ORIGINAL CONTRIBUTION

Low Blood Pressure and Risk of Dementia in the Kungsholmen Project

A 6-Year Follow-up Study

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Background: Previous studies have reported a higher prevalence of dementia in persons with low blood pressure.

Objective: To examine whether low blood pressure is prospectively associated with the occurrence of Alzheimer disease and dementia in elderly people.

Subjects and Methods: A community-based, dementia-free cohort (n=1270) aged 75 to 101 years was longitudinally examined twice within 6 years to detect incident dementia using the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria. Cox proportional hazards models were used to analyze blood pressure in association with dementia after adjustment for several potential confounders.

Results: During the 6-year period, 339 subjects were diagnosed with dementia, including 256 persons with Alzheimer disease. Subjects with very high systolic pressure (>180 vs 141-180 mm Hg) had an adjusted relative risk of 1.5 (95% confidence interval [CI], 1.0-2.3; $P=.07$) for Alzheimer disease, and 1.6 (95% CI, 1.1-2.2) for dementia. Low systolic pressure (≤140 mm Hg) was not related to incident dementia. In contrast, high diastolic pressure (>90 mm Hg) was not associated with dementia incidence, whereas extremely low diastolic pressure (≤65 vs 66-90 mm Hg) produced an adjusted relative risk of 1.7 (95% CI, 1.1-2.4) for Alzheimer disease and 1.5 (95% CI, 1.0-2.1; $P=.03$) for dementia. The latter association was pronounced particularly in persons who used antihypertensive drugs.

Conclusions: Both low diastolic and high systolic pressure are associated with an increased risk of Alzheimer disease and dementia in this elderly population. The atherosclerotic process may explain the observed associations. In addition, low diastolic pressure may increase dementia risk by affecting cerebral perfusion.

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SEVERAL LONGITUDINAL studies have shown that hypertension or elevated blood pressure, occurring in either middle age or late-life, increases the risk of Alzheimer disease or other types of dementia.[1-5] Conversely, an increased prevalence of Alzheimer disease and dementia has been reported in persons with low blood pressure.[6,7] Two possible hypotheses may explain the observed cross-sectional association: (1) Low blood pressure is a consequence of dementia, as the dementia process itself may lower blood pressure;[2,6] and (2) low blood pressure increases the risk of Alzheimer disease and dementia. Few population-based prospective studies have specifically explored the latter topic so far. In a cohort of Japanese American men, low blood pressure (especially low diastolic pressure) during middle age, as well as elevated blood pressure, has been found to be associated with an increased risk for developing Alzheimer disease and dementia in late life, particularly among those who were never treated with antihypertensive medication.[3] The pooled data from 2 studies in Europe have also shown an inverse relationship between level of blood pressure and incidence of dementia, especially in persons who used antihypertensive drugs.[8] A recent community study from East Boston found no evidence for the association between high blood pressure and increased risk of Alzheimer disease. In contrast, blood pressure level measured 4 years prior to dementia diagnosis was inversely associated with the risk of subsequent Alzheimer disease in this population.[9] These studies indicate that low blood pressure may predispose the risk of Alzheimer disease and dementia.

In a 3-year follow-up study performed on a random sample from the Kungsholmen population in Stockholm, Sweden, we found that the association between low systolic pressure (≤140 mm Hg) and

increased incidence of dementia was very dependent on initial cognitive functioning,[10] which supports the hypothesis that low blood pressure may be an early correlate of the dementia process. The present study aims to further explore whether low blood pressure is prospectively associated with occurrence of Alzheimer disease and dementia by using the 6-year follow-up data from the entire cohort of the Kungsholmen Project.

METHODS

STUDY POPULATION

The Kungsholmen Project is a community-based, longitudinal study on aging and dementia. All phases of the project received approval from the Ethics Committee of Karolinska Institutet. The baseline data collection, the inception of the dementia-free cohort, and the follow-up examinations concerning the project have been described in detail elsewhere.[11,12] In brief, the initial population of this project included all registered inhabitants who were living in the Kungsholmen district of Stockholm and who were 75 years and older in October 1987. Of all 1810 participants at the baseline survey (1987-1989), 1440 subjects with available blood pressure readings were diagnosed as being free of dementia through a 2-phase design procedure. Of these subjects, 170 either refused to participate in the first follow-up examination or had moved out of Stockholm before the examination (1991-1993). Therefore, the study population for the current analysis consisted of 1270 dementia-free subjects at baseline. During the first follow-up period, 303 subjects died. Among those who underwent an extensive clinical examination at first follow-up (n=967), 772 individuals remained free of dementia, and these subjects were followed up for 3 years further. Of these persons, 170 died during the second follow-up period, and 43 persons refused to participate in the second follow-up examination (1994-1996).

BASELINE DATA COLLECTION

Arterial blood pressure (ie, 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 the subject in a sitting position after at least a 5-minute rest.[6] If the first reading was abnormal (ie, 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. Pulse pressure was calculated as the difference between systolic pressure and diastolic pressure.

Data on age, sex, education, and cognitive functioning (assessed with the Mini-Mental State Examination [MMSE][13]) were collected at baseline interview according to standardized protocols.[11,12] Educational level was measured by the maximum years of formal schooling and was categorized as less than 8 years (elementary or vocational training) or 8 years or more (high school or university).[14] Information on vascular disorders at baseline was derived from the computerized Stockholm Inpatient Register system that encompassed all hospitals in the Stockholm area since 1969. Vascular diseases were diagnosed based on the *International Classification of Diseases, Eighth Revision (ICD-8)*, including heart disease (*ICD-8* codes 410-414, 427, and 428), cerebrovascular disease (*ICD-8* codes 430-438), and diabetes mellitus (*ICD-8* code 250). Information on medical drug use (both prescription and nonprescription) in the 2 weeks prior to the baseline interview was collected, and the drug containers and prescriptions were inspected to verify this information. Drug use was coded and classified according to the Anatomical Therapeutic Chemical (ATC) classification system.[15] Antihypertensive drugs were defined as all medicines potentially used for lowering blood pressure (ie, ATC codes C02, C03, and C07).

DIAGNOSIS OF INCIDENT DEMENTIA AND ALZHEIMER DISEASE

Cases of incident dementia involved all individuals who developed dementia during the 2 follow-up periods. At each follow-up examination, all participants underwent an extensive evaluation following a standardized protocol, including a structured interview by trained nurses, a comprehensive clinical examination by physicians, and psychological assessments.[12,16]

The diagnosis of incident dementia was made according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)* criteria.[17] A 3-step diagnostic procedure was used at both follow-up examinations (ie, 2 examining physicians independently made the preliminary diagnoses, and a third opinion was requested in case of disagreement).[12,16] The subjects who completely fulfilled the *DSM-III-R* criteria were diagnosed as having "clinically definite dementia," in contrast with a category of "questionable dementia," which was used when there was evident memory impairment but dysfunction of a second cognitive ability was questionable. The diagnosis of Alzheimer disease requires gradual onset, progressive deterioration, and lack of any other specific causes of dementia. Our criteria for Alzheimer disease were similar to those from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association[18] for probable Alzheimer disease.

For those who had died before each follow-up examination, information about health status during the follow-up period was obtained from the Stockholm Inpatient Register system, and individual hospital records, as well as death certificates, were collected. The diagnosis of dementia or Alzheimer disease was made by reviewing the medical records and death certificates.

STATISTICAL ANALYSIS

The incidence rates were calculated as the number of events (Alzheimer disease or dementia) divided by the follow-up time (person-years at risk).[12] We considered the different types of dementia as competing causes of dementia, which meant that a subject who developed any type of dementia was no longer at risk of developing other types of dementia. Cox proportional hazards models were used to estimate the relative risk of developing Alzheimer disease or dementia in relation to baseline blood pressure. Blood pressure levels were first grouped into 5 categories following the criteria used in a previous study,[6] with a minor modification (ie, instead of >95 mm Hg, a cutoff of >90 mm Hg was used due to limited numbers in the original category). Preliminary analysis showed that some adjacent groups had a similar incidence of dementia; for instance, subjects with systolic pressure between 141 and 160 mm Hg, and those with 161 to 180 mm Hg had a dementia incidence of 58.4 and 55.3 per 1000 person-years, respectively. These groups were then merged, leading to a final model with 3 categories of blood pressure (ie, systolic pressure: ≤140, 141-180 [reference], and >180 mm Hg; diastolic pressure: ≤65, 66-90 [reference], and >90 mm Hg). Age, sex, education, vascular disease, baseline MMSE score, antihypertensive drug use, and systolic pressure or diastolic pressure were included as covariates in all multiple regression models. As further adjustment for squared age and pulse pressure (as an indicator variable with 3 categories of <70, 70-84, >84 mm Hg based on the tertiles) did not substantially affect the estimate of the association between blood pressure and risk of dementia, we only reported the results determined without controlling for squared age, and pulse pressure.

Table 1. Baseline Characteristics of the Initial 1270 Dementia-Free Cohort in the Kungsholmen Project According to Dementia Status Diagnosed During 6 Years of Follow-up

Baseline Characteristic	Demented Subjects (n = 339)	Nondemented Subjects (n = 931)	*P* Value
Mean (SD) age, y	82.5 (4.6)	81.1 (5.1)	.02
Female, No. (%)	277 (81.7)	677 (72.7)	.001
Education ≥8 years, No. (%)	108 (31.9)	409 (43.9)	<.001
Vascular disease, No. (%)*	81 (23.9)	192 (20.6)	.21
Antihypertensive drug use, No. (%)	135 (39.8)	432 (46.4)	.04
Mean (SD) MMSE score†	25.7 (3.2)	27.0 (2.4)	<.001
Mean (SD) systolic pressure, mm Hg	156.3 (23.0)	155.2 (21.1)	.15
Mean (SD) diastolic pressure, mm Hg	80.6 (10.9)	81.2 (10.7)	.59
Mean (SD) pulse pressure, mm Hg	75.7 (19.5)	74.0 (17.9)	.15

Abbreviation: MMSE, Mini-Mental State Examination.
*At least one of the following was present: heart disease, cerebrovascular disease, and diabetes mellitus.
†MMSE score ranged from 0 (worst) to 30 (best).

Table 2. Incidence Rates, Relative Risks, and 95% Confidence Intervals (CIs) of Alzheimer Disease and All Types of Dementia by Baseline Blood Pressure Levels*

Blood Pressure, mm Hg	No. of All Subjects	Alzheimer Disease			All Types of Dementia		
		No. of Subjects	IR	RR (95% CI)	No. of Subjects	IR	RR (95% CI)
Systolic pressure							
≤140	393	83	52.3	1.0 (0.8-1.3)	108	65.4	1.0 (0.8-1.3)
141-180	767	145	44.9	1.0 (Reference)	192	57.0	1.0 (Reference)
>180	110	28	65.7	1.5 (1.0-2.3)†	39	87.3	1.6 (1.1-2.2)
Diastolic pressure							
≤65	132	34	73.9	1.7 (1.1-2.4)	40	83.4	1.5 (1.0-2.1)‡
66-90	958	191	47.8	1.0 (Reference)	255	61.1	1.0 (Reference)
>90	180	31	39.6	0.8 (0.5-1.2)	44	54.3	0.9 (0.6-1.2)

Abbreviations: IR, incidence rate; RR, relative risk.
*Both RR and 95% CI were estimated after adjustment for age (in years), sex, education (<8 vs ≥8 years), vascular disease (yes vs no), use of antihypertensive drugs (yes vs no), baseline Mini-Mental State Examination score (continuous variable), and if applicable, diastolic or systolic pressure.
†*P* = .07.
‡*P* = .03.

In addition, the results of the preliminary analysis indicated that "questionable dementia" and "clinically definite dementia" were related to blood pressure in a very similar way (ie, similar results were obtained when the category of "questionable dementia" was excluded from the analysis). Thus, in this study, both groups were considered to have dementia. All types of dementia and Alzheimer disease were used as separate outcomes in all Cox regression analyses.

RESULTS

Across a total of 5465 person-years (median, 5 years) of follow-up, 339 subjects were diagnosed with dementia, including 256 individuals with Alzheimer disease. Subjects who developed dementia during the follow-up period were older, more likely to be female, less educated, and with lower MMSE scores, and there were fewer persons with antihypertensive therapy at baseline than those who remained nondemented. However, the 2 groups did not differ significantly in terms of the frequency of vascular disease and means of systolic pressure, diastolic pressure, and pulse pressure (**Table 1**).

Table 2 presents the crude incidence rates and the adjusted relative risks of Alzheimer disease and all dementias by baseline blood pressure levels. For systolic pressure, very high systolic pressure (>180 vs 141-180 mm Hg) was significantly related to an increased incidence of dementia, while the relative risk for Alzheimer disease was marginally statistically significant. Subjects with low systolic pressure (≤140 vs 141-180 mm Hg) had the age-, sex-, and education-adjusted relative risks of 1.3 (95% confidence interval [CI],1.0-1.7; *P* = .09) for Alzheimer disease and 1.2 (95% CI, 1.0-1.6; *P* = .09) for dementia. However, these relative risks considerably decreased after further adjustment for other potential confounders, especially baseline MMSE score and diastolic pressure (Table 2). High diastolic pressure (>90 vs 66-90 mm Hg) was not related to the risk of Alzheimer disease and dementia, but extremely low diastolic pressure (≤65 vs 66-90 mm Hg) was significantly associated with an increased incidence of Alzheimer disease and dementia, even when several potential confounders were taken into account (Table 2). These analyses were repeated using less extreme cut-offs for blood pressure, which produced results similar to those presented in Table 2. Compared with less than 130 mm Hg, for instance, systolic pressure between 130 and 159 mm Hg, and 160 mm Hg or greater was related to adjusted relative risks of 1.4 (95% CI, 0.9-2.2) and 1.4 (95% CI, 0.9-2.4) for Alzheimer disease, and 1.3 (95% CI, 0.9-2.0) and 1.3 (95%

Table 3. Relative Risks and 95% Confidence Intervals (CIs) of Alzheimer Disease and All Types of Dementia Associated With Baseline Blood Pressure Levels by Antihypertensive Drug Use*

	No Use of Antihypertensive Drugs					Use of Antihypertensive Drugs				
		Alzheimer Disease		All Dementias			Alzheimer Disease		All Dementias	
Blood Pressure, mm Hg	No. of Subjects	No. of Subjects	RR (95% CI)	No. of Subjects	RR (95% CI)	No. of Subjects	No. of Subjects	RR (95% CI)	No. of Subjects	RR (95% CI)
Systolic pressure										
≤140	230	52	1.0 (0.7-1.4)	66	1.0 (0.8-1.4)	163	31	1.0 (0.7-1.6)	42	1.0 (0.7-1.5)
141-180	415	92	1.0 (Reference)	116	1.0 (Reference)	352	53	1.0 (Reference)	76	1.0 (Reference)
>180	58	19	1.6 (0.9-2.6)	22	1.5 (0.9-2.4)	52	9	1.4 (0.7-2.9)	17	1.7 (1.0-2.9)†
Diastolic pressure										
≤65	69	17	1.3 (0.8-2.2)	20	1.2 (0.8-2.0)	63	17	2.5 (1.4-4.3)	20	1.9 (1.1-3.1)
66-90	534	122	1.0 (Reference)	154	1.0 (Reference)	424	69	1.0 (Reference)	101	1.0 (Reference)
>90	100	24	1.0 (0.6-1.6)	30	1.0 (0.7-1.6)	80	7	0.5 (0.2-1.1)	14	0.6 (0.4-1.1)

Abbreviation: RR, relative risk.
*Both RR and 95% CI were estimated after adjustment for age, sex, education, vascular disease, baseline Mini-Mental State Examination score, and if applicable, diastolic or systolic pressure.
†$P = .06$.

CI, 0.9-2.0) for dementia, respectively. The corresponding figures related to diastolic pressure less than 70 and 90 mm Hg or greater (in comparison with 70-89 mm Hg) were 1.8 (95% CI, 1.2-2.6) and 0.9 (95% CI, 0.7-1.2) for Alzheimer disease, and 1.5 (95% CI, 1.1-2.2) and 1.0 (95% CI, 0.7-1.3) for dementia.

Antihypertensive treatment at baseline was significantly related to a reduced incidence of Alzheimer disease (relative risk=0.7; 95% CI, 0.5-0.9) and dementia (relative risk=0.8; 95% CI, 0.6-1.0; $P = .03$). We further examined the relationship between blood pressure level and dementia incidence by stratification of baseline antihypertensive treatment (**Table 3**). The use of antihypertensive drugs did not greatly modify the association between systolic pressure and risk of dementia. However, the increased incidence of Alzheimer disease and dementia related to low diastolic pressure was statistically significant only among persons who used antihypertensive drugs (Table 3).

Additional analyses were performed to further evaluate the potential influence of baseline cognitive functioning on the association between blood pressure and dementia. First, as some very mild dementia cases might have been missed at baseline and been included in the initial dementia-free cohort, we repeated the analyses using only the incident cases diagnosed at the second follow-up examination (n=729, 121 dementia cases, 94 Alzheimer disease cases). Subjects with high systolic pressure (>180 vs 141-180 mm Hg) had adjusted relative risks of 1.7 (95% CI, 0.9-3.4) for Alzheimer disease and 1.4 (95% CI, 0.7-2.6) for dementia. The corresponding relative risks related to low diastolic pressure (≤65 vs 66-90 mm Hg) were 1.5 (95% CI, 0.8-2.9) for Alzheimer disease and 1.4 (95% CI, 0.8-2.5) for dementia. These results were quite close to those from the entire population (Table 2), although they were not statistically significant, probably due to the limited statistical power. Further, all analyses were repeated in the subgroup of persons with a baseline MMSE score of 24 or higher (n=1183, 293 dementia cases, 219 Alzheimer disease cases), which also yielded results similar to the entire population (data not shown). All these additional analyses were adjusted for major potential confounders, including baseline MMSE score.

COMMENT

In this elderly Swedish population, aged 75 years and older, we found that not only high systolic pressure, but also low diastolic pressure, was associated with an increased incidence of Alzheimer disease and dementia. The risk effect of low diastolic pressure on dementia was pronounced particularly among antihypertensive drug users. These results could be confirmed even when blood pressure was measured at least 6 years before diagnosis.

Numerous population-based studies have examined the longitudinal relationship between blood pressure and risk of dementia.[1-5,8-10] Although the findings from these studies have been inconsistent, an association between elevated blood pressure and increased incidence of Alzheimer disease or other dementias is reported in most previous studies,[1-5,10] suggesting that high blood pressure (especially high systolic pressure) may be a risk factor for Alzheimer disease and dementia. These findings from observational studies are supported by a randomized placebo-controlled clinical trial (Syst-Eur[19]), which showed that active treatment of isolated systolic hypertension in elderly persons decreased the dementia incidence by 50% throughout 2 years. Our population-based study provides further evidence for the association between high systolic pressure and elevated dementia incidence. In addition, we could confirm our previous report of a protective effect of antihypertensive therapy against Alzheimer disease and dementia in the general elderly population.[20] However, we found that antihypertensive medication could not substantially modify the increased dementia risk in subjects with high systolic pressure. This suggests that very elderly people with hypertension (especially systolic hypertension) whose high blood pressure is treated, but not well controlled, remain at an increased risk for developing dementing disorders. The etiological role of hypertension in vascular

dementia has been well documented. Elevated blood pressure may be also connected with Alzheimer disease in different ways. First, the neuropathological studies have linked elevated blood pressure to the density of neuritic plaques and neurofibrillary tangles,[21,22] which are the histopathological hallmarks of Alzheimer disease. Second, long-standing hypertension may be linked to Alzheimer disease by contributing to atherosclerosis,[23] white matter lesions,[24] blood-brain barrier disturbance,[25] and brain atrophy.[26] Third, cerebrovascular disease secondary to hypertension may accelerate the clinical expression of Alzheimer disease in the presence of coexisting Alzheimer pathological changes in the brain.[27,28]

An association between low blood pressure and high risk of subsequent Alzheimer disease or other dementias has been previously suggested.[3,8-10] Our follow-up data further indicate that low, rather than high, diastolic pressure is prospectively associated with an increased incidence of Alzheimer disease and dementia. These findings are in good line with the East Boston study,[9] in which low, but not high, diastolic pressure (<70 mm Hg) tended to increase the risk of subsequent Alzheimer disease. Furthermore, we found that the association between low diastolic pressure and increased risk of Alzheimer disease and dementia was evident particularly among the users of antihypertensive drugs. Different mechanisms may underlie this association. First, evidence has shown that cerebral hypoperfusion seems to precede the neurodegenerative pathological changes[29]; therefore, it is likely that in advanced ages, a reduction in cerebral blood flow associated with hypotension, particularly when treated with antihypertensive drugs, may play a critical role in the pathogenesis of Alzheimer disease and dementia.[30,31] An alternative explanation relies on the fact that low diastolic pressure, as well as high systolic pressure, is an indicator of increased large arterial stiffness and widespread atherosclerosis in elderly people.[32-34] These pathological changes have already been linked to dementia and Alzheimer disease.[23,35] As expected, heart disease, cerebrovascular disease, and diabetes mellitus were more common among antihypertensive drug users than nonusers in this population (32.1% vs 12.9%, $P<.001$). It is therefore biologically plausible that the association between low diastolic pressure and increased risk of Alzheimer disease and dementia may be stronger in individuals affected by these vascular disorders.

The finding of low diastolic pressure in association with Alzheimer disease and dementia in elderly people may have relevant implications for clinical practice and dementia prevention. First, diastolic pressure needs to be closely monitored when high systolic pressure is targeted with clinical treatment. The protective effect of appropriate antihypertensive treatment on cardiovascular disease and stroke has been well established.[36] In terms of dementia prevention, however, our findings may call into question the presumption that for antihypertensive treatment in the very elderly, "the lower the better." Second, as low diastolic pressure may predispose a subpopulation to Alzheimer disease and dementia, low diastolic pressure can be used to identify high-risk individuals.

Several potential limitations of this study deserve mentioning. First, the defined population of the current study consisted of subjects with a minimum age of 75 years at entry. The pathophysiological implications of blood pressure levels are largely age-dependent.[33,37] Our findings may therefore not totally apply to younger age groups. Second, the diagnosis of Alzheimer disease and dementia was made on a clinical basis, as the use of imaging techniques was unfeasible in a large-scale population study started in the 1980s. However, the cerebral vascular lesions detected with neuroimaging are difficult to determine as causes of dementia since the coexistence of Alzheimer disease or dementia and vascular changes in the brain are quite common in the very elderly.[27,38] Third, dementia cases might have been under-diagnosed among the deceased subjects, which could only have resulted in an underestimation of the association between both low and high blood pressure and incidence of dementia due to the selective survival related to blood pressure levels.[39] Finally, the blood pressure measurement made on a single occasion might diminish the data accuracy, which could attenuate the association between blood pressure and dementia.

In summary, our data indicate that both high systolic and low diastolic pressure are possible risk factors for Alzheimer disease and dementia in elderly people. In view of the clinical implications, further investigations are imperative to elucidate whether the antihypertensive treatment could strengthen the association between low diastolic blood pressure and risk of dementia.

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REFERENCES

1. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology.* 1995;45:1161-1168.
2. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. *Lancet.* 1996;347:1141-1145.
3. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging.* 2000;21:49-55.

4. Kivipelto M, Helkala E-L, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ*. 2001; 322:1447-1451.
5. Posner HB, Tang M-X, 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.
6. Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: the Kungsholmen project. *BMJ*. 1996;312:805-808.
7. Morris MC, Scherr PA, Hebert LE, et al. The cross-sectional association between blood pressure and Alzheimer's disease in a biracial community population of older persons. *J Gerontol A Biol Sci Med Sci*. 2000;55:M130-M136.
8. Ruitenberg A, Skoog I, Ott A, et al. 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.
9. 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.
10. Guo Z, Viitanen M, Winblad B, Fratiglioni L. Low blood pressure and incidence of dementia in a very old sample: dependent on initial cognition. *J Am Geriatr Soc*. 1999;47:723-726.
11. Fratiglioni L, Viitanen M, Bäckman L, Sandman P-O, Winblad B. Occurrence of dementia in advanced age: The study design of the Kungsholmen Project. *Neuroepidemiology*. 1992;11(suppl 1):29-36.
12. Fratiglioni L, Viitanen M, von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. *Neurology*. 1997;48:132-138.
13. 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.
14. Qiu CX, Bäckman L, Winblad B, Agüero-Torres H, Fratiglioni L. The influence of education on clinically diagnosed dementia: Incidence and mortality data from the Kungsholmen Project. *Arch Neurol*. 2001;58:2034-2039.
15. Nordic Council on Medicines. *Guidelines for ATC Classification*. Uppsala, Sweden: Nordic Council on Medicines; 1985. NLN Publication No. 16.
16. Fratiglioni L, Wang H-X, Ericsson K, Maytan M, Winblad B. Influence of social network on occurrence of dementia: a community-based longitudinal study. *Lancet*. 2000;355:1315-1319.
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987.
18. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Service Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
19. Forette F, Seux M, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet*. 1998;352:1347-1351.
20. Guo Z, Fratiglioni L, Zhu L, Fastbom J, Winblad B, Viitanen M. Occurrence and progression of dementia in a community population aged 75 years and over: relation of antihypertensive medication use. *Arch Neurol*. 1999;56:991-996.
21. Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker III JC. Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. *J Neurol Sci*. 1995;131:162-169.
22. Petrovitch H, White LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiol Aging*. 2000;21:57-62.
23. Hofman A, Ott A, Breteler MMB, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet*. 1997; 349:151-154.
24. de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain*. 2002;125(pt 4):765-772.
25. Skoog I, Wallin A, Fredman P, et al. A population study on blood-brain barrier function in 85-year-olds: relation to Alzheimer's disease and vascular dementia. *Neurology*. 1998;50:966-971.
26. Skoog I, Andreasson L, Landahl S, Lernfelt B. A population-based study on blood pressure and brain atrophy in 85-year-olds. *Hypertension*. 1998;32:404-409.
27. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. *JAMA*. 1997;277:813-817.
28. Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet*. 1999;354:919-920.
29. de la Torre JC. Alzheimer disease as a vascular disorder: nosological evidence. *Stroke*. 2002;33:1152-1162.
30. Ballard C, O'Brien J, Barber B, et al. Neurocardiovascular instability, hypotensive episodes, and MRI lesions in neurodegenerative dementia. *Ann N Y Acad Sci*. 2000;903:442-445.
31. Zuccalà G, Onder G, Pedone C, et al. Hypotension and cognitive impairment: selective association in patients with heart failure. *Neurology*. 2001;57:1986-1992.
32. Bots ML, Witteman JCM, Hofman A, de Jong PTVM, Grobbee DE. Low diastolic blood pressure and atherosclerosis in elderly subjects: the Rotterdam Study. *Arch Intern Med*. 1996;156:843-848.
33. Franklin SS, Gustin IV W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation*. 1997;96: 308-315.
34. van Popele NM, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis: the Rotterdam Study. *Stroke*. 2001;32:454-460.
35. Bots ML, van Swieten JC, Breteler MMB, et al. Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *Lancet*. 1993;341:1232-1237.
36. Staessen JA, Wang J-G, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet*. 2001;358:1305-1315.
37. Tate RB, Manfreda J, Krahn AD, Cuddy TE. Tracking of blood pressure over a 40-year period in the University of Manitoba follow-up study, 1948-1988. *Am J Epidemiol*. 1995;142:946-954.
38. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS): pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet*. 2001; 357:169-175.
39. 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.