Original Article

OPEN

The association between SBP and mortality risk differs with level of cognitive function in very old individuals

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Objective: Cognitive impairment and dementia are highly prevalent in very old populations. Cardiovascular disease is a common cause of death in people with dementia. This study investigated whether the association of blood pressure (BP) with mortality differed with respect to mini-mental state examination (MMSE) score in a representative sample of very old individuals.

Methods: The sample consisted of 1115 participants aged 85, 90, and at least 95 years from the Umeå85+/GErontological Regional DAtabase cohort study. The main outcome was all-cause mortality within 2 years according to BP and MMSE score, using Cox proportional-hazard regression models adjusted for sociodemographic and clinical characteristics associated with death.

Results: Mean age, MMSE score, and SBP and DBP were 89.4 ± 4.6 years, 21.1 ± 7.6, 146.1 ± 23.4 mmHg, and 74.1 ± 11.7 mmHg, respectively. Within 2 years, 293 (26%) participants died. BP was not associated independently with mortality risk, except among participants with MMSE scores of 0–10 among whom mortality risk was increased in association with SBP at least 165 mmHg and 125 mmHg or less, compared with 126–139 mmHg (adjusted hazard ratio 4.54, 95% confidence interval = 1.52–13.60 and hazard ratio 2.23, 95% confidence interval = 1.12–4.45, respectively). In age and sex-adjusted analyses, SBP 125 mmHg or less was associated with increased mortality risk in participants with MMSE scores at least 18.

Conclusion: In people aged at least 85 years, the association of SBP with mortality appears to differ with respect to MMSE score. Very old individuals with very severe cognitive impairment and low or high BP may have increased mortality risk.

Keywords: aged 80 and over, cognition disorders, dementia, hypertension, hypotension, mortality

Abbreviations: ADLs, activities in daily living; BP, blood pressure; CI, confidence interval; GERDA, gerontological regional database; MMSE, mini-mental state examination

INTRODUCTION

With an aging population, cognitive decline and dementia are becoming major public health issues [1]. An estimated 35.6 million people were affected by dementia in 2010, and this number is projected to almost double every 20 years [2]. Cognitive decline may involve one or several cognitive domains, such as memory, attention, and language [3], as well as functional abilities, such as activities in daily living (ADLs) [4]. Cognitive decline commonly coexists with cardiovascular disease, which seems to play a major role in the development and progress of cognitive decline and dementia [5–9]. Cardiovascular disease is also the most common cause of death in people with vascular dementia and mixed dementia [10,11]. In very old (age ≥ 80 years) individuals, cognitive impairment is associated with low systolic BP (SBP) [12–15]. As both low SBP and cognitive impairment are separately associated with increased mortality risk [16–21], the mortality risk associated with blood pressure (BP) may differ with respect to level of cognitive function.

Systematic reviews of randomized controlled trials have investigated the effects of antihypertensive therapy in patients with dementia aged at least 65 years [22] and more than 80 years [23], but limited statistical power prevented the authors from drawing definitive conclusions. A population-based study of older people (age ≥ 75 years; mean age, 83 years) revealed an independent association between low BP and increased mortality risk in cognitively impaired participants [24], defined by mini-mental state examination (MMSE) scores less than 24. Other population-based studies with somewhat younger participants (age ≥ 65 years; mean ages, 74 and 76 years) showed associations between diastolic BP (DBP), but not SBP and mortality that differed with respect to MMSE score [25,26]. This discrepancy may be because of age-related changes in SBP level [27,28] and the type of dementia [29–31]. Owing to these processes, extrapolation of results from younger populations to the very old may be misleading. The aim of this study was to investigate whether the association of BP with mortality differs with respect to MMSE score in a representative sample of very old individuals, including those with severe cognitive impairment.

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METHODS

Setting

Baseline data for this study were taken from the population-based, prospective Umeå 85+/GErontological Regional DAtabase (GERDA) study, conducted by Umeå University, Sweden, in collaboration with Åbo Akademi University and the University of Vaasa, Finland. The Umeå85+/GERDA study has been described in detail elsewhere [32]. It was approved by the Regional Ethical Review Board in Umeå (§99–326, §05–063 mol/l, §09–178 mol/l, §2015-296-31) and the Ethics Committee of Vaasa Central Hospital (§05–87). The objective of the GERDA study is to increase knowledge of the living conditions of very old people, increase quality of life in this population, and provide data to support planning of future eldercare.

Design

Every other inhabitant of eight municipalities in northern Sweden and western Finland aged 85 years, and all of those aged 90 and at least 95 years, as listed in national population and tax registers, were invited to participate. All participants provided informed oral consent and relatives also provided informed oral consent when appropriate. Baseline data for Swedish participants in the present study were collected in three rounds, commencing in the years 2000, 2005, and 2010, and those for Finnish participants were collected in one round commencing in 2005. Trained assessors with medical education collected data using a standardized questionnaire and assessments at participants' homes or care facilities and medical records. Data were also collected from care personnel and relatives of cognitively impaired individuals as proxy respondents when possible. The questionnaire included subjective and objective questions and covers sociodemographic, socioeconomic, and medical factors; quality of life; and attitudes toward aging, participants' current situation, and the current situation with eldercare.

Participants

Participants in the Umeå85+/GERDA study from whom SBP measurements and MMSE scores were collected during home visits were included in the present study. For those who participated in more than one round of data collection, the first sets of data from home visits were included in this study. All participants were followed to determine survival status after 2 years.

Measures

The study outcome was all-cause mortality within 2 years. Dates of death were collected from death certificates, population registers, and medical records. Information on cohabitation, education, and smoking status was collected from the respondent. Information on diagnoses, medical conditions, and drug prescriptions collected from the respondent was verified and complemented using medical records from hospitals, general practitioners, and care facilities. A specialist in geriatric medicine verified and complemented diagnoses using all collected data, including assessments, tests, pharmacological treatments, and medical records. Dementia and depression were diagnosed according to the 'Diagnostic and Statistical Manual of Mental Disorders,' fourth edition, text revision [33] criteria. Participants' height and weight were measured to calculate BMI (kg/m^2). The Barthel ADL index was used to assess dependency in daily activities on a scale of 0–20, with a score of 20 indicating total independence in personal ADLs [34].

BP was measured using a calibrated manual sphygmomanometer and stethoscope after 5 min rest in a supine position. Pulse pressure was calculated by subtracting DBP from SBP. To allow for detection of nonlinear associations with mortality, SBP, and pulse pressure were classified in quintiles ($\leq$125, 126–139, 140–149, 150–164, and $\geq$165 mmHg and $\leq$55, 56–65, 66–75, 76–90, and $>$90 mmHg, respectively). DBP was classified in quartiles because of its narrower distribution ($<$70, 70–74, 75–80, and $>$80 mmHg).

Cognitive impairment was assessed using the MMSE, a validated and commonly used screening tool for cognitive impairment [35,36]. In community and primary care settings, the MMSE has 82–88% sensitivity for dementia and 86% specificity [37,38] in pooled analyses (most common cutoff value, 23/24). MMSE scores range from 0 to 30, with higher scores indicating better cognitive function. Participants were classified into four subcohorts based on MMSE score (0–10, 11–17, 18–23, and 24–30). MMSE score cutoff values of 17 or less and at least 24 are commonly used to differentiate severe, mild, and no cognitive impairment, respectively [36]. To investigate differences within the MMSE score = 0–17 group, an additional cutoff value of 10 or less designating very severe cognitive impairment was used; this threshold has been used previously to indicate severe dementia [39,40].

Statistical analysis

Associations between all-cause mortality and categorized BP variables were analyzed using Cox proportional-hazard regression models. The BP category with the lowest risk was used as reference. Two models were developed: a basic model, including only age, sex, and BP (model 1) and a fully adjusted model, including age, sex, baseline characteristics associated with death, and BP (model 2). BP variables (SBP, DBP, and pulse pressure) were entered separately into each model. Baseline characteristics potentially associated with death (Table 1) were identified from previous research. Associations between baseline characteristics and 2-year mortality were tested using Student's *t*-test and Pearson's χ^2 test. Bivariate correlations were tested between all baseline characteristics associated with death, and the dementia and antidepressants variables were removed because of strong correlations ($r > 0.6$) with MMSE score and depression, respectively. The BMI variable was removed because of missing values. Remaining baseline characteristics associated with death at a significance level of $P \leq 0.15$ were entered in a multivariate analysis using Cox proportional-hazard regression models. To reduce the number of variables [41], only baseline characteristics associated with death at a significance level of $P \leq 0.05$ in the multivariate analysis were entered into

TABLE 1. Baseline sociodemographic and clinical characteristics of the study population

Characteristic	Total ($n = 1115$)	MMSE score			
		0–10 ($n = 118$)	11–17 ($n = 166$)	18–23 ($n = 289$)	24–30 ($n = 542$)
Age (years)	89.4 ± 4.6	92.5 ± 4.8	91.1 ± 4.9	89.8 ± 4.4	87.9 ± 3.9
Sex (female)	742 (67)	99 (84)	113 (68)	184 (64)	346 (64)
Living alone ($n = 1112$)	875 (79)	108 (92)	142 (86)	229 (80)	396 (73)
Education < 8 years ($n = 1086$)	791 (73)	88 (85)	120 (77)	230 (80)	353 (65)
Current smoker ($n = 1109$)	35 (3)	1 (1)	2 (1)	10 (4)	22 (4)
Former smoker ($n = 1109$)	324 (29)	16 (14)	44 (27)	84 (29)	180 (33)
Diagnoses and medical conditions					
Diabetes	178 (16)	18 (15)	29 (18)	46 (16)	85 (16)
Congestive heart failure ($n = 1114$)	348 (31)	46 (39)	69 (42)	89 (31)	144 (27)
Atrial fibrillation	270 (24)	22 (19)	56 (34)	60 (21)	132 (24)
MI in the previous year	31 (3)	2 (2)	4 (2)	9 (3)	16 (3)
Angina pectoris	471 (42)	58 (49)	78 (47)	123 (43)	212 (39)
Cerebrovascular disease	243 (22)	33 (28)	41 (25)	62 (22)	107 (20)
Cancer in the previous 5 years ($n = 1113$)	141 (13)	11 (9)	15 (9)	33 (11)	82 (15)
Dementia	389 (35)	116 (98)	153 (92)	104 (36)	16 (3)
Hip fracture	201 (18)	43 (36)	36 (22)	45 (16)	77 (14)
COPD ($n = 1114$)	196 (18)	15 (13)	28 (17)	55 (19)	98 (18)
Depression	385 (35)	54 (46)	85 (51)	118 (41)	128 (24)
Rheumatic disorders	154 (14)	11 (9)	25 (15)	38 (13)	80 (15)
Routine prescription medications					
ACE inhibitors	224 (20)	17 (14)	43 (26)	69 (24)	95 (18)
β blockers	478 (43)	35 (30)	62 (37)	128 (44)	253 (47)
Calcium channel blockers	189 (17)	11 (9)	23 (14)	49 (17)	106 (20)
Diuretics	604 (54)	61 (52)	102 (61)	161 (56)	280 (52)
Benzodiazepines	287 (26)	33 (28)	48 (29)	81 (28)	125 (23)
Antidepressants	198 (18)	42 (36)	54 (33)	51 (18)	51 (9)
ASA	469 (42)	40 (34)	69 (42)	126 (44)	234 (43)
Neuroleptics	132 (12)	43 (36)	32 (19)	32 (11)	25 (5)
Warfarin	102 (9)	5 (4)	14 (8)	22 (8)	61 (11)
Opioids ($n = 1114$)	144 (13)	21 (18)	22 (13)	46 (16)	55 (10)
NSAIDs	68 (6)	4 (3)	5 (3)	20 (7)	39 (7)
Paracetamol	385 (35)	81 (69)	87 (52)	98 (34)	119 (22)
Statins	129 (12)	2 (2)	12 (7)	30 (10)	85 (16)
No. of prescribed drugs ($n = 1108$)	6.5 ± 4.0	7.5 ± 3.4	7.6 ± 4.2	6.8 ± 4.4	5.8 ± 3.7
Assessments					
BMI ($n = 1080$)	25.4 ± 4.4	23.5 ± 4.8	25.2 ± 4.8	25.8 ± 4.2	25.6 ± 4.2
MMSE score (range, 0–30)	21.1 ± 7.6	4.1 ± 3.9	14.5 ± 1.9	20.9 ± 1.7	26.8 ± 1.9
Barthel ADL index (range, 0–20; $n = 1113$)	16.4 ± 5.5	6.7 ± 5.9	12.3 ± 6.1	17.4 ± 3.7	19.1 ± 2.0
SBP (mmHg)	146.1 ± 23.4	131.3 ± 19.4	139.3 ± 22.5	145.0 ± 22.9	152.0 ± 22.7
DBP (mmHg; $n = 1110$)	74.1 ± 11.7	68.3 ± 12.9	73.3 ± 11.6	74.2 ± 11.5	75.6 ± 11.1
Pulse pressure (mmHg; $n = 1110$)	72.0 ± 20.0	63.0 ± 17.7	66.1 ± 19.0	70.8 ± 18.8	76.4 ± 20.3

Data are presented as *n* (%) or mean ± standard deviation. Total number is presented in parentheses after characteristics with some missing data. ACE, angiotensin-converting enzyme; ADL, activities in daily living; ASA, acetylsalicylic acid; BP, blood pressure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; MMSE, mini-mental state examination.

model 2, together with BP. The Schoenfeld residuals test was used to identify time-dependent variables [42]. Interaction effects between BP and MMSE score were tested by entering an interaction term into each model. These analyses were performed using SPSS Statistics software (version 22.0; IBM Corporation, Armonk, New York, USA). Associations of mortality with SBP and MMSE score in the total sample were explored graphically with flexible parametric models (knots in default position) using STATA statistical software (release 12; StataCorp 2011, College Station, Texas, USA). All analyses were two tailed and $P < 0.05$ was considered to be significant.

RESULTS

The flow of study participation is shown in Fig. 1. In total, 1115 participants were included in the present study population (participation rate, 66% of those who received invitations), of whom 293 (26%) participants died within 2 years (mean ± SD, 1.73 ± 0.53 years). The numbers of deaths were about equally distributed among MMSE score subcohorts, but larger proportions of participants in the lower than in the higher MMSE score subcohorts died (mortality rates: MMSE = 0–10, 0.593; MMSE = 11–17, 0.506; MMSE = 18–23, 0.239; MMSE = 24–30, 0.129). Compared with the study population, individuals who declined participation or from whom no SBP measurement or MMSE score was obtained did not differ significantly in age (89.8 ± 4.8 vs. 89.4 ± 4.6 years, $P = 0.064$), but the proportion of women was larger (75.0 vs. 66.5%, $P < 0.001$).

Table 1 shows the baseline characteristics of the study population according to MMSE score. Age and prevalence of dementia showed increasing trends with decreasing MMSE score, whereas BP, pulse pressure, and Barthel ADL index showed decreasing trends. Individuals with MMSE scores of 0–10 showed the highest prevalence of

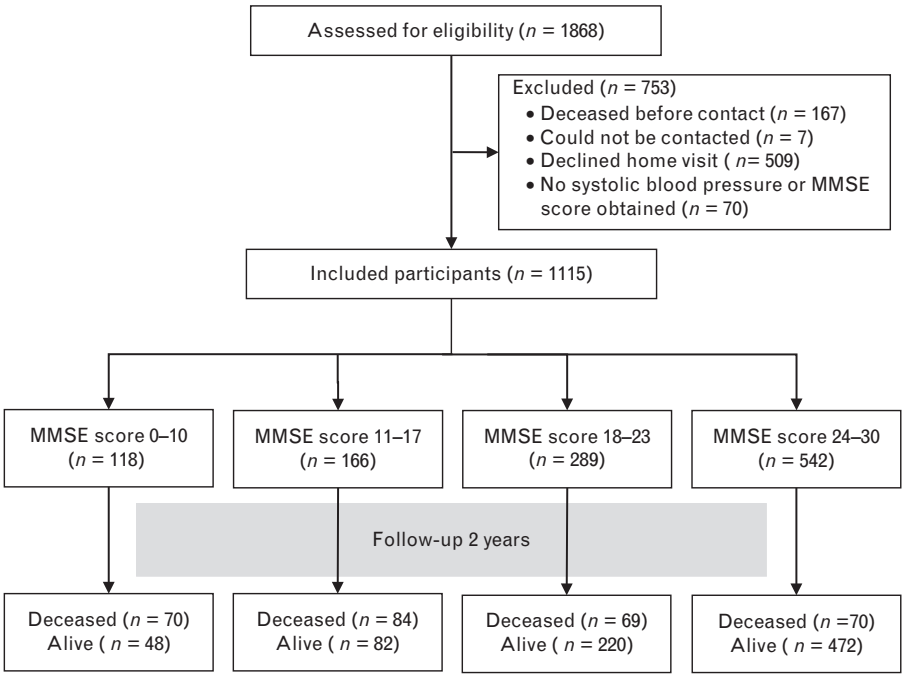

FIGURE 1 Flow chart of study participation. MMSE, mini-mental state examination.

cerebrovascular disease, hip fracture, and angina pectoris and the lowest prevalence of atrial fibrillation. Individuals with MMSE scores of 11–17 had the highest prevalence of depression, atrial fibrillation, and congestive heart failure, and the highest mean number of prescribed drugs.

Figure 2 shows survival curves based on flexible parametric models according to SBP and MMSE score in the total sample. As can be seen, mortality risk was increased primarily among individuals with low SBP (Fig. 2a) or MMSE score less than 21 (population mean, Fig. 2b). The survival curve according to MMSE score had a sigmoidal shape; maximum risk was approximately 3.4, among individuals with MMSE scores less than 5.

Model 2 included age, sex, atrial fibrillation, depression, and Barthel ADL index. No time-dependent variables were identified. Interaction effects between MMSE score subcohorts and SBP categories were borderline significant in models 1 ($P = 0.069$), and 2 ($P = 0.068$). Interaction effects between MMSE score subcohorts and DBP and pulse pressure categories respectively were not significant in model 1 or 2 (data not shown).

Table 2 presents hazard ratios for death according to SBP category and MMSE score subcohort. Survival curves based on Cox proportional-hazard regression models are shown in Fig. 3. Among participants with MMSE scores of 0–10, SBP at least 165 and 125 mmHg or less were associated with increased mortality risk [model 2: hazard ratio 4.54, 95% confidence interval (CI) = 1.52–13.60 and hazard ratio 2.23, 95% CI = 1.12–4.45, respectively], compared with SBP of 126–139 mmHg in the fully adjusted model. In model 1, SBP 125 mmHg or less was associated with increased mortality risk also among participants with MMSE scores of 18–23 and 24–30, compared with SBP at least 165 mmHg (hazard ratio 2.81, 95% CI = 1.20–6.54 and hazard ratio 2.19, 95% CI = 1.09–4.40, respectively). For DBP and pulse pressure, the only significant associations were with MMSE scores of

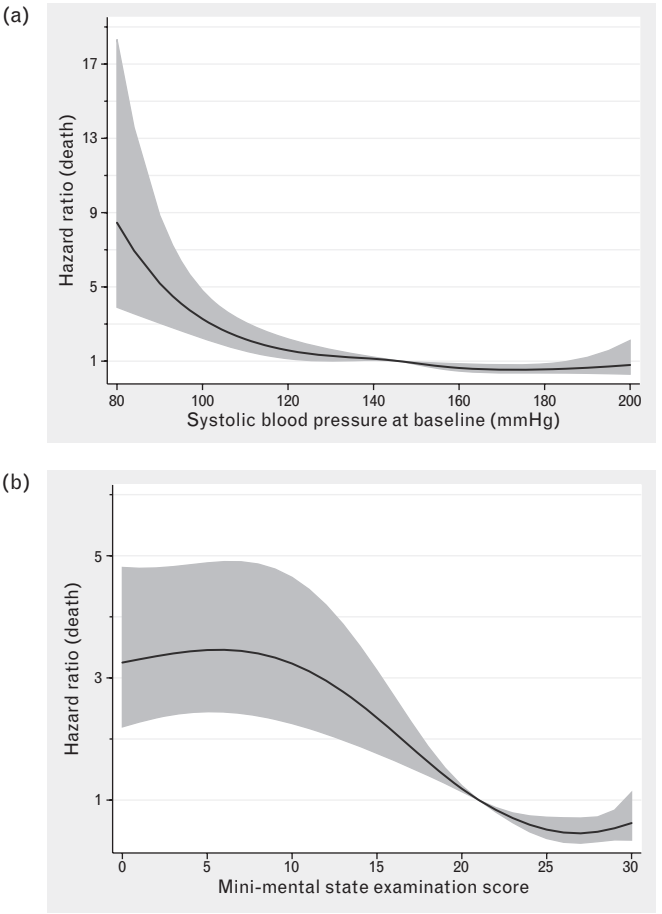

FIGURE 2 Survival curves according to SBP (a) and mini-mental state examination score (b), based on flexible parametric models in the total sample. Mean values are used as reference points.

TABLE 2. Hazard ratios for death according to SBP and Mini-Mental State Examination score subcohort[a]

	MMSE 0–10			MMSE 11–17			MMSE 18–23			MMSE 24–30		
SBP (mmHg)	Total (no. of events)	Hazard ratio (95% CI)	*P*	Total (no. of events)	Hazard ratio (95% CI)	*P*	Total (no. of events)	Hazard ratio (95% CI)	*P*	Total (no. of events)	Hazard ratio (95% CI)	*P*
Model 1	118 (70)			166 (84)			289 (69)			542 (70)		
≤125		2.41 (1.23–4.72)	0.011		1.45 (0.62–3.37)	0.389		2.81 (1.20–6.54)	0.017		2.19 (1.09–4.40)	0.029
126–139		1			1.41 (0.58–3.41)	0.449		1.97 (0.76–5.10)	0.161		1.23 (0.56–2.73)	0.604
140–149		1.73 (0.74–4.02)	0.203		1.48 (0.62–3.51)	0.379		1.87 (0.74–4.76)	0.187		1.06 (0.48–2.34)	0.883
150–164		1.65 (0.71–3.85)	0.242		1.23 (0.51–2.98)	0.645		1.42 (0.58–3.48)	0.446		1.28 (0.65–2.53)	0.480
≥165		4.48 (1.51–13.23)	0.007		1			1			1	
Model 2	117 (69)			165 (83)			289 (69)			542 (70)		
≤125		2.23 (1.12–4.45)	0.023		1.18 (0.47–2.93)	0.729		1.99 (0.84–4.73)	0.121		1.60 (0.72–3.53)	0.247
126–139		1			1.33 (0.52–3.39)	0.549		1.55 (0.59–4.10)	0.378		1.13 (0.47–2.72)	0.788
140–149		2.25 (0.91–5.57)	0.081		1.45 (0.57–3.69)	0.433		1.47 (0.58–3.77)	0.420		1	
150–164		1.63 (0.68–3.87)	0.272		1.35 (0.53–3.45)	0.528		1.36 (0.55–3.34)	0.507		1.16 (0.53–2.54)	0.714
≥165		4.54 (1.52–13.60)	0.007		1			1			1.05 (0.47–2.31)	0.911

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, atrial fibrillation, depression, and Barthel Activities of Daily Living index. MMSE, mini-mental state examination.
[a]Calculated using Cox proportional-hazard regression models.

18–23 in model 1; increased mortality risk was observed for DBP less than 70 mmHg compared with 75–80 mmHg (hazard ratio 1.96, 95% CI = 1.04–3.70) and pulse pressure 55 mmHg or less compared with more than 90 mmHg (hazard ratio 2.84, 95% CI = 1.08–7.45).

DISCUSSION

In this study of 1115 very old individuals, the association between SBP and mortality differed with respect to MMSE score. BP was not associated independently with mortality risk, except among participants with MMSE scores of 0–10. Among these participants, high (≥165 mmHg) and low (≤125 mmHg) SBP were associated independently with mortality risk, compared with intermediate (126–139 mmHg) SBP. In age and sex-adjusted analyses, low SBP was also associated with increased mortality risk in participants with MMSE scores at least 18.

To our knowledge, the association of BP and mortality has not previously been analyzed separately in individuals with MMSE scores 10 or less. In contrast to those with higher cognitive function, these individuals seem to be vulnerable to the harmful effects of high and low SBP, indicating a nonlinear association. Larger studies are needed to confirm the risks associated with high and low SBP in people with very severe cognitive impairment, but this finding indicates that BP research in general very old populations may not be extrapolated to those with very severe cognitive impairment. Previously, an independent association of low SBP with 5-year mortality was shown to pertain exclusively to very old individuals with MMSE scores less than 24, as opposed to those with scores at least 24 [24]. The results of the present study indicate that the association of SBP with mortality pertains to individuals with much lower cognitive function than previously known, and that BP may not be an individual risk factor for 2-year mortality in individuals with MMSE scores more than 10, which is the great majority of the population. The previous findings of independent associations between low DBP and mortality risk that differed with respect to MMSE score [24–26] were not replicated in the present study.

Low SBP was a marker for increased mortality risk in individuals with MMSE scores at least 18. These results are consistent with some previous BP research among very old individuals, the majority of which have no or mild cognitive impairment [19–21]. Specifically, atrial fibrillation, depression, and dependency in ADLs seem to account for mortality risk associated with low SBP in the present study, as the associations were not robust against adjustments for these factors. Notably, low SBP was not a marker or risk factor for mortality risk in individuals with MMSE scores of 11–17, in contrast to those with higher and lower scores. This inconsistency across MMSE score subcohorts may imply that different mechanisms underlie the mortality risk associated with low SBP in very old individuals with MMSE scores less than 11 and more than 17.

The increased mortality risk with high and low SBP in individuals with very severe cognitive impairment may be mediated by cerebrovascular disease, such as microinfarctions, hemorrhages, and white matter hyperintensities. Cerebrovascular disease accounts for 12–17% of

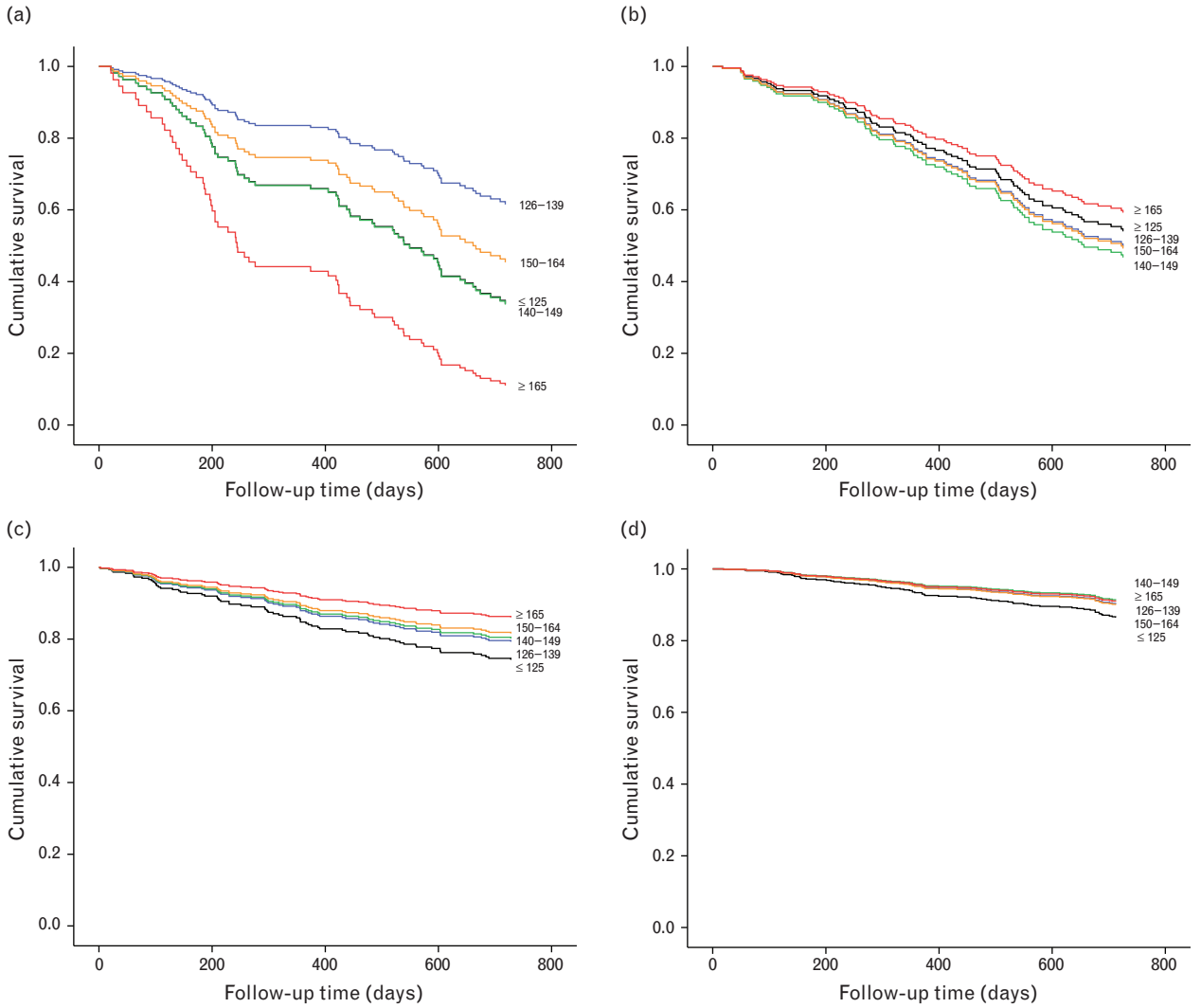

FIGURE 3 Survival curves according to SBP (mmHg) in mini-mental state examination score subcohorts (a) 0–10, (b) 11–17, (c) 18–23, and (d) 24–30, based on Cox proportional-hazard regression models adjusted for age, sex, atrial fibrillation, depression, and Barthel Activities of Daily Living index.

cardiovascular causes of death in people with vascular or mixed dementia [11]. Individuals with very severe cognitive impairment are more likely to have reduced cerebral autoregulation of BP because of severe dementia [43,44]. This reduced autoregulation may predispose individuals to further cerebrovascular damage, caused by dissociations in cerebral blood flow and demand [10,45–49]. Individuals with high or low SBP in combination with reduced cerebral autoregulation of BP may be at greater risk of such cerebrovascular damage [49,50], particularly in the presence of arterial stiffness [51].

The strengths of the present study include the use of specially trained assessors, who maintained the high quality of data collection and home visitation to minimize healthy user bias. The classification of BP values and MMSE scores using multiple categories allowed for interpretation of nonlinear associations, but resulted in potentially limited statistical power of some analyses and the inability to examine the impacts of age, sex, and BP treatment. The study has other limitations. Single measurement of MMSE score and BP did not capture variability in these measures over time, but was likely sufficient for group-level statistical analysis. A 24-h BP monitoring could have given valuable information about BP variability and episodic hypotension [52]. BP was measured with participants in a supine position, which may have yielded higher values relative to a seated position because of the high prevalence of orthostatic hypotension in very old people [53]. The proportion of women was smaller in the study sample compared with individuals who declined participation or from whom no SBP measurement or MMSE score was obtained, which may impede the generalizability of the results. The underrepresentation of women in the study sample has probable consequences for the generalizability of the results, such as the lower-than-average prevalence of conditions with female predominance (e.g. dementia) [54]. Because the MMSE has higher sensitivity for severe than for mild cognitive impairment, people with mild cognitive impairment may have been misclassified [36], potentially interfering with comparability among subcohorts. The validity of MMSE scores in terms of cognitive impairment is affected by several factors that may be relevant for our study population, such as age, length of

education, verbal fluency, sensory impairment, cultural background, institutional living, and depression [36,55,56].

In conclusion, in very old individuals, the association between SBP and mortality appears to differ with level of cognitive function. Very old individuals with very severe cognitive impairment and low or high SBP may have increased mortality risk. Low SBP may be a marker for increased mortality risk in individuals with no or mild cognitive impairment. Larger studies are needed to confirm these results, but the results of BP research in the general very old population should not be extrapolated to those with very severe cognitive impairment. To better target groups potentially benefitting from intervention, we need to define easily distinguishable groups within this heterogeneous population with and without increased risk for negative outcomes of high or low BP. The issue of treatment individualization is particularly important in very old people, who are especially susceptible to adverse drug reactions and polypharmacy.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Anderson LA, McConnell SR. Cognitive health: an emerging public health issue. *Alzheimers Dement* 2007; 3 (2 Suppl):S70–S73.
2. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and meta-analysis. *Alzheimers Dement* 2013; 9:63–75.
3. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, *et al.* Mild cognitive impairment: beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004; 256:240–246.
4. Njegovan V, Man-Son-Hing M, Mitchell SL, Molnar FJ. The hierarchy of functional loss associated with cognitive decline in older persons. *J Gerontol A Biol Sci Med Sci* 2001; 56:M638–M643.
5. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol* 2015; 12:267–277.
6. Kling MA, Trojanowski JQ, Wolk DA, Lee VMY, Arnold SE. Vascular disease and dementias: paradigm shifts to drive research in new directions. *Alzheimers Dement* 2013; 9:76–92.
7. Nelson L, Gard P, Tabet N. Hypertension and inflammation in Alzheimer's disease: close partners in disease development and progression!. *J Alzheimers Dis* 2014; 41:331–343.
8. Kalaria RN. Cerebrovascular disease and mechanisms of cognitive impairment: evidence from clinicopathological studies in humans. *Stroke* 2012; 43:2526–2534.
9. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease: lessons from pathology. *BMC Med* 2014; 12:206.
10. Attems J, Konig C, Huber M, Lintner F, Jellinger KA. Cause of death in demented and nondemented elderly inpatients; an autopsy study of 308 cases. *J Alzheimers Dis* 2005; 8:57–62.
11. Brunnström HR, Englund EM. Cause of death in patients with dementia disorders. *Eur J Neurol* 2009; 16:488–492.
12. Nilsson SE, Read S, Berg S, Johansson B, Melander A, Lindblad U. Low systolic blood pressure is associated with impaired cognitive function in the oldest old: longitudinal observations in a population-based sample 80 years and older. *Aging Clin Exp Res* 2007; 19:41–47.
13. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005; 4:487–499.
14. Molander L, Gustafson Y, Lövheim H. Low blood pressure is associated with cognitive impairment in very old people. *Dement Geriatr Cogn Disord* 2010; 29:335–341.
15. Sabayan B, Oleksik AM, Maier AB, van Buchem MA, Poortvliet RK, de Ruijter W, *et al.* High blood pressure and resilience to physical and cognitive decline in the oldest old: the Leiden 85-plus Study. *J Am Geriatr Soc* 2012; 60:2014–2019.
16. Börjesson-Hanson A, Gustafson D, Skoog I. Five-year mortality in relation to dementia and cognitive function in 95-year-olds. *Neurology* 2007; 69:2069–2075.
17. Gussekloo J, Westendorp RGJ, Remarque EJ, Lagaay AM, Heeren TJ, Knook DL. Impact of mild cognitive impairment on survival in very elderly people: cohort study. *BMJ* 1997; 315:1053–1054.
18. O'Donnell M, Teo K, Gao P, Anderson C, Sleight P, Dans A, *et al.* Cognitive impairment and risk of cardiovascular events and mortality. *Eur Heart J* 2012; 33:1777–1786.
19. Weidung B, Boström G, Toots A, Nordström P, Carlberg B, Gustafson Y, *et al.* Blood pressure, gait speed, and mortality in very old individuals: a population-based cohort study. *J Am Med Dir Assoc* 2015; 16:208–214.
20. Jacobs JM, Stessman J, Ein-Mor E, Bursztyn M. Hypertension and 5-year mortality among 85-year-olds: the Jerusalem Longitudinal Study. *J Am Med Dir Assoc* 2012; 13:759.
21. Boshuizen HC, Izaks GJ, van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older: community based study. *BMJ* 1998; 316:1780–1784.
22. Beishon LC, Harrison JK, Harwood RH, Robinson TG, Gladman JR, Conroy SP. The evidence for treating hypertension in older people with dementia: a systematic review. *J Hum Hypertens* 2014; 28:283–287.
23. van der Wardt V, Logan P, Conroy S, Harwood R, Gladman J. Antihypertensive treatment in people with dementia. *J Am Med Dir Assoc* 2014; 15:620–629.
24. Guo Z, Viitanen M, Winblad B. Low blood pressure and five-year mortality in a Stockholm cohort of the very old: possible confounding by cognitive impairment and other factors. *Am J Public Health* 1997; 87:623–628.
25. Cacciatore F, Abete P, de Santis D, Longobardi G, Ferrara N, Rengo F. Mortality and blood pressure in elderly people with and without cognitive impairment. *Gerontology* 2005; 51:53–61.
26. Post Hospers G, Smulders YM, Maier AB, Deeg DJ, Muller M. Relation between blood pressure and mortality risk in an older population: role of chronological and biological age. *J Intern Med* 2015; 277:488–497.
27. Molander L, Lövheim H. Blood pressure change and antihypertensive treatment in old and very old people: evidence of age, sex and cohort effects. *J Hum Hypertens* 2013; 27:197–203.
28. Lernfelt B, Svanborg A. Change in blood pressure in the age interval 70–90. Late blood pressure peak related to longer survival. *Blood Press* 2002; 11:206–212.
29. Jellinger KA, Attems J. Prevalence and pathology of dementia with Lewy bodies in the oldest old: a comparison with other dementing disorders. *Dement Geriatr Cogn Disord* 2011; 31:309–316.
30. James BD, Bennett DA, Boyle PA, Leurgans S, Schneider JA. Dementia from Alzheimer disease and mixed pathologies in the oldest old. *JAMA* 2012; 307:1798–1800.
31. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuropathology, and dementia. *N Engl J Med* 2009; 360:2302–2309.

32. von Heideken Wagert P, Gustavsson JM, Lundin-Olsson L, Kallin K, Nygren B, Lundman B, *et al*. Health status in the oldest old. Age and sex differences in the Umea 85+ Study. *Aging Clin Exp Res* 2006; 18:116–126.
33. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 4th ed Washington, DC: American Psychiatric Publishing, Inc; 2000.
34. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL index: a reliability study. *Int Disabil Stud* 1988; 10:61–63.
35. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12:189–198.
36. Tombaugh TN, McIntyre NJ. The Mini-Mental-State-Examination: a comprehensive review. *J Am Geriatr Soc* 1992; 40:922–935.
37. Lin JS, O'Connor E, Rossom RC, Perdue LA, Burda BU, Thompson M, *et al*. *Screening for cognitive impairment in older adults: an evidence update for the U.S. Preventive Services Task Force. Evidence Syntheses No. 107*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2013.
38. Mitchell AJ. A meta-analysis of the accuracy of the Mini-Mental State Examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009; 43:411–431.
39. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. *Ann Neurol* 2005; 58:773–776.
40. Cutler RG, Kelly J, Storie K, Pedersen WA, Tammara A, Hatanpaa K, *et al*. Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proc Natl Acad Sci U S A* 2004; 101:2070–2075.
41. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995; 48:1503–1510.
42. Kleinbaum DG, Klein M. *Survival analysis: a self-learning text.*, 3rd ed New York, NY: Springer; 2012.
43. Claassen JA, Zhang R. Cerebral autoregulation in Alzheimer's disease. *J Cereb Blood Flow Metab* 2011; 31:1572–1577.
44. Sabayan B, Jansen S, Oleksik AM, van Osch MJ, van Buchem MA, van Vliet P, *et al*. Cerebrovascular hemodynamics in Alzheimer's disease and vascular dementia: a meta-analysis of transcranial Doppler studies. *Ageing Res Rev* 2012; 11:271–277.
45. van Beek A, Sijbesma JC, Jansen R, Rikkert M, Claassen J. Cortical oxygen supply during postural hypotension is further decreased in Alzheimer's disease, but unrelated to cholinesterase-inhibitor use. *J Alzheimers Dis* 2010; 21:519–526.
46. Jellinger KA. Prevalence and impact of cerebrovascular lesions in Alzheimer and Lewy body diseases. *Neurodegener Dis* 2010; 7:112–115.
47. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, *et al*. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011; 42:2672–2713.
48. Costanza A, Xekardaki A, Kövari E, Gold G, Bouras C, Giannakopoulos P. Microvascular burden and Alzheimer-type lesions across the age spectrum. *J Alzheimers Dis* 2012; 32:643–652.
49. Gasecki D, Kwarciany M, Nyka W, Narkiewicz K. Hypertension, brain damage and cognitive decline. *Curr Hypertens Rep* 2013; 15:547–558.
50. Muller M, van der Graaf Y, Visseren FL, Vlek AL, Mali WP, Geerlings MI, *et al*. Blood pressure, cerebral blood flow, and brain volumes. The SMART-MR study. *J Hypertens* 2010; 28:1498–1505.
51. Scuteri A, Tesauro M, Guglini L, Lauro D, Fini M, Di Daniele N. Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. *Int J Cardiol* 2013; 169:371–377.
52. Scuteri A, Modestino A, Frattari A, Di Daniele N, Tesauro M. Occurrence of hypotension in older participants. Which 24-h ABPM parameter better correlate with? *J Gerontol A Biol Sci Med Sci* 2012; 67:804–810.
53. Low PA. Prevalence of orthostatic hypotension. *Clin Auton Res* 2008; 18 (Suppl 1):8–13.
54. Corrada MM, Brookmeyer R, Berlau D, Paganini-Hill A, Kawas CH. Prevalence of dementia after age 90: results from the 90+ study. *Neurology* 2008; 71:337–343.
55. Orrell M, Howard R, Payne A, Bergmann K, Woods R, Everitt BS, *et al*. Differentiation between organic and functional psychiatric-illness in the elderly: an evaluation of 4 cognitive tests. *Int J Geriatr Psychiatr* 1992; 7:263–275.
56. Pradier C, Sakarovitch C, Le Duff F, Layese R, Metelkina A, Anthony S, *et al*. The Mini Mental State Examination at the time of Alzheimer's disease and related disorders diagnosis, according to age, education, gender and place of residence: a cross-sectional study among the French National Alzheimer database. *PLoS One* 2014; 9:e103630.

Reviewer's Summary Evaluation

Reviewer 2

This observational study aimed at investigating the association of BP with all cause mortality in subjects over 85 years with different MMSE scores (four subgroups). Subjects were a representative sample of the population in Sweden and Finland (GERDA study), including 1115 individuals. After 2 years follow-up 26% of subjects had died. The higher mortality risk was observed among those with the most severe dementia. Mortality risk in subjects with MMSE 10 or less was not linear and increased in patients with SBP of 125 mmHg or less, or at least 165 mmHg compared with intermediate SBP (126–139 mmHg) values following a 'J'-shaped curve. Despite several limitations (BP measured in supine position overestimates BP values; underrepresentation of women; MMSE much more sensitive for severe cognitive decline than for mild cognitive impairment), the non-linearity relationship between SBP and mortality in very old subjects with dementia has implications for treatment of these patients.