</td>
<td>Mini-Nutritional Assessment</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NOMAS</td>
<td>Northern Manhattan Study</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PP</td>
<td>Pulse pressure</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
</tbody>
</table>
List of original papers


IV. Weidung B, Toots A, Nordström P, Carlberg B, Gustafson Y. Systolic blood pressure decline in the very old is explained by deteriorating health: Longitudinal changes from Umeå 85+/GERDA. Manuscript.

The original papers are reprinted in this thesis with the kind permission of the respective publishers.
Introduction

Overview

High blood pressure (BP) is the leading risk factor for disease and mortality worldwide.¹ However, whether these risks pertain to the very old population is unclear. Adverse outcomes associated with high BP may be influenced by age-related physiological changes, morbidity, and polypharmacy. Poor health may also increase the risk of adverse reactions to BP-lowering drug treatments, which may cause more suffering than benefit.² To avoid unnecessary interventions, determination of the properties of the associations between BP and adverse outcomes in very old age is important.

BP levels change throughout life. Longitudinal BP change may be physiological or a consequence of disease. To better separate these two etiologies, the study of normal BP changes is important. The etiology of such change may be understood by identifying the factors associated with it.

The population is aging, due to increasing life expectancy and declining fertility rates.³ In Europe, the proportion of individuals aged ≥ 80 years was 5% in 2015 and is expected to double before 2050.⁴ Very old age may be defined as ≥ 80 or ≥ 85 years. As the population of very old individuals grows, health care systems face the challenge of accommodating its specific needs.

Blood pressure

Physiology and definitions

Arterial BP is measured in relation to the pulse wave, which is created as the contractions of the left ventricle of the heart eject blood into the proximal aorta. The pulse wave travels along the arteries and propels the blood forward. BP increases toward the peripheral arteries due to increasing arterial stiffness. Due to impedance mismatch at distal reflection sites, the pulse wave is reflected at the terminations of arteries into smaller arterioles and travels back to the heart.⁵,⁶

Systolic blood pressure (SBP) is the peak pressure of the blood in the arteries during the passing pulse wave, and diastolic blood pressure (DBP) is the pressure between pulse waves. Pulse pressure (PP) is the difference between SBP and DBP. In other words, SBP and DBP are the upper and lower limits of the PP generated by the passing pulse wave. Mean arterial pressure (MAP) is the average value during the cardiac cycle and can be approximated as the sum of two-thirds DBP and one-third SBP. The World
Health Organization defines hypertension as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg in individuals not taking antihypertensive medication.7

BP may be measured directly using an intra-arterial catheter, or indirectly using a sphygmomanometer, together with a stethoscope or digital device. The indirect method generally produces higher SBP and lower DBP measures compared with the direct method.8 BP may be measured on a single occasion or continuously over several days. In this thesis, unless otherwise stated, BP signifies arterial BP measured on a single occasion by sphygmomanometer in the brachial artery, which is the established measurement site for clinical applications. BP measurement is affected by several factors, including posture, situation, rest time before measurement, and calibration of the measuring device.8,9

Average blood pressure in the very old population

Average BP in very old individuals varies greatly among studies. SBP is generally higher among very old women than among men10-14 and may differ regionally.15 Evidence of temporal trends and a cohort effect, in which average BP is lower in later investigation years and younger birth cohorts, has also been reported.10,15-19 The following text describes average BP among individuals aged ≥ 80 years in population-based studies central to this thesis, which are summarized in Table 1.

The Umeå 85+/Gerontological Regional Database (GERDA) study includes individuals aged 85, 90, and ≥ 95 years from the regions of Västerbotten, Sweden, and Österbotten/Pohjanmaa, Finland. Recruitment has been conducted every 5 years since 2000. This study is described in further detail in the Methods section. A previous study showed that SBP declined 0.44 mm Hg per year between 1981 and 2005 in a combined sample of 397 Umeå 85+/GERDA study participants and 341 participants in the U70 study, which examined a population-based sample of individuals aged ≥ 70 years.17 Among Umeå 85+/GERDA participants, BP (SBP/DBP) decreased from 148/75 to 143/72 mm Hg between 2000 and 2005. Sex differences were not presented, but the sample included 75% women in 2000 and 71% in 2005. BP was measured in the supine position. In this study, BP was measured twice in 84 individuals.

The H70 study14 included individuals aged 70 years living in Göteborg, Sweden, in 1971–1972 and 1976–1977. Average BP was 151/79 mm Hg among men and 155/79 mm Hg among women at the age of 85 years. No significant difference in SBP or DBP was found between sexes after the age of 82 years.

The population-based Tromsø Study10 included inhabitants of Tromsø, Norway. Average SBP and DBP were lower in younger birth cohorts. Among
Table 1. Population characteristics for population-based cohort studies of individuals aged ≥ 80 years

<table>
<thead>
<tr>
<th>Study a</th>
<th>Region</th>
<th>Age, years</th>
<th>Investigation year</th>
<th>Birth cohort</th>
<th>N</th>
<th>Position for BP measurement</th>
<th>Mean BP, systolic/diastolic, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umeå 85+/GERDA</td>
<td>Västerbotten, Sweden, and Österbotten/Pohjanmaa, Finland</td>
<td>85, 90, ≥ 95</td>
<td>2000</td>
<td>1915, 1910, ≤ 1905</td>
<td>224</td>
<td>Supine</td>
<td>148/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2005</td>
<td>1920, 1915, ≤ 1910</td>
<td>229</td>
<td>Supine</td>
<td>143/72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2001</td>
<td>1912–1921</td>
<td>–</td>
<td>Seated</td>
<td>151/85 157/84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2001</td>
<td>1912–1921</td>
<td>–</td>
<td>Seated</td>
<td>151/85 157/84</td>
</tr>
<tr>
<td>Helsinki Ageing</td>
<td>Helsinki/Helsingfors and Vantaa/Vanda, Finland</td>
<td>80, 85</td>
<td>1989</td>
<td>1909</td>
<td>111</td>
<td>–</td>
<td>158/85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1989</td>
<td>1904</td>
<td>169</td>
<td>–</td>
<td>155/77</td>
</tr>
<tr>
<td>Vantaa 85+</td>
<td>Vantaa/Vanda, Finland</td>
<td>≥ 85</td>
<td>1991</td>
<td>≤ 1906</td>
<td>521</td>
<td>Seated</td>
<td>144/80 150/82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1991</td>
<td>≤ 1892</td>
<td>561</td>
<td>Seated</td>
<td>144/83 154/84</td>
</tr>
<tr>
<td>Tampere</td>
<td>Tampere/Tammerfors, Finland</td>
<td>≥ 85</td>
<td>1977–1978</td>
<td>≤ 1892</td>
<td>599</td>
<td>Seated</td>
<td>155/77</td>
</tr>
<tr>
<td>Leiden 85+</td>
<td>Leiden, the Netherlands</td>
<td>85</td>
<td>1997–1999</td>
<td>1912–1914</td>
<td>1159</td>
<td>Seated</td>
<td>147/74</td>
</tr>
<tr>
<td>Jerusalem Longitudinal Study</td>
<td>Western Jerusalem, Israel</td>
<td>85</td>
<td>2005–2006</td>
<td>1920–1921</td>
<td>213</td>
<td>Supine</td>
<td>156/65</td>
</tr>
<tr>
<td>Framingham Heart</td>
<td>Framingham, Boston, USA</td>
<td>≥ 80</td>
<td>2002–2008</td>
<td>≤ 1928</td>
<td>1088</td>
<td>Seated</td>
<td>146/74 146/74</td>
</tr>
<tr>
<td>NHANES</td>
<td>Primary sampling units of metropolitan statistical areas or groups of counties in the USA</td>
<td>≥ 80</td>
<td>1988–1994</td>
<td>≤ 1914</td>
<td>1026</td>
<td>Seated</td>
<td>148/61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1999–2004</td>
<td>≤ 1924</td>
<td>1048</td>
<td>Seated</td>
<td>140/59</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; GERDA, Gerontological Regional Database; EPESE, Established Populations for Epidemiological Studies of the Elderly; NHANES, National Health and Nutrition Examination Survey.

aPopulation characteristics for the Umeå 85+/GERDA study from Molander and Lövheim,17 for the H70 study from Lernfelt and Svanborg,14 for the Tromsø Study from Hopstock et al.,10 for the Helsinki Ageing Study from Strandberg and Tilvis,20 for the Vantaa 85+ Study from Rastas et al.,12 for the Tampere study from Mattila et al.,11 for the Leiden 85+ Study from van Bemmel et al.,21 for the Jerusalem Longitudinal Study from Jacobs et al.,22 for the Framingham Heart Study from Mitchell et al.,23 for the EPESE project from Satish et al.,13 and for the NHANES from Bromfield et al.19
participants aged 80–89 years, average SBP decreased significantly between 1994–1995, 2001, and 2007–2008 among women (from 169 to 159 mm Hg), but not among men. Average DBP decreased from 90 to 81 mm Hg among women and from 85 to 82 mm Hg among men.

The Helsinki Ageing Study was a population-based prospective cohort study of individuals aged 65, 75, 80, and 85 years living in Helsinki/Helsingfors and Vantaa/Vanda, Finland, in 1988. Average SBP in 1989 was 158 mm Hg among 80-year-olds and 155 mm Hg among 85-year-olds. The proportions of women in these cohorts were 74% and 79%, respectively.

The Vantaa 85+ Study was a prospective, longitudinal population-based study of individuals aged ≥ 85 years residing in Vantaa/Vanda, Finland, in 1991. Average BP in 1991 was 144/80 mm Hg among men and 150/82 mm Hg among women.

A population-based study investigated individuals aged ≥ 85 years residing in Tampere/Tammerfors, Finland, in 1977–1978. Average BP in 1977–1978 was 154/84 mm Hg among women and 144/83 mm Hg among men.

The population-based Leiden 85+ Study examined average BP among very old individuals. It included 85-year-old residents of Leiden, the Netherlands, from the 1912–1914 birth cohorts. At the age of 85 years, average BP was 155/77 mm Hg. The sample included 66% women.

The Jerusalem Longitudinal Study was a prospective observational study of residents of western Jerusalem, Israel. The cohort was highly heterogeneous in origin. The third wave included individuals aged 85 years in 2005–2006. At this age, average BP was 147/74 mm Hg. The sample included 55% women.

The Framingham Heart Study originally included 5209 individuals without previous cardiovascular disease living in Framingham, MA, USA, in 1948. It has been expanded with new cohorts. Average BP was presented for second- and third-generation participants aged ≥ 80 years; it was 156/65 mm Hg in 2002–2008, measured in the supine position.

The Established Populations for Epidemiological Studies of the Elderly (EPESE) project was a population-based, longitudinal study of inhabitants aged ≥ 65 years in East Boston, MA; New Haven, CT; Iowa and Washington counties, IA, and Piedmont, NC; USA. BP was measured in 1981–1987 and 1986–1987. Among participants aged ≥ 85 years, average BP was 146/74 mm Hg in men and the same in women.

The National Health and Nutrition Examination Survey (NHANES) is a program of studies investigating health in the USA. In a study of 3238 NHANES participants aged ≥ 80 years, average BP decreased from 147/70 mm Hg in 1988–1994 to 140/59 mm Hg in 2005–2010. The proportions of
women in different time periods ranged from 63% to 65%. Individuals living in residential care facilities were excluded.

Although average BP in very old individuals differs among studies, SBP is consistently in the hypertensive range. The prevalence of hypertension may differ between high- and low-income countries. The NHANES also presented the prevalence of controlled hypertension among very old individuals, which also seemed to be increasing, from 69% in 1988–1994 to 77% in 2005–2010.

**Average longitudinal blood pressure changes in the very old population**

SBP increases with age and seems to peak on average around the age of 75 years, with great variation within and among study populations. DBP may peak at a younger age. In contrast to the trend in younger populations, BP seems to be declining in very old populations. The average SBP change (ΔSBP) in very old age may be −1.5 to −2.9 mm Hg/year, according to findings from the Leiden 85+ Study, a previous Umeå 85+/GERDA study, and the Helsinki Ageing Study. The average DBP change may be −1.0 to −1.4 mm Hg/year. Although mean SBP trajectories seem to be declining, not every individual shows declining SBP. About two-thirds (69%) of very old individuals may show SBP declines of ≥5 mm Hg over 5 years, according to the findings of the Umeå 85+/GERDA study. In the Helsinki Ageing Study, SBP declined over 5 years in 33% of men and 60% of women aged 85 years.

Declining SBP in old age may precede adverse outcomes, such as mortality, cardiovascular events, and dementia. These associations may be causal or effects of other factors causing both the decline and the adverse events. A study from the EPESE projet showed associations of SBP decline with later all-cause mortality risk, cardiovascular mortality, and cardiovascular events, which depended on adjustments or were better explained by other factors, particularly impairment in activities of daily living (ADL). The Leiden 85+ Study showed a greater mortality risk with declining SBP among care facility residents compared with other participants.

**Determinants of blood pressure**

BP is determined by a combination of cardiovascular factors. The amplitude of the pulse wave is determined by left ventricle stroke volume, ejection velocity, large artery stiffness, pulse wave reflection, and heart rate. DBP is determined by large artery stiffness and vascular resistance, which involves the ability of small arteries to accept runoff of blood from the
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aorta.25 These factors are controlled by a complex interplay between long- and short-term regulatory mechanisms of the autonomic nervous system, kidneys, adrenal glands, pituitary glands, lungs, heart, and local tissues.37 The factors with the largest impacts on BP and BP dysregulation in very old age have not been identified clearly. Furthermore, the effects of individual factors may not be independent of each other.

**Arterial stiffening**

Arterial stiffness is a consequence of age-related changes in the proximal arteries. These changes include degeneration of elastin fibers in the media, which rupture due to repeated strain from the pulse wave. Over time, the vessels lose some elasticity due to accumulated damage. Due to the rupture of elastin fibers, the vessel is dilated and the media is remodeled with an increase in more-rigid collagen fibers.5,6

Increased large artery stiffness may influence BP in several ways. First, the pulse wave amplitude and resulting SBP may be increased in the aorta. Second, decreased elastic capacity of the aorta may also cause DBP to decrease due to greater peripheral runoff of blood during systole.25 Third, increased arterial stiffness causes increased pulse wave velocity, which affects the timing of the forward and reflected pulse waves and pressure amplification at different levels of the arterial tree. In addition, the pulse wave may be reflected to a lesser extent due to decreased impedance mismatch at distal reflection sites, as the stiffness of the proximal arteries approaches that of more distal ones.5 Finally, stiffness in the carotid arteries may impair baroreceptor sensitivity, which interferes with the regulatory intrinsic reflexes of the autonomic nervous system.38

**Determinants of average blood pressure in very old individuals**

BP is associated with age-related changes, diseases, medication use, and lifestyle factors, which may differ in very old and younger populations. Common age-related changes that may influence BP levels include increased arterial stiffness39,40 and decreased renin level,39,41 aldosterone levels,39,41 and glomerular filtration rate.39,41,42

Common diseases in very old age that may impair BP regulation39 include renal disorders,43-44 heart failure,45,46 ischemic heart disease,47,48 cerebrovascular disease,49,50 diabetes mellitus,51 cancer,52 obstructive sleep apnea,53 chronic obstructive pulmonary disease (COPD),54 cognitive impairment,55-57 and depressive disorders.58 Less common causes include primary aldosteronism,59,60 Cushing’s disease,60 thyroid disorders,60,61 aortic calcification,62 and tachycardia.5 Autonomic dysfunction is common with hypertension and heart failure,63 and may cause decreased heart rate.
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variability, increased BP variability, or orthostatic hypo- or hypertension.

Medications that may affect BP levels include non-steroidal anti-inflammatory drugs (NSAIDs), steroids, antidepressants, and neuroleptics. Lifestyle factors that may affect BP levels include dietary salt intake, alcohol consumption, waist circumference and body mass index (BMI), physical activity, sedentary behavior, and smoking. Pain may increase BP levels.

Determinants of longitudinal blood pressure changes

The age-related increase in SBP before very old age and simultaneous decline in DBP are likely consequences of arterial stiffening, but this factor may not explain SBP decline in very old age. Findings from previous population-based studies suggest that health-related factors are associated with SBP decline. However, the ability of factors related to individual diseases, drugs, and health-related assessments to predict ∆SBPs independently of each other is unclear.

A previous study conducted with a combined sample from the Umeå 85+/GERDA study and the population-based U70 study showed that declining SBP was associated with older age, male sex, and higher baseline SBP, which were all of the investigated factors. In the Helsinki Ageing Study age, SBP, health status after 5 years, and decreasing blood lipid levels were associated independently with declining SBP over 5 years. A multivariate analysis conducted as part of a substudy from the EPESE project showed that age, geographic location, baseline SBP, and self-rated health were associated independently with SBP decline, but that hospitalization in the previous year, BMI, smoking status, ADL dependency, sex, ethnicity, and antihypertensive medication use were not.

Findings from less-adjusted analyses suggest that SBP decline is also associated with medication use, antihypertensive medication use, poor health, depressive disorder, anxiety, ventricular hypertrophy, socioeconomic status, and transfer to a care facility. SBP may also decline with Mini-Mental State Examination (MMSE) score. Whether these associations are independent of other factors is unknown.

Blood pressure and adverse outcomes

High BP was the leading risk factor for disease and mortality worldwide in 2015, with 212 million disability-adjusted life years attributable to this condition. High BP is a risk factor for cerebrovascular disease, ischemic heart disease, heart failure, atrial fibrillation, aortic aneurysm, peripheral artery disease, dementia, chronic kidney disease, ophthalmological
disorders, and quality of life issues among individuals aged ≥ 65 years.\textsuperscript{39,85} However, whether these risks pertain to the very old population is unclear.

The development of cardiovascular disease in old age has been suggested to be a manifestation of life-long cumulative exposure to vascular risk factors, including hypertension.\textsuperscript{85,86} The mechanism linking hypertension to cardiac outcomes is thought to involve arterial stiffness, increased cardiac load, hypertrophy, shortened diastolic period, and ischemia, even in the absence of coronary artery disease.\textsuperscript{6,40,45} Highly perfused organs, such as the brain and kidney, may sustain damage to the microcirculation as the arteries' ability to cushion the pulsatile energy of the pulse wave is decreased with greater arterial stiffness.\textsuperscript{5,6,40,87,88} The damage to the microcirculation may involve ischemia, microinfarctions, hypoperfusion, and inflammation.\textsuperscript{5,6,40,87,88}

**Mortality risk**

All-cause mortality risk is a comprehensive estimation of the risk of any condition or event with a fatal outcome. The leading causes of death in 2012 were stroke and ischemic heart disease, including acute myocardial infarction (AMI).\textsuperscript{89}

**Observational studies**

In contrast to findings in younger populations,\textsuperscript{13,90} those from population-based observational studies of very old people indicate an inverse association between BP and mortality risk; low SBP and DBP are associated with increased mortality risk compared with high BP.\textsuperscript{11–13,21,22,28,91–93} In addition, the EPESE project\textsuperscript{13} and Umeå 85+/GERDA\textsuperscript{93} studies found non-linear associations between SBP and mortality, where mortality risk was increased with both high and low SBP.

The inverse association between SBP and mortality risk was independent of confounders in the Tampere,\textsuperscript{11} Vantaa 85+,\textsuperscript{12} Umeå 85+/GERDA,\textsuperscript{93} and EPESE project\textsuperscript{13} studies and in one Leiden 85+ Study.\textsuperscript{21} In contrast, this association was dependent on confounders in the Jerusalem Longitudinal Study,\textsuperscript{22} in two studies from Leiden,\textsuperscript{28,91} and in the Longitudinal Ageing Study Amsterdam (LASA).\textsuperscript{92} The inverse association of mortality with DBP was independent of adjustments in the Tampere,\textsuperscript{11} Umeå 85+/GERDA,\textsuperscript{93} and Vantaa 85+\textsuperscript{12} studies, LASA,\textsuperscript{92} and one Leiden 85+ Study.\textsuperscript{21} In one study from Leiden,\textsuperscript{91} the association was not independent of adjustments.

The LASA\textsuperscript{92} is a prospective population-based cohort study of residents of Amsterdam, the Netherlands, aged ≥ 55 years in 1992–1993. BP measurements were introduced in 1995–1996 for 1466 participants aged ≥ 65 years, of whom 464 participants were aged ≥ 80 years. Participants were
followed for up to 17 years. The association of BP and mortality risk was investigated in relation to age groups and indicators of physical and cognitive function.

The different Leiden 85+ studies have produced different results. The first study examined mortality risk in 599 participants aged 85 years who were followed for 5–7 years, and revealed independent inverse associations between combined measures of categorized SBP and DBP and mortality risk. It also showed a tendency toward increased mortality risk with high DBP, indicating a non-linear association. The second Leiden 85+ Study investigated mortality risk and SBP in 271 participants aged 90 years who were followed for 5 years. Mortality risk increased with SBP ≤ 150 mm Hg compared with SBP > 150 mm Hg. This association was not independent of adjustments. An earlier population-based study of Leiden inhabitants included 835 individuals aged ≥ 85 years in 1986 who were followed for 5–7 years. In that study, inverse associations were found between categories of SBP and DBP, respectively, and mortality risk, which were not independent of adjustments.

Although these observational studies have revealed inverse associations between BP and mortality risk, whether these associations are independent of adjustment for confounders remains unclear. The linearity or non-linearity of the associations is also unclear, due to mixed findings.

**Interventional studies**

The largest randomized controlled trial (RCT) to investigate these issues in very old individuals to date, the Hypertension in the Very Elderly Trial (HYVET), demonstrated a significant decrease in total mortality with antihypertensive treatment to a target BP of 150/80 mm Hg, compared with placebo, in individuals aged ≥ 80 years. In contrast, a large systematic review from the Cochrane Collaboration and a meta-analysis of RCTs conducted with patients aged ≥ 80 years, including the HYVET, showed that BP reduction by antihypertensive treatment was not associated with a reduced mortality risk in individuals aged ≥ 80 years. Specific causes of mortality, including coronary and cardiovascular death, were not significantly associated with BP reduction by antihypertensive treatment. However, significant heterogeneity was detected between the findings of the HYVET and the other RCTs, which was attributed to variation in the degree of BP reduction and intensity of therapy. In addition, treatment effects were significant only among participants with, and not among those without, previous antihypertensive treatment, indicating a possible negative effect of treatment discontinuation, rather than a treatment benefit.

The HYVET sample may not be representative of very old individuals with multimorbidity, due to the exclusion of individuals with medical conditions...
(recent hemorrhagic stroke, treatment-requiring heart failure, disturbed serum creatinine or serum potassium level, gout, and dementia) and those requiring nursing care. This exclusion resulted in the underrepresentation of individuals in poor health, as demonstrated by comparisons of study sample characteristics between the HYVET and the Jerusalem Longitudinal Study and NHANES. However, investigations of the importance of a frailty index in the HYVET sample showed no interaction with treatment effect.

**Stroke risk**

Stroke is defined as an episode of acute neurological dysfunction caused by focal cerebral, spinal cord, or retinal infarction or intracerebral hemorrhage, excluding trauma, with a duration ≥ 24 h. Stroke was ranked as the second most common cause of death and disability in 2015, following ischemic heart disease. About 10–20% of individuals aged ≥ 80 years have had a previous stroke. Reports of stroke incidence vary among studies; most studies have shown that this incidence is 11–32/1000 person-years among very old individuals, but an incidence of 57/1000 person-years was reported in the H70 study. Very old individuals have more severe strokes, longer hospital stays, and a lesser likelihood of being discharged to their original residences compared with younger populations. In addition, they have greater risks of stroke-related mortality and disability compared with younger old people.

High BP is the strongest risk factor for stroke in the general adult population. Other risk factors include current smoking, abdominal obesity, unhealthy diet, low physical activity, diabetes mellitus, high alcohol consumption, psychosocial stress, depressive disorder, cardiac causes (a composite of atrial fibrillation or flutter, previous AMI, rheumatic valve disease, and prosthetic heart valve use), and blood lipid unbalance. However, whether risk factors for stroke in very old age differ from those in the general adult population has not been determined.

**Observational studies**

Several observational studies of very old individuals have shown no association between BP and stroke risk, but one study did reveal an association with SBP.

A substudy of 513 participants from the Leiden 85+ Study showed that SBP and DBP were not associated with 5-year stroke risk, but revealed a significant inverse association between PP and stroke risk. Adjustments were made for sex, cardiovascular disease, diabetes mellitus, antihypertensive medication, and smoking.
A substudy of the Framingham Heart Study,\textsuperscript{121} which investigated stroke risk related to cardiovascular conditions in the original cohort, showed that among the potential risk factors of hypertension, coronary heart disease, cardiac failure, and atrial fibrillation, only atrial fibrillation was associated significantly with stroke risk among individuals aged 80–89 years (2084 person-bienniums). The relative risk of stroke associated with hypertension was found to decrease with age.

The Northern Manhattan Study (NOMAS)\textsuperscript{120} was designed to investigate the impacts of risk factors for vascular disease in initially stroke-free individuals aged > 39 years living in Manhattan, NY, USA. According to findings from a substudy of 562 NOMAS participants aged ≥ 80 years,\textsuperscript{120} neither hypertension nor diabetes mellitus contributed significantly to the population-attributable risk of stroke. The median follow-up time was 12 years.

The H70 study\textsuperscript{103} investigated risk factors for stroke in 494 individuals aged ≥ 85 years living in Göteborg, Sweden, and found that SBP was associated with 3-year stroke risk. SBP and female sex were the only significant risk factors for stroke among the investigated factors, which also included treated hypertension, DBP, diabetes mellitus, high cholesterol, overweight, smoking, atrial fibrillation, AMI, and alcohol consumption.

Furthermore, a large meta-analysis of observational studies from the Prospective Studies Collaboration\textsuperscript{122} found significant associations of SBP and DBP with the risk of fatal stroke, particularly hemorrhagic stroke, in participants aged 80–89 years. The associations were significant in men and women separately. The meta-analysis excluded individuals with previous vascular disease.

A study based on observational data from the Cardiovascular Research using Linked Bespoke Studies and Electronic Health Records (CALIBER) study\textsuperscript{123} investigated associations between BP and adverse outcomes in individuals aged ≥ 30 years in 1997–2010 who were initially free of cardiovascular disease. Findings from this study indicate that SBP was associated with an increased risk of ischemic, but not hemorrhagic, stroke in individuals aged ≥ 80 years. DBP was associated with both ischemic and hemorrhagic stroke.

Previous studies have produced contrasting results regarding the association between BP and stroke in very old individuals. Due to small samples, lack of adjustment for confounders, and/or exclusion criteria, whether high BP is a risk factor for stroke in very old individuals remains unclear. Findings of some studies suggest that the risk of stroke associated with BP is attenuated with increasing age.\textsuperscript{120–123}
**Interventional studies**

The HYVET\(^94\) found significant reductions in the risk of fatal stroke, but not stroke overall (fatal and nonfatal), with antihypertensive treatment. The large systematic review from the Cochrane Collaboration\(^95\) and the meta-analysis of RCTs\(^96\) conducted with patients aged ≥ 80 years showed that BP reduction with antihypertensive treatment was associated with a 25–35% reduced risk of stroke (fatal or nonfatal), but not with a reduced risk of fatal stroke, among individuals aged ≥ 80 years. As previously stated, significant heterogeneity exists between the results of the HYVET and other RCTs, which may be due to differences related to methodologies and exclusion criteria.\(^39,96\)

**Other adverse outcomes**

Other adverse outcomes of high BP may also differ with respect to age. Cardiovascular diseases, such as heart failure, atrial fibrillation, ischemic heart disease, chronic kidney disease, and peripheral artery disease, are highly prevalent among very old individuals.\(^42,45,47,124-126\) According to the CALIBER study,\(^123\) SBP is associated with increased risks of stable angina pectoris, AMI, heart failure, and peripheral artery disease in individuals aged ≥ 80 years. In contrast, unstable angina pectoris, transient ischemic attack, and abdominal aorta aneurysm were not associated with SBP in this age group. DBP was associated with stable angina pectoris, AMI, heart failure, transient ischemic attack, and abdominal aorta aneurysm, but not with unstable angina pectoris or peripheral artery disease.

The Cochrane review of RCTs\(^95\) documented a reduction in total cardiovascular mortality and morbidity (a combined measure of coronary heart disease and cerebrovascular morbidity and mortality) associated with antihypertensive treatment in individuals aged ≥ 80 years. The meta-analysis of RCTs in patients aged ≥ 80 years showed that antihypertensive treatment reduced the occurrence of cardiovascular events and heart failure, but not coronary events.\(^96\)

Dementia disorders, such as Alzheimer’s disease, are common among very old individuals and may affect about one-fourth to one-third of those aged ≥ 85 years.\(^127,128\) In very old individuals, dementia usually includes cerebrovascular pathologies, such as infarctions, microbleeds, and white matter lesions.\(^87\) Previous findings suggest that mid-life hypertension is a stronger risk factor than late-life hypertension for cognitive decline and dementia.\(^87,129-131\) Furthermore, BP has been found to decrease several years before the appearance of clinical symptoms.\(^36,134,132\) In very old age, low BP may be associated with cognitive impairment.\(^29,56,129\)
Some adverse outcomes, such as dementia, may result from long-standing hypertension and other cardiovascular risk factors, in which case these pathologies may be independent of BP levels in very old age. Stroke may develop after a relatively short exposure time and is thus a highly relevant adverse outcome of BP in the very old population.\textsuperscript{122} Several adverse outcomes, such as atrial fibrillation,\textsuperscript{124} ischemic heart disease,\textsuperscript{133} and heart failure,\textsuperscript{134} may be fatal and as such are included in all-cause mortality. This thesis focuses on mortality and stroke risk. However, other adverse outcomes of BP are highly relevant in very old age and should not be ignored.

\textit{Age-related differences with relevance for adverse outcomes of blood pressure}

Associations between BP and adverse outcomes have been established in younger populations, but very old populations differ from these populations in ways that may influence these associations. Due to these differences, results from younger age groups may not be directly applicable to the very old population.

BP dysregulation due to increased arterial stiffness and other age-related morbid conditions has already been mentioned. The increased levels of morbidity and polypharmacy among very old individuals may also interact with BP in the associations with adverse outcomes.\textsuperscript{39}

Older age is related to reductions in organ capacity reserves and decreased responsiveness in regulatory functions, which may cause health status to fluctuate or to deteriorate suddenly in response to a relatively minor insult, such as infection.\textsuperscript{135} This relative instability in health status may cause baseline measurements to seem invalid after a shorter time period than in younger populations.

In addition, the shorter average life expectancy in the very old population compared with younger populations leads potential adverse outcomes associated with BP to be more relevant over a short time period, compared with long-term risks.

Very old individuals are also likely to have different risk factor profiles compared with younger populations, which may confound the associations with adverse outcomes. For example, very old stroke patients are more likely than younger stroke patients to have atrial fibrillation, heart failure, and hypertension at hospital admission, but they have lower prevalences of diabetes mellitus and hyperlipidemia.\textsuperscript{111,113} Finally, very old individuals may constitute a selected population of individuals with low vulnerability to traditional risk factors, which may have allowed them to reach very old age.
Heterogeneity within the very old population

Although the designation “very old age” seems to define a clinically relevant group, age alone may not be an optimal indicator of risks of adverse outcomes, due to differences within the very old population. The very old population is heterogeneous in terms of health status, which can range from terminal disease, strong dependency on help from others, and complex comorbidity to high function, independence, and long life expectancy.

Results from previous studies suggest that the associations of BP with mortality and stroke differ according to indicators of health status. Gait speed at usual pace, measured over a short distance, has emerged as a possible indicator of health status. It is an objective assessment that integrates physical function with multiple system functions, including circulation, respiration, and cognition. Gait speed at usual pace is associated with BP and increased risks of adverse outcomes, such as mortality and stroke.

The MMSE is a screening test for cognitive impairment. Its 11 items are used to test different cognitive domains, such as orientation, memory, attention, execution, language, calculation, and constructional ability. MMSE scores have been associated with BP, mortality risk, and stroke risk. In general, episodic and working memory decline in old age, although these declines vary among individuals. Cognition may also be impaired by dementia, which in very old age usually involves cerebrovascular pathology. MMSE scores may therefore be indicators of the extent of cerebrovascular pathology among very old individuals.

ADL refers to basic self-care tasks and other fundamental activities in daily living, such as dressing, walking, and using the toilet. Dependency in ADL is associated with chronic disease, antihypertensive treatment, arterial stiffness, and cerebrovascular pathology, indicating that it plays an important role in health status in general, and cardiovascular health in particular. Other indicators of health status, such as frailty assessments, may also be important for associations of BP with adverse outcomes.

Gait speed, blood pressure, and mortality risk

A thorough search of the relevant literature produced no previous study investigating the association between BP and mortality with respect to gait speed in populations aged ≥ 80 years. Some findings from studies of individuals aged ≥ 65 years are available; gait speed has been shown to moderate the association of mortality risk with SBP in the NHANES, the Peñagrande cohort, and in results from Rozzini and Trabucci, but not in the LASA or the Cardiovascular Health Study (CHS). Gaït speed was
shown to moderate the association of mortality risk with DBP in the LASA\textsuperscript{92} and the Peñagrande cohort,\textsuperscript{162} but not in the CHS.\textsuperscript{164}

A study from the NHANES\textsuperscript{143} investigated the association of BP with mortality with respect to gait speed, measured over 6 m, in 2340 individuals aged ≥ 65 years. Participants were followed for 4–7 years. The authors showed that gait speed ≥ .8 m/s could be used to identify individuals with increased mortality risk associated with high SBP. SBP and DBP did not appear to be associated with mortality among slower-walking participants (gait speed < .8 m/s). Among participants who did not complete the gait speed test, independent inverse associations with mortality were found for SBP and DBP.

In contrast, in a study from the LASA\textsuperscript{92} of 1466 participants followed for 15–16 years, DBP and mortality risk were associated inversely among slower-walking (gait speed < .8 m/s, measured over 6 m, including a turn) participants aged ≥ 65 years in age-, sex-, and education-adjusted analyses. The association was not significant in fully adjusted analyses or among faster-walking participants (gait speed ≥ .8 m/s). No association between SBP and mortality was found in any gait speed group. Among participants who did not complete the gait speed test, an independent inverse association with mortality was found for DBP, but not for SBP.

The Peñagrande cohort\textsuperscript{162} included individuals aged ≥ 65 years who lived in Peñagrande, Spain, in 2008. A study of 814 individuals from this cohort showed independent inverse associations of SBP and DBP with 6-year mortality risk among slower-walking participants (gait speed < .8 m/s over 3 m or inability to complete the gait speed test), but not among faster-walking participants (gait speed ≥ .8 m/s).

Rozzini and Trabucci\textsuperscript{163} reported findings from 461 patients without stroke or hip fracture admitted to a geriatric rehabilitation ward in Brescia, Italy. The mean age was 79 years. Self-reported hypertension was associated independently with decreased 12-month mortality risk among slower-walking participants (gait speed < .6 m/s, measured over 15 m) and those unable to perform the gait speed test, but no association was found among faster-walking participants (gait speeds .6–.9 and ≥ 1.0 m/s).

The CHS\textsuperscript{164} included community-dwelling individuals aged > 65 years who lived in four counties in North Carolina, California, Maryland, and Pennsylvania, USA. The study was conducted in two waves from 1989 to 1993. Associations between BP and 9-year mortality risk were investigated with respect to gait speed (measured over 4.6 m) in 3547 participants. Associations between BP and mortality risk did not differ according to gait speed (≥ 1.0, .60–.99, and < .60 m/s).

Previous studies of individuals aged ≥ 65 years have produced inconsistent results. The commonly used gait speed cutoff of .8 m/s may be too high for meaningful definition of groups of very old individuals.
Furthermore, findings from populations aged ≥ 65 years may not be applicable to individuals aged ≥ 80 years, due to higher levels of age-related morbidity.

**Mini-Mental State Examination score, blood pressure, and mortality risk**

Previous studies have shown that the MMSE score moderates the associations of SBP\textsuperscript{165,166} and DBP\textsuperscript{92,165,167} with mortality in individuals aged ≥ 65 years\textsuperscript{92,167,168} and ≥ 75 years.\textsuperscript{165} One study of individuals aged ≥ 75 years revealed no difference with respect to MMSE score in the association of SBP or DBP with mortality.\textsuperscript{169}

The Swedish National study on Aging and Care in Kungsholmen,\textsuperscript{165} or Kungsholmen Project, is a population-based study including individuals living in the Kungsholmen district, Stockholm, Sweden, aged ≥ 60 years. In 1810 participants, aged ≥ 75 years in 1987, the association between SBP and 5-year mortality was found to differ with MMSE scores; SBP and DBP were associated inversely with 5-year mortality risk among participants with cognitive impairment (MMSE score < 24), but not associated with mortality among those without cognitive impairment (MMSE score ≥ 24). Another study\textsuperscript{166} from the Kungsholmen Project investigated the association between BP and mortality risk in relation to combined measures of MMSE score and gait speed, measured over 2.4 or 6 m at a self-selected pace, in 3014 participants aged ≥ 60 years in 2001-2004. In fully adjusted analysis, low SBP (< 130 mm Hg), vs. lower intermediary SBP (130-139 mm Hg) was associated with increased all-cause mortality risk among participants with low MMSE scores (≤ 26) or gait speeds (≤ .8 m/s), but associated with decreased risk in those with both high MMSE scores (> 26) and high gait speeds (> .8 m/s). The association of DBP with all-cause mortality risk did not differ with combined measures of MMSE score and gait speed.

The LASA study\textsuperscript{92} found no association between SBP and mortality risk in subcohorts based on tertiles of MMSE score (≤ 26, 27 and 28, and > 28). In age-, sex-, and education-adjusted analyses, lower DBP (≤ 70 mm Hg) was associated with increased mortality risk compared with intermediary DBP (71–90 mm Hg) in the MMSE score ≤ 26 subcohort. In a fully adjusted analysis, higher DBP (> 90 mm Hg) was associated with an increased risk compared with intermediary DBP in the MMSE score > 28 subcohort.

The Osservatorio Geriatrico Regione Campania study\textsuperscript{167} included 1332 individuals living in 40 municipalities of Campania, Italy, who were aged ≥ 65 years in 1991. Findings from this study showed no association between categories of SBP and 6-year mortality risk in subcohorts based on MMSE scores ≥/≤ 24. In the MMSE score < 24 subcohort, high and low DBP were associated with mortality risk compared with lower intermediary DBP; in the
MMSE score $\geq 24$ subcohort, only low DBP was associated with increased mortality risk compared with lower intermediary DBP.

The Milan Geriatrics 75+ Cohort Study\textsuperscript{169} is a prospective, hospital-based study including outpatients of a geriatric unit in Milan, Italy, aged $\geq 75$ years between 2000 and 2004. In 1587 participants, the association between SBP and 10-year mortality was found to differ with MMSE and Katz ADL scores; SBP was associated inversely with mortality risk among participants with combined low scores (MMSE $< 24$ and Katz ADL $\leq 5$), but not in those with one low score or those with high scores (MMSE $> 24$ and/or Katz ADL $> 5$).

The Kangwa cohort\textsuperscript{168} included residents of Kangwa County, South Korea, aged $\geq 55$ years in 1985. A follow-up study was conducted in 1994. A study based on data from the 1994 follow-up investigated the association of BP with 12-year mortality risk with respect to MMSE score in participants aged $\geq 64$ years. BP was classified according to combined measures of SBP and DBP. Independent associations of increased mortality risk with intermediary and high BP categories were found for men and women without cognitive impairment in all classes of MMSE score, compared with low BP among participants without cognitive impairment. The associations seemed to be stronger in women with mild or severe cognitive impairment than in those with no cognitive impairment. The associations appeared to be non-linear among men.

The results of previous studies suggest that BP, and especially DBP, is associated inversely or non-linearly with mortality risk among individuals with cognitive impairment. The association of BP with mortality risk is less clear among participants with higher MMSE scores. Findings regarding the association of SBP with mortality risk are inconsistent. Whether the association of BP with mortality risk is moderated by MMSE score among individuals aged $\geq 85$ years is unclear.

**Mini-Mental State Examination score, blood pressure, and stroke risk**

The Leiden 85+ substudy\textsuperscript{119} investigating the association between BP and stroke is the only study to have examined the impact of MMSE score on this association. SBP was associated inversely with stroke risk among individuals with MMSE scores $\leq 26$ (median), but not among those with higher scores. Participants with higher scores had greater stroke risk in association with higher DBP. These findings need to be corroborated in different samples.

**Activities of daily living, blood pressure, and stroke risk**

Dependency in ADL was also found to moderate the association of BP with stroke risk in 85-year-old individuals in the Leiden 85+ Study.\textsuperscript{119} SBP, PP,
and MAP were associated inversely with stroke risk among individuals with higher dependency in ADL, assessed using relevant items of the Groningen Activity Restriction Scale. These results contrast with those obtained for the total sample, in which no association between BP and stroke was found. The analyses were adjusted for sex, cardiovascular disease, diabetes mellitus, antihypertensive medication use, and smoking.

The CHS also investigated the association of BP with cardiovascular events with respect to ADL dependency. ADL dependency did not significantly interact with SBP or DBP in the association with the risk of cardiovascular events. However, significant associations were found with SBP among participants without ADL dependency, and with DBP among participants with ADL dependency. These results suggest that dependency in ADL influences the association of BP with stroke risk in very old individuals. However, these findings need to be corroborated in different samples.

**Recommendations for blood pressure management**

Recommendations have been made to lower BP in otherwise healthy very old individuals with no tendency for orthostatic hypotension or other adverse drug reaction, to prevent cardiovascular disease. In its 2013 guidelines, the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology recommends SBP reduction to ≤ 140–150 mm Hg in healthy individuals aged ≥ 80 years with initial SBP ≥ 160 mm Hg. In its 2011 consensus document on hypertension in elderly individuals, the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents recommended SBP reduction to ≤ 140–145 mm Hg, and avoidance of SBP < 130/65 mm Hg, in this population.

Evidence supporting guidelines for BP-lowering treatment in very old individuals, especially those in poor health, is lacking. Older individuals are particularly susceptible to adverse drug reactions, such as electrolyte disturbances, hypotension, renal impairment, fatigue, confusion, cough, diabetes, arrhythmia, and heart failure. These risks are particularly prominent with comorbidity and polypharmacy. Adverse reactions to BP-lowering drugs may be crippling, and treatment could thus cause more suffering than benefit.
Rationale

Few studies have investigated ΔSBPs in very old individuals. Previous findings indicate that SBP declines in very old age and that health-related factors have important effects on this change. However, the ability of factors related to individual diseases, drugs, and health-related assessments to predict ΔSBPs in multivariate models is unclear.

The properties of the association between BP and all-cause mortality in very old age have not yet been established, due to the contrasting results obtained in previous studies. Previous observational studies may not have adjusted sufficiently for confounding factors or investigated non-linear associations.

Risk factors for stroke have not been investigated extensively in very old individuals. Due to contrasting results of previous studies, whether high BP remains a risk factor for stroke in this age group, or whether this association becomes attenuated with advanced age, is unclear. Previous observational studies have been characterized by small samples, lack of adjustment for confounders, or application of exclusion criteria interfering with the applicability of the results.

The impacts of indicators of health status on the associations of BP with mortality and stroke are unclear, as few studies have investigated these issues and findings have been inconsistent. Furthermore, few studies have focused on the very old population. Currently available findings do not indicate whether the associations of all-cause mortality and stroke risk with BP are moderated by gait speed, dependency in ADL, and/or MMSE score among individuals aged ≥ 85 years.

Findings from studies of younger populations may not be applicable to very old individuals, due to age-related changes in life expectancy, arterial stiffness, instability in health status, risk factor profiles, and generally more disease and medication use. The applicability of results of previous clinical trials to this population may be compromised by the exclusion of individuals in poor health. Larger observational studies that are representative of very old individuals, including those with multimorbidity and care facility residents, that are of adequate size, involve proper adjustment, and investigate non-linear associations are needed to determine whether high or low BP is an independent risk factor for mortality and/or stroke in very old individuals.

The Umeå 85+/GERDA study involved the collection of representative cross-sectional and longitudinal data, including information on diseases, drug prescriptions, and assessments of health status, from more than 1400 unique very old individuals during 2000–2012. Earlier research based on the Umeå 85+/GERDA study has shown significant temporal trends in BP,
its determinants, and associated adverse outcomes. These results may now be extended to larger samples of the Umeå 85+/GERDA study, which allows comprehensive adjustment and the investigation of subcohorts within the very old population.
Aims

The overall aim of this thesis was to contribute to a better understanding of the determinants of ΔSBP, the risks of adverse outcomes associated with different BP levels, and the importance of comorbidity and heterogeneity of health status for these risks in very old age.

Specific aims were:

- To investigate longitudinal ΔSBPs in individuals aged ≥ 85 years who were followed for 5 years, and identify factors associated independently with ΔSBP in a multivariate model (paper IV).

- To investigate the association of BP with mortality risk in a representative sample of individuals aged ≥ 85 years, and determine whether this association differs with respect to gait speed (paper I) and/or MMSE score (paper II).

- To investigate the association of BP with stroke risk in a representative sample of individuals aged ≥ 85 years, and determine whether this association differs with respect to the Barthel ADL index and/or MMSE score (paper III).
Methods

The studies reported on in all four papers were based on epidemiological data from the population-based Umeå 85+/GERDA study. Statistical models were employed to explore the aims. An overview of sampling from the Umeå 85+/GERDA study and methods employed with respect to the aims of this thesis is presented in Table 2.

Ethical approval

The Umeå 85+/GERDA study, including the studies comprising this thesis, was reviewed and approved by the Regional Ethical Review Board in Umeå (§99-326, §05-063M, §09-178M, §2014-221-31M, and §2015-296-31) and the Ethics Committee of Vaasa/Vasa Central Hospital (§05-87, §10-54), on several occasions.

The Umeå 85+/GERDA study

The Umeå 85+ study was started in 2000 by Umeå University, with the objective to investigate medical and rehabilitational aspects of elder care and living conditions of very old individuals. In 2003, the Umeå 85+ study was succeeded by the GERDA study, conducted by Umeå University in collaboration with Åbo Akademi University, the Novia University of Applied Sciences, and the University of Vaasa/Vasa. The GERDA study expanded data collection to nearby Finnish areas and involved the collection of all information in a single database. The objectives of the Umeå 85+/GERDA study are to increase knowledge of the health and living conditions of very old people, improve their quality of life, and provide data to support the planning of future elder care.

Data collection has been repeated every 5 years since the start of the study; three rounds were completed in 2000–2002, 2005–2007, and 2010–2012 and an ongoing fourth round commenced in 2015. Each round involves the addition of cross-sectional data from a new cohort to the database and longitudinal follow-up of individuals who have already participated. The GERDA study includes a questionnaire-based study of individuals aged 65, 70, 75, and 80 years. These data were not used in this thesis and are not described further.

Participants

The sampling criteria of the Umeå 85+/GERDA study were based on age and geographic area of residence. Individuals aged 85, 90, and ≥ 95 years were
### Table 2. Overview of papers and methods

<table>
<thead>
<tr>
<th>Sample</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample, gait speed subcohorts</td>
<td>MMSE score subcohorts</td>
<td>Total sample</td>
<td>Total sample</td>
</tr>
<tr>
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<td>Follow-up period</td>
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<td>2 years</td>
<td>5 years</td>
<td>5 years</td>
</tr>
<tr>
<td>Main outcome</td>
<td>Mortality risk</td>
<td>Mortality risk</td>
<td>Stroke risk</td>
<td>SBP changes</td>
</tr>
<tr>
<td>Main statistical method</td>
<td>Cox proportional-hazard regression models</td>
<td>Cox proportional-hazard regression models</td>
<td>Cox proportional-hazard regression models</td>
<td>Linear regression models</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; SBP, systolic blood pressure; MMSE, Mini-Mental State Examination; GERDA, Gerontological Regional Database.

eligible for participation in their respective age cohorts. Half of 85-year-olds and all individuals aged 90 and ≥ 95 years were invited to participate, with the aim of creating an age-balanced database.

Geographic areas of residence were selected to include urban and rural areas with individuals of fairly similar cultural and socioeconomic backgrounds. They are six municipalities in Västerbotten, Sweden (Umeå, Sorsele, Storuman, Malå, Vilhelmina, and Dorotea), two municipalities in Österbotten/Pohjanmaa, Finland (Vaasa/Vasa and Mustasaari/Korsholm) since 2005, and two additional municipalities in Österbotten/Pohjanmaa (Korsnäs and Malax/Maalahti) since 2010.

**Procedure**

Eligible participants were identified using population registers from the Swedish Tax Agency and the Finnish Population Register Center. Every second 85-year-old from a randomized starting point, and all individuals aged 90 and ≥ 95 years were invited to participate in the study.

Beginning with the oldest eligible participants, each individual was sent an informational letter by mail. About 1 week later, these individuals were contacted by telephone to provide further information, obtain decisions about participation, and schedule home visits with consenting participants. When an eligible participant was suspected to be unable to provide informed consent him- or herself, as in the case of severe cognitive impairment, a close relative was also informed and asked to provide consent.
Trained assessors with medical knowledge, such as medical doctors, medical students, physiotherapists, and nurses, collected data. Participating individuals were visited at their homes and care facilities for data collection. The data were collected using standardized questionnaires and tests, and included information on sociodemographic, socioeconomic, and medical characteristics; quality of life; and attitudes toward aging, participants’ current situations, and the current situation with elder care. Objective data were also collected from medical records and proxy respondents (i.e., relatives and health care professionals). When a participant could not answer a question or was unsure of his or her answer, a relative or health care professional (in the case of care facility residency) was asked. Participants could choose to decline data collection from any source, including home visitation. They could choose to terminate participation at any time or to continue data collection at a different time.

**Measures**

The Umeå 85+/GERDA study has involved the collection of data for a great number of variables. Only those relevant to this thesis are described here. Information on cohabitation, education, and smoking status was collected from participants or proxy respondents. Length of education was dichotomized as $\leq g 8$ years, as not all respondents knew the exact number of years.

**Diagnoses, medical conditions, and drug prescriptions**

Information on diagnoses, medical conditions, and drug prescriptions was collected from participants or proxy respondents, and medical records from hospitals, general practitioners, and care facilities. All diagnoses were verified and complemented by a specialist in geriatric medicine using all available data, including assessments, tests, pharmacological treatments, and medical records. Angina pectoris was considered to be present based on a diagnosis of angina pectoris or prescription of nitroglycerin.

Dementia and depressive disorder were verified and complemented according to the Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th Edition, Text Revision criteria. The diagnostic criteria for dementia were adapted by removing the criterion of significant impairment in social or occupational functioning due to cognitive deficit, as participants generally did not have occupations and the cause of impairment in social functioning is difficult to determine in individuals receiving high levels of support. Since the start of the Umeå 85+/GERDA study, a 5th edition of the DSM has been released, with new terminology and a new set of diagnostic criteria related to dementia. The terminology of the 4th edition is used in...
this thesis, as it relates to the diagnostic criteria used in the Umeå 85+/GERDA study and most of the cited research.

Assessments

SBP and DBP were measured in the upper arm using a calibrated manual sphygmomanometer (12 x 35 cm, AB Henry Eriksson, Sweden) and stethoscope according to Korotkoff phases I and V, respectively, with the participants in the supine position after 5 min rest.

Gait speed was measured at usual pace from a standstill starting position. Each participant was timed twice using a digital stopwatch as he or she walked for a distance of 2.4 m, and the mean measure was used. Walking aids, but no other means of support, were permitted.

The MMSE was administered following the standard procedure. Total scores, ranging from 0 to 30, were used, with higher scores indicating better cognitive function. Total scores < 23 or 24 have shown 82–88% sensitivity and 86% specificity for the identification of dementia in pooled analyses in community and primary care settings.

Dependency in personal ADL was assessed using total Barthel ADL index scores. Total scores range from 0 to 20, with higher scores indicating higher levels of independence.

Depressive symptoms were assessed using total Geriatric Depression Scale (GDS) scores, which range from 0 to 15. Higher scores indicate more depressive symptoms.

Nutritional status was assessed using the Mini-Nutritional Assessment (MNA). Total scores range from 0 to 30, with higher scores indicating better nutritional status.

The chair stand test was used to assess lower limb strength. Participants were timed while rising from a seated position and sitting down on a chair three times, without using the arms or any other means of support.

Height and weight were measured using a measuring stick and digital portable scales, respectively. BMI (in kilograms/meter squared) was then calculated.

Outcome measures

Dates of death were collected from death certificates, medical records, and population registers for up to 5 years after initial participation.

Dates of stroke events were collected from death certificates and the inpatient diagnosis register for up to 5 years after initial participation. In addition, the longitudinal follow-up component of the Umeå 85+/GERDA study provided indication of stroke events for participants in more than one round of data collection, in which cases the dates were extracted from
medical records. Stroke events were classified according to the International Classification of Diseases, 10th Revision, and included ischemic and hemorrhagic stroke, but not transient ischemic attack or traumatic intracerebral hemorrhage.

$\Delta$SBP was determined by calculating the difference between SBP values obtained at baseline and at the 5-year longitudinal follow-up.

**Sampling**

The flow of first-time participants from invitation to inclusion is presented in Figure 1.

The study described in paper I was based on data from the first and second rounds of data collection. Umeå 85+/GERDA participants with registered SBP measures obtained during home visits were included. Based on gait speed assessment, two gait speed subcohorts were defined: faster-walking ($\geq .5$ m/s) and slower-walking ($< .5$ m/s) participants. The gait speed cutoff value of .5 m/s was found to have 74% sensitivity and 64% specificity against mortality among individuals aged $\geq 85$ years in a previous Umeå 85+/GERDA study. Participants who were unable to complete the gait speed assessment due to habitual physical impairment of gait function were included in the slower-walking subcohort.

The study reported on in paper II was based on data collected in the first to third rounds of the study, except for data collected from Finnish participants in round three, which were not available at the time. Umeå 85+/GERDA participants with registered SBP measures and MMSE scores collected during home visits were included. Participants were divided into four subcohorts based on MMSE score (0–10, 11–17, 18–23, and 24–30). The subcohorts were intended to differentiate very severe, severe, mild, and no cognitive impairment, respectively.

The study reported on in paper III was based on data from Swedish participants in the first to third rounds of data collection. Umeå 85+/GERDA participants who received home visits were included.

For individuals who had participated in more than one round of data collection, the first set of data that qualified for inclusion was used in the analyses reported on in papers I–III.

The study reported on in paper IV was based on baseline data from the first to third rounds of the study and follow-up data from the second to fourth rounds. Follow-up of participants included in the third round had been completed only for Swedish participants included in 2010 at the time of sampling. Individuals who participated in at least two rounds of data collection, with registered SBP measures collected during home visits, were
Figure 1. Flow of first-time participants
METHODS

Analyses were based on the earliest set of data from two consecutive rounds of data collection.

Derived variables

The numeric BP variables were classified to investigate possible non-linear associations with the outcome. In the analyses reported on in papers I and II, SBP was classified in quintiles (≤ 125, 126–139, 140–149, 150–164, and ≥ 165 mm Hg) and DBP was classified in quartiles (< 70, 70–74, 75–80, and > 80 mm Hg). In the analyses reported on in paper III, an alternative classification of BP was used (SBP: < 140, 140–159, and ≥ 160 mm Hg; DBP: < 90 and ≥ 90 mm Hg). PP was calculated by subtracting DBP from SBP. MAP was calculated as the sum of two-thirds DBP and one-third SBP. Quadrated terms of numeric BP variables were also calculated to investigate non-linear associations.

In the analyses reported on in paper III, cases in which gait speed could not be assessed due to physical impairment were assigned a value of .01 for this variable. In the analyses reported on in paper IV, scores for incomplete GDS assessments with 10–14 answered items were imputed using individual mean scores.

Changes were calculated for all variables (∆variables), and could be positive or negative. Binominal variables took three possible values: –1 (removed diagnosis or discontinued drug prescription during follow-up), 0 (no change), and 1 (new diagnosis or drug prescription during follow-up), which were treated as an ordinal scale. Three ∆variables were kept binominal to reflect whether the event had occurred or not occurred during follow-up: ∆cerebrovascular disease, ∆AMI, and ∆hip fracture.

Statistical analyses

Statistical analyses were performed using SPSS Statistics software (versions 20.0, 22.0, and 23.0; IBM Corporation, Armonk, NY, USA) and the R software (version 3.0.2; The R Foundation, Vienna, Austria). All analyses were two tailed, and p < .05 was considered to be significant.

Bivariate associations

In the analyses reported on in papers I, II, and IV, baseline differences between independent groups were investigated using Student’s t test, the Mann–Whitney U test, Pearson’s chi-squared test, and one-way analysis of variance. In the analyses reported on in paper IV, longitudinal differences within groups were investigated using the paired samples t test, Wilcoxon signed rank test, and McNemar’s test. In the analyses reported on in paper
III, bivariate associations between variables and the outcome were analyzed using bivariate Cox proportional-hazard regression models. Bivariate correlations were tested using Pearson or Spearman correlations. The normality of variables was checked using histograms. Non-parametric statistics were used for variables with non-normally distributed values and <30 observations, according to the central limit theorem. To investigate possible bias in the study samples, differences in age and sex between individuals included and not included in samples were examined.

**Multivariate linear regression models**

Multivariate linear regression models were developed to test factors associated with ∆SBP in the analyses reported on in paper IV. Baseline variables and ∆variables associated bivariately with ∆SBP at the level of p ≤ .15 were entered into separate multivariate models (1 and 2, respectively), together with baseline age, sex, investigation year, and baseline SBP. In cases of high correlation between variables (r > .5, rho > .5), the variable with the strongest association with the outcome was kept and the correlating variable was removed. A final model (3) included variables associated with ∆SBP at the level of p ≤ .15 in models 1 and 2, together with baseline age, sex, investigation year, and baseline SBP. Residuals were linear and distributed normally in all models.

**Cox proportional-hazard regression models**

Cox proportional-hazard regression models were used to analyze associations between BP and mortality (analyses for papers I and II) or stroke (analysis for paper III), based on the times to death and the first stroke event, respectively. In the analysis reported on in paper III, participants who were deceased before the first stroke event were censored. Complete case analysis was used due to small proportions of missing values.180

In the analyses reported on in papers I and II, two models were developed: a basic model including age, sex and BP (model 1), and a fully adjusted model for the total sample including age, sex, BP, and baseline variables associated with the outcome at the level of p ≤ .15 (model 2).

In the analyses reported on in paper III, three models were developed with increasing numbers of baseline variables associated with the outcome at the level of p ≤ .05, in order of increasing number of missing values (basic, intermediate, and comprehensive models).

Bivariate correlations between variables were tested, and one of the correlating variables was removed in cases of high correlation (analyses for papers I and II: r > .6, rho > .6; analyses for paper III: r > .5, rho > .5).
To avoid model instability in subcohort analyses, the maximum number of variables included in a model was controlled by removing variables associated less significantly with the outcome. Only variables associated with the outcome at the level of $p \leq .05$ in total-sample multivariate models were retained in subcohort models. Measures of BP were entered separately in each model.

The models were tested for violations against assumptions of the Cox proportional-hazard models using the Schoenfeld test. Time-dependent variables were handled by entering the product of each variable and follow-up time in extended models.

Interaction effects were tested by entering an interaction term (the product of the variables tested for interaction) in each model, together with the variables tested for interaction. BP was tested for interactions with age, sex, categories of gait speed (analysis for paper I: $< .5$ vs. $\geq .5$ m/s), MMSE score (analysis for paper II: $0–10$, $11–17$, $18–23$, and $24–30$; analysis for paper III: $< 24$ vs. $\geq 24$), and Barthel ADL index (analysis for paper III: $< 24$ vs. $\geq 24$). The models were tested in the total sample and in subgroups of gait speed (analysis for paper I) and MMSE score (analysis for paper II).

**Additional analyses**

Additional analyses were performed for this thesis. Baseline factors associated with baseline SBP were investigated in all first-time participants using a multivariate linear regression model. Baseline variables associated bivariately with baseline SBP at the level of $p \leq .15$ were entered into a multivariate model, together with age, sex, and investigation year. Independent predictors of $\Delta$SBP were investigated further by replacing the antidepressants variable with depressive disorder and removing the Barthel ADL variable in the multivariate models.

Associations between BP and mortality were investigated in the total sample reported on in paper II. The importance of confounders for the significance of associations between SBP and mortality risk was investigated by removing covariates associated significantly with mortality in model 2, separately and together, in the samples reported on in papers I and II. Linear associations were tested by replacing the categorical BP variable with a linear term for BP in the multivariate models examining mortality risk. Non-linear associations were tested by including a quadrated term of BP together with the numeric term in these models. Interaction effects between BP and gait speed were tested in the samples reported on in paper III according to the previously described method.
Results

Descriptive characteristics and the main results reported in papers I–IV are presented below according to outcome. Results of additional analyses are presented in a separate section.

Descriptive characteristics of the Umeå 85+/GERDA sample

The Umeå 85+/GERDA database contained data from 1425 first-time participants, collected in 2000–2002, 2005–2007, and 2010–2012 in Sweden and 2005–2007 in Finland. The participation rate was 84% of those who received invitations. Of all first-time participants, 283 (20%) declined home visitation. Descriptive baseline characteristics of all first-time participants in the Umeå 85+/GERDA study in 2000–2012 and of the samples reported on in papers I–IV are shown in Table 3.

The mean (± standard deviation) age of all first-time participants was 89 ± 4.7 years, and about two-thirds (69%) of participants were women. Age and sex did not differ significantly between all first-time Umeå 85+/GERDA participants and eligible non-participants, but women were underrepresented in the samples reported on in papers II (67% vs. 72%, p < .010) and III (66% vs. 72%, p = .028). Participants were younger than eligible non-participants in the samples reported on in papers II (89 ± 4.6 vs. 90 ± 4.8 years, p < .032) and IV (87 ± 3.3 vs. 90 ± 4.8 years, p < .001). The majority of all first-time participants were Swedish (83% vs. 17% Finnish).

Of all first-time participants, 39% were care facility residents, 80% lived alone, 31% had heart failure, and 23% had atrial fibrillation. The average number of drugs prescribed was 7.7 ± 4.6. Angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and calcium channel blockers were prescribed to 19%, 32%, and 15% of participants, respectively. The average gait speed was .53 ± .23 m/s and the median MMSE score was 23 (interquartile range, 17–27). These characteristics were very similar across samples, except for the sample reported on in paper IV.

Mean SBP is presented according to sex, age group, and investigation year in Table 4 and Figure 2. Among all first-time participants, mean SBP was 146 ± 23 mm Hg and mean DBP was 74 ± 11 mm Hg. BP varied among samples; SBP values ranged from 146 ± 23 to 152 ± 22 mm Hg and DBP values ranged from 74 ± 11 to 76 ± 11 mm Hg.
<table>
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<tr>
<th>Characteristic</th>
<th>All first-time participants</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
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<td>806</td>
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<td>561 (70)</td>
<td>742 (67)</td>
<td>629 (66)</td>
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<td>Care facility residency</td>
<td>530 (39)</td>
<td>315 (39)</td>
<td>407 (37)</td>
<td>351 (37)</td>
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<tr>
<td>Living alone</td>
<td>1044 (80)</td>
<td>653 (81)</td>
<td>875 (79)</td>
<td>753 (79)</td>
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<tr>
<td>Education &lt; 8 years</td>
<td>841 (74)</td>
<td>573 (74)</td>
<td>791 (73)</td>
<td>692 (76)</td>
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<td>Current smoker</td>
<td>39 (3)</td>
<td>27 (3)</td>
<td>35 (3)</td>
<td>32 (3)</td>
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<td>Former smoker</td>
<td>344 (28)</td>
<td>210 (27)</td>
<td>324 (29)</td>
<td>298 (31)</td>
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</table>

### Diagnoses and medical conditions

<table>
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<tr>
<th>Diagnosis</th>
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<th>Paper III</th>
<th>Paper IV, baseline</th>
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<td>Diabetes</td>
<td>206 (15)</td>
<td>113 (14)</td>
<td>178 (16)</td>
<td>148 (16)</td>
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<td>Heart failure</td>
<td>446 (31)</td>
<td>238 (30)</td>
<td>348 (31)</td>
<td>287 (29)</td>
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<td>Atrial fibrillation</td>
<td>329 (23)</td>
<td>180 (22)</td>
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<tr>
<td>Myocardial infarction</td>
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<td>23 (3)</td>
<td>31 (3)</td>
<td>29 (3)</td>
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<td>Cerebrovascular event</td>
<td>305 (21)</td>
<td>160 (20)</td>
<td>243 (22)</td>
<td>219 (23)</td>
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<tr>
<td>Cancer previous 5 yrs</td>
<td>178 (13)</td>
<td>86 (11)</td>
<td>141 (13)</td>
<td>116 (12)</td>
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<tr>
<td>Dementia</td>
<td>277 (20)</td>
<td>277 (34)</td>
<td>389 (35)</td>
<td>321 (34)</td>
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<td>Hip fracture</td>
<td>270 (19)</td>
<td>142 (18)</td>
<td>201 (18)</td>
<td>194 (20)</td>
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<td>COPD</td>
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<td>134 (17)</td>
<td>196 (18)</td>
<td>165 (17)</td>
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<td>Depressive disorder</td>
<td>478 (34)</td>
<td>258 (32)</td>
<td>385 (35)</td>
<td>335 (35)</td>
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<td>Rheumatic disorder</td>
<td>190 (13)</td>
<td>110 (14)</td>
<td>154 (14)</td>
<td>136 (14)</td>
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<td>Angina pectoris</td>
<td>508 (36)</td>
<td>350 (43)</td>
<td>471 (42)</td>
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### Drug prescriptions

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<th>Paper III</th>
<th>Paper IV, baseline</th>
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<tbody>
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<td>ACE inhibitors</td>
<td>271 (19)</td>
<td>139 (17)</td>
<td>224 (20)</td>
<td>177 (19)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>461 (32)</td>
<td>262 (33)</td>
<td>478 (43)</td>
<td>361 (38)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>217 (15)</td>
<td>103 (13)</td>
<td>189 (17)</td>
<td>142 (15)</td>
</tr>
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<td>Diuretics</td>
<td>704 (49)</td>
<td>394 (49)</td>
<td>604 (54)</td>
<td>484 (51)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>361 (25)</td>
<td>246 (31)</td>
<td>287 (26)</td>
<td>232 (24)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>275 (19)</td>
<td>136 (17)</td>
<td>198 (18)</td>
<td>171 (18)</td>
</tr>
<tr>
<td>ASA</td>
<td>558 (39)</td>
<td>337 (42)</td>
<td>469 (42)</td>
<td>396 (42)</td>
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<td>Opioids</td>
<td>210 (15)</td>
<td>157 (19)</td>
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<td>143 (15)</td>
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<td>177 (12)</td>
<td>115 (14)</td>
<td>132 (12)</td>
<td>111 (12)</td>
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<td>Warfarin</td>
<td>114 (8)</td>
<td>71 (9)</td>
<td>102 (9)</td>
<td>55 (6)</td>
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<td>Paracetamol</td>
<td>496 (35)</td>
<td>375 (47)</td>
<td>385 (35)</td>
<td>348 (36)</td>
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<tr>
<td>NSAIDs</td>
<td>88 (6)</td>
<td>64 (8)</td>
<td>68 (6)</td>
<td>61 (94)</td>
</tr>
<tr>
<td>Statins</td>
<td>136 (10)</td>
<td>44 (6)</td>
<td>129 (12)</td>
<td>87 (9)</td>
</tr>
<tr>
<td>Total no. of drugs</td>
<td>7.7 ± 4.6</td>
<td>6.5 ± 4.3</td>
<td>6.5 ± 4.0</td>
<td>6.6 ± 4.1</td>
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</table>

### Assessments

<table>
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<tr>
<th>Assessment</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV, baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>25 ± 4.4</td>
<td>25 ± 4.4</td>
<td>25 ± 4.4</td>
<td>25 ± 4.4</td>
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<tr>
<td>MMSE score</td>
<td>23 (17–27)</td>
<td>23 (17–27)</td>
<td>23 (17–27)</td>
<td>23 (17–27)</td>
</tr>
<tr>
<td>GDS score</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
</tr>
<tr>
<td>Barthel ADL index</td>
<td>19 (13–20)</td>
<td>19 (15–20)</td>
<td>19 (15–20)</td>
<td>19 (17–22)</td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
<td>.53 ± .23</td>
<td>.52 ± .21</td>
<td>.53 ± .23</td>
<td>.46 ± .27</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>146 ± 23</td>
<td>147 ± 24</td>
<td>146 ± 23</td>
<td>146 ± 23</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>74 ± 11</td>
<td>75 ± 11</td>
<td>74 ± 12</td>
<td>74 ± 12</td>
</tr>
</tbody>
</table>

**Abbreviations:** GERDA, Gerontological Regional Database; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; NSAID, non-steroidal anti-inflammatory drug; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; ADL, activities of daily living; BP, blood pressure.

*Data are presented as n (%), mean ± standard deviation, or median (interquartile range).


*Ever.

*Previous year.
RESULTS

Changes in systolic blood pressure

Longitudinal trends in average SBP among followed participants are presented according to age group and investigation year in Table 5 and Figure 3. \(\Delta\)SBPs according to 10 mm Hg categories of baseline SBP are shown in Table 6 and Figure 4. The majority (65%) of participants were followed between the ages of 85 and 90 years. During the 5-year (mean, 4.7 ± .33 years) follow-up period, the mean \(\Delta\)SBP was –12 ± 25 mm Hg. The average annual decline was 2.6 ± 5.4 mm Hg. Almost two-thirds (62%) of participants showed SBP declines ≥ 5 mm Hg during the follow-up period. About one-fourth (26%) of participants showed SBP increases ≥ 5 mm Hg.

Selective serotonin reuptake inhibitors (SSRIs) formed the most prevalent class of antidepressants prescribed at baseline (SSRIs: n = 20, 77%; tricyclic antidepressants: n = 2, 7.7%; other [including mianserin and mirtazapine]: n = 5, 20%).

Table 7 presents multivariate associations of variables included in models 1–3 with \(\Delta\)SBP. Model 1, constructed to examine \(\Delta\)SBP prediction, included the baseline variables age, sex, investigation year, SBP, care facility residency, cerebrovascular disease, rheumatic disorder, and antidepressants. The depressive disorder diagnosis and warfarin variables were removed due to strong correlations with antidepressants and atrial fibrillation, respectively. Significant regression equations were found (F[8, 288] = 30.815, \(p < .001\), \(r^2 = .461\)). Significant variables were SBP (B = –.75, standard error [SE] = .05, \(p < .001\)), investigation year (B = –.63, SE = .32, \(p = .048\)), and antidepressants (B = –12, SE = 3.9, \(p = .002\)). All B values presented are unstandardized.

Model 2 examining \(\Delta\)SBP prediction included the baseline variables age, sex, investigation year, and SBP and the \(\Delta\)variables \(\Delta\)diabetes, \(\Delta\)heart failure, \(\Delta\)atrial fibrillation, \(\Delta\)AMI, \(\Delta\)dementia, \(\Delta\)ACE inhibitors, \(\Delta\)beta blockers, \(\Delta\)diuretics, \(\Delta\)benzodiazepines, \(\Delta\)neuroleptics, \(\Delta\)total number of drugs, \(\Delta\)MMSE score, \(\Delta\)GDS score, and \(\Delta\)Barthel ADL index. Significant regression equations were found (F[18, 247] = 15.483, \(p < .001\), \(r^2 = .530\)). Significant variables were \(\Delta\)AMI (B = –8.8, SE = 3.7, \(p = .017\)), \(\Delta\)Barthel ADL index (B = .73, SE = .32, \(p = .025\)), investigation year (B = –1.1, SE = .34, \(p = .002\)), age (B = .84, SE = .37, \(p = .024\)), and SBP (B = –.71, SE = .05, \(p < .001\)).

Model 3 included the baseline variables age, sex, investigation year, SBP, rheumatic disorder, and antidepressants and the \(\Delta\)variables \(\Delta\)AMI, \(\Delta\)Barthel ADL index, \(\Delta\)diuretics, and \(\Delta\)neuroleptics. Significant regression equations were found (F[10, 282] = 29.878, \(p < .001\), \(r^2 = .497\)). Significant variables were investigation year (B = –.81, SE = .31, \(p = .009\)), SBP (B = –.75, SE = .05, \(p < .001\)), antidepressants (B = –9.9, SE = 3.8, \(p = .011\)), \(\Delta\)AMI (B = –10, SE = 3.4, \(p = .003\)), \(\Delta\)diuretics (B = –4.4, SE = 2.2, \(p = .044\)), and \(\Delta\)Barthel
### Table 4. Average SBP, according to age group, sex, and investigation year

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>All</td>
<td>Men</td>
<td>Women</td>
<td>N</td>
<td>All</td>
<td>Men</td>
<td>Women</td>
<td>N</td>
<td>All</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Total</td>
<td>423</td>
<td>148 ± 24</td>
<td>148 ± 23</td>
<td>148 ± 24</td>
<td>549</td>
<td>146 ± 24</td>
<td>144 ± 22</td>
<td>146 ± 25</td>
<td>929</td>
<td>145 ± 21</td>
<td>144 ± 21</td>
<td>145 ± 21</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85 years</td>
<td>173</td>
<td>156 ± 23</td>
<td>155 ± 23</td>
<td>157 ± 23</td>
<td>251</td>
<td>150 ± 23</td>
<td>143 ± 18</td>
<td>153 ± 24</td>
<td>346</td>
<td>149 ± 20</td>
<td>148 ± 20</td>
<td>150 ± 20</td>
</tr>
<tr>
<td>90 years</td>
<td>148</td>
<td>145 ± 24</td>
<td>144 ± 22</td>
<td>146 ± 24</td>
<td>150</td>
<td>146 ± 25</td>
<td>145 ± 27</td>
<td>146 ± 24</td>
<td>305</td>
<td>143 ± 20</td>
<td>141 ± 21</td>
<td>143 ± 19</td>
</tr>
<tr>
<td>≥ 95 years</td>
<td>102</td>
<td>137 ± 22</td>
<td>133 ± 19</td>
<td>138 ± 23</td>
<td>148</td>
<td>138 ± 23</td>
<td>144 ± 23</td>
<td>136 ± 22</td>
<td>278</td>
<td>142 ± 23</td>
<td>141 ± 23</td>
<td>142 ± 23</td>
</tr>
</tbody>
</table>

Abbreviations: SBP, systolic blood pressure.

*SBP is presented as mean ± standard deviation, in mm Hg.

### Table 5. Average SBP of followed participants at baseline and follow-up, according to age group and investigation year

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>98</td>
<td>155 ± 22</td>
<td>141 ± 21</td>
<td>135</td>
<td>152 ± 23</td>
<td>143 ± 19</td>
<td>64</td>
<td>146 ± 18</td>
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<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85 years</td>
<td>61</td>
<td>159 ± 20</td>
<td>141 ± 21</td>
<td>86</td>
<td>152 ± 25</td>
<td>142 ± 19</td>
<td>45</td>
<td>148 ± 17</td>
</tr>
<tr>
<td>90 years</td>
<td>31</td>
<td>149 ± 26</td>
<td>142 ± 20</td>
<td>37</td>
<td>151 ± 21</td>
<td>144 ± 19</td>
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<td>144 ± 19</td>
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<tr>
<td>≥ 95 years</td>
<td>6</td>
<td>149 ± 19</td>
<td>145 ± 26</td>
<td>12</td>
<td>149 ± 21</td>
<td>144 ± 21</td>
<td>3</td>
<td>127 ± 27</td>
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</tbody>
</table>

Abbreviations: SBP, systolic blood pressure.

*SBP is presented as mean ± standard deviation, in mm Hg.

*The 2011–2012 part of the cohort has not yet been followed.
**RESULTS**

**Figure 2.** Average cross-sectional systolic blood pressure according to sex, age group, and investigation year

**Figure 3.** Average systolic blood pressure of followed participants at baseline and the 5-year follow-up, according to age group and investigation year
Table 6. Average SBP of followed participants at baseline and follow-up, according to 10-mm Hg categories of baseline SBP.

<table>
<thead>
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<th>SBP category</th>
<th>N</th>
<th>Baseline</th>
<th>5-year follow-up</th>
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<tr>
<td>&lt; 120</td>
<td>11</td>
<td>109 ± 6</td>
<td>129 ± 14</td>
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<tr>
<td>120–129</td>
<td>25</td>
<td>122 ± 3</td>
<td>131 ± 20</td>
</tr>
<tr>
<td>130–139</td>
<td>45</td>
<td>132 ± 3</td>
<td>135 ± 19</td>
</tr>
<tr>
<td>140–149</td>
<td>53</td>
<td>142 ± 3</td>
<td>137 ± 16</td>
</tr>
<tr>
<td>150–159</td>
<td>47</td>
<td>152 ± 3</td>
<td>142 ± 18</td>
</tr>
<tr>
<td>160–169</td>
<td>48</td>
<td>162 ± 3</td>
<td>141 ± 19</td>
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<td>170–179</td>
<td>29</td>
<td>171 ± 2</td>
<td>146 ± 22</td>
</tr>
<tr>
<td>180–189</td>
<td>26</td>
<td>181 ± 2</td>
<td>145 ± 22</td>
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<tr>
<td>≥ 190</td>
<td>13</td>
<td>207 ± 17</td>
<td>156 ± 25</td>
</tr>
</tbody>
</table>

Abbreviations: SBP, systolic blood pressure.

aSBP is presented as mean ± standard deviation, in mm Hg.

Figure 4. Average systolic blood pressure of followed participants at baseline and the 5-year follow-up, according to 10-mm Hg categories of baseline systolic blood pressure.
### Table 7. Multivariate associations with SBP changea

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Unstandardized B</th>
<th>SE</th>
<th>Standardized beta</th>
<th>p</th>
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</thead>
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<td>(Constant)</td>
<td>1329.94</td>
<td>641.09</td>
<td>.0</td>
<td>.039</td>
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<tr>
<td>Investigation year</td>
<td>−63</td>
<td>.32</td>
<td>−.09</td>
<td>.048</td>
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<tr>
<td>Age</td>
<td>.35</td>
<td>.34</td>
<td>.05</td>
<td>.303</td>
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<tr>
<td>Sex (female vs. male)</td>
<td>3.60</td>
<td>2.36</td>
<td>.07</td>
<td>.128</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>−.75</td>
<td>.05</td>
<td>−.67</td>
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<td>Care facility residency</td>
<td>1.95</td>
<td>3.69</td>
<td>.03</td>
<td>.597</td>
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<td>Cerebrovascular disease</td>
<td>−.14</td>
<td>2.89</td>
<td>−.02</td>
<td>.963</td>
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<tr>
<td>Rheumatic disorder</td>
<td>5.85</td>
<td>3.37</td>
<td>.08</td>
<td>.083</td>
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<td>Antidepressants</td>
<td>−11.96</td>
<td>3.91</td>
<td>−3.06</td>
<td>.002</td>
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</tbody>
</table>

<table>
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<th></th>
</tr>
</thead>
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<td>(Constant)</td>
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<td>Investigation year</td>
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<td>−.15</td>
<td>.002</td>
</tr>
<tr>
<td>Age</td>
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<td>.37</td>
<td>.11</td>
<td>.024</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>3.36</td>
<td>2.42</td>
<td>.06</td>
<td>.167</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>−.71</td>
<td>.05</td>
<td>−.64</td>
<td>&lt;.001</td>
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<tr>
<td>∆Diabetes</td>
<td>5.05</td>
<td>4.71</td>
<td>.05</td>
<td>.285</td>
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<td>∆Heart failure</td>
<td>−.92</td>
<td>2.69</td>
<td>−.02</td>
<td>.732</td>
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<td>∆Atrial fibrillation</td>
<td>−2.12</td>
<td>3.32</td>
<td>−.03</td>
<td>.525</td>
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<td>∆AMI</td>
<td>−8.79</td>
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<td>−.11</td>
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<td>∆Dementia</td>
<td>−.56</td>
<td>3.36</td>
<td>−.01</td>
<td>.868</td>
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<tr>
<td>∆ACE inhibitors</td>
<td>−.4.39</td>
<td>3.19</td>
<td>−.06</td>
<td>.170</td>
</tr>
<tr>
<td>∆Beta blockers</td>
<td>−3.44</td>
<td>2.59</td>
<td>−.06</td>
<td>.185</td>
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<td>∆Diuretics</td>
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<td>2.50</td>
<td>−.07</td>
<td>.130</td>
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<tr>
<td>∆Benzodiazepines</td>
<td>1.94</td>
<td>2.89</td>
<td>.03</td>
<td>.502</td>
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<td>∆Neuroleptics</td>
<td>−9.14</td>
<td>4.70</td>
<td>−.09</td>
<td>.054</td>
</tr>
<tr>
<td>∆Total number of drugs</td>
<td>−.27</td>
<td>.33</td>
<td>−.04</td>
<td>.421</td>
</tr>
<tr>
<td>∆MMSE score</td>
<td>.41</td>
<td>.31</td>
<td>.08</td>
<td>.194</td>
</tr>
<tr>
<td>∆GDS score</td>
<td>−.19</td>
<td>.45</td>
<td>−.02</td>
<td>.679</td>
</tr>
<tr>
<td>∆Barthel ADL index</td>
<td>.73</td>
<td>.32</td>
<td>.12</td>
<td>.025</td>
</tr>
</tbody>
</table>

| Model 3                      |                   |      |                  |      |
| (Constant)                   | 1667.84           | 624.37 |                 | .008 |
| Investigation year           | −.81              | .31   | −.11              | .009 |
| Age                          | .61               | .33   | .08               | .063 |
| Sex (female vs. male)        | 3.09              | 2.27  | .06               | .175 |
| SBP (mm Hg)                  | −.75              | .05   | −.66              | <.001|
| Rheumatic disorder           | 5.50              | 3.22  | .07               | .089 |
| Antidepressants              | −9.85             | 3.83  | −.11              | .011 |
| ∆AMI                         | −10.12            | 3.44  | −.12              | .003 |
| ∆Barthel ADL index           | .86               | .24   | .16               | <.001|
| ∆Diuretics                   | −.4.44            | 2.19  | −.09              | .044 |
| ∆Neuroleptics                | −5.75             | 4.40  | −.06              | .192 |

Abbreviations: SBP, systolic blood pressure; SE, standard error; AMI, acute myocardial infarction; ADL, activities of daily living; ACE, angiotensin-converting enzyme; MMSE, mini-mental state examination; GDS, geriatric depression scale.

aCoefficients and p values were calculated using multiple linear regression; follow-up time was 5 years.
ADL index (B = .86, SE = .24, p < .001). Results from some variations on model 3 are presented in the Additional analyses section.

**Mortality risk**

All significant associations of categorized SBP and DBP with mortality risk from the multivariate models are presented in this section. Analyses conducted with numeric and quadrated BP variables are presented in the Additional analyses section.

**Total sample**

Within 5 years, 490 (61%) participants in the study reported on in paper I had died (mean follow-up time, 3.3 ± 1.7 years). Within 2 years, 293 (26%) participants in the study reported on in paper II had died (mean follow-up time, 1.7 ±.53 years). Results for the total sample are presented in Table 8 and Figure 5 (SBP), and in Table 9 (DBP).

Model 2, reported on in paper I, included age, age × follow-up time, sex, BP, heart failure, atrial fibrillation, AMI, cancer, depressive disorder, angina pectoris, BMI, MMSE score, care facility residency, living alone, education, education × follow-up time, cerebrovascular disease, hip fracture, ACE inhibitors, calcium channel blockers, diuretics, benzodiazepines, neuroleptics, warfarin, analgesics, statins, number of drugs, and gait speed subcohort. The Barthel ADL index variable was removed due to strong correlation with care facility residency, MMSE score, dementia, and gait speed subcohort. The dementia variable was removed due to strong correlation with MMSE score. The antidepressants variable was removed due to the high risk of an overlap effect with depressive disorder diagnosis.

In the model 1 analysis reported on in paper I, SBP appeared to be associated inversely with 5-year mortality in the total sample, with up to 50% decreased mortality risk in the highest SBP category compared with the lowest (SBP ≥ 165 vs. ≤ 125 mm Hg: hazard ratio [HR] = .50, 95% confidence interval [CI] = .38–.66, p < .001). In model 2, SBP was not associated significantly with mortality risk.

In model 1, lower DBP categories were associated significantly with increased 5-year mortality risk in the total sample, compared with the higher intermediary category (DBP < 70 vs. 75–80 mm Hg: HR = 1.42, 95% CI = 1.11–1.81, p = .005; DBP 70–74 vs. 75–80 mm Hg: HR = 1.32, 95% CI = 1.03–1.69, p = .031). In model 2, lower intermediary DBP was associated significantly with increased 5-year mortality risk, compared with higher intermediary DBP (DBP 70–74 vs. 75–80 mm Hg: HR = 1.37, 95% CI = 1.03–1.83, p = .031).
In the analyses reported on in paper I, the same covariates were associated independently with increased mortality risk in model 2 for SBP and DBP: male sex, heart failure, atrial fibrillation, AMI, cancer, depressive disorder, absence of angina pectoris, lower BMI, lower MMSE score, and lower gait speed. Analyses conducted in total sample described in paper II and some variations on model 2 are presented in the Additional analyses section.

**Gait speed**

The results are presented according to gait speed subcohort in Table 8 and Figure 5 (SBP) and in Table 9 (DBP). Model 2 examining the gait speed subcohorts included age, age × follow-up time, sex, BP, heart failure, atrial fibrillation, AMI, cancer, depressive disorder, angina pectoris, BMI, and MMSE score. The models for SBP and DBP were identical, although developed separately.

Interaction effects between categorized SBP and gait speed subcohort were significant in model 1 (p = .031), but not in model 2. No interaction effects between DBP and mortality was found in either model.

**Gait speed < .5 m/s**

In the gait speed < .5 m/s subcohort, SBP and DBP were not associated significantly with mortality risk in model 2.

Higher SBP categories were associated significantly with up to 49% decreased 5-year mortality risk, compared with the lowest category (SBP ≥ 165 vs. ≤ 125 mm Hg: HR = .51, 95% CI = .35–.72, p < .001), in model 1.

The higher intermediary category of DBP was associated significantly with decreased 5-year mortality risk, compared with the lowest category (DBP 75–80 vs. < 70 mm Hg: HR = .71, 95% CI = .53–.96, p = .024), in model 1.

Mortality risk was independently increased with male sex, heart failure, atrial fibrillation, cancer, depressive disorder, absence of angina pectoris, lower MMSE score, in model 2 examinations of SBP and DBP.

**Gait speed ≥ .5 m/s**

In the gait speed ≥ .5 m/s subcohort, the intermediary and highest SBP categories in model 2 had more than doubled 5-year mortality risks, compared with the lower intermediary category (SBP 140–149 vs. 126–139 mm Hg: HR = 2.25, 95% CI = 1.03–4.94, p = .042; SBP ≥ 165 vs. 126–139 mm Hg: HR = 2.13, 95% CI = 1.01–4.49, p = .048).
The highest DBP category in model 2 was associated significantly with increased 5-year mortality risk, compared with higher intermediary DBP (DBP > 80 vs. 75–80 mm Hg: HR = 1.76, 95% CI = 1.07–2.90, p = .026).

Mortality risk was independently increased with male sex, heart failure, atrial fibrillation, lower BMI, and lower MMSE score in model 2 examining SBP. In model 2 examining DBP, the same variables and AMI were associated independently with mortality risk.

**Mini-Mental State Examination score**

The maximum follow-up time was reduced to 2 years in the analyses reported on in paper II, due to time dependence in the association of MMSE score with mortality risk for longer follow-up times. The results for SBP are presented according to MMSE score subcohort in Table 10 and Figure 6.

Model 2, examining MMSE score subcohorts, included age, sex, BP, atrial fibrillation, depressive disorder, and Barthel ADL index.

Interaction effects between categorized BP and MMSE score subcohorts were borderline significant for SBP, but not DBP, in the basic model (p = .069) and the fully adjusted model (p = .068).

**MMSE score 0–10**

In model 1, 2-year mortality risk was more than doubled in the lowest SBP category and more than quadrupled in the highest category, compared with lower intermediary SBP (≥ 165 vs. 126–139 mm Hg; HR = 4.48, 95% CI = 1.51–13.23, p = .007; ≤ 125 vs. 126–139 mm Hg: HR = 2.41, 95% CI = 1.23–4.72, p = .011).

In model 2, 2-year mortality risk was doubled in the lowest SBP category and more than quadrupled in the highest category, compared with lower intermediary SBP (≥ 165 vs. 126–139 mm Hg; HR = 4.54, 95% CI = 1.52–13.60, p = .007; ≤ 125 vs. 126–139 mm Hg: HR = 2.23, 95% CI = 1.12–4.45, p = .023).

DBP was not associated significantly with mortality risk in model 1 or 2.

Only age was associated independently with mortality risk in model 2 examining categorized SBP. No covariate was associated independently with mortality risk in model 2 examining categorized DBP.

**MMSE score 11–17**

SBP and DBP were not associated significantly with mortality risk in model 1 or 2. Covariates associated independently with mortality risk in model 2 examining categorized SBP were age, atrial fibrillation, and Barthel ADL index. Covariates associated independently with mortality risk in model 2 examining categorized DBP were age, atrial fibrillation, and Barthel ADL index.
Table 8. Hazard ratios for death for SBP in the total sample and gait speed subcohorts\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>SBP (mm Hg)</th>
<th>Total sample</th>
<th>Gait speed &lt; .5 m/s</th>
<th>Gait speed ≥ .5 m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Model 1</td>
<td>806</td>
<td>1</td>
<td>433</td>
</tr>
<tr>
<td>≤ 125</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>126–139</td>
<td>.70 (.53–.93)</td>
<td>.014</td>
<td>.78 (.56–1.08)</td>
</tr>
<tr>
<td>140–149</td>
<td>.63 (.48–.83)</td>
<td>.001</td>
<td>.70 (.50–.99)</td>
</tr>
<tr>
<td>150–164</td>
<td>.59 (.45–.76)</td>
<td>&lt; .001</td>
<td>.56 (.40–.77)</td>
</tr>
<tr>
<td>≥ 165</td>
<td>.50 (.38–.66)</td>
<td>&lt; .001</td>
<td>.51 (.35–.72)</td>
</tr>
<tr>
<td>Model 2</td>
<td>698</td>
<td>1</td>
<td>399</td>
</tr>
<tr>
<td>≤ 125</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>126–139</td>
<td>.87 (.62–1.23)</td>
<td>.439</td>
<td>.89 (.62–1.27)</td>
</tr>
<tr>
<td>140–149</td>
<td>1.07 (.78–1.48)</td>
<td>.668</td>
<td>.94 (.65–1.35)</td>
</tr>
<tr>
<td>150–164</td>
<td>.97 (.71–1.32)</td>
<td>.828</td>
<td>.78 (.55–1.11)</td>
</tr>
<tr>
<td>≥ 165</td>
<td>1.03 (.74–1.44)</td>
<td>.860</td>
<td>.85 (.57–1.27)</td>
</tr>
</tbody>
</table>

Abbreviations: SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval.
\textsuperscript{a}Data from J Am Med Dir Assoc. 2015;16(3):208–214. ©2015 AMDA – The Society for Post-Acute and Long-Term Care Medicine. CC BY-NC-ND 3.0.
\textsuperscript{b}Calculated using Cox proportional-hazard regression models; follow-up time was 5 years. The blood pressure reference category was chosen based on graphical interpretation of initial age- and sex-adjusted analyses in the total sample and in each gait speed group.
\textsuperscript{c}Comprises participants with gait speeds < .5 m/s and those unable to complete the walking test due to habitual impairment of gait function.
\textsuperscript{d}Model 1 was adjusted for age and sex.
\textsuperscript{e}In gait speed subcohorts, adjusted for age, age × follow-up time, sex, heart failure, atrial fibrillation, acute myocardial infarction, cancer, depressive disorder, angina pectoris, body mass index, and Mini-Mental State Examination score. In the total sample, additionally adjusted for care facility residency; living alone; education; education × follow-up time; cerebrovascular disease; hip fracture; prescription of angiotensin-converting enzyme inhibitors, calcium channel inhibitors, diuretics, benzodiazepines, neuroleptics, warfarin, analgesics, and statins; number of drugs; and gait speed subcohort.
### Table 9. Hazard ratios for death for DBP in the total sample and gait speed subcohorts$^{a,b}$

<table>
<thead>
<tr>
<th>DBP (mm Hg)</th>
<th>Total sample</th>
<th>Gait speed &lt; .5 m/s</th>
<th>Gait speed ≥ .5 m/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N HR (95% CI) P</td>
<td>N HR (95% CI) P</td>
<td>N HR (95% CI) P</td>
</tr>
<tr>
<td>Model 1$^d$</td>
<td>805</td>
<td>432</td>
<td>312</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>1.42 (.11–1.81) .005</td>
<td>1.23 (.70–2.16) .468</td>
<td>1.34 (.99–1.81) .058</td>
</tr>
<tr>
<td>70–74</td>
<td>1.32 (.03–1.69) .031</td>
<td>1.10 (.80–1.52) .552</td>
<td>1.46 (.87–2.45) .155</td>
</tr>
<tr>
<td>75–80</td>
<td>1</td>
<td>.71 (.53–.96) .024</td>
<td>.75 (.54–1.06) .103</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>1.14 (.88–1.49) .321</td>
<td>1.10 (.80–1.52) .552</td>
<td>1.65 (1.01–2.69) .045</td>
</tr>
</tbody>
</table>

Model 2$^e$ 697 398 311

| < 70        | 1.15 (.87–1.53) .337 | 1.23 (.70–2.16) .468 | 1.10 (.80–1.52) .552 |
| 70–74       | 1.37 (.03–1.83) .031 | 1.10 (.80–1.52) .552 | 1.46 (.87–2.45) .155 |
| 75–80       | 1            | .83 (.60–1.15) .251 | .94 (.65–1.36) .735 |
| > 80        | 1.34 (.99–1.81) .058 | 1.76 (1.07–2.90) .026 | 1.76 (1.07–2.90) .026 |

Abbreviations: DBP, diastolic blood pressure; HR, hazard ratio; CI, confidence interval.


$^b$Calculated using Cox proportional-hazard regression models; follow-up time was 5 years. The blood pressure reference category was chosen based on graphical interpretation of initial age- and sex-adjusted analyses in the total sample and in each gait speed group.

$^c$Comprises participants with gait speeds < .5 m/s and those unable to complete the walking test due to habitual impairment of gait function.

$^d$Model 1 was adjusted for age and sex.

$^e$In gait speed subcohorts, adjusted for age, age × follow-up time, sex, heart failure, atrial fibrillation, acute myocardial infarction, cancer, depressive disorder, angina pectoris, body mass index, and Mini-Mental State Examination score. In the total sample, additionally adjusted for care facility residency; living alone; education; education × follow-up time; cerebrovascular disease; hip fracture; prescription of angiotensin-converting enzyme inhibitors, calcium channel inhibitors, diuretics, benzodiazepines, neuroleptics, warfarin, analgesics, and statins; number of drugs; and gait speed subcohort.
RESULTS

Figure 5. Survival curves for systolic blood pressure categories (mm Hg) in the total sample and gait speed subcohorts

Data from *J Am Med Dir Assoc.* 2015;16(3):208–214. ©2015 AMDA – The Society for Post-Acute and Long-Term Care Medicine. CC BY-NC-ND 3.0. Survival curves were based on Cox proportional-hazard regression models. A: Total sample, adjusted for age and sex. B: Total sample, adjusted for age; age × follow-up time; sex; heart failure; atrial fibrillation; acute myocardial infarction; cancer; depressive disorder; angina pectoris; body mass index; Mini-Mental State Examination score; care facility residency; living alone; education; education × follow-up time; cerebrovascular disease; hip fracture; prescription of angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, benzodiazepines, neuroleptics, warfarin, analgesics, and statins; number of drugs; and gait speed subcohort. C: < .5 m/s gait speed subcohort (also including those unable to complete the walking test due to habitual impairment of gait function); adjusted for age, age × follow-up time, sex, heart failure, atrial fibrillation, acute myocardial infarction, cancer, depressive disorder, angina pectoris, body mass index, and Mini-Mental State Examination score. D: ≥ .5 m/s gait speed subcohort, same adjustments as in C.
RESULTS

examining categorized DBP were age, atrial fibrillation, and Barthel ADL index.

**MMSE score 18–23**

In model 1, the lowest SBP category was associated with an increased mortality risk, compared with the highest category (SBP ≤ 125 vs. ≥ 165 mm Hg: HR = 2.81, 95% CI = 1.20–6.54, p = .017). SBP was not associated with mortality risk in model 2. Covariates associated independently with mortality risk in model 2 examining categorized SBP were age, sex, atrial fibrillation, and Barthel ADL index.

In model 1, low DBP was associated significantly with increased 2-year mortality risk, compared with higher intermediary DBP (< 70 vs. 75–80 mm Hg: HR = 1.96, 95% CI = 1.04–3.70, p = .038). In model 2, DBP was not associated with mortality risk. Covariates associated independently with mortality risk in model 2 examining categorized DBP were age, sex, atrial fibrillation, and Barthel ADL index.

**MMSE score 24–30**

In model 1, the lowest SBP category was associated significantly with increased 2-year mortality risk, compared with the highest category (SBP ≤ 125 vs. ≥ 165 mm Hg: HR = 2.19, 95% CI = 1.09–4.40, p = .029). In model 2, SBP was not associated significantly with mortality risk. Covariates associated independently with mortality risk in model 2 examining categorized SBP were sex, atrial fibrillation, depressive disorder, and Barthel ADL index.

DBP was not associated significantly with mortality risk in model 1 or 2. Covariates associated independently with mortality risk in model 2 examining numerical DBP were sex, atrial fibrillation, depressive disorder, and Barthel ADL index.

**Stroke risk**

At baseline, 23% of the participants in the study reported on in paper III had previously had strokes. Baseline stroke prevalence did not differ significantly according to age or sex or between residents of Sweden and Finland. Within 5 years, 94 (9.8%) participants had had strokes, the majority (75%) of which were ischemic. The stroke incidence rate was 34/1000 person-years and did not differ significantly according to age or sex.

The basic model included BP, atrial fibrillation, previous stroke, and heart failure. The intermediate model additionally included MMSE score category (0–18, 19–23, 24–30) and MNA score. The comprehensive model
| SBP (mm Hg) | MMSE 0–10 | | | MMSE 11–17 | | | MMSE 18–23 | | | MMSE 24–30 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | HR (95% CI) | P | N | HR (95% CI) | P | N | HR (95% CI) | P | N | HR (95% CI) | P |
| Model 1 | 118 | | | | | | | | | | |
| ≤ 125 | 118 | 2.41 (1.23–4.72) | .011 | 166 | 1.45 (0.62–3.37) | .389 | 289 | 2.81 (1.20–6.54) | .017 | 542 | 2.19 (1.09–4.40) | .029 |
| 126–139 | 1 | 1.41 (0.58–3.41) | .449 | 1 | 1.97 (.76–5.10) | .161 | 1 | 1.23 (.56–2.73) | .604 | 1 | 1 | . |
| 140–149 | 1.73 (.74–4.02) | .203 | 1.48 (.62–3.51) | .379 | 1.87 (.74–4.76) | .187 | 1.06 (.48–2.34) | .883 | 1 | 1 | . |
| 150–164 | 1.65 (.71–3.85) | .242 | 1.23 (.51–2.98) | .645 | 1.42 (.58–3.48) | .446 | 1.28 (.65–2.53) | .480 | 1 | 1 | . |
| ≥ 165 | 4.48 (1.51–13.23) | .007 | 1 | 1 | 1 | 1 | . |
| Model 2 | 117 | | | | | | | | | | |
| ≤ 125 | 117 | 2.23 (1.12–4.45) | .023 | 165 | 1.18 (.47–2.93) | .729 | 289 | 1.99 (.84–4.73) | .121 | 542 | 1.60 (.72–3.53) | .247 |
| 126–139 | 1 | 1.33 (.52–3.39) | .549 | 1 | 1.55 (.59–4.10) | .378 | 1 | 1.13 (.47–2.72) | .788 | 1 | 1 | . |
| 140–149 | 2.25 (.91–5.57) | .081 | 1.45 (.57–3.69) | .433 | 1.47 (.58–3.77) | .420 | 1 | 1 | . |
| 150–164 | 1.63 (.68–3.87) | .272 | 1.35 (.53–3.45) | .528 | 1.36 (.55–3.34) | .507 | 1 | 1.16 (.53–2.54) | .714 | 1 | 1 | . |
| ≥ 165 | 4.54 (1.52–13.60) | .007 | 1 | 1 | 1 | 1.05 (.47–2.31) | .911 | 1 | 1 | . |

Abbreviations: SBP, systolic blood pressure; MMSE, Mini-Mental State Examination; HR, hazard ratio; CI, confidence interval.


bHRs, CIs, and p values were calculated using Cox proportional-hazard regression models; follow-up time was 2 years.

cModel 1 was adjusted for age and sex.

dModel 2 was adjusted for age, sex, atrial fibrillation, depressive disorder, and Barthel Activities of Daily Living index.
Figure 6. Survival curves for systolic blood pressure categories (mm Hg) in Mini-Mental State Examination score subcohorts

RESULTS

Additionally included gait speed and GDS score. The dementia and delirium variables were removed due to strong correlations with MMSE score. The Barthel ADL index variable was removed due to strong correlations with the MNA and MMSE scores and gait speed. Among other variables, classes of antihypertensive drug (beta blockers, calcium channel blockers, ACE inhibitors, and type 1 angiotensin II receptors) were not associated bivariately with incident stroke and thus were not included in the multivariate models.

Interaction effects between SBP, DBP, PP, and MAP and sex, Barthel ADL index, and MMSE score were not significant in any model. Additional interaction effects are presented in the next section.

Multivariate associations with incident stroke are presented for models examining numeric SBP in Table 11 and for additional BP measures in Table 12. BP and atrial fibrillation were associated significantly with increased stroke risk in all three multivariate models. In the comprehensive model, stroke risk was increased by 19%, 26%, 17%, and 32% per 10 mm Hg increase in SBP, DBP, PP, and MAP, respectively (SBP: HR = 1.19, 95% CI = 1.08–1.30, p < .001; DBP: HR = 1.26, 95% CI = 1.05–1.52, p = .013; PP: HR = 1.17, 95% CI = 1.04–1.31, p = .006; MAP: HR = 1.32, 95% CI = 1.13–1.54, p < .001). Atrial fibrillation was associated with 85% increased stroke risk in the comprehensive model (HR = 1.85, 95% CI = 1.07–3.19, p < .027). Previous stroke was also associated significantly with increased stroke risk in the intermediate and basic models. Quadrated BP terms, together with corresponding numeric BP variables showed no significant association in any model.

In all three models, SBP ≥ 160 mm Hg was associated with a more than doubled stroke risk compared with SBP < 140 mm Hg (basic: HR = 2.20, 95% CI = 1.27–3.84, p = .005; intermediate: HR = 2.51, 95% CI = 1.43–4.42, p = .001; comprehensive: HR = 2.80, 95% CI = 1.53–5.14, p < .001). DBP ≥ 90 mm Hg was also associated with increased stroke risk compared with DBP < 90 mm Hg in all three models (basic: HR = 2.08, 95% CI = 1.28–3.41, p = .003; intermediate: HR = 2.33, 95% CI = 1.41–3.85, p < .001; comprehensive: HR = 2.45, 95% CI = 1.47–4.08, p < .001). Additional associations are presented in the next section.

Additional analyses

Baseline systolic blood pressure

In bivariate analyses, mean SBP and DBP did not differ according to the sex or nationality (Swedish vs. Finnish) of all first-time participants. Mean SBP and DBP showed decreasing trends with age (SBP: Pearson r = –.22; DBP: Pearson r = –.18; both p < .001), age group (both p < .001), and later
### Table 11. Multivariate associations with incident stroke<sup>a,b</sup>

<table>
<thead>
<tr>
<th></th>
<th>Basic model</th>
<th>Intermediate model</th>
<th>Comprehensive model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>SBP (/10-mm Hg increase)</td>
<td>909</td>
<td>1.16 (1.06–1.27)</td>
<td>.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.78 (1.09–2.93)</td>
<td>.022</td>
<td>1.79 (1.08–2.99)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.77 (1.13–2.77)</td>
<td>.013</td>
<td>1.61 (1.01–2.56)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.50 (0.94–2.41)</td>
<td>.092</td>
<td>1.56 (0.96–2.52)</td>
</tr>
<tr>
<td>MMSE &lt; 18 (vs. ≥ 24)</td>
<td>1.82 (0.95–3.50)</td>
<td>.073</td>
<td>1.50 (0.72–3.12)</td>
</tr>
<tr>
<td>MMSE 18–23 (vs. ≥ 24)</td>
<td>1.42 (0.86–2.33)</td>
<td>.170</td>
<td>1.36 (0.81–2.29)</td>
</tr>
<tr>
<td>MNA (score)</td>
<td>0.97 (0.92–1.03)</td>
<td>.405</td>
<td>0.97 (0.91–1.04)</td>
</tr>
<tr>
<td>Gait speed (m/s)</td>
<td>.39 (0.13–1.16)</td>
<td>.092</td>
<td>1.04 (0.35–1.14)</td>
</tr>
<tr>
<td>MNA (&lt; 18 vs. ≥ 24)</td>
<td>1.04 (0.95–1.14)</td>
<td>.394</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; MMSE, Mini-Mental State Examination; MNA, Mini-Nutritional Assessment; GDS, Geriatric Depression Scale.


<sup>b</sup>HRs, CIs, and p values were calculated using Cox proportional-hazard regression models; follow-up time was ≤5 years.

### Table 12. Multivariate associations of additional blood pressure measures with incident stroke<sup>a,b</sup>

<table>
<thead>
<tr>
<th></th>
<th>Basic models&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Intermediate models&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Comprehensive models&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>SBP ≥ 160 mm Hg (vs. &lt; 140)</td>
<td>2.20 (1.27–3.84)</td>
<td>.005</td>
<td>2.51 (1.43–4.42)</td>
</tr>
<tr>
<td>SBP 140–159 mm Hg (vs. &lt; 140)</td>
<td>1.63 (0.93–2.86)</td>
<td>.089</td>
<td>1.60 (0.90–2.85)</td>
</tr>
<tr>
<td>DBP ≥ 90 mm Hg (vs. &lt; 90)</td>
<td>2.08 (1.28–3.41)</td>
<td>.003</td>
<td>2.33 (1.41–3.85)</td>
</tr>
<tr>
<td>DBP (/10-mm Hg increase)</td>
<td>1.21 (1.01–1.45)</td>
<td>.037</td>
<td>1.24 (1.04–1.49)</td>
</tr>
<tr>
<td>PP (/10-mm Hg increase)</td>
<td>1.14 (1.03–1.27)</td>
<td>.015</td>
<td>1.18 (1.05–1.31)</td>
</tr>
<tr>
<td>MAP (/10-mm Hg increase)</td>
<td>1.27 (1.09–1.48)</td>
<td>.002</td>
<td>1.32 (1.13–1.54)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; MAP, mean arterial pressure.


<sup>b</sup>HRs, CIs, and p values were calculated using Cox proportional-hazard regression models; follow-up time was ≤5 years.

<sup>c</sup>The basic models included atrial fibrillation, previous stroke, and heart failure.

<sup>d</sup>The intermediate models additionally included categorical Mini-Mental State Examination and Mini-Nutritional Assessment scores.

<sup>e</sup>The comprehensive models additionally included Geriatric Depression Scale score and usual gait speed.
investigation year (SBP: Pearson r = −.13; DBP: Pearson r = −.15; both p < .001).

A multivariate model examining baseline SBP prediction included the baseline variables age, female sex, investigation year, living alone, education, former smoking, heart failure, atrial fibrillation, AMI, cerebrovascular disease, cancer, hip fracture, COPD, depressive disorder, angina pectoris, ACE inhibitors, calcium channel blockers, diuretics, neuroleptics, paracetamol, NSAIDs, MMSE score, BMI, MNA score, GDS score, and gait speed. The baseline antidepressants, warfarin, and number of drugs variables were removed due to strong correlations with depressive disorder, atrial fibrillation, and diuretics, respectively. The dementia variable was removed due to strong correlation with MMSE score. The Barthel ADL index variable was removed due to strong correlations with MMSE score and care facility residency.

Among all first-time participants, baseline variables associated independently with SBP were age (B = −.62, SE = .21, p = .003), female sex (B = 6.32, SE = 1.92, p = .001), former smoking (B = 3.96, SE = 1.82, p = .030), heart failure (B = −6.56, SE = 2.17, p = .003), atrial fibrillation (B = −.42, SE = 2.08, p = .034), and MMSE score (B = .42, SE = .20, p = .032). Regression equations were significant (F[26, 737] = 4.520, p < .001, r² = .138).

**Change in systolic blood pressure**

Removal of the Barthel ADL index variable produced significant associations between MMSE score and ΔSBP in models 2 and 3 (B = .53, SE = .19, p = .002). Replacement of the antidepressants variable with the depressive disorder variable did not produce a significant association between depressive disorder and ΔSBP in model 3 (p = .166).

**Mortality risk**

In an additional analysis of the total sample reported on in paper I, the removal of any covariate associated significantly with mortality in model 2 did not produce a significant association between any SBP category and mortality risk. The removal of all covariates associated significantly with mortality in model 2, except age and sex, did not produce a significant association between any SBP category and mortality risk.

The associations between BP and mortality risk were investigated in the total sample described in paper II. Mortality risk was associated significantly with SBP (≥ 165 vs. ≤ 125 mm Hg: HR = .38, 95% CI = .24−.59, p < .001), but not with DBP, in model 1. Model 2 included age, sex, BP, living alone, heart failure, atrial fibrillation, hip fracture, depressive disorder, angina
RESULTS

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pectoris, ACE inhibitors, beta blockers, diuretics, benzodiazepines, neuroleptics, opioids, paracetamol, statins, number of drugs, Barthel ADL index, and MMSE score. The dementia and antidepressants variables were removed due to strong correlations with MMSE score and depressive disorder, respectively. The models examining SBP and DBP were identical, although developed separately. Covariates associated independently with mortality risk in model 2 were age, male sex, atrial fibrillation, depressive disorder, lower Barthel ADL index, and lower MMSE score. Model 2 yielded no significant association between any BP category and mortality risk in this sample. The removal of all covariates associated significantly with mortality in model 2, except age and sex, produced significant associations between the two highest SBP categories and mortality, compared with the lowest SBP category (150–164 vs. < 126 mm Hg: HR = .67, 95% CI = .51–.89, p = .005; ≥ 165 vs. < 126 mm Hg: HR = .66, 95% CI = .49–.89, p = .006).

Replacement of the categorical SBP variable with a numeric variable resulted in a significant association with mortality risk in model 1 for the total samples reported on in papers I (per 10 mm Hg: HR = .90, 95% CI = .86–.95, p < .001) and II (HR = .86, 95% CI = .81–.91, p < .001), as well as in the gait speed < .5 m/s subcohort (per 10 mm Hg: HR = .91, 95% CI .86–.97, p = .001) and the MMSE score 18–23 subcohort (HR = .87, 95% CI .78–.96, p = .009). Replacement of the categorical DBP variable with a numeric variable resulted in a significant association with mortality risk in model 1 for the total sample described in paper II (per 10 mm Hg: HR = .84, 95% CI = .76–.93, p = .001) and the MMSE score 24–30 subcohort (per 10 mm Hg: HR = .77, 95% CI = .62–.97, p = .023). The numeric SBP and DBP variables were not associated with mortality risk in model 2.

The addition of a quadrated SBP term to a model including a numeric SBP variable resulted in a significant association with mortality risk in the MMSE score 0–10 (models 1 and 2, p < .001) and 24–30 (model 1, p = .023) subcohorts. The addition of a quadrated DBP term to a model including a numeric DBP variable resulted in a significant association with mortality risk in the MMSE score 18–23 subcohort in models 1 (p = .022) and 2 (p = .037).

**Stroke risk**

Stroke risk among participants with SBP 140–159 mm Hg did not differ from that of participants with SBP < 140 or ≥ 160 mm Hg in any model. Interaction effects on the association with stroke risk were not significant between the numeric or categorized SBP or DBP variable and gait speed or MMSE score subcohort in the basic model.
Discussion

The discussion is organized around the three aims of this thesis; the first concerns determinants of SBP, the second concerns the association of BP with mortality risk, and the third concerns the association of BP with stroke risk. It also includes a section on optimal BP in relation to these risks. The main findings are discussed in relation to previous findings and possible pathophysiological mechanisms. Methodological considerations, ethical considerations, and clinical implications are discussed separately. Implications for future research are described at the end of the discussion, together with a summary of the conclusions.

Main findings

The average annual SBP decline among followed participants was 2.6 ± 5.4 mm Hg. The majority (62%) of participants experienced SBP declines ≥ 5 mm Hg during the 5-year follow-up period. Within 5 years, 61% of participants had died and 10% had had incident strokes.

SBP declined with later investigation year, higher baseline SBP, baseline antidepressant drug use, incident AMI during follow-up, declining Barthel ADL index scores during follow-up, and use of a new diuretic drug during follow-up.

Lower SBP and DBP were associated with increased mortality risk in the total sample and among slower-walking participants, but the associations with SBP were dependent on adjustment. Among faster-walking participants, higher SBP and DBP were associated significantly with mortality risk in the fully adjusted analyses. Interaction effects on the association with mortality risk were significant between SBP, but not DBP, and gait speed.

In participants with very severe cognitive impairment, high and low SBP were associated significantly with increased mortality risk, compared with lower intermediary SBP, in the fully adjusted analyses. Interaction effects on the association with mortality risk were borderline significant between SBP, but not DBP, and MMSE score subcohort.

Significant and independent associations were found between stroke risk and higher SBP, DBP, PP, MAP, and atrial fibrillation in multivariate models. Interaction effects on the association with stroke risk between measures of BP and dependency in ADL and cognitive impairment were not significant.
Determinants of systolic blood pressure

Average SBP ranged from 133 to 157 mm Hg in groups defined by sex, age, and investigation year. These levels are congruent with findings from several other population-based studies.\textsuperscript{10-14,19,21,22,24} Higher SBP was observed in the Tromsø Study,\textsuperscript{10} possibly due to the younger age range of 80–89 years.

Longitudinal SBP decline was expected among very old individuals, given observations from previous longitudinal studies.\textsuperscript{14,17,26-28,32} The average annual SBP change of $-2.6 \pm 5.4$ mm Hg in the current study population is in line with previous findings of $-1.5$ to $-2.9$ mm Hg/year from the Leiden 85+ Study,\textsuperscript{28} the Helsinki Ageing Study,\textsuperscript{30} and a previous Umeå 85+/GERDA study.\textsuperscript{32} Many fewer (26\%) participants in the sample reported on in paper IV experienced a $\geq 5$ mm Hg increase in SBP during the follow-up period, compared with those who had declining SBP.

The proportion (62\%) of participants with SBP declines $\geq 5$ mm Hg over 5 years is somewhat smaller than reported in a previous Umeå 85+/GERDA study (69\%).\textsuperscript{32} That study had a marginally longer follow-up time compared with the study reported on in paper IV (mean 4.8 vs. 4.7 years), which may explain this difference. In addition, it had fewer participants ($n = 102$ vs. 297). Still, the mean SBP changes were larger in the sample described in paper IV than in 85-year-olds in the Helsinki Ageing Study.\textsuperscript{30}

Determinants of cross-sectional SBP are discussed first, followed by a discussion of the determinants of longitudinal SBP changes.

**Baseline systolic blood pressure is determined by age and morbidity**

In a multivariate model, higher baseline SBP was associated with younger age, female sex, and former smoking, and lower baseline SBP was associated with heart failure, atrial fibrillation, and lower MMSE score. However, only 14\% of the variation was explained by the model, and factors not accounted for are likely important predictors of baseline SBP.

The observation of higher SBP among women than among men is in accordance with the findings of previous studies of very old individuals.\textsuperscript{10-14} Sex differences in SBP and DBP were significant in multivariate analyses adjusted for age, investigation year, and region. These results are in accordance with those of a Vantaa study,\textsuperscript{12} in which significant sex differences in SBP were found among $\geq 85$-year-old participants. In contrast, average BP may be higher among men than among women in younger populations.\textsuperscript{182}

The observed effects of age, former smoking, heart failure, and MMSE score on SBP are in line with previous observations.\textsuperscript{39-41,46,55-57,78,183} Atrial fibrillation was also found to be associated with lower SBP. The effects of age
may be explained by the interference of age-related conditions with BP regulation. The trend of declining SBP with later investigation year, observed in a bivariate analysis, is also in line with previous results. However, investigation year was not associated independently with baseline SBP in the multivariate model, suggesting that temporal trends in cross-sectional SBP are not very strong among very old individuals, and may be better explained by other variables included in the model.

No class of BP-lowering medication had a significant effect in the multivariate model, suggesting that other factors included in the model, such as heart failure, have stronger effects on SBP in very old age. BP levels have been found to differ regionally, but they did not differ between Swedish and Finnish participants in the Umeå 85+/GERDA study.

**Temporal trends of systolic blood pressure change**

Although investigation year was not associated independently with cross-sectional SBP, it was an independent predictor of longitudinal SBP decline in the study reported on in paper IV, in line with the findings of a previous study of individuals aged ≥ 65 years from the Florida Geriatric Research Program. The association between investigation year and SBP change indicates a temporal trend, in which later investigation year is associated with greater SBP decline in very old individuals. The temporal trends of SBP may be due to external exposures, such as dietary, lifestyle, and environmental factors, or the use of BP-lowering medication.

Age was not associated independently with longitudinal SBP change in the final model reported on in paper IV. This finding is in contrast to previous findings from the Umeå 85+/GERDA, EPESE project, and Helsinki Ageing studies, in which greater age was shown to predict SBP decline. The previously observed association between greater age and SBP decline may be confounded by temporal trends, as the analyses were not adjusted for investigation year, or were performed with all participants included in the same year, rendering associations with age and time indistinguishable. The association between age and SBP decline may also be confounded by age-related morbidity, which was not adjusted for in the previous Umeå 85+/GERDA study. Disease attenuated the age-related increase in SBP in a sample of initially disease-free community-resident individuals aged ≥ 70 years from the Healthy Old People in Edinburgh cohort.

Surprisingly, longitudinal SBP increase was associated with greater age in model 2 in the study reported on in paper IV. This association was independent of investigation year. In model 3, it was only borderline significant, indicating that it was influenced by the baseline factors that were added in model 3. This association may indicate that, in the absence of
disease, SBP continues to increase with age into very old age, possibly due to the age-related progression of arterial stiffness. Additional studies are needed to adequately determine the importance of this trend.

**Morbidity predicts systolic blood pressure decline**

In line with previous findings, several health-related factors were associated with SBP changes in the present research.\(^{29,30,32,33,58,80-84}\) SBP declined with baseline factors indicating poorer health and with changes toward increased morbidity. The general trends were of increasing morbidity and declining SBP, rather than improving health and increasing SBP, although the opposite occurred in some individuals.

In contrast to previous findings, SBP change was not associated independently with sex, transfer to a care facility, or changes in levels of cognitive performance and depressive symptoms.\(^{29,30,32,82-84}\) The associations of SBP change with care facility transfer and changes in levels of cognitive performance and depressive symptoms were significant in bivariate analyses, but they did not seem to be independent of adjustment among very old people. In particular, they may be confounded by changes in the Barthel ADL index, which is closely related to these factors.\(^{184,185}\) The removal of this variable from the multivariate models revealed significant associations between MMSE score changes and SBP changes.

The role of antidepressant drug use in SBP decline may be explained by the effects of these drugs on autonomic regulatory cardiac control. Although different classes of antidepressant drugs may shift autonomic cardiac control in different directions, SSRIs, the most prevalent class in the sample reported on in paper IV, have been found to decrease sympathetic control and may thereby reduce SBP.\(^{69,70}\) Alternative explanations include underlying depressive disorder or anxiety, for which antidepressants may be prescribed, which may be associated with SBP decline.\(^{58,81}\) However, replacement of the antidepressants variable with the depressive disorder variable produced no significant association with SBP change in model 3, suggesting that depressive disorder is not an independent determinant of SBP change in very old age.

The association between new diuretic drug prescription and SBP decline may be therapeutic. This result is in line with a previous finding of an association between antihypertensive medication use and SBP decline.\(^{30}\) Different BP-lowering drug classes, i.e., ACE inhibitors and beta blockers, were not associated independently with SBP decline; the effect on BP change seems to be better explained by other factors included in the models. The association of SBP change with the use of calcium channel blockers was not significant in bivariate or multivariate analyses. The effects of different BP-
lowering drug classes on SBP level may be influenced by dosage, combined treatment, and treatment indication.

SBP decline with incident AMI may be due to secondary heart failure. It may also be due to secondary prevention, which involves the use of BP-lowering drugs.

Decreasing Barthel ADL index was associated with decreasing SBP. As decreases in this index indicate loss of independence in ADL and increased morbidity, this result is congruent with the other observed associations of increasing morbidity with SBP decline. The association may be explained by an underlying factor, such as debilitating end-stage cardiac disease, dementia development, or cerebrovascular pathology, which may interfere with BP regulatory mechanisms. The heart failure and dementia variables were not associated significantly with SBP change in multivariate analyses. However, these variables were not specific to severe heart failure and preclinical dementia, respectively, which may still influence the association with SBP change.

Although morbidity seemed to predict SBP decline among followed participants in the present study, this sample was not representative of the general very old population due to the survival bias inherent in longitudinal studies. The extent to which this bias affected the results is not clear. In addition, half of the variation was not explained by the final model and additional factors may be important in predicting SBP change. The findings contribute novel information about the ability of individual health-related factors to predict SBP changes among 5-year survivors in a comprehensively adjusted model.

**Higher systolic blood pressure predicts later decline**

In line with previous findings, SBP declined with higher baseline SBP in the present research. Baseline SBP explained 66% of the variation in the final model and was by far the strongest predictor of SBP change. This association may be explained by reversed causality, in which an adverse outcome causes a reduction in the primary risk factor. Higher baseline SBP may increase the risk of cardiovascular disease, which in turn may cause a reduction in SBP. Cardiovascular disease may include heart failure, which in the end stages may cause a reduction in SBP due to low cardiac output. As stated previously, despite the lack of an association between the heart failure variable and SBP decline in multivariate analyses, severe heart failure may still influence this association, as the variable was not stratified according to disease severity.

However, the association between higher baseline SBP and SBP decline may also be explained by regression toward the mean. As the sample of followed participants seems to have been affected by selection of individuals
with higher baseline SBP, likely due to survival bias, any measurement error in the baseline SBP variable may have caused regression toward the mean in follow-up assessments.

Blood pressure, mortality risk, and subgroups

*Low systolic blood pressure may be a risk marker for mortality due to other factors in very old people*

SBP and DBP were associated inversely with mortality in the studies described in papers I and II. These results are supported by previous observations from population-based studies of very old individuals.\(^{11-13,21,22,28,91-93}\) The previously found non-linear associations between SBP and mortality risk in the EPESE project\(^3\) and Umeå 85+/GERDA\(^93\) study were not replicated in the total samples in the analyses described in papers I and II.

The inverse association between SBP and mortality risk lost significance with comprehensive adjustment for confounders, indicating that the association is dependent on other factors. This result is supported by findings from the Jerusalem Longitudinal Study,\(^{22}\) two studies from Leiden,\(^{28,91}\) and the LASA.\(^{92}\)

In contrast, independent associations between SBP and mortality risk were found in the Tampere,\(^{11}\) Vantaa 85+,\(^{12}\) Umeå 85+/GERDA,\(^{93}\) and EPESE project\(^3\) studies and in one Leiden 85+ Study.\(^{21}\) These studies involved less extensive adjustment than the analysis described in paper I, which may explain the results. The previous Umeå 85+/GERDA study\(^{93}\) involved the evaluation of largely the same confounders, but fewer confounders qualified for inclusion in the multivariate model, likely due to the smaller sample of 248 participants compared with the 806 and 1115 participants in the studies described in papers I and II, respectively.

Other differences between studies may also explain the diverging results. The EPESE project\(^3\) study sample seems to have been healthier than the sample reported on in paper I, as demonstrated by the lower prevalence of diseases such as stroke, which was 8–10% among participants aged ≥ 85 years in the EPESE project sample compared with 20% in the sample reported on in paper I. However, sample characteristics in other studies that produced divergent results seem to have been similar to those in the study reported on in paper I.\(^{11,12,21,93}\)

In short, findings of population-based studies indicate that low SBP is associated with increased mortality risk in very old people. This association was independent in several studies, perhaps due to underadjustment. The extent of adjustment may determine whether the association is perceived to be dependent or independent of other factors.
Comorbidity may confound the association between systolic blood pressure and mortality risk

Any covariate in the model may confound the association between SBP and mortality risk, although those associated more strongly with the outcome are more likely to influence the association. Specifically, male sex, heart failure, atrial fibrillation, AMI, cancer, depressive disorder, absence of angina pectoris, lower BMI, lower MMSE score, and lower gait speed were associated significantly with increased mortality risk in the multivariate model described in paper I. Sex does not likely explain the absence of an independent association between SBP and mortality risk in the general very old population, as it was also included in model 1. Corresponding variables in the larger sample reported on in paper II were atrial fibrillation, depressive disorder, lower Barthel ADL index, and lower MMSE score.

Additional analyses were performed to test whether these factors were confounders. Although the removal of any one of these factors did not produce a significant association between SBP and mortality risk, the removal of all of them together did. These results highlight the importance of multimorbidity in the association of SBP with mortality; it may contribute to mortality more quickly than does hypertension.

No clear pattern of adjustment for these factors in previous studies that would distinguish the presence from the absence of an independent association between SBP and mortality can be identified, further supporting the argument that multimorbidity may confound this association. However, studies showing independent associations\textsuperscript{11-13,21,93} did not involve the same extent of adjustment for cardiovascular morbidity as did studies showing dependent associations\textsuperscript{22,28,91,92} For instance, adjustment for atrial fibrillation was performed in the previous Umeå 85+/GERDA study,\textsuperscript{93} but several studies showing independent associations included composite cardiovascular disease\textsuperscript{21,28,92} or antiarrhythmic drug variables.\textsuperscript{91} Two of five studies\textsuperscript{21,93} showing independent associations and three of four studies\textsuperscript{28,91,92} showing dependent associations involved adjustment for atrial fibrillation in some form. This may indicate a central confounding role of cardiovascular disease in the association of SBP with mortality.

Other cardiovascular diseases implicated in this association include heart failure, angina pectoris, and AMI. The seemingly protective effect of angina pectoris may be explained by positive effects of its treatment with nitroglycerin, the prescription of which was an additional classification criterion for this variable. Heart failure was shown to have no influence on the association of low SBP with increased mortality risk in a Leiden 85+ Study.\textsuperscript{187} BMI,\textsuperscript{188} gait speed,\textsuperscript{189} MMSE score,\textsuperscript{87} ADL dependency,\textsuperscript{159,160} and depressive disorder\textsuperscript{190} are also associated with cardiovascular disease. They
may also affect the association of BP with mortality through some other mechanism.

In addition to being associated independently with mortality risk, the depressive disorder, dependency in ADL, and AMI covariates were implicated in SBP decline. Based on these patterns, depressive disorder and increased ADL dependency may be important confounders of the previously observed associations of SBP decline with mortality risk.14,28,31,33 This issue remains to be determined.

Multimorbidity seems to be very important in the association of BP with mortality. Consequently, the health status of a study sample will greatly influence the results obtained. Differences in health status may explain differences in the association between low BP and mortality with age and among populations.

*Low diastolic blood pressure may be associated with increased mortality risk*

The findings of inverse associations between DBP and mortality in the studies reported on in papers I and II are in line with previous observations from the Tampere,11 Umeå 85+/GERDA,93 Vantaa 85+,12 and Leiden 85+ studies,21,91 and the LASA.92 Whether this association is independent of adjustment remains unclear. Lower intermediary DBP was associated significantly with increased 5-year mortality risk, compared with higher intermediary DBP, in the fully adjusted model described in paper I, whereas no independent association was found in the analysis of the total sample reported on in paper II, or between numeric DBP variables and mortality in either sample. Of the previous population-based studies investigating this association, only one study,91 from Leiden, showed that the association was not independent of adjustment.

Further studies are needed to determine whether the association between DBP and mortality risk in very old age is independent of adjustment. A possible causal relationship between lower DBP and mortality risk could be explained by reduced perfusion of the heart during diastole. Heart failure and adverse drug reactions due to intensive antihypertensive therapy may also explain the association.40 However, individual BP-lowering drug classes were not associated with mortality risk in the models.

*Gait speed and Mini-Mental State Examination score moderate associations between blood pressure and mortality risk*

A thorough search of the relevant literature produced no previous study investigating the association between BP and mortality with respect to gait
speed or MMSE score in individuals aged ≥ 80 years. Thus, comparisons are made with studies of younger individuals.

The observation that gait speed had a moderating effect on the association of SBP with mortality risk in this research is in line with previous observations in individuals aged ≥ 65 years from the NHANES, the Peñagrande cohort, and the sample examined by Rozzini and Trabucci. The LASA and CHS produced contrasting results; in these studies, the association between SBP and mortality risk did not differ according to gait speed. The divergence of these results may be explained by differences in samples and methods, such as lower levels of comorbidity in younger samples and the use of different cutoff values.

The moderating effect of MMSE score on the association of SBP with mortality is unclear, due to the borderline significant interaction effect. Most previous studies have documented no difference in the association of SBP with mortality risk among MMSE score subcohorts. The Kungsholmen Project did show such differences, but they were among participants with mild or no cognitive impairment, which did not appear to differ in the sample described in paper II. In the study reported on in paper II, the association between SBP and mortality risk appeared to differ the most between the very severe cognitive impairment subcohort and the other subcohorts. Previous researchers have not differentiated participants with MMSE scores < 24, but the prevalence of severe and very severe cognitive impairment was likely comparatively low in their younger samples.

The results of the present research suggest that the association between DBP and mortality does not differ according to gait speed or MMSE score. This finding is in contrast to most observations in younger samples, in which differences according to gait speed and MMSE score have been found.

Another study from the Kungsholmen Project found a moderating effect of combined measures of MMSE score and gait speed on the association of SBP with mortality risk, in individuals aged ≥ 60 years. The results of this study may not be comparable with the findings of the present research, due to categorization of participants according to combined measures of MMSE and gait speed, but they highlight the importance of these factors in the association of SBP with mortality risk.

In summary, the results of this research suggest that gait speed moderates the association between SBP and mortality in very old individuals. As conclusions cannot be drawn from single observations, this finding needs to be corroborated in different samples of very old individuals. The association of SBP with mortality risk may differ among MMSE score subcohorts, but this issue needs to be investigated further. The extrapolation of these results
from the general very old population to individuals with very severe cognitive impairment may be inappropriate.

**Low systolic blood pressure may be a risk marker for mortality due to other factors in subgroups with low gait speed or better cognitive performance**

The findings of inverse associations between BP and mortality among slower-walking participants are in line with previous observations of slower-walking individuals and those who did not complete the gait speed test in studies of individuals aged ≥ 65 years. However, contrasting results were obtained for participants without cognitive impairment. Other studies have documented no association between SBP and mortality risk among individuals with mild cognitive impairment. The divergent findings among MMSE score subcohorts may be due to age-related differences among samples, such as the level of comorbidity, which may influence the association in older populations.

The findings of inverse and non-linear associations between DBP and mortality risk among participants with mild cognitive impairment are in line with most previous observations. Contrasting results were reported for the Kangwa cohort, in which mortality risk was associated independently with higher BP in women with mild or severe cognitive impairment, and one Kungsholmen Project study, in which low SBP was associated independently with decreased all-cause mortality risk in participants with high MMSE scores and high gait speeds. Comparison of these results with the present findings is difficult because the Kangwa researchers classified BP according to combined consideration of SBP and DBP and the Kungsholmen researchers used a combined measure of MMSE score and gait speed.

In conclusion, slower-walking individuals seem to have an increased mortality risk in association with lower BP, according to the present study findings and previous findings among individuals aged ≥ 65 years. Similar associations may pertain to individuals with mild or no cognitive impairment, but findings are divergent. These associations correspond with those from the total samples in the present research.
High systolic and diastolic blood pressures may increase mortality risk among faster-walking individuals

The finding of an independent association between high SBP and mortality risk among faster-walking participants is supported by results from a younger NHANES sample. It is also in line with the results from a younger Kungsholmen Project study, but differences in mortality risk were only observed between lower categories of SBP in the Kungsholmen Project. Other studies investigating this issue have shown no association between mortality and SBP or DBP in faster-walking individuals. This disparity may be explained by differences in study samples, methods, and adjustment.

Performance of the gait speed test with an insufficient distance has been suggested to influence gait speed assessment and its ability to moderate the association of BP with mortality. However, the relatively short distance (2.4 m) of the Umeå 85+/GERDA gait speed test was sufficient to demonstrate a positive association. This distance was shorter than those used in the LASA and CHS, which revealed no moderating effect of gait speed on the association of SBP with mortality. Other differences in the gait speed test that may influence the assessment are related to the starting attitude (standing still vs. walking), inclusion of turning, and the use of walking aids. The gait speed cutoff value of .5 m/s used in the study described in paper I is lower than the .8 m/s used in most previous studies, but seems to be relevant in the very old population.

The categorization of BP may also influence the results, as demonstrated in additional analyses for the study described in paper I, in which the use of numeric variables produced non-significant results. This factor alone may not explain the differing results, as BP was categorized in the LASA and CHS in almost the same way as in the present study, although with fewer categories, and those studies showed no association between BP and mortality in faster-walking participants. The findings of Rozzini and Trabucci and the Kungsholmen Project may not be comparable with those of the other studies because they were based on self-reported hypertension or combined measures of MMSE score and gait speed, respectively.

The results of the present study suggest that the independent association between high BP and mortality risk pertains only to individuals in better health, as indicated by higher gait speed or, perhaps, another indicator of health status. Due to methodological differences among previous studies, further studies are needed to corroborate these findings.
Heterogeneity of health status affects the association between blood pressure and mortality risk

The dependent, inverse associations of SBP and DBP with mortality among slower-walking participants and those with mild or no cognitive impairment correspond with those found in the total sample in the present research. As these subgroups constituted the majorities of the samples, associations found within them may have had major impacts on the associations observed in the total sample.

Surprisingly, associations were comparable among slower-walking participants, who are thought to have poorer health status, and participants with better cognitive performance. These findings may indicate that gait speed is a more comprehensive indicator of health status than is the MMSE score, at least in relation to multimorbidity, which seems to affect the association of low BP with mortality risk among very old individuals. In this regard, the subcohorts of participants with mild or no cognitive impairment may have included individuals with good or poor health status, compared with the total sample.

In younger populations, the level of comorbidity is generally lower and the ratio of faster- to slower-walking individuals may be higher, as demonstrated in the NHANES.143 Accordingly, the associations found for faster-walking individuals may have major impacts in younger samples, in which independent associations between higher SBP and mortality risk are usually found.13,90 However, the transition from good to poor health is complex and not likely determined by any single measure or cutoff value. Nevertheless, findings from total samples of old and very old populations may be misleading due to heterogeneity of health status. Given the importance of this heterogeneity in the association between BP and mortality risk, increasing ratios of individuals with multimorbidity may explain the apparent change in this association with increasing age.

Extreme systolic blood pressure may increase mortality risk in individuals with very severe cognitive impairment

Very low MMSE scores seemed to identify a group of very old individuals with independently increased mortality risk associated with both high and low SBP in the present research. The Kungsholmen Project165 generated similar findings; SBP < 130 mm Hg was associated with an increased 5-year mortality risk compared with SBP ≥ 130 mm Hg in very old individuals with MMSE scores < 24, but not in those with scores ≥ 24. Because of further stratification of MMSE scores in the study reported on in paper II, a group showing independent associations between BP and mortality could be delineated using scores ≤ 10, as no association was found in the subcohort
with MMSE scores of 11–17. These differences are likely gradual and not reflected by absolute cutoff values. However, the ability of the MMSE score ≤/≥ 10 cutoff to differentiate levels of cognitive impairment has not been tested.

Several previous studies of younger populations showed no association between SBP and mortality among participants with cognitive impairment.92,165,167,169 This discrepancy may be due to age-related differences among study populations, as mean ages were lower than in the sample described in paper II and the Kungsholmen Project165 sample. Such differences may include lower levels of comorbidity in younger populations.

Adjustment was not extensive in the present study due to the small size of some subcohorts, and this association may depend on other factors. In addition, 95% CIs were large in the MMSE score ≤ 10 subcohort, indicating a lack of analytical power. The significance of this finding needs to be confirmed in larger samples. Still, the results of the analyses conducted with the categorized variable are supported by those conducted with the quadrated numerical variable, in which statistical power was not limited by categorization.

The increased mortality risk associated with extreme SBP could be explained by factors associated with cognitive impairment, such as cerebrovascular disease and reduced cerebral autoregulation of BP.50,191 Reduced cerebral autoregulation may expose the cerebral circulation to the adverse effects of high and low SBP, which may involve atherosclerosis, white matter lesions, and hypoperfusion of brain tissue.192-198

**Blood pressure and stroke risk**

At baseline, 23% of individuals in the sample reported on in paper III had previously had strokes. This prevalence is somewhat higher than the 21% found among all first-time participants in 2000–2012 because stroke prevalence was complemented with data from death certificates in this sample. Both prevalences were higher than the previously observed 10–20% among very old individuals.103-105

Ten percent of participants had strokes, the majority of which were ischemic, during the follow-up period. The stroke incidence of 34/1000 person-years was higher than most previous observations,106-110 but lower than in the H70 study.103 Some previously reported incidences were for first-ever stroke,107-110 which may be lower than the incidence of any stroke.
High blood pressure is an independent risk factor for stroke in very old individuals

The results of the present research indicate that stroke risk increases linearly with BP. However, the lower boundary of this association remains unclear due to conflicting results. The linear association was not shown in participants with SBP < 140 mm Hg. In contrast, SBP < 140 mm Hg was associated with decreased stroke risk compared with SBP ≥ 160 mm Hg. In addition, the stroke risk associated with SBP of 140–159 mm Hg is unclear, as it did not differ from that observed for the < 140 and ≥ 160 mm Hg categories.

The observation of an increased stroke risk associated with higher BP is in line with previous findings from younger populations and with the results of the Prospective Studies Collaboration. The findings of independent associations with SBP are supported by those from the H70 study but not by findings from the Leiden 85+ Study, Framingham Heart Study, or NOMAS. Two observational studies showed no association with DBP, but the Leiden 85+ Study documented associations with PP.

In the study described in paper III, SBP ≥ 160 mm Hg was associated with increased stroke risk compared with SBP < 140 mm Hg only in the multivariate analysis. This result suggests that adjustment affected the association of SBP with stroke and may explain the difference from previous results. The H70 study involved the most extensive adjustment and is the only previous population-based study to show associations between SBP and stroke. The Leiden 85+ Study also involved comprehensive adjustment, but the inclusion of a composite cardiovascular disease variable (including ischemic heart disease, intermittent claudication, vascular surgery, arrhythmia, and heart failure) may have interfered with the results. Differences in adjustment approaches may explain the contrasting results.

Differences in population characteristics may also influence the observed associations, particularly in unadjusted analyses. The NOMAS sample may differ from other samples in that it was multiethnic and was derived from densely populated Manhattan. Compared with the Umeå /GERDA sample reported on in paper III, the NOMAS sample had about half the prevalence of angina pectoris, lower BMI, and a higher proportion of smokers. The Leiden 85+ Study sample had half the prevalence of heart failure, compared with the sample reported on in paper III, and higher SBP, DBP, MMSE score, and BMI. The Framingham Heart Study sample of 80–89-year-olds had only one-third the heart failure prevalence and less than half the prevalence of atrial fibrillation relative to the sample described in paper III. These differences may also have contributed to the divergence of results.
In summary, the results of observational studies are divergent and only partially consistent with the present study results. Stroke risk seems to increase independently with BP among very old individuals, but comorbidity appears to influence the association. Furthermore, the lower boundary of this association has not been determined.

**Heterogeneity may not affect the association between blood pressure and stroke**

The previous findings of differing associations between BP and stroke in subgroups of ADL dependency and MMSE score from the Leiden 85+ Study were not corroborated in the Umeå 85+/GERDA study. The CHS documented different associations between BP and cardiovascular events in subgroups of ADL dependency, but interactions between BP and ADL status were not significant, in line with the present study results.

Methodological differences between the Leiden 85+ Study and the present study may explain the different results. ADL dependency was assessed using the Groningen Activity Scale in the Leiden 85+ Study, and the Barthel ADL index in the present study. Cognitive impairment was assessed using the MMSE in both studies, but it was categorized differently: \( \leq \) median (26) in the Leiden 85+ Study and \( \geq 24 \) in the Umeå 85+/GERDA study. The study samples and adjustment strategies also seem to differ somewhat, as stated above.

Due to these differing results, whether the association of BP with stroke risk is moderated by ADL dependency and/or cognitive impairment remains unclear. Further studies are needed to examine this issue.

**Optimal blood pressure levels**

In this research, optimal BP levels for survival seem to differ among subgroups of very old individuals. Slower-walking individuals appear to have increased survival with higher SBP up to \( \geq 165 \) mm Hg, compared with \( \leq 125 \) mm Hg; this benefit is detectable at 140–149 mm Hg. The same SBP levels may be optimal for survival in individuals with mild or no cognitive impairment, although the associations were less clear among those with no cognitive impairment. Among faster-walking individuals and those with very severe cognitive impairment, the optimal SBP for survival may be 126–139 mm Hg, compared with \( \geq 165 \) mm Hg and \( \leq 125 \) mm Hg.

DBP of 75–80 mm Hg seem to be associated with increased survival among slower-walking participants and individuals with mild cognitive impairment, compared with \(< 70 \) mm Hg. The optimal DBP among faster-walking individuals may be the same as among slower-walking individuals (75–80 mm Hg), but in comparison with \( > 80 \) mm Hg.
Lower BP, at least to a certain level, seems to be optimal for decreased stroke risk. This level has not been determined but it may lie somewhere below 160 mm Hg for SBP. In addition, optimal BP for decreased stroke risk may not differ according to sex, ADL dependency, or cognitive impairment.

Although optimal BP levels seem to vary with outcome and among subgroups, SBP of about 126–140 mm Hg and DBP of about 75–80 mm Hg do not seem to be associated with increased risk in any subgroup and are associated with decreased stroke and mortality risks in some subgroups. However, other BP levels may be optimal to reduce the risks of other adverse outcomes, such as cognitive decline.

These cutoffs are arbitrary and should be interpreted with caution. They do, however, provide indications of approximate BP intervals with possible clinical implications. Furthermore, these values relate to BP measured with participants in the supine position and may be lower for BP measured with participants in the standard seated position. Optimal BP levels do not constitute recommendations for antihypertensive treatment targets, as they are not based on results from intervention studies, or necessarily on independent associations.

**Ethical considerations**

As the Umeå 85+/GERDA study has no exclusion criteria, it includes individuals who are unable to provide informed consent to participate. The very old population contains a significant proportion of individuals with age-related cognitive disorders, such as dementia. Individuals with advanced cognitive disorders may not fully understand the implications of study participation and are therefore at increased risk of abuse. Individuals with cognitive impairment may also have difficulty understanding why personal questions are asked, and they may underestimate their own limitations in testing situations. The ability to understand the situation may fluctuate from day to day or within the hour, further complicating interaction with researchers.

These risks associated with the inclusion of individuals who are unable to provide informed consent should be outweighed by advantages for the individuals or patient groups. The advantages of participation include social stimulus, personal attention, and a sense of meaningful contribution to society. Participation may also lead to the detection of serious medical issues, in which cases participants’ regular doctors would be alerted. Conversely, the exclusion of these individuals from the study would effectively deprive the larger group of individuals with cognitive disorders of the potential benefits of scientific research, including the possibility of receiving better-tailored medical care. As very old people with cognitive impairment seem to differ from cognitively intact individuals in terms of
various health-related aspects, scientific results may not be directly transferrable between groups.

The risks of participation include injury during physical tests, such as the chair stand test and gait speed assessment, and discomfort during BP measurement. Some questions concerning participants’ personal economic situations and religious beliefs may be offensive to some individuals, and other questions, such as those included in the GDS, may be depressing. In addition, the length of the assessment protocol may be overwhelming. The data collected include sensitive information which potentially could be distributed illegally. Finally, follow-up to determine survival status and stroke event dates 2–5 years after data collection is conducted without obtaining renewed consent from participants, which could be taken as an insult to their personal integrity.

Great effort has been made to avoid these risks, mainly by training competent assessors who can ensure that tests are performed with minimal risk of injury and that difficult themes are handled professionally and with empathy. Participants could choose to terminate participation at any time. All data are confidential and handled with great care. Due to these efforts, study participation is not believed to have caused individuals any harm.

Methodological considerations

The Umeå 85+/GERDA study has sampled a population of relatively homogeneous ethnicity, culture, and geographic distribution. It has no inherent selection bias, as it has no exclusion criteria. However, individuals may have declined participation for systematic reasons, introducing bias. Such reasons may involve the lack of energy, time, or ability to understand the implications of study participation; skepticism about scientific research; and fear of engagement. Groups of very old individuals that may be underrepresented include those with cognitive impairment, depressive disorder, low socioeconomic status, low self-esteem, and low educational level, respectively.

In the Umeå 85+/GERDA sample examined in this research, participants did not differ from non-participants in terms of age or sex. Individuals who died before the first contact could not be included, which caused a slight underrepresentation of individuals with end-stage terminal disease.

Recall bias may have been introduced, as this population may find it difficult to recall past events. This bias was minimized by reviewing the medical records of all consenting participants. However, some conditions may have been underregistered in these records, as very old individuals and care facility residents may not visit the hospital or general practitioner for investigation of all health issues. Observer bias, potentially introduced by the
assessors, was minimized by using a standardized protocol and procedures and by training the assessors in data collection methods.

**Samples**

Sampling from the Umeå 85+/GERDA study may also have introduced bias. Exclusion criteria were kept to a minimum, but individuals who declined home visitation or whose BP was not measured were excluded from most analyses. Twenty percent of all first-time participants declined home visitation. Reasons for declining home visitation may have included lack of energy or time, which may have resulted in underrepresentation of individuals with morbidity or medication use related to fatigue, and those of very advanced age. Among data from first-time participants who agreed to home visitation, 3–5% of baseline BP values were missing. Among data from followed participants in the sample described in paper IV, follow-up SBP values were missing for 6% of survivors who agreed to home visitation. Missing BP values were suspected to reflect participants’ declination of BP measurement due to fatigue, which may be more common in individuals of more advanced age and/or multimorbidity, and may therefore have introduced bias.

Twenty-one participants without MMSE scores and 61 participants without gait speed assessments were excluded from the respective subsamples. Missing gait speed values may be due to cognitive, severe vision, or hearing impairment; environmental limitations; or session interruption. Reasons for missing MMSE scores may have included hearing impairment, aphasia, and apraxia. These exclusions were necessary to enable performance of the analyses, but they could have introduced bias. The study reported on in paper IV excluded participants without 5-year follow-up data, which introduced survival bias. This bias is inherent to longitudinal studies, but it could have been reduced by collecting follow-up data between the baseline and 5-year follow-up timepoints.

Women were underrepresented in the samples reported on in papers II and III, with possible consequences for the generalizability of the results. The mean ages of participants were significantly lower than those of eligible non-participants in the samples reported on in papers II and IV, but the sizes of the differences do not seem to be clinically relevant.

**Measures**

Single assessments do not incorporate variations over time in BP, MMSE score, and other variables or reflect the durations of diseases and drug treatments, which should be kept in mind when interpreting the results. BP was measured with participants in the supine position, which may impede
comparison with other studies in which it was measured with participants in the standard sitting position, and limit the applicability of the findings to clinical settings. However, the high prevalence of orthostatic hypotension in very old people may narrow the distribution of BP values obtained with participants in the seated position to within a lower range, compared with values obtained with participants in the supine position.\textsuperscript{199} A substudy from the Helsinki Ageing Study\textsuperscript{200} showed that the association of BP with mortality risk in an older population was not affected by the measurement position (supine, seated, or standing). The effect of the “white-coat phenomenon,”\textsuperscript{40} in which BP is increased by medical settings, may have been small due to BP measurement in participants’ homes, but a residual effect due to the influence of the assessors and the testing situation is likely present. PP, pulse wave velocity, BP variability, and BP instability may be better indicators of cardiovascular risk than are SBP and DBP.\textsuperscript{40,201-203} BP measurement with a sphygmomanometer may have resulted in the acquisition of systematically higher DBP values due to arterial stiffness, compared with intra-arterial measurement.\textsuperscript{40} However, brachial SBP and DBP measures obtained by sphygmomanometer are used widely in clinical settings.

Mortality data were reliable due to the comprehensive registration of deaths in the Swedish and Finnish population registers. Stroke cases may have been under- or overreported in medical records and/or death certificates. However, incidence rates were comparable to most previous findings. Some stroke cases may have been misclassified when radiological evaluation was not performed. Cause of death and type of stroke were not differentiated, resulting in a lack of precision in the outcome measure, which may be problematic if unrelated mechanisms are involved in its associations with different outcomes.

The usual gait speed assessment may lead to overestimation of participants’ usual gait speeds, due to the excitement of the testing situation or desire to impress the assessor. However, the assessments remain applicable to clinical testing situations, in which the same conditions usually apply. Participants who were unable to perform the gait speed assessment due to habitual causes were classified as slower-walking, which may have compromised the integrity of this group. However, these individuals have been shown to have increased mortality risk.\textsuperscript{144}

The MMSE has shown greater sensitivity for the detection of severe than of mild cognitive impairment.\textsuperscript{179} This difference increases the risk of misclassification of individuals with mild cognitive impairment, which may interfere with comparability among MMSE score subcohorts. Furthermore, the validity of MMSE scores in terms of cognitive impairment may be compromised by age, education, verbal fluency, sensory impairment, and other factors that are relevant in the very old population.\textsuperscript{179,204,205} The
impacts of such factors were minimized by not administering the MMSE when it was deemed unsuitable.

**Missing values**

The proportion of missing values for most variables in the samples analyzed was < 5%, which was considered to be unlikely to affect the results. In some samples, ≥ 10% of gait speed values and GDS scores were missing.

Proportions of missing baseline gait speed values were 24% and 21% in the samples reported on in papers I and III, respectively. In the analysis described in paper I, the categorization of the gait speed variable to form two gait speed subcohorts and inclusion of habitually non-walking participants in the slower-walking subcohort reduced the proportion of missing gait speed values to 8%. In the analysis described in paper III, the variable was kept numerical and cases in which gait speed could not be assessed due to physical impairment were assigned the value of .01, which also reduced the proportion of missing values to 8%. In the analysis described in paper IV, 21% of Δgait speed values were missing. Assigning the value of .01 to cases in which gait speed could not be assessed due to physical impairment and recalculating Δgait speed would have reduced the proportion of missing values only to 19%. ΔGait speed was not associated with the outcome in the bivariate analysis, and thus was not included in the multivariate models. However, whether potential bias interfered with the model building process is unclear. The reasons for missing Δgait speed values were known in 24% of cases, in which physical impairment or lack of motivation prevented the assessment.

In the samples reported on in papers II and IV, 14% and 17% of GDS scores, respectively, were missing. In the analysis described in paper IV, imputation using individual mean scores for participants who answered ≥ 10 items decreased the proportion to 3%. After imputation, the ΔGDS variable had 10% missing values. ΔGDS did not qualify for inclusion in the final model, but whether potential bias interfered with the model building process is unclear. Missing GDS values may have been due to impaired cognition, as some questions can be difficult to understand, and may therefore have introduced bias.

**Statistical models**

Great numbers of diseases, prescriptions, and assessments were incorporated in the multivariate models. However, important variables may have been omitted. This factor is reflected in the poor fit of the model examining the prediction of baseline SBP and the less-than-optimal fit of the model examining the prediction of SBP changes, which left half of the
variation unexplained. The omission of important variables from the models examining the associations of BP with mortality and stroke may have resulted in underadjustment. Relevant factors include lipid levels, renal disease, anxiety, adrenal dysfunction, ventricular hypertrophy, autonomic dysfunction, severity of heart failure, markers of preclinical dementia, obstructive sleep apnea, thyroid disease, dietary factors, and arterial stiffness. The selection of covariates for inclusion in the models may have been better performed using directed acyclic graphs.207

The interaction analyses may have been affected by the non-linear tendencies in some subcohorts. Non-linear associations may have been better modelled using another statistical method, such as generalized additive modeling.208

The categorization of BP and other variables may have compromised the data or statistical power. To compensate, analyses were repeated using numeric variables. Finally, the statistical power of subcohort analyses may also have been limited.

Clinical implications

Knowledge of average longitudinal SBP changes in very old age may serve as a reference for the detection of pathological changes. Increased understanding of determinants of longitudinal SBP change may help clinicians understand the etiology of SBP decline in very old age. Due to the lack of evidence for antihypertensive treatment among very old individuals with comorbidity, observational data on adverse outcomes associated with BP may have to guide clinical decision making.

High gait speed may be useful in distinguishing very old individuals with increased mortality risk associated with high BP from those without such risk, but whether this group benefits from antihypertensive treatment has not been determined. Individuals with very severe cognitive impairment may require special considerations to help maintain BP at a certain level, although how BP should be managed in these individuals has not been determined. Stroke risk seems to be associated with high BP in all individuals, including slower-walking very old individuals. This risk could be decreased by antihypertensive treatment. However, no association was found between different classes of antihypertensive medication and decreased stroke risk.

Any potential benefit of BP reduction must be balanced with the risk of adverse drug reactions, which is particularly high among very old individuals.39 Current guidelines recommend the initiation of pharmacological treatment with a low dosage and only one or two drug classes.39,85 Treatment effects and possible adverse drug reactions should be monitored closely. Non-pharmacological interventions, such as salt
restriction, moderation of alcohol consumption, weight reduction, exercise, and smoking cessation, may be suitable alternatives to pharmacological treatment.\textsuperscript{39,85}

Low BP may serve as an indicator of comorbidity, which may require attention. No subgroup of the very old population in which low BP was associated independently with increased mortality or stroke risk was identified, except for those with very severe cognitive impairment. Nevertheless, low BP may have other adverse outcomes.

**Implications for future research**

Cardiovascular disease is highly prevalent in the very old population and a major source of disease and mortality. With the expected growth of the very old population, future health care systems must be prepared to manage age-related diseases in an effective and safe manner. Further research is needed to determine the specific mechanisms of BP decline and associations of BP with adverse outcomes among very old individuals.

The indication of a continued increase in SBP with increasing age, in the absence of morbidity, requires further investigation in other longitudinal samples of very old individuals. Factors not accounted for in the models constructed for the present research, such as renal disease and autonomic dysfunction, need to be investigated to fully understand the etiology of SBP decline. In addition, the major impacts of baseline SBP and dependency in ADL remain to be explained; this may involve the reliable assessment of heart failure severity and early detection of preclinical dementia.

In addition, whether SBP decline is associated independently with adverse outcomes in very old age remains to be determined. Furthermore, the prevention of determinants of SBP decline should be studied, including investigation of whether such prevention can reduce the decline or associated adverse outcomes. Non-pharmacological treatment of depressive disorders or primary prevention of AMI and dependency in ADL could be the focus of such prevention. Furthermore, whether SBP decline is associated with greater risks of adverse outcomes than is stable low SBP or increased BP variability is not known.

More research is needed to establish which BP-related adverse outcomes are relevant in the very old population, with respect to heterogeneity of health status, and how such factors should be managed. The very old population is characterized by marked heterogeneity of health status, which needs to be taken into account when interpreting the results of total-sample investigations. As morbidity was found to confound the association of BP with mortality, adequate adjustment for morbidity in analyses is important. Specifically, heart failure, atrial fibrillation, AMI, cancer, depressive disorder, angina pectoris, BMI, MMSE score, and gait speed or dependency
in ADL may be important confounders of the association between BP and mortality in very old individuals.

Larger samples are needed to determine whether MMSE scores moderate the association between SBP and mortality, and to determine the properties of this association among individuals with very severe cognitive impairment. The finding of a moderating effect of gait speed on the association of SBP with mortality in very old individuals needs to be corroborated in additional samples.

The optimal BP to reduce stroke risk remains to be determined. Due to the incongruence of results among studies, whether the association between BP and stroke risk is moderated by ADL dependency and/or cognitive impairment remains unclear.

Ultimately, interventional studies including very old individuals with morbidity are needed to determine whether antihypertensive treatment is beneficial for subgroups with increased risks of adverse outcomes associated with high BP. Such studies cannot be conducted with individuals with very severe cognitive impairment in Sweden, where drug treatment studies involving individuals who cannot provide informed consent are not permitted.
Conclusions

SBP decline seems to be associated with higher baseline SBP, later investigation year, antidepressant drug use, incident AMI, use of a new diuretic drug, and increased dependency in ADL in very old individuals. Baseline SBP was the strongest predictor of SBP decline in the present research. The impact of investigation year on longitudinal SBP change indicates a temporal trend of larger SBP decline with later investigation year.

Morbidity and heterogeneity of health status seem to be very important for mortality risk associated with BP in very old age. High SBP does not seem to be an independent risk factor for mortality in the general very old population or among very old individuals with low gait speeds. However, low BP may be a risk marker for short life expectancy due to multimorbidity. In particular, heart failure, atrial fibrillation, AMI, cancer, depressive disorder, angina pectoris, BMI, and MMSE score may confound the association of BP with mortality risk in very old age. Very old individuals with high gait speeds may have an independently increased mortality risk associated with high SBP, consistent with findings in younger populations. These findings may be explained by the better health status of individuals with higher gait speeds.

Whether MMSE scores moderate the association of BP with mortality remains unclear, but the results suggest that individuals with very severe cognitive impairment are sensitive to high and low SBP, in contrast to individuals with higher cognitive function. Results from the general very old population may therefore not be applicable to individuals with very severe cognitive impairment.

Higher BP seems to be an independent risk factor for stroke in very old age. The association of BP with stroke risk did not differ according to ADL dependency, cognitive impairment, or gait speed in the present research. These findings may contribute to an increased understanding of the etiology of SBP decline and the importance of individualized health care in very old age. Further research is needed to understand BP decline and the associations of BP with adverse outcomes in very old age.
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