Table 3. Association Between Midlife Blood Pressure and the Risk of Dementia in Late Life

Midlife BP Levels Defined by JNC-7	No. of Events	No. of Participants	Age-, Sex-, and Education-Adjusted		Multivariable-Adjusted*	
			HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause dementia						
Normal	38	122	1.00 (reference)		1.00 (reference)	
Prehypertension	56	185	0.92 (0.60 to 1.40)	0.68	0.92 (0.60 to 1.41)	0.71
Stage 1 hypertension	66	153	1.51 (1.00 to 2.29)	0.05	1.73 (1.12 to 2.65)	0.01
Stage 2 hypertension	33	74	1.79 (1.11 to 2.90)	0.02	1.95 (1.18 to 3.24)	0.01
P for trend			0.001		<0.001	
Vascular dementia						
Normal	4	122	1.00 (reference)		1.00 (reference)	
Prehypertension	15	185	2.29 (0.75 to 6.99)	0.15	2.38 (0.77 to 7.30)	0.13
Stage 1 hypertension	26	153	5.12 (1.76 to 14.93)	0.003	5.96 (2.00 to 17.77)	0.001
Stage 2 hypertension	18	74	8.92 (2.95 to 26.93)	<0.001	10.07 (3.25 to 31.25)	<0.001
P for trend			<0.001		<0.001	
Alzheimer disease						
Normal	26	122	1.00 (reference)		1.00 (reference)	
Prehypertension	33	185	0.80 (0.47 to 1.35)	0.4	0.77 (0.45 to 1.31)	0.34
Stage 1 hypertension	31	153	1.09 (0.63 to 1.87)	0.76	1.26 (0.72 to 2.21)	0.42
Stage 2 hypertension	12	74	0.97 (0.48 to 1.96)	0.94	1.05 (0.50 to 2.22)	0.89
P for trend			0.72		0.45	

BP indicates blood pressure; HR, hazard ratio; JNC-7, the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.

*Data were adjusted for potential confounding covariates in late life, namely, age, sex, education level, use of antihypertensive agents, diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

in the very elderly, BP lowering did not increase the risk of dementia, but the BP levels achieved in the intervention group were still >140/90 mm Hg.[23] Therefore, BP lowering for very elderly people may be implemented with caution. To date, it might be said that there is no strong evidence to indicate that elevated late-life BP is a risk factor for dementia.

Several longitudinal studies have examined the associations between midlife BP and the risk of dementia.[24–28] The

Table 4. Effects of Change in Blood Pressure Levels From Midlife to Late Life on the Risk of Dementia

BP Levels, mm Hg			No. of Events	No. of Participants	Percentage of Use of Antihypertensive Agents		Age-, Sex-, and Education-Adjusted		Multivariable-Adjusted*	
Midlife		Late-Life			Midlife	Late-Life	HR (95% CI)	*P*	HR (95% CI)	*P*
All-cause dementia										
<140/90	→	<140/90	59	197	0.5	9.2	1.00 (reference)		1.00 (reference)	
<140/90	→	≥140/90	35	110	3.6	21.8	1.05 (0.69 to 1.61)	0.81	1.13 (0.73 to 1.75)	0.58
≥140/90	→	<140/90	35	78	10.3	42.3	1.74 (1.14 to 2.66)	0.01	1.88 (1.19 to 2.96)	0.007
≥140/90	→	≥140/90	64	149	17.5	55.0	1.68 (1.17 to 2.42)	0.005	1.64 (1.09 to 2.46)	0.02
Vascular dementia										
<140/90	→	<140/90	6	197	0.5	9.2	1.00 (reference)		1.00 (reference)	
<140/90	→	≥140/90	13	110	3.6	21.8	3.71 (1.40 to 9.83)	0.008	3.29 (1.21 to 8.94)	0.02
≥140/90	→	<140/90	14	78	10.3	42.3	6.68 (2.55 to 17.52)	<0.001	5.32 (1.9 to 14.89)	0.001
≥140/90	→	≥140/90	30	149	17.5	55.0	6.94 (2.86 to 16.88)	<0.001	4.72 (1.83 to 12.17)	0.001
Alzheimer disease										
<140/90	→	<140/90	41	197	0.5	9.2	1.00 (reference)		1.00 (reference)	
<140/90	→	≥140/90	18	110	3.6	21.8	0.79 (0.45 to 1.39)	0.41	0.91 (0.51 to 1.62)	0.74
≥140/90	→	<140/90	14	78	10.3	42.3	1.00 (0.54 to 1.85)	1.00	1.23 (0.64 to 2.34)	0.53
≥140/90	→	≥140/90	29	149	17.5	55.0	1.16 (0.71 to 1.90)	0.55	1.29 (0.74 to 2.26)	0.37

BP indicates blood pressure; HR, hazard ratio.

*Data were adjusted for potential confounding covariates in late life, namely, age, sex, education level, use of antihypertensive agents, diabetes mellitus, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

Honolulu-Asia Aging Study revealed that the risks for both AD and VaD increased in Japanese-American men with untreated hypertension in midlife.[24,25] The results of community-based studies conducted in Finland[26] and in China[27] also showed that elevated systolic BP in midlife increased the risk of AD in late life. Conversely, the Hiroshima Study[28] in Japan demonstrated that higher midlife systolic BP was linked to late-life onset of VaD but not to AD. This finding is in accord with ours. The discrepancies in the findings among these studies may be attributable to the difficulty of distinguishing between dementia subtypes. Patients with dementia sometimes have mixed neurodegenerative and vascular pathology.[29] Recently, cognitive impairment in association with vascular factors has received much attention as a treatable condition and has been termed "vascular cognitive impairment," which can occur either alone or in association with AD.[11] Careful ascertainment of the dementia type, using clinical information, neuroimaging, and brain autopsy, may be necessary to assess the true effects of vascular risk factors on the development of dementia. Therefore, we have ascertained the relationship between BP and each dementia subtype in the sensitivity analysis using only definite cases determined by autopsy. Another possible explanation is that the diverse findings may reflect that controlling for confounding factors such as diabetes mellitus and metabolic disorders was lacking or insufficient in the previous studies.

Most notably, the present study demonstrated that subjects with midlife BP of ≥140/90 mm Hg still had a greater risk of VaD, even if their late-life BP was reduced to <140/90 mm Hg. Elevated BP has been found likely to cause small-vessel disease and white-matter lesions.[30,31] Long exposure to poorly controlled midlife hypertension presumably worsens arteriolosclerotic changes and lipohyalinosis in the deep subcortical white matter circuit, which may be less reversible by BP reduction once these changes are established.[13,32] The present findings, therefore, strongly support that hypertension and relevant cardiovascular morbidity in midlife have a great impact on the etiology of VaD.

The strengths of our study include its longitudinal population-based design, long follow-up, evaluation of midlife BP as well as late-life BP, and the availability of neuropathology and neuroimaging data where needed for the ascertainment of dementia types. On the other hand, several limitations of the present study should be noted. First, the fact that there were only 3 measurements of BP on only one occasion in midlife and on another in late life may have led to some degree of misclassification of BP levels. Such a limitation would weaken the association found in the present study, biasing the results toward the null hypothesis. To obtain a precise estimate of the association, a study in which multiple measurements of BP are taken on separate occasions is needed. Second, we were unable to obtain potential confounding factors, such as depressed mood and apolipoprotein E genotype. The lack of this information would result in a bias toward overdiagnosis of dementia and reduce the accuracy of our findings.

Perspectives

The present study clearly demonstrated that elevated midlife and late-life BP levels are significant risk factors for the late-life onset of VaD but not for AD in a general Japanese population. Higher midlife BP is especially considered to be strongly associated with greater risks of all-cause dementia and VaD, regardless of BP levels in late life. These findings highlight certain important facts, that BP-related pathophysiological processes of dementia begin many years before any symptoms appear and that a clinical history of hypertension and related comorbid disease at that point is likely to have a great impact on the establishment of the disease. To the extent that the adverse effects of long-standing hypertension on small brain vessels and the subsequent development of dementia are less reversible, optimal management of hypertension as early as possible in the life cycle may be an effective approach to preventing late-life dementia in the general population.

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Disclosures

None.

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ONLINE SUPPLEMENT

Title: Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama Study

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Short Title: Late-life and midlife blood pressure and dementia

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EXPANDED MATERIALS AND METHODS

Follow-up survey

The subjects were followed up prospectively for 17 years, from December 1988 to November 2005. Details about the follow-up survey on dementia have been described elsewhere.[1,2] Briefly, we established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office.[3] Regular health checks were given annually to obtain information on any stroke or dementia missed by the monitoring network. Health status was also checked yearly by mail or telephone for any subject who did not undergo regular examinations or who had moved out of town. Additionally, comprehensive surveys of cognitive function including neuropsychological tests (Hasegawa's dementia scale [HDS],[4] its revised version [HDS-R],[5] and the Mini-Mental State Examination [MMSE][6]) were conducted in 1985, 1992, 1998, and 2005. All the participation rates of these surveys were more than 90% of the total population aged 65 years or more. The examination was performed in the public hall of Hisayama town or in their home. The study physicians also visited the hospital or health care facilities for examining hospitalized people.

Diagnosis of dementia

Because the neuropsychological tests were likely to cause the over-diagnosis of cognitive impairment by the several factors (e.g. low education, hearing loss, etc.)[7], we performed two-step procedures on the diagnosis of dementia.[1,2] First, the neuropsychological tests were performed by trained nurses or physicians. When the test scores were below the cut-off points (22/32.5 for HDS,[4] 21/30 for the HDS-R[5] and MMSE[6]) or new neurological symptoms including cognitive impairment were suspected, the subject was carefully evaluated by the study physician and psychiatrist, who conducted comprehensive investigations including interviews of the family or attending physician, physical and neurological examinations, and a review of the clinical records. Diagnoses of dementia and its subtypes were based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition,[8] the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association,[9] and the criteria of the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences[10] Every dementia case was adjudicated by expert neurologists and psychiatrists. Possible or probable dementia subtypes were diagnosed with clinical information including neuroimaging. Definite dementia subtypes were also determined on the basis of clinical and neuropathological information in deceased dementia subjects who underwent autopsy. The diagnostic procedure for autopsy cases has been reported previously.[11] A neuropathological diagnosis of AD was made following the National Institute on Aging–Reagan Institute criteria,[12] where the frequencies of senile plaques and neurofibrillary tangles were evaluated using the criteria of the Consortium to Establish a Registry for Alzheimer's Disease[13] and the Braak stage.[14] Definite VD cases were confirmed with causative stroke or cerebrovascular change.

Other risk factors

At the baseline examination, each participant completed a self-administered questionnaire covering educational status, medical history, anti-hypertensive treatment, smoking habits, and alcohol consumption. Educational status was categorized as ≤6 year, 7-9 years, and ≥10 years. Because only 45 subjects had an academic background of ≥12 years, of which 10 subjects attended university, these subjects were included in the category of ≥10 years. Smoking habits and alcohol consumption were classified as either current use or not. History of stroke was determined as preexisting a sudden onset of nonconvulsive and focal neurological deficit

persisting for >24 hours on the basis of all available clinical data including medical records, neurological examination, and brain imaging. Body height and weight were measured in light clothing without shoes, and body mass index (kg/m^2) was calculated. Diabetes was defined by fasting glucose concentrations ≥ 7.0 mmol/L), postprandial glucose concentrations ≥ 11.1 mmol/L, and/or medical history of diabetes in 1973-1974, and by the criteria of the American Diabetes Association[15] for subjects undergoing a 75-g oral glucose tolerance test or the foregoing definition for subjects not undergoing the tolerance test in 1988. Chronic kidney disease was defined as estimated glomerular filtration rate of <60 ml/min/1.73 m^2, which was calculated using the 3-variable equation, proposed by the Japanese Society of Nephrology.[16] Serum total cholesterol levels were measured by the Zurkowski method in 1973-1974 and by the enzymatic method in 1988. The data of serum homocysteine levels was only available in 1988, which were assayed the high-performance liquid chromatography method.

Statistical analysis

The software package SAS (version 9.2, SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. The linear trends in the mean values and the frequencies of risk factors across the blood pressure levels were tested using linear regression analysis and logistic regression analysis, respectively. The incidence rates of dementia were calculated by a person-year method and adjusted for the age and sex distribution of the overall study population using the direct method; the differences among blood pressure levels were tested using the Cox proportional hazards model including age and sex. The age- and sex-adjusted or multivariate-adjusted hazard ratios with 95% confidence intervals of blood pressure levels for the development of dementia were also estimated using the Cox proportional hazards model. The heterogeneity in the relationship between subgroups was tested by adding multiplicative interaction terms to the relevant Cox model. The risk estimates per every 10 mmHg increment in systolic and diastolc blood presure were computed using the relavant Cox model including each variable taken as a continuous variable. Two-sided $p<0.05$ was considered statistically significant in all analyses.

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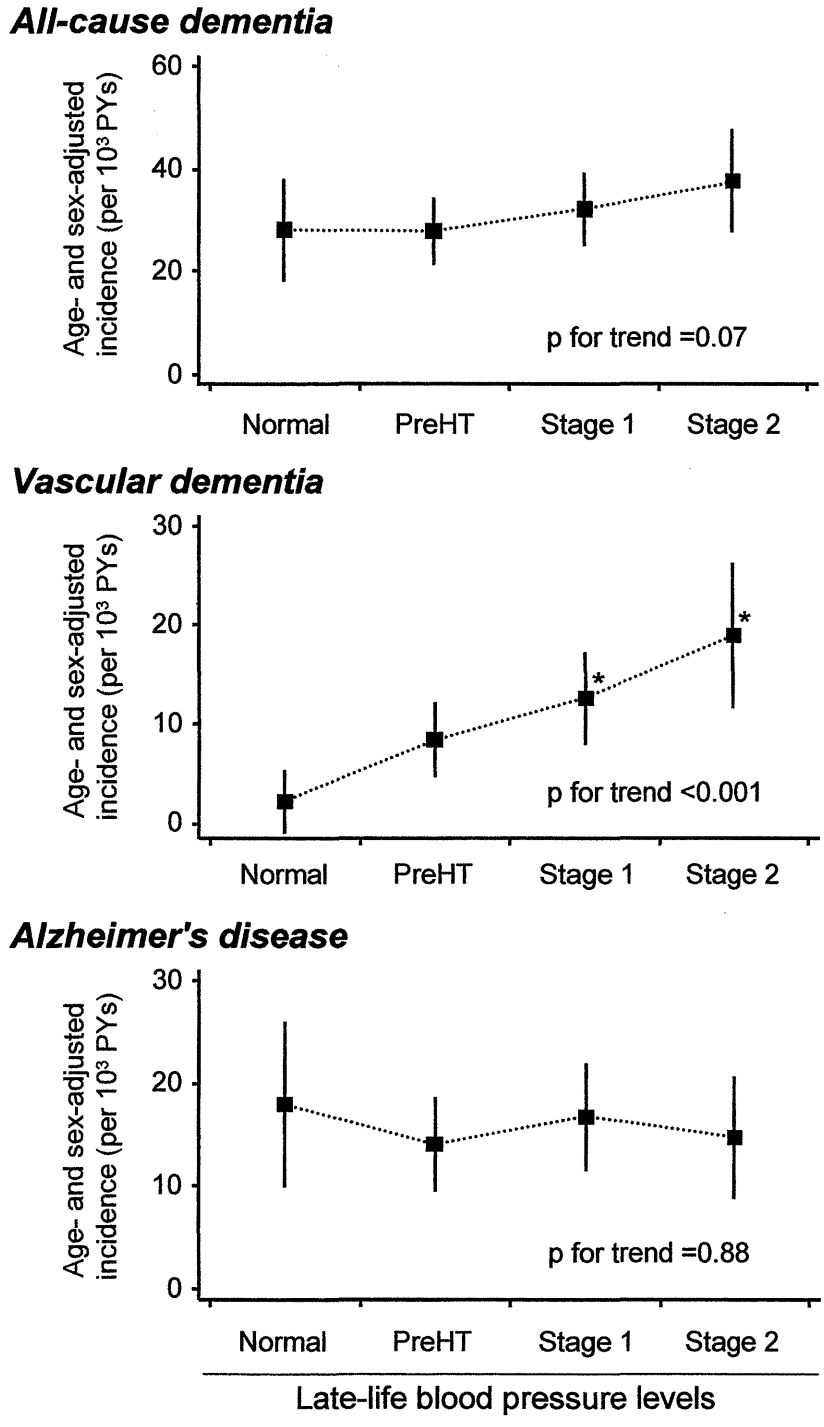

Figure S1: Age- and sex-adjusted incidence rates of dementia and its subtypes according to blood pressure categories in late life
Vertical bars represented 95% confidence intervals of incidence rates.
PreHT, prehypertension; PYs, person-years*p<0.01 vs. normal

A)

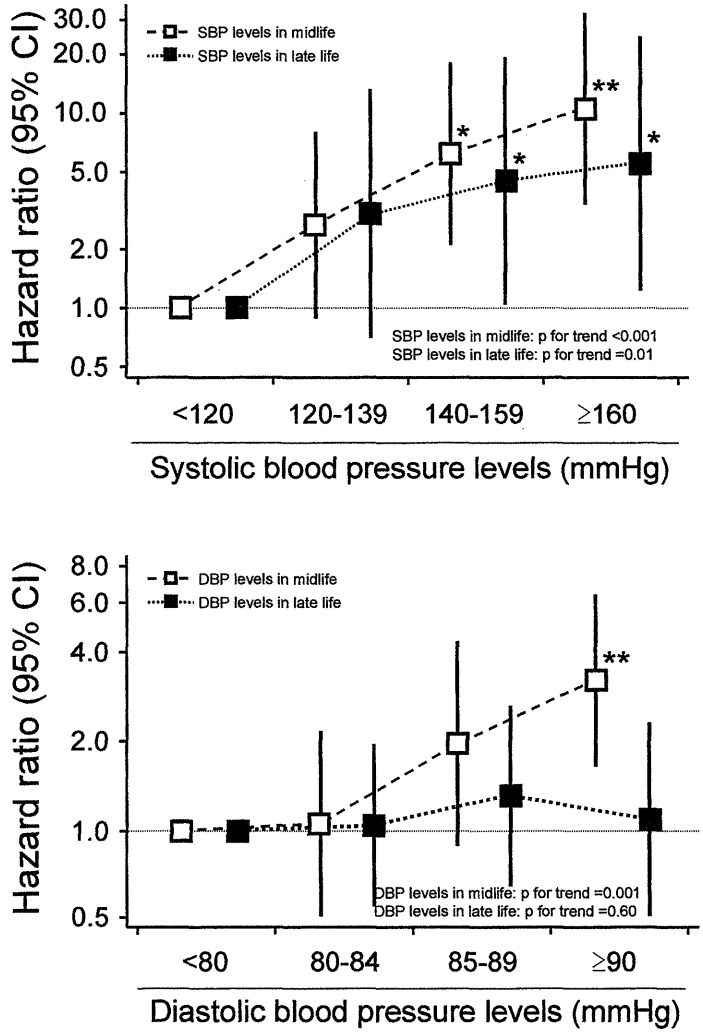

Figure S2: Multivariate-adjusted hazard ratios of vascular dementia according to systolic (A) and diastolic (B) blood pressure levels in midlife and late life
Vertical bars represented 95% confidence intervals of hazard ratios.

The risk estimates were adjusted for potential confounding covariates in midlife or late life : namely, age, sex, education level, use of anti-hypertensive agents, diabetes, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake. CI, confidence interval

*p<0.05, **p<0.01 vs. systolic blood pressure <120 mmHg or diastolic blood pressure <80 mmHg

Table S1: Multivariate-adjusted HRs of late-life and midlife blood pressure levels for late-life onset of dementia determined by autopsy

BP levels defined by JNC-7	Late-life BP				Midlife BP			
	No of events	HR (95% CI)	p	p for trend	No of events	HR (95% CI)	p	p for trend
All-cause dementia								
Normal	14	1.00 (reference)			19	1.00 (reference)		
Prehypertension	40	1.11 (0.58-2.10)	0.76	0.67	26	0.87 (0.48-1.60)	0.66	0.005
Stage1 hypertension	33	0.98 (0.50-1.93)	0.96		42	2.06 (1.15-3.70)	0.01	
Stage2 hypertension	29	1.26 (0.60-2.66)	0.54		16	1.86 (0.91-3.83)	0.09	
Vascular dementia								
Normal	1	1.00 (reference)			4	1.00 (reference)		
Prehypertension	14	4.12 (0.52-32.38)	0.18	0.03	7	1.11 (0.32-3.84)	0.87	<0.001
Stage1 hypertension	17	4.76 (0.61-37.44)	0.14		21	4.86 (1.59-14.85)	0.006	
Stage2 hypertension	19	7.68 (0.94-62.84)	0.06		13	7.05 (2.17-22.88)	0.001	
Alzheimer's disease								
Normal	7	1.00 (reference)			10	1.00 (reference)		
Prehypertension	20	1.36 (0.55-3.37)	0.51	0.92	16	1.03 (0.46-2.32)	0.94	0.87
Stage1 hypertension	13	1.01 (0.38-2.71)	0.98		14	1.37 (0.57-3.31)	0.48	
Stage2 hypertension	10	1.19 (0.39-3.65)	0.76		2	0.49 (0.10-2.38)	0.37	

BP, blood pressure; HR, hazard ratio; CI, confidence interval

The risk estimates were adjusted for potential confounding covariates in midlife or late life: namely, age, sex, education level, use of anti-hypertensive agents, diabetes, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

Endpoints were only definite dementia cases determined by autopsy.

Table S2: Multivariate-adjusted HRs of systolic or diastolic blood pressure levels in late life and midlife for late-life onset of dementia

	Late-life BP						Midlife BP					
BP levels (mmHg)	Median of SBP or DBP (mmHg)	No of events	No of partici pants	HR (95% CI)	p	HR per 10 mmHg increment in SBP or DBP (95% CI)	Median of SBP or DBP (mmHg)	No of events	No of particip ants	HR (95% CI)	p	HR per 10 mmHg increment in SBP or DBP (95% CI)
All-cause dementia												
SBP <110	105	15	47	1.06 (0.53-2.12)	0.87		105	17	59	0.85 (0.45-1.62)	0.62	
SBP 110-119	114	18	60	1.00 (reference)			115	22	69	1.00 (reference)		
SBP 120-139	130	72	228	0.88 (0.52-1.49)	0.63	1.06 (1.00-1.13), p=0.06	129	60	193	0.91 (0.55-1.51)	0.72	1.09 (1.03-1.16), p=0.006
SBP 140-159	148	74	198	1.10 (0.64-1.89)	0.73		148	61	140	1.60 (0.96-2.66)	0.07	
SBP ≥160	173	53	135	1.16 (0.64-2.10)	0.62		173	33	73	1.87 (1.05-3.32)	0.03	
p for trend				0.28						<0.001		
DBP <70	63	64	182	0.88 (0.63-1.23)	0.44		64	30	94	0.88 (0.56-1.38)	0.57	
DBP 70-79	74	92	258	1.00 (reference)			74	62	183	1.00 (reference)		
DBP 80-84	82	35	108	0.85 (0.57-1.27)	0.44	1.02 (0.90-1.16), p=0.74	81	42	105	1.27 (0.85-1.91)	0.24	1.20 (1.05-1.36), p=0.008
DBP 85-89	87	17	53	0.83 (0.49-1.41)	0.50		87	18	62	1.12 (0.65-1.92)	0.68	
DBP ≥90	93	24	67	0.99 (0.62-1.59)	0.97		95	41	90	2.29 (1.50-3.51)	<0.001	
p for trend				0.94						<0.001		

Vascular dementia												
SBP <110	105	1	47	1.13 (0.07-18.11)	0.93		105	2	59	1.19 (0.17-8.48)	0.86	
SBP 110-119	114	1	60	1.00 (reference)			115	2	69	1.00 (reference)		
SBP 120-139	130	19	228	3.24 (0.43-24.71)	0.26	1.18 (1.07-1.31), p=0.002	129	17	193	2.94 (0.67-12.95)	0.15	1.24 (1.12-1.37), p<0.001
SBP 140-159	148	29	198	4.81 (0.64-36.34)	0.13		148	24	140	6.82 (1.57-29.58)	0.01	
SBP ≥160	173	26	135	6.00 (0.77-46.95)	0.09		173	18	73	11.68 (2.61-52.22)	0.001	
p for trend				0.01						<0.001		
DBP <70	63	12	182	0.45 (0.22-0.91)	0.03		64	7	94	0.67 (0.27-1.66)	0.39	
DBP 70-79	74	31	258	1.00 (reference)			74	18	183	1.00 (reference)		
DBP 80-84	82	14	108	0.78 (0.4-1.52)	0.46	1.21 (0.98-1.49), p=0.07	81	12	105	0.93 (0.43-2.01)	0.86	1.37 (1.09-1.72), p=0.007
DBP 85-89	87	10	53	0.98 (0.46-2.06)	0.95		87	9	62	1.74 (0.75-4.01)	0.2	
DBP ≥90	93	9	67	0.85 (0.39-1.86)	0.69		95	17	90	2.85 (1.38-5.90)	0.005	
p for trend				0.16						0.001		
Alzheimer's disease												
SBP <110	105	12	47	1.66 (0.71-3.88)	0.24		105	12	59	0.83 (0.39-1.80)	0.65	
SBP 110-119	114	10	60	1.00 (reference)		1.01 (0.92-1.1), p=0.83	115	15	69	1.00 (reference)		1.02 (0.93-1.12), p=0.72
SBP	130	39	228	0.93	0.84		129	34	193	0.72	0.31	

120-139				(0.46-1.89)						(0.39-1.35)		
SBP 140-159	148	39	198	1.22 (0.59-2.53)	0.58		148	29	140	1.13 (0.59-2.17)	0.72	
SBP ≥160	173	23	135	1.06 (0.47-2.40)	0.89		173	12	73	0.99 (0.44-2.23)	0.98	
p for trend				0.91						0.47		
DBP <70	63	40	182	1.06 (0.69-1.65)	0.78		64	18	94	0.91 (0.50-1.63)	0.74	
DBP 70-79	74	51	258	1.00 (reference)			74	36	183	1.00 (reference)		
DBP 80-84	82	15	108	0.70 (0.39-1.26)	0.24	0.88 (0.73-1.06), p=0.18	81	22	105	1.31 (0.76-2.26)	0.33	1.12 (0.93-1.34), p=0.25
DBP 85-89	87	8	53	0.89 (0.42-1.89)	0.76		87	9	62	1.01 (0.48-2.13)	0.98	
DBP ≥90	93	9	67	0.74 (0.35-1.55)	0.42		95	17	90	1.67 (0.90-3.10)	0.1	
p for trend				0.21						0.09		

BP, blood pressure; HR, hazard ratio; CI, confidence interval

The risk estimates were adjusted for potential confounding covariates in midlife or late life: namely, age, sex, education level, use of anti-hypertensive agents, diabetes, chronic kidney disease, serum total cholesterol, body mass index, history of stroke, smoking habits, and alcohol intake.

Original Article

Albuminuria as a Risk Factor for Peripheral Arterial Disease in a General Population

— The Hisayama Study

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Aims: To elucidate the relationship between albuminuria and the prevalence of peripheral arterial disease (PAD), and to examine the effect of albuminuria on the ability to assess the likelihood of PAD in a general Japanese population.

Methods: In 3,061 community-dwelling subjects aged ≥ 40 years, we investigated the association of urinary albumin-creatinine ratio (UACR) levels with the prevalence of PAD, defined as an ankle-brachial index <0.9. The odds ratio for the presence of PAD was estimated using the logistic regression model. To compare the accuracy of the assessment for the likelihood of prevalent PAD between models adjusted for potential risk factors with and without UACR levels, the receiver operating characteristic (ROC) curves were plotted.

Results: Overall, 1.47% of the study participants had PAD. The age- and sex-adjusted prevalence of PAD increased linearly for UACR levels of <5.6, 5.6-10.8, 10.9-29.9, 30.0-300.0, and >300.0 mg/g, being 0.34, 0.80, 2.02, 2.50, and 2.53%, respectively (p for trend <0.001). The multivariate-adjusted odds ratio for the presence of PAD was 1.85 (95% confidence interval 1.12-3.06) for every 10-fold increment in UACR. The area under the ROC curve significantly increased when UACR levels were incorporated into a model with potential risk factors for PAD (0.80 vs. 0.77, p=0.02).

Conclusion: Greater UACR levels are associated linearly with a higher prevalence of PAD, even within the normoalbuminuric range, in the general Japanese population, and combining UACR levels with potential risk factors substantially improves the performance to assess the likelihood of PAD.

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Key words; Peripheral arterial disease, Albuminuria, Cross-sectional study, General populations

Introduction

Peripheral arterial disease (PAD) is a manifestation of atherosclerosis. PAD in a clinical stage develops ulceration, pain, claudication, necrosis, and subsequent amputation of the lower extremities, which is one of the causes of disability among diabetic and elderly persons[1]. Recently, several studies have demonstrated that PAD is associated with higher risks of cardiovascular morbidity and mortality[2,3].

It has been acknowledged that cardiovascular risk factors, such as aging, smoking, hypertension, diabetes, dyslipidemia, and inflammation, are linked to the presence of PAD[4]. Clinical information on these risk factors would be useful in the assessment for the risk of PAD.

The importance of kidney disease as a risk factor

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for atherosclerotic disease is increasingly recognized[5, 6]. Albuminuria has been shown to be linked to increased risks of cardiovascular disease, systemic atherosclerosis, and death not only in patients with diabetes or hypertension, but also in general populations[4, 7-9]. Hence, it would be of great interest to elucidate whether albuminuria substantially improves the ability to assess the likelihood for the presence of PAD beyond a model based on the known potential risk factors. Herein we present the findings of cross-sectional analyses from the Hisayama Study, which is a population-based cohort study of cardiovascular disease in Japan. The aims of this study were to investigate the relationship between albuminuria and the presence of PAD, and to evaluate the influence of albuminuria on the performance to assess the likelihood of PAD in a general Japanese population.

Methods

Study population

The Hisayama Study is a population-based prospective study of cardiovascular disease and its risk factors in the town of Hisayama, a suburb of Fukuoka City in southern Japan. The design of the study has been described in detail elsewhere[10]. The present cross-sectional study was based on a screening survey conducted in 2002. A total of 3,328 residents aged 40 years or over (77.6% of the total population of this age group) participated in the health examination and underwent a comprehensive assessment including determination of the ankle-brachial index (ABI). After the exclusion of 30 subjects who did not consent to participate in the study, 84 subjects without urine samples, and 153 subjects without information on their ankle blood pressure, the remaining 3,061 subjects (1,342 men, 1,719 women) were enrolled in the study. This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from all participants.

Definition of peripheral arterial disease

Blood pressure measurement for calculation of the ABI was obtained using volume-plethysmographic equipment (Form PWV/ABI; Colin, Tokyo, Japan)[11]. The ABI was calculated as ankle blood pressure divided by arm blood pressure, where the higher of the blood pressure values between the right and left arms was used. PAD was defined as ABI <0.9 in either leg[4].

Urine albumin and creatinine ratio

A spot urine sample was obtained at the health examination visit. Urine creatinine and albumin were measured using the turbidimetric immmunoassay method. The urine albumin-creatinine ratio (UACR, in mg/g) was calculated by dividing the urinary albumin values by the urinary creatinine concentrations. UACR was categorized as normoalbuminuria (UACR <30.0 mg/g), microalbuminuria (UACR 30.0-300.0 mg/g), and macroalbuminuria (UACR >300.0 mg/g) using common cut-off points[12]. UACR levels in the normoalbuminuric range were further divided into the following tertile levels: low-normal (<5.6 mg/g), medium-normal (5.6-10.8 mg/g), and high-normal (10.9-29.9 mg/g).

Measurement of risk factors

A self-administered questionnaire concerning the current use of antihypertensive agents, insulin, oral glucose-lowering agents, and oral medication for hyperlipidemia, smoking habits, and alcohol intake was completed in advance of the examination by each participant and was checked by trained interviewers at the screening. These variables were classified as being either habitual or not. A history of cardiovascular disease was defined as any previous events of stroke or coronary heart disease, including myocardial infarction and coronary intervention, all of which were adjudicated on the basis of clinical information including medical records and imaging.

Blood pressure was measured three times after the subject had rested for at least 5 min in the sitting position. The mean of the three measurements was used for the present analysis. Hypertension was defined as a systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, and/or current use of antihypertensive agents. Body height and weight were measured in light clothing without shoes, and the body mass index (kg/m^2) was calculated. Obesity was defined as a body mass index $\geq$ 25.0 kg/m^2.

Serum total cholesterol concentration was determined enzymatically. Hypercholesterolemia was defined as serum total cholesterol $\geq$ 5.68 mmol/l (220 mg/dL) and/or current use of oral medication for hyperlipidemia. Fasting and casual blood glucose were measured by the glucose oxidase method. Diabetes mellitus was defined as fasting plasma glucose levels of $\geq$ 7.0 mmol/L (126 mg/dL), 2-h post-loaded or casual glucose levels of $\geq$ 11.1 mmol/L (200 mg/dL), and/or current use of insulin or oral glucose-lowering agents. High-sensitivity C-reactive protein (HS-CRP) was measured using a modification of the Behring Latex-Enhanced CRP assay on a Behring Nephelometer

Table 1. Mean values or frequencies of relevant factors according to urinary albumin-creatinine ratio levels

Variables	Urinary albumin-creatinine ratio levels (mg/g)					p for trend
	<5.6 (n=821)	5.6-10.8 (n=825)	10.9-29.9 (n=822)	30.0-300.0 (n=520)	>300.0 (n=73)	
Age, yr	55 (11)	59 (11)	63 (11)	66 (12)	66 (12)	<0.001
Men, %	55.5	37.9	37.7	42.9	54.8	<0.001
Systolic blood pressure, mmHg	123 (17)	126 (19)	136 (19)	145 (22)	153 (21)	<0.001
Diastolic blood pressure, mmHg	75 (10)	76 (11)	80 (11)	84 (13)	89 (14)	<0.001
Antihypertensive drug, %	12.4	14.5	29.1	41.3	46.6	<0.001
Hypertension, %	23.4	30.9	53.5	70.2	78.1	<0.001
Diabetes mellitus, %	10.4	12.1	19.6	30.3	52.1	<0.001
Hypercholesterolemia, %	33.0	36.8	39.9	40.1	54.8	<0.001
Obesity, %	19.7	25.0	29.3	36.5	37.0	<0.001
High high-sensitivity C-reactive protein, %	18.8	22.4	26.0	34.1	48.0	<0.001
History of cardiovascular disease, %	1.9	3.4	4.6	8.3	11.0	<0.001
Smoking habits, %	31.3	19.9	19.2	19.2	21.9	<0.001
Alcohol intake, %	53.8	43.8	41.0	40.8	43.8	<0.001

Values are the means (SD) or frequencies.

BN-100 (Behring Diagnostics, Westwood, MA). High HS-CRP was defined as a serum HS-CRP level ≥ 1.0 mg/L[13].

Statistical analysis

The trends in the mean values or frequencies of risk factors across UACR levels were tested using a linear or logistic regression model, respectively, with evenly spaced numeric codes for UACR levels. The prevalence of PAD was adjusted for the age and sex distribution of the overall study population enrolled in this study using a direct method. The statistical differences in prevalence and their trends among UACR levels were estimated using the logistic regression model, where age and sex were included. The age- and sex-adjusted or multivariate-adjusted odds ratio (OR) and its 95% confidence interval (CI) for the presence of PAD were assessed by fitting the logistic regression model with adjustment for potential confounding covariates. The confounding covariates included in the relevant model, such as hypertension, diabetes mellitus, hypercholesterolemia, obesity, high HS-CRP, history of cardiovascular disease, smoking habits, and alcohol intake, were used as binary categorical variables. The heterogeneity in the relationship between subgroups was tested by adding a multiplicative interaction term to the relevant statistical model. To compare the accuracy of the ability to assess the likelihood of PAD between the models adjusted for potential risk factors with and without UACR levels, the receiver operating characteristic (ROC) curves were plotted. The consistency of the area under the ROC curve among models was estimated using DeLong's method[14]. All the statistical analyses were performed using the SAS software package, release 9.2 (SAS Institute, Cary, USA). A two-tailed value of $p<0.05$ was considered statistically significant.

Results

The prevalence of microalbuminuria and macroalbuminuria was 17.0% and 2.4%, respectively, in this population. The clinical characteristics of the study population are summarized in **Table 1** according to UACR levels. The mean values of age, systolic and diastolic blood pressures, and the frequencies of the following parameters increased significantly with elevated UACR levels: use of antihypertensive drugs, hypertension, diabetes, hypercholesterolemia, obesity, high HS-CRP, and a history of cardiovascular disease. Decreasing trends in the frequencies of men, smoking habits, and alcohol intake were found in higher UACR levels.

Overall, 45 (1.47%) of the study participants had PAD. The age- and sex-adjusted prevalence of PAD increased linearly for higher UACR levels of < 5.6, 5.6-10.8, 10.9-29.9, 30.0-300.0, and >300.0 mg/g, being 0.34, 0.80, 2.02, 2.50, and 2.53%, respectively (p for trend <0.001) (**Fig. 1**). After adjusting for potential confounding factors, namely, age, sex, hypertension, diabetes, hypercholesterolemia, obesity, high HS-CRP, history of cardiovascular dis-

Table 2. The relationship between albuminuria levels and odds ratios for the presence of peripheral arterial disease

UACR levels (mg/g)	*N* of PAD/ *N* of subjects	Age- and sex-adjusted			Multivariate-adjusted [a]		
		OR (95% CI)	*p*	*p* for trend	OR (95% CI)	*p*	*p* for trend
<5.6	3/821	1.00 (reference)			1.00 (reference)		
5.6-10.8	5/825	1.38 (0.33-5.84)	0.66		1.36 (0.32-5.77)	0.68	
10.9-29.9	17/822	3.88 (1.11-13.61)	0.03	<0.001	3.56 (1.00-12.65)	0.05	0.005
30.0-300.0	17/520	5.35 (1.51-19.00)	0.009		4.44 (1.21-16.26)	0.02	
>300.0	3/73	6.27 (1.20-32.79)	0.03		4.64 (0.84-25.66)	0.08	
Every 10-fold increment in UACR	45/3061	2.21 (1.37-3.54)	0.001		1.85 (1.12-3.06)	0.02	

UACR, urinary albumin-creatinine ratio; PAD, peripheral arterial disease; OR, odds ratio; CI, confidence interval
[a] Adjusted for age, sex, hypertension, diabetes mellitus, hypercholesterolemia, obesity, high high-sensitivity C-reactive protein, history of cardiovascular disease, smoking habits, and alcohol intake.

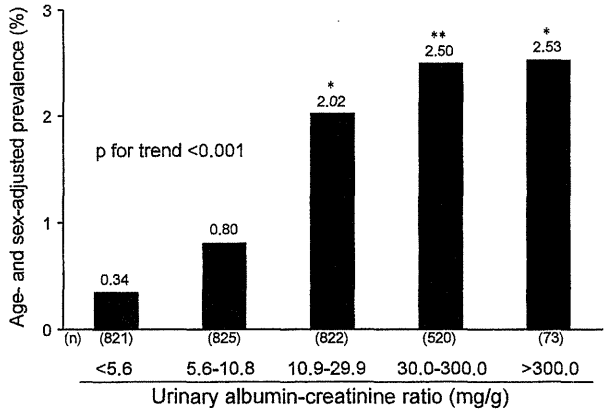


Fig. 1. Age- and sex-adjusted prevalence of peripheral arterial disease in 3,061 subjects, the Hisayama Study

*$p<0.05$, **$p<0.01$ vs. urinary albumin-creatinine ratio of <5.6 mg/g

ease, smoking habits, and alcohol intake, the OR for the presence of PAD increased progressively as UACR levels became elevated (**Table 2**). The multivariate-adjusted OR for the presence of PAD was 1.85 (95% CI, 1.12-3.06) for every 10-fold increment in UACR. The sensitivity analyses, excluding subjects with macroalbuminuria ($n=73$) or subjects having a much higher ABI of ≥ 1.4 ($n=2$), did not make any material differences in the findings of this study (data not shown).

We also performed subgroup analyses to estimate the effect of cardiovascular risk factors on the relationship between PAD and UACR (**Table 3**). Overall, there was no evidence for statistically significant differences in the magnitudes of the multivariate-adjusted ORs across UACR levels for the risk of prevalent PAD among subgroups of cardiovascular risk factors (all p for interaction >0.09); however, the association between UACR and PAD tended to be stronger in current smokers than in non-smokers (p for interaction =0.097).

Finally, we assessed the effect of UACR on the assessment for the likelihood of prevalent PAD by comparing the areas under the ROC curves between the models with and without UACR (**Fig. 2**). The area under the ROC curve significantly increased when UACR levels were incorporated into a model with potential risk factors for PAD (0.80 vs. 0.77, $p=0.02$). The same was true after excluding subjects with a history of cardiovascular disease (0.79 vs. 0.74, $p=0.03$).

We also performed sensitivity analyses including systolic blood pressure taken as a continuous variable and use of antihypertensive medication in the relevant model, instead of the binary variable of hypertension. As a result, the finding was not altered substantially: the multivariate-adjusted OR for the presence of PAD for every 10-fold increment in UACR was 1.71 (95% CI, 1.02-2.89), and the area under the ROC curve for the model assessing the likelihood of PAD increased when UACR was added to the model (0.80 vs. 0.78, $p=0.05$).

Discussion

In the present study, we clearly demonstrated that albuminuria was associated linearly with an increasing likelihood for the presence of PAD, even in the normoalbuminuric range. This association remained unchanged even after controlling for the potential confounding factors, namely, age, sex, hypertension, diabetes, hypercholesterolemia, high HS-CRP, history of cardiovascular disease, smoking habits, and alcohol intake. Importantly, our findings re-

Table 3. Multivariate-adjusted odds ratios and their 95% confidence intervals for the presence of peripheral arterial disease for every 10-fold increment in urinary albumin-creatinine ratio according to subgroups of risk factors

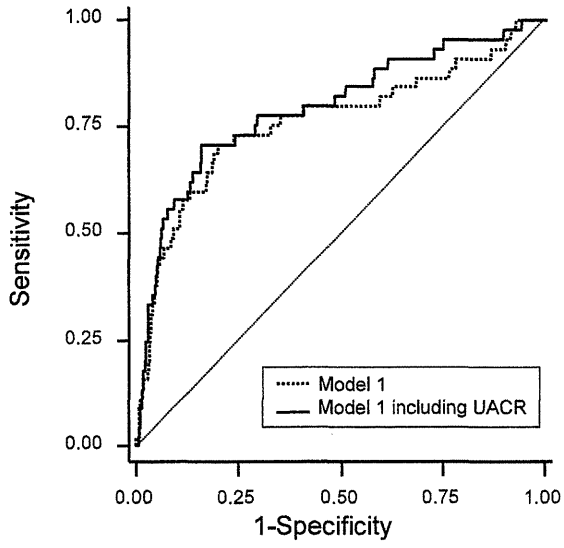
Subgroups	*N* of PAD/ *N* of subjects	Age- and sex-adjusted prevalence (%)	Age- and sex-adjusted			Multivariate-adjusted [a]		
			OR for every 10-fold increment in UACR (95% CI)	*p*	*p* for interaction	OR for every 10-fold increment in UACR (95% CI)	*p*	*p* for interaction
Hypertension								
Absence	14/1752	0.8	1.99 (0.70-5.66)	0.20	0.52	1.88 (0.64-5.56)	0.25	0.62
Presence	31/1309	1.8	2.01 (1.13-3.57)	0.02		1.79 (1.01-3.19)	0.047	
Diabetes mellitus								
Absence	29/2519	1.2	2.01 (1.05-3.86)	0.04	0.78	1.84 (0.91-3.72)	0.09	0.73
Presence	16/541	2.5	2.05 (0.98-4.31)	0.06		1.92 (0.91-4.08)	0.09	
Hypercholesterolemia								
Absence	28/1909	1.4	2.08 (1.09-3.98)	0.03	0.58	1.84 (0.91-3.69)	0.09	0.45
Presence	17/1151	1.6	2.35 (1.16-4.76)	0.02		1.91 (0.91-4.03)	0.09	
Obesity								
Absence	38/2235	1.6	2.36 (1.41-3.95)	0.001	0.94	1.89 (1.09-3.27)	0.02	0.95
Presence	7/826	1.0	2.26 (0.67-7.71)	0.19		1.42 (0.36-5.55)	0.62	
High HS-CRP								
Absence	28/2295	1.3	1.94 (1.00-3.76)	0.049	0.44	1.77 (0.86-3.65)	0.12	0.56
Presence	17/765	1.7	2.52 (1.25-5.08)	0.009		1.98 (0.95-4.11)	0.07	
History of cardiovascular disease								
Absence	37/2928	1.3	2.34 (1.39-3.95)	0.001	0.32	2.25 (1.28-3.95)	0.005	0.33
Presence	8/133	3.9	1.27 (0.42-3.80)	0.68		1.15 (0.34-3.85)	0.82	
Smoking habits								
Absence	35/2366	1.4	1.79 (1.02-3.15)	0.04	0.07	1.55 (0.85-2.83)	0.15	0.097
Presence	10/695	1.3	4.71 (1.83-12.10)	0.001		3.30 (1.12-9.73)	0.03	
Alcohol intake								
Absence	24/1677	1.3	3.04 (1.61-5.74)	<0.001	0.21	2.63 (1.35-5.12)	0.004	0.16
Presence	21/1384	2.0	1.56 (0.76-3.21)	0.23		1.18 (0.54-2.56)	0.68	

PAD, peripheral arterial disease; OR, odds ratio; UACR, urinary albumin-creatinine ratio; CI, confidence interval; HS-CRP, high-sensitivity C-reactive protein

[a] Adjusted for age, sex, hypertension, diabetes mellitus, hypercholesterolemia, obesity, high HS-CRP, history of cardiovascular disease, smoking habits, and alcohol intake. The variable relevant to the subgroup was excluded from each model.

vealed that the incorporation of albuminuria to a model with potential risk factors significantly improved the assessment of the likelihood for the presence of PAD in a general population. To the best of our knowledge, this is the first study statistically elucidating the clinical value of albuminuria in the likelihood assessment for PAD. These findings therefore highlight the potential additive value of the measurement of albuminuria in the risk assessment for PAD for the general population, especially for individuals with smoking habits.

There has been conflicting evidence in the literature regarding the association between albuminuria and the presence of PAD, especially according to the diabetic status[8, 9, 15]. The Islington Diabetes Survey first suggested that the prevalence of PAD defined as ABI <0.9 was higher in subjects with albuminuria among non-diabetic subjects[16]. The Strong Heart Study, in which about half of the study population had diabetes, showed that the magnitude of the effect



Model	Area under curve (95% CI)	p value (vs. Model 1)
Model 1	0.77 (0.68-0.85)	-
Model 1 including UACR levels	0.80 (0.72-0.88)	0.02

Fig. 2. Comparison of the assessment of the likelihood of the presence of peripheral arterial disease between models with and without urinary albumin-creatinine ratio levels

Model 1 included age, sex, hypertension, diabetes mellitus, hypercholesterolemia, obesity, high high-sensitivity C-reactive protein, history of cardiovascular disease, smoking habits, and alcohol intake.
Abbreviations: UACR, urinary albumin-creatinine ratio; CI, confidence interval

of albuminuria on the risk for the presence of PAD was comparable to that of other cardiovascular risk factors, such as hypertension, diabetes, and smoking in Native Americans[4]. Some cross-sectional studies in large community-derived populations found that diabetic subjects with albuminuria had approximately twice the risk for the presence of PAD than those without albuminuria, but this relationship was absent in non-diabetic subjects[8, 15]. By contrast, the recent results from the National Health and Nutrition Examination Surveys (NHANES) 1999-2004 revealed that the association of albuminuria with the risk of prevalent PAD applied to non-diabetic subjects but not to diabetic subjects[9]. The present study indicated that higher UACR levels were associated with an increased risk of the presence of PAD, without any clear evidence of heterogeneity in the association between subgroups of subjects with diabetes in a general Japanese population. These diverse findings may arise from insufficient statistical power to perform a reliable subgroup analysis due to the small number of PAD cases in these studies, including ours. Further large-scale community-based studies or meta-analyses are needed to clarify this issue.

Most notably, the present study clearly demonstrated that adding albuminuria to a model involving potential risk factors significantly improved the assessment of the likelihood of the presence of PAD. A recent statement about the clinical scientific research[17] recommends that studies of a novel risk marker should report whether the incorporation of the new marker improves the risk assessment performance provided by established risk markers, but there have been limited studies assessing the improvement by the new marker so far. Additionally, the risk assessment for PAD may be more clinically useful in people without a history of cardiovascular disease rather than those with it, because people with prior cardiovascular disease are obviously considered as a high-risk population of any other vascular diseases. Importantly, our sensitivity analysis revealed that the incorporation of UACR levels into the model significantly improved the risk assessment ability for PAD even in people without a history of cardiovascular disease. Therefore, we believe that our findings provide strong evidence that albuminuria should be evaluated as an important factor in the risk assessment of PAD.

The mechanism through which the relationship between albuminuria and PAD may be mediated is an area of great interest. Albuminuria is suggested to be a manifestation of systemic endothelial dysfunction, which reflects the severity of vascular disease[18]. It has been acknowledged that subjects with greater albuminuria also show a higher prevalence of traditional cardiovascular risk factors, such as aging, hypertension, diabetes, dyslipidemia, and smoking habits[15, 19]. Additionally, chronic inflammation has been shown to be involved in the relationship between albuminuria and PAD[20]. The burden of these risk factors is likely to cause endothelial dysfunctions and subsequent vascular damage. Furthermore, the fact that the significant relationship between albuminuria and PAD was still observed after adjusting for these risk factors in the present study may suggest the existence of residual confounders such as the involvement of oxidative stress or asymmetric dimethylarginine[21] and the duration of the underlying disease. Further studies are warranted to better elucidate the mechanism underlying the relationship between albuminuria and PAD.

In the present study, the effect of albuminuria on the likelihood of prevalent PAD tended to be greater in current smokers than in non-smokers, although the

statistical power of this tendency was insufficient to show a significant difference in the effects. The results from the NHANES Ⅲ and a case-control study conducted in 82 hypertensive patients revealed that heavy current smokers were likely to have a greater amount of albuminuria among hypertensive subjects[22, 23]. Smoking has numerous effects, such as oxidative stress, systemic inflammation, hemostatic and coagulation activation[24, 25], and deteriorating vascular disease in parallel with the induction of albuminuria. Our findings imply the importance of paying particular attention to subjects with smoking habits and albuminuria as a population at higher risk of PAD.

Several limitations should be noted. First, the cross-sectional study design limits the interpretation of causality between albuminuria and PAD. Second, albuminuria levels were determined by a single measurement, which may not be accurately representative of the status of the study participants. This weakens the association found in this study, biasing the results toward the null hypothesis. Third, the diagnosis of PAD was determined on the basis of ABI, but not angiography; however, it has been well acknowledged that ABI is a noninvasive and reproducible procedure for detecting preclinical PAD, and it is suitable for mass screening. Fourth, our study was unable to identify the relationship between albuminuria and extremely high ABI, which is also considered to signify advanced arteriosclerosis, because very few subjects ($n=2$) had an ABI of ≥ 1.4 in this study; however, sensitivity analysis excluding subjects with ABI of ≥ 1.4 did not alter the findings substantially.

Conclusion

In conclusion, greater UACR levels, even in the normoalbuminuric range, are associated linearly with a higher prevalence of PAD in the general Japanese population. Routine measurement of albuminuria therefore improves the current tools available for the likelihood assessment of PAD. Our findings suggest that the clinical assessment of and early intervention for PAD should be considered in people with albuminuria.

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Disclosure

The authors report no conflicts of interest.

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