Low Diastolic Pressure and Risk of Dementia in Very Old People: A Longitudinal Study

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Key Words

Blood pressure • Dementia • Alzheimer's disease • Longitudinal study

Abstract

Background/Aim: Midlife high blood pressure is linked to late-life dementia. We sought to investigate the temporal relation of blood pressure to the risk of dementia and Alzheimer's disease (AD) among older adults. **Methods:** A dementia-free cohort (n = 422) aged ≥ 81 years was followed for 3 years to detect dementia and AD cases (Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised criteria). The blood pressure was measured 4 times over a 9-year period starting from ≥ 75 years of age. The data were analyzed with Cox models controlling for potential confounders. **Results:** During the 954 person-years of follow-up, 89 subjects developed dementia (72 AD cases). Low diastolic pressure (<70 vs. 70–89 mm Hg) was associated with a multiaadjusted hazard ratio of 2.13 [95% confidence interval (CI) = 1.05–4.32] for dementia and 2.16 (95% CI = 0.98–4.73) for AD occurring over a 6-to 9-year period, whereas high diastolic pressure (≥ 90 mm Hg) was marginally related to a decreased hazard ratio of 0.58 (95% CI = 0.33–1.02) for dementia and 0.57 (95% CI = 0.30–1.09) for AD. Systolic pressure was not significantly related to dementia risk. Subjects who

developed dementia had a greater decline in blood pressure than persons who did not, mainly during the 3-year period before dementia diagnosis. **Conclusion:** Low diastolic pressure predicts the risk of dementia among very old people, and the blood pressure exhibits a substantial decline over around 3 years before the dementia syndrome becomes clinically evident.

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Introduction

The relationship between blood pressure and risk of dementia may depend on the patients' age when the blood pressure is measured as well as the time interval between the assessments of blood pressure and dementia status [1–3]. Several studies have found that elevated blood pressure in midlife is associated with an increased risk of dementia and Alzheimer's disease (AD) later in life [4–6]. Follow-up studies of late-life blood pressure and risk of dementia have yielded mixed results, depending largely on the time interval between the 2 measurements. Studies with a relatively short period of follow-up (e.g. 2–5 years) often found no relationship or an inverse association of blood pressure with the risk of dementia [7–10]. The 15-year follow-up study on a cohort of 70-year-old

people in Gothenburg, Sweden, showed that subjects who developed dementia at the ages of 79–85 years had a higher level of blood pressure at 70 years than people who did not [11]. In the 6-year follow-up study of people aged ≥ 75 years, we found that low diastolic pressure (< 70 mm Hg) was associated with an increased risk of dementia and AD [12], which is in accordance with the findings from another independent cohort study of ≥ 75 -year-old people [13]. However, clinicopathological research revealed that degeneration of brain neurons that regulate the blood pressure might alter the blood pressure [14]. Epidemiologic study also indicated that neurodegenerative processes, even in the preclinical phase of dementia, may lower the blood pressure [11]. Thus, the hypothesis that low blood pressure is longitudinally associated with an increased risk of dementia and AD among older adults needs to be confirmed by studies with a relatively long time gap between blood pressure measurement and dementia onset. In this study, we had the opportunity to examine the temporal relation of low blood pressure to the risk of dementia and AD in very old people within the Kungsholmen Project.

Methods

Study Population

The study population was derived from the Kungsholmen Project, a community-based cohort study of aging and dementia on people aged ≥ 75 years in Stockholm, Sweden [15]. After the 2-phase designed baseline survey (1987–1989, time 1), a full dementia workup was applied twice to the whole cohort during 1991–1993 (time 2) and 1994–1996 (time 3). The follow-up data concerning blood pressure and dementia until time 3 have been fully reported elsewhere [12]. At time 3, 453 survivors aged ≥ 81 years remained free of dementia. Of those, 31 (6.8%) refused to participate in the subsequent follow-up evaluation that was carried out during 1997–1998 (time 4), and 104 had died before the time 4 evaluation. Medical records and death certificates were available for all deceased persons to determine their dementia status at the time when they died. Thus, this analysis included 422 subjects who were free of dementia and were aged ≥ 81 years at time 3. All parts of the Kungsholmen Project received approval from the Ethics Committee at Karolinska Institutet, Stockholm, Sweden.

Measurements of Blood Pressure

At time 1, arterial blood pressure (systolic Korotkoff phase I and diastolic phase V) was measured on the right arm by trained nurses using a standardized random-zero mercury sphygmomanometer, with subjects in the sitting position after at least a 5-min rest [12]. If the first reading was abnormal (systolic pressure ≥ 160 mm Hg or diastolic pressure ≥ 95 mm Hg), 2 additional readings were then taken. The mean of the second and third readings was used for analysis. The same procedure was used for measuring the blood pressure at all follow-up occasions from time 2 to time 4.

Covariates

At time 3, which was considered as baseline of the follow-up study, data on demographic features were collected from the subjects. Global cognitive function was assessed with the Mini-Mental State Examination (MMSE). History of stroke, cardiovascular disease and diabetes until time 3 was ascertained using the computerized Stockholm inpatient register system. Presence of vascular morbidity was defined as having any of stroke, heart disease and diabetes. Functional status was measured by the Katz index of activities of daily living, and functional dependence was defined as the need of assistance in ≥ 2 activities [16]. Information on medical drug use in the 2 weeks preceding the time 3 survey was collected, and was verified by checking prescriptions and drug containers. Drugs were classified following the Anatomical, Therapeutic and Chemical classification system. Antihypertensive drugs were defined as all medications potentially used for lowering blood pressure (Anatomical, Therapeutic and Chemical codes C02, C03 and C07) [12]. Genomic DNA was prepared from peripheral blood samples that were taken at time 1, and the APOE allelic status was determined following a standard procedure [17].

Diagnosis of Dementia and AD

At time 4, all participants undertook extensive clinical examinations and comprehensive cognitive tests that were carried out by physicians and neuropsychologists [15]. We followed the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised criteria [18] to define dementia cases with a validated 3-step diagnostic procedure [19]. Briefly, 2 examining physicians independently made a preliminary diagnosis, and in the case of disagreement, a third opinion from a specialist was asked to reach a concordant diagnosis. The diagnosis of AD required gradual onset, progressive deterioration and lack of any other specific causes of dementia. Our diagnostic criteria for AD were similar to those in the international standardized criteria for probable AD [20]. For the deceased subjects, 2 physicians made a diagnosis of dementia or AD through thoroughly reviewing medical records and death certificates.

Statistical Analysis

Baseline characteristics were compared with the χ^2 test for categorical variables and with the *t* test for continuous variables controlling for age. Cox proportional hazards models were constructed to examine dementia and AD diagnosed at time 4 in association with blood pressure measured at time 1, in which the follow-up time over the time 3 and time 4 interviews was used as time scale. Specifically, for the nondemented subjects, the follow-up time was calculated from the date of the time 3 interview to the date of the time 4 evaluation or death (censored). For the demented subjects, half of the follow-up time was assumed due to insidious onset of dementia [15]. The blood pressure was categorized in similar ways as we had done previously [12]. We presented the results from 3 models: model 1 included only systolic and diastolic pressure, model 2 was adjusted for demographics (age, sex and education), and in model 3 we introduced additional covariates that might potentially explain or modify the association between blood pressure and dementia, which included MMSE score, vascular morbidity, use of antihypertensive drugs, functional dependence and APOE $\epsilon 4$ allele. All covariates were measured at time 3 because we considered time 3 to be the baseline survey of this follow-up study. In addition, because blood pres-

sure might be associated with mortality, and dementia cases were underdiagnosed among deceased individuals, the survival status at time 4 was also included in model 3. We assessed statistical interaction by incorporating the independent variables and their cross-product term into the same model. Dementia and AD were used as separate outcomes in all Cox regression analyses. Finally, we described dynamic variations in the age- and sex-adjusted mean systolic and diastolic pressures over a 9-year period by dementia status determined at time 4 by plotting linear graphs.

Results

Table 1 shows the characteristics of the study participants at time 3. After controlling for age, subjects who subsequently developed dementia had a lower MMSE score compared to individuals who did not, but the 2 groups had no significant differences in demographics, vascular morbidity, functional status, APOE ϵ 4 allele and use of antihypertensive drugs.

During a total of 954 person-years of follow-up from time 3 to time 4 [mean time per person = 2.3 years; standard deviation (SD) = 0.9], 89 subjects were diagnosed as having dementia, including 72 with AD, 4 with vascular dementia and 11 with mixed dementia. Cox regression analysis showed no significant association of systolic pressure measured at time 1 with the risk of dementia and AD diagnosed at time 4. After controlling for major potential confounders, however, low diastolic pressure (<70 vs. 70–89 mm Hg) measured at time 1 was significantly or marginally associated with a 2-fold increased risk of dementia and AD, whereas high diastolic pressure ($\geq$ 90 vs. 70–89 mm Hg) was marginally related to a decreased risk of dementia and AD (table 2). The mean time interval between the time 1 and time 4 examinations was 9.0 years (SD = 1.0; range = 6.3–10.5).

When blood pressure was used as continuous variables, the multiaadjusted hazard ratio (HR) related to each increment of 10 mm Hg in systolic pressure was 1.01 (95% CI = 0.89–1.15) for dementia and 0.99 (95% CI = 0.86–1.14) for AD; the corresponding figures related to each increment of 10 mm Hg in diastolic pressure were 0.87 (95% CI = 0.67–1.11) and 0.84 (95% CI = 0.63–1.12), respectively. We tested the nonlinear relationship between blood pressure as a continuous variable (per increment of 10 mm Hg) and the risk of dementia and AD by including the blood pressure variable and its quadratic term in the Cox regression model. The p values related to the quadratic term of systolic and diastolic pressure ranged from 0.05 to 0.24, which suggested a nonlinear or a potential for a nonlinear relationship between them.

Table 1. Characteristics of the study participants at baseline (time 3) by dementia status diagnosed at the follow-up (time 4)

Characteristics	Dementia (n = 89)	No dementia (n = 333)	Age- adjusted p value
Mean age $\pm$ SD, years	86.2 $\pm$ 4.0	86.1 $\pm$ 3.8	0.917
Female sex	74 (83.1)	253 (76.0)	0.153
Educational level $\geq$ 8 years	39 (43.8)	173 (52.0)	0.172
Vascular morbidity ^a	29 (32.6)	80 (24.0)	0.103
Antihypertensive drug use	41 (46.1)	166 (49.8)	0.509
Functional dependence ^b	4 (4.5)	14 (4.2)	0.912
APOE ϵ 4 allele ^c	22 (26.2)	73 (22.9)	0.524
Mean MMSE score $\pm$ SD	24.9 $\pm$ 3.6	26.7 $\pm$ 2.6	<0.001

APOE = Apolipoprotein E gene; SD = standard deviation. Figures in parentheses are percentages. ^a Vascular morbidity was defined as the presence of at least one of heart disease, stroke and diabetes. ^b Functional dependence was defined as the need of assistance in $\geq$ 2 activities in the Katz index of activities of daily living. ^c Information on APOE genotype was missing for 20 subjects, and they were included in the non- ϵ 4 allele category in the subsequent analysis.

No statistical interaction was detected between blood pressure and use of antihypertensive drugs, APOE ϵ 4 allele, or vascular morbidity and the risk of dementia.

The main results could be roughly confirmed when the analyses were confined to the subjects who were alive at the time 4 examination (n = 318, 75 dementia cases, including 64 AD cases; mean time interval between blood pressure and dementia assessments = 9.2 years, SD = 0.8, range = 7.1–10.5; data not shown). Furthermore, because low blood pressure at time 1 might be related to low body mass index (i.e. measured weight in kilograms divided by squared height in meters) [21], depression and use of antihypertensive drugs at the same time, and since pulse pressure (difference between systolic and diastolic pressure) might be superior to systolic or diastolic pressure in predicting dementia risk [22], we made additional adjustments for these variables assessed at time 1, which did not substantially alter the main results (data not shown). Finally, when the follow-up data in this study were integrated with the data from the first 6-year follow-up that had previously been reported [12] (total participants n = 1,270, over a 9-year follow-up period, 428 subjects were diagnosed as having dementia, including 328 AD cases), the multiaadjusted hazard ratios related to high ($\geq$ 90 mm Hg) and low (<70 vs. 70–89 mm Hg) diastolic pressure were 0.80 (95% CI = 0.63–1.01; p = 0.063) and 1.47 (95% CI = 1.07–2.01) for dementia, and 0.74 (95% CI = 0.56–

Table 2. Hazard ratio (95% CI) of dementia and AD associated with systolic and diastolic pressure measured 9 years before dementia diagnosis

Blood pressure	Sub- jects	Dementia				Alzheimer's disease			
		cases	model 1	model 2	model 3	cases	model 1	model 2	model 3
<i>Systolic pressure</i>									
<140 mm Hg	67	12	0.68 (0.35–1.32)	0.69 (0.36–1.35)	0.77 (0.39–1.51)	10	0.62 (0.30–1.28)	0.63 (0.31–1.30)	0.69 (0.33–1.45)
140–159 mm Hg	154	34	1.00 (reference)	1.00 (reference)	1.00 (reference)	31	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥160 mm Hg	201	43	1.23 (0.76–1.98)	1.21 (0.75–1.96)	1.38 (0.83–2.29)	31	0.99 (0.56–1.69)	0.98 (0.58–1.67)	1.18 (0.67–2.06)
<i>Diastolic pressure</i>									
<70 mm Hg	30	10	1.70 (0.85–3.39)	1.65 (0.82–3.29)	2.13 (1.05–4.32)	8	1.64 (0.76–3.52)	1.60 (0.74–3.45)	2.16 (0.98–4.73) ^a
70–89 mm Hg	272	60	1.00 (reference)	1.00 (reference)	1.00 (reference)	50	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥90 mm Hg	120	19	0.55 (0.32–0.96)	0.55 (0.32–0.95)	0.58 (0.33–1.02) ^a	14	0.53 (0.28–1.00)	0.53 (0.28–0.99)	0.57 (0.30–1.09) ^b

Model 1 included only systolic and diastolic pressure; model 2 was adjusted for age, sex and education, and in model 3 additional adjustment was made for MMSE score, vascular morbidity, use of antihypertensive drugs, functional dependence, APOE ε4 allele and follow-up survival status.

^a $p = 0.06$. ^b $p = 0.09$.

0.97) and 1.67 (95% CI = 1.18–2.37) for AD. Systolic pressure ≥ 160 or <140 mm Hg, in comparison with 140–159 mm Hg, was not significantly associated with the risk of dementia and AD.

In order to determine at which time point the blood pressure might be affected by the dementia process in its preclinical phase, we plotted linear graphs to describe the trends of the age- and sex-adjusted mean systolic and diastolic pressures over a 9-year period by dementia status determined at time 4. As shown in figure 1, there was no substantial difference between these 2 groups in the changes in either systolic or diastolic pressure over 3–9 years before dementia diagnosis. Compared with persons who remained free of dementia at time 4, however, individuals who developed dementia at this point in time did show a greater decline in blood pressure, especially in systolic pressure, during an approximately 3-year period before dementia diagnosis ($p < 0.001$).

Discussion

This population-based follow-up study suggests that among very old adults low diastolic pressure (<70 mm Hg) is associated with an increased risk of dementia and

AD occurring over the period of 6–9 years after blood pressure measurement. Furthermore, blood pressure, especially systolic pressure, shows substantial decline during an approximately 3-year period before dementia becomes clinically evident, but there is no evidence to suggest that such a decline would occur >6 years before dementia onset. This implies that the temporal relation of low diastolic pressure to an increased risk of dementia and AD observed in this study is not likely to be due to the influence of preclinical dementia. Our findings support the notion that late-life low diastolic pressure predicts the risk of dementia including AD. Finally, this study also indicates that very old adults with high diastolic pressure (≥ 90 mm Hg) are less likely to develop dementia during a subsequent period of 6–9 years.

Longitudinal studies with a short follow-up period suggest an inverse relationship between level of blood pressure and risk of dementia [7–10]. However, such an association cannot be directly interpreted as an effect of low blood pressure on the development of dementia because the blood pressure could be lowered by the dementia process, even at the preclinical stage [11, 23]. The temporal relationship between low blood pressure and an increased risk of dementia can be supported by research with a longer follow-up period such as the current study,

Fig. 1. Changes in the age- and sex-adjusted mean systolic (a) and diastolic (b) pressures over a 9-year period from time 1 to time 4 by dementia status ascertained at time 4. There were approximately 3 years over each time period. Note: blood pressure readings were missing in 4 subjects at time 2, in 6 subjects at time 3 and in 112 subjects (104 were due to death) at time 4.

in which the time gap between blood pressure measurement and dementia diagnosis is long enough to assure that the blood pressure is less likely to be affected by the disease process. In fact, our data show that the blood pressure could be affected just around 3 years before dementia onset, and we found no evidence that the blood pressure might have been affected in the early preclinical phase of dementia, especially over the period of 6–9 years before the dementia syndrome is clinically manifested. A few studies have indicated that high systolic pressure in midlife is associated with an elevated risk of dementia [4–6]. A recent evaluation found that high systolic pressure (≥ 160 mm Hg) was associated with an increased risk of dementia only in younger-old people (65–74 years) but not in the very old (≥ 75 years). Diastolic pressure was not significantly linked with the risk of dementia in all age strata, although very old individuals (≥ 75 years) with high diastolic pressure (≥ 90 mm Hg) tended to have a decreased risk of dementia [3], which is in line with our findings. Our results are also consistent with those from the Bronx Aging Study [13], where a cohort of community-dwelling volunteers aged ≥ 75 years was followed for a median of 6.7 years (range = 1–21). Both studies found that low diastolic pressure (< 70 mm Hg) was associated with an approximately 2-fold increased risk of dementia and AD, whereas high diastolic pressure (≥ 90 mm Hg) led to an approximately 40% reduced risk of dementia. In the Bronx Aging Study the association of low diastolic pressure with an increased risk of dementia was also confirmed by excluding dementia cases detected during the first 2 years of follow-up. The main discrepancy was that

we found no significant association between level of systolic pressure and risk of dementia, whereas the Bronx Aging Study suggested that people with systolic pressure ≥ 140 mm Hg were less likely to develop dementia [13]. As a substantial decline in systolic pressure is shown in our study during the preclinical phase of dementia, it is unclear to what extent the inverse association of systolic pressure with dementia risk observed in the Bronx cohort might be due to the influence of preclinical dementia.

The major advantage of this community-based study is the relatively long-term follow-up period, especially the long time gap between blood pressure and dementia assessments, which allows us to determine the temporal relationship between low blood pressure and the risk of dementia and AD. However, the lack of neuroimaging data limits our understanding of the biological mechanisms linking low blood pressure to dementia. In addition, it may also affect the accuracy of diagnosis for AD (but not for dementia in general); some Alzheimer patients would have been reclassified as having mixed dementia if neuroimaging data had been available. Indeed, neuropathological study confirmed that mixed pathologies of Alzheimer pathological changes and cerebrovascular disease account for the majority of dementia cases in community-dwelling older persons [24]. The study from our project also suggested that when major vascular disorders (e.g. hypertension, diabetes, cerebrovascular disease and heart disease) were taken into consideration, only approximately half of the AD patients were reclassified as pure AD cases without any vascular component [25]. Thus, the association with 'AD' observed in our study

might have represented a relation with mixed dementia. Finally, our finding of low diastolic pressure in association with an elevated risk of dementia and AD, which was based on a relatively small group of interests (i.e. very old individuals with diastolic pressure <70 mm Hg), warrants confirmation in studies with larger samples.

Long-standing high blood pressure starting from middle age can lead to a spectrum of cerebrovascular disease such as white matter lesions, silent brain infarcts and clinical stroke. These ischemic brain lesions could act either independently or in combination with late-life brain neurodegenerative changes to cause cognitive impairment and to promote clinical expression of the dementia syndrome [26, 27]. However, the pathophysiological influence of late-life blood pressure on cognition may be different from that of midlife blood pressure [1]. Neuroimaging and neuropathological studies suggest that low blood pressure in older adults can be linked to dementia and AD through various pathways. First, large-scale population-based neuroimaging studies found that low diastolic pressure (<70 mm Hg) was associated with more white matter lesions and severer atrophy of the hippocampus, especially among persons with antihypertensive treatments [28, 29]. All these brain lesions have been linked to dementia and AD [30, 31]. Second, very old people often experience impaired autoregulation of cerebral blood perfusion due to microvascular disease, microangiopathy or neurodegeneration in the brain [32, 33]. Thus, orthostatic hypotension and episodic or persistent hypotension may further impair cerebral blood perfusion and lead to a condition of more extensive brain ischemia, which in turn accelerates the clinical expression of the dementia syndrome [34, 35]. Finally, low diastolic pressure may indicate the presence of severer atherosclerosis, a condition that has been linked to cerebral neurodegen-

erative markers and clinical expression of the dementia syndrome [36–38]. In this context, cerebral atherosclerosis and arteriosclerosis may mediate the association between low diastolic pressure and an elevated risk of dementia and AD.

Isolated high systolic blood pressure is the most prevalent type of hypertension among older adults, and control of high systolic pressure often is the target of antihypertensive therapy, which may result in low diastolic pressure. We have previously reported that the association of low diastolic pressure with an increased risk of dementia and AD is evident mainly among individuals who took antihypertensive drugs [12]. This is in agreement with neuroimaging studies which found that the association between low diastolic pressure and severer cerebral white matter lesions and brain atrophy was particularly strong among persons who were treated with antihypertensive medications [30, 31]. Therefore, the establishment of a temporal relation of low diastolic pressure to an increased risk of dementia and AD among very old people has relevant implications for clinical practice and dementia prevention. For instance, among very old adults it may help reduce the risk of dementia and cognitive deterioration to take precautions to avoid low diastolic pressure.

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References

- 1 Qiu C, Winblad B, Fratiglioni L: The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* 2005;4:487–499.
- 2 Petitti DB, Crooks VC, Buckwalter JG, Chiu V: Blood pressure levels before dementia. *Arch Neurol* 2005;62:112–116.
- 3 Li G, Rhew IC, Shofer JB, Kukull WA, Breitner JC, Peskind E, Bowen JD, McCormick W, Teri L, Crane PK, Larson EB: Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study. *J Am Geriatr Soc* 2007;55:1161–1167.
- 4 Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, Havlik RJ: Midlife blood pressure and dementia: the Honolulu-Asia Aging Study. *Neurobiol Aging* 2000;21:49–55.
- 5 Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A: Midlife vascular risk factors and Alzheimer's disease in late life: longitudinal, population-based study. *BMJ* 2001;322:1447–1451.
- 6 Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K: Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005;64:277–281.
- 7 Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, van Harskamp F, Hofman A, Breteler MM: Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord* 2001;12:33–39.
- 8 Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA: Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. *Arch Neurol* 2001;58:1640–1646.

- 9 Posner HB, Tang MX, Luchsinger R, Lantigua R, Stern Y, Mayeux R: The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology* 2002;58:1175–1181.
- 10 Shah RC, Wilson RS, Bienias JL, Arvanitakis Z, Evans DA, Bennett DA: Relation of blood pressure to risk of incident Alzheimer's disease and change in global cognitive function in older persons. *Neuroepidemiology* 2006; 26:30–36.
- 11 Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, Persson G, Odén A, Svanborg A: 15-year longitudinal study of blood pressure and dementia. *Lancet* 1996; 347:1141–1145.
- 12 Qiu C, von Strauss E, Fastbom J, Winblad B, Fratiglioni L: Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Arch Neurol* 2003;60: 223–228.
- 13 Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ: Low blood pressure and the risk of dementia in very old individuals. *Neurology* 2003;61:1667–1672.
- 14 Burke WJ, Coronado PG, Schmitt CA, Gillespie KM, Chung HD: Blood pressure regulation in Alzheimer's disease. *J Auton Nerv Syst* 1994;48:65–71.
- 15 Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B: Very old women at highest risk of dementia and Alzheimer disease: incidence data from the Kungsholmen project, Stockholm. *Neurology* 1997;48:132–138.
- 16 Von Strauss E, Fratiglioni L, Viitanen M, Forsell Y, Winblad B: Morbidity and comorbidity in relation to functional status: a community-based study of the oldest old (90+ years). *J Am Geriatr Soc* 2000;48:1462–1469.
- 17 Qiu C, Kivipelto M, Agüero-Torres H, Winblad B, Fratiglioni L: Risk and protective effects of APOE gene towards Alzheimer's disease in the Kungsholmen project: variation by age and sex. *J Neurol Neurosurg Psychiatry* 2004;75:828–833.
- 18 American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised (DSM-III-R)*. Washington, American Psychiatric Association, 1987.
- 19 Fratiglioni L, Grut M, Forsell Y, Viitanen M, Winblad B: Clinical diagnosis of Alzheimer's disease and other dementias in a population survey: agreement and causes of disagreement in applying the DSM-III-R Criteria. *Arch Neurol* 1992;49:927–932.
- 20 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Service Task Force on Alzheimer Disease. *Neurology* 1984;34:939–944.
- 21 Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L: Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. *J Am Geriatr Soc* 2008;56:111–116.
- 22 Qiu C, Winblad B, Viitanen M, Fratiglioni L: Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. *Stroke* 2003;34:594–599.
- 23 Qiu C, von Strauss E, Winblad B, Fratiglioni L: Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. *Stroke* 2004;35: 1810–1815.
- 24 Schneider JA, Arvanitakis Z, Bang W, Bennett DA: Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007;69: 2197–2204.
- 25 Agüero-Torres H, Kivipelto M, von Strauss E: Rethinking the dementia diagnoses in a population-based study: what is Alzheimer's disease and what is vascular dementia? A study from the Kungsholmen Project. *Dement Geriatr Cogn Disord* 2006;22:244–249.
- 26 Vermeer SE, den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM: Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* 2003;34:392–396.
- 27 Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM: Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348: 1215–1222.
- 28 Van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A: The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension* 2004;44:625–630.
- 29 Den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, Breteler MM: Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005;64:263–267.
- 30 Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM: Cerebral white matter lesions and the risk of dementia. *Arch Neurol* 2004; 61:1531–1534.
- 31 Geerlings MI, den Heijer T, Koudstaal PJ, Hofman A, Breteler MM: History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease. *Neurology* 2008;70:1258–1264.
- 32 Sorond FA, Khavari R, Serrador JM, Lipsitz LA: Regional cerebral autoregulation during orthostatic stress: age-related differences. *J Gerontol A Biol Sci Med Sci* 2005;60:M1484–M1487.
- 33 Bakker SL, de Leeuw FE, den Heijer T, Koudstaal PJ, Hofman A, Breteler MM: Cerebral haemodynamics in the elderly: the Rotterdam study. *Neuroepidemiology* 2004;23: 178–184.
- 34 Ruitenberg A, den Heijer T, Bakker SL, Swieten JC, Koudstaal PJ, Hofman A, Breteler MM: Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. *Ann Neurol* 2005;57:789–794.
- 35 Yap PL, Niti M, Yap KB, Ng TP: Orthostatic hypotension, hypotension and cognitive status: early comorbid markers of primary dementia? *Dement Geriatr Cogn Disord* 2008; 26:239–246.
- 36 Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, Pandya Y, Esh C, Connor DJ, Sabbagh M, Walker DG, Roher AE: Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. *Acta Neuropathol* 2007;113:13–21.
- 37 Laurin D, Masaki KH, White LR, Launer LJ: Ankle-to-brachial index and dementia: the Honolulu-Asia Aging Study. *Circulation* 2007;116:2269–2274.
- 38 Van Oijen M, de Jong FJ, Wittman JC, Hofman A, Koudstaal PJ, Breteler MM: Atherosclerosis and risk for dementia. *Ann Neurol* 2007;61:403–410.