Home Blood Pressure Variability as Cardiovascular Risk Factor in the Population of Ohasama

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Abstract—Blood pressure variability based on office measurement predicts outcome in selected patients. We explored whether novel indices of blood pressure variability derived from the self-measured home blood pressure predicted outcome in a general population. We monitored mortality and stroke in 2421 Ohasama residents (Iwate Prefecture, Japan). At enrollment (1988–1995), participants (mean age, 58.6 years; 60.9% women; 27.1% treated) measured their blood pressure at home, using an oscillometric device. In multivariable-adjusted Cox models, we assessed the independent predictive value of the within-subject mean systolic blood pressure (SBP) and corresponding variability as estimated by variability independent of the mean, difference between maximum and minimum blood pressure, and average real variability. Over 12.0 years (median), 412 participants died, 139 of cardiovascular causes, and 223 had a stroke. In models including morning SBP, variability independent of the mean and average real variability (median, 26 readings) predicted total and cardiovascular mortality in all of the participants ($P \leq 0.044$); variability independent of the mean predicted cardiovascular mortality in treated ($P=0.014$) but not in untreated ($P=0.23$) participants; and morning maximum and minimum blood pressure did not predict any end point ($P \geq 0.085$). In models already including evening SBP, only variability independent of the mean predicted cardiovascular mortality in all and in untreated participants ($P \leq 0.046$). The R^2 statistics, a measure for the incremental risk explained by adding blood pressure variability to models already including SBP and covariables, ranged from <0.01% to 0.88%. In a general population, new indices of blood pressure variability derived from home blood pressure did not incrementally predict outcome over and beyond mean SBP. (*Hypertension*. 2013;61:61-69.) • Online Data Supplement

Key Words: blood pressure variability ■ variability independent of the mean index ■ average real variability ■ general population ■ home blood pressure ■ risk factors

Current guidelines propose out-of-office blood pressure measurement as the standard in the diagnosis and management of hypertension.[1–3] Self-measurement of the blood pressure at home offers several of the well-recognized advantages of the more complex approach of ambulatory monitoring.[4–6] The greater number of readings and the minimization of the white coat effect, observer bias, and measurement error all contribute to better diagnostic accuracy compared with office blood pressure measurement. Similar to visit-to-visit variability in clinic blood pressure,[7] multiple home blood pressure measurements[8–10] provide information on day-to-day blood pressure variability in the relatively controlled home environment.

We demonstrated previously that the within-subject SD of blood pressure predicted mortality.[10] However, the SD is highly dependent on the mean.[7,11] Rothwell et al[7,11] therefore proposed blood pressure variability independent of the mean (VIM) as a new index, which might be a better predictor of cardiovascular outcome over and beyond blood pressure level. The aim of the present study was to test the hypothesis that new indices of blood pressure variability,[7,11] derived from the self-measured home blood pressure in a general population instead of the office blood pressure in selected hypertensive or high-risk patients,[7,11,12] would predict outcome.

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Methods

Study Design

As described in detail elsewhere,[5] from 1988 until 1995, we contacted 4969 individuals who resided in 4 districts of Ohasama, a rural community in Iwate Prefecture, Japan, and who were ≥35 years old. Residents were not eligible if they were not at home during normal working hours (n=1057) or if they were hospitalized (n=166) or incapacitated (n=94). Of the remaining 3652 residents, 3090 (84.6%) participated in baseline and follow-up examinations. The study complies with the Declaration of Helsinki, and the study protocol was approved by the institutional review board of Tohoku University School of Medicine and by the Ohasama Town Government Department of Health. Participants gave written informed consent. We excluded 669 participants from analysis because they had not measured their home blood pressure (n=218), had obtained <5 morning or evening readings (n=322), or because at enrollment they had a history of stroke (n=129). Thus, the number of participants statistically analyzed totaled 2421.

Data Collection

Physicians and public health nurses instructed participants how to measure their home blood pressure using a validated oscillometric device (OMRON HEM 401C, Omron Healthcare Co Ltd, Kyoto, Japan).[13] Participants were asked to record their blood pressure for 4 weeks after ≥2 minutes of rest in the morning within 1 hour after awakening and, if applicable, before taking their blood pressure–lowering medications, and in the evening just before going to bed.[5] The first reading obtained on each occasion was used for analysis.

At public health centers, study nurses measured anthropometric characteristics. Body mass index was weight in kilograms divided by the square of height in meters. The nurses also administered questionnaires inquiring into each participant's medical history, intake of medications, and smoking and drinking habits. Venous blood samples were analyzed for total cholesterol and blood glucose. Diabetes mellitus was a fasting or random blood glucose level of ±7.0 or 11.1 mmol/L or the use of insulin or oral antidiabetic drugs.[14] Hypercholesterolemia was a serum level of ≥5.68 mmol/L or use of lipid-lowering agents. Previous cardiovascular disease included coronary heart disease, atrial fibrillation, and heart failure.

Follow-Up and Risk Assessment

We ascertained outcome until December 31, 2004, based on the Ohasama residents' registration cards, which in Japan provide access to social security and retirement benefits; the National Japanese Mortality Registry of causes of death; the Stroke Registration System of Iwate Prefecture; and questionnaires sent every 4 years to each participant. End points were all-cause and cardiovascular mortality and stroke events. Cardiovascular mortality included deaths from cerebrovascular and cardiac causes. Stroke events included, in addition to fatal events, nonfatal stroke but not transient ischemic attack. End points were adjudicated by checking the medical charts at Ohasama Hospital, where >90% of participants had regular health checkups.

Statistical Analysis

For database management and statistical analysis, we used the SAS system, version 9.3 (SAS Institute Inc, Cary, NC). We limited our analyses to systolic blood pressure, because this is the overriding risk factor in middle-aged and older people.[15] We used all of the available home readings of the self-measured blood pressure. We analyzed the morning and evening blood pressures separately, because previous studies showed that they have a different prognostic meaning.[5] In sensitivity analyses, we used 5 home readings in the morning and 5 in the evening (10 readings) according to European population studies[16] and the Japanese randomized trial.[17]

For descriptive purposes, we computed the within-participant blood pressure variability from the SD and coefficient of variation. We based our analyses on VIM, difference between maximum minus minimum blood pressure (MMD), and average real variability (ARV). Coefficient of variation is the within-participant SD divided by the within-participant mean. VIM[7,11] is SD divided by the mean to the power^x. Power x is modeled as SD = a × mean^x and was derived by nonlinear regression analysis as implemented in the PROC NLIN procedure of the SAS package. ARV is the average of the absolute differences between consecutive day blood pressure measurements.[18,19]

We compared means and proportions using the standard normal z test for large samples and the Fisher exact test, respectively. Kruskal-Wallis test was used to assess differences between quartiles of VIM. We plotted incidence rates by fourths of the blood pressure variability distribution while standardizing rates for sex and age by the direct method. In multivariable-adjusted Cox regression, we derived standardized relative hazard ratios that expressed the change in risk associated with 1-SD increase in mean blood pressure or in variability. Covariables were sex, age, body mass index, heart rate, smoking and drinking, diabetes mellitus, total cholesterol, history of cardiovascular disease, and treatment with antihypertensive drugs. For 608 participants without known alcohol use, we interpolated drinking status based on sex and age (continuous). We checked the proportional hazards assumption by testing the interaction terms between follow-up duration and the variable of interest. Finally, we applied the generalized R^2 statistic[20] to assess the additional risk explained in Cox regression by adding the indices of blood pressure variability to models already including the mean systolic blood pressure level and covariables. The formula for the calculation of generalized R^2 is as follows:

$$R^2 = 1 - \exp\left\{\frac{-2}{n}[\ln L(X_2) - \ln L(X_1)]\right\} = 1 - \exp\left\{\frac{-\chi^2}{n}\right\}$$

where n is the number of participants, ln $L(X_2)$ and ln $L(X_1)$ are the log likelihood statistics of the full model and the basic model, respectively, and χ^2 is the likelihood ratio chi-square.

Results

Baseline Characteristics

Of the 2421 participants, 656 (27.1%) were treated with antihypertensive drugs at baseline, 475 (19.6%) were current smokers, 219 (9.1%) had diabetes mellitus, and 635 (26.2%) had hypercholesterolemia. The median number of days with self-measured blood pressure readings available for analysis was 26 (interquartile range, 21 to 28) in the morning and 26 (interquartile range, 22 to 28) in the evening. The self-measured systolic blood pressure was 2.15 mm Hg (95% confidence interval [CI], 1.88–2.42 mm Hg; P<0.0001) higher in the morning than evening. In patients on antihypertensive drug treatment, this difference was to 3.55 mm Hg (95% CI, 2.91–4.18 mm Hg; P<0.0001). For the morning blood pressure, the VIM formulas were (123.8^1.22) × SD/(mean^1.22) in all participants, (119.9^1.12) × SD/(mean^1.12) in 1765 untreated subjects, and (134.6^0.78) × SD/(mean^0.78) in 656 patients on antihypertensive drug treatment. For the evening blood pressure, the corresponding formulas were (121.7^1.15) × SD/(mean^1.15), (118.2^1.08) × SD/(mean^1.08) and (131.1^0.73) × SD/(mean^0.73), respectively.

Table 1 lists the baseline characteristics of the 2421 participants by sex-specific quartiles of VIM based on systolic blood pressure in the morning. The average morning blood pressure was similar across VIM quartiles (P=0.61), whereas the other indices of variability significantly increased with higher VIM (P<0.0001). These trends were similar across quartiles of VIM based on systolic blood pressure in the evening (Table S1, available in the online-only Data Supplement). The proportion of participants on antihypertensive drug treatment increased (P<0.0001) from low to high VIM (Table 1 and Table S1). All of the indices of variability were significantly (P<0.0001) higher in 656 treated compared with 1765 untreated participants (Table S2). The morning and evening blood pressures were lower (P<0.0001) in women than in men

Table 1. Baseline Characteristics of Participants by Fourths of the Distribution of Overall Systolic Variability Independent of the Mean in the Morning

Characteristic	Categories of Systolic Blood Pressure Variability				*P* Value
Limits, units					
Women	0.79–6.78	6.78–8.61	8.61–10.5	10.5–22.3	
Men	0.86–6.32	6.32–7.81	7.83–9.67	9.67–24.6	
Number of participants, %					
All participants in category	604	606	606	605	
Antihypertensive treatment	118 (19.5)	142 (23.4)	181 (29.9)*	215 (35.5)*	<0.0001
Smokers	123 (20.4)	122 (20.1)	124 (20.5)	106 (17.5)	0.52
Drinking alcohol	111 (26.1)	129 (27.9)	125 (26.2)	106 (23.6)	0.52
Diabetes mellitus	45 (7.5)	66 (10.9)*	53 (8.8)	55 (9.1)	0.22
Cardiovascular disease	11 (1.8)	18 (3.0)	15 (2.5)	26 (4.3)	0.068
Mean (SD) of characteristic					
Age, y	55.2 (12.0)	56.6 (11.3)	59.6 (12.2)†	62.8 (12.5)†	<0.0001
Body mass index, kg/m^2	23.9 (2.9)	23.6 (2.8)	23.2 (2.9)	23.1 (2.9)	<0.0001
Serum total cholesterol, mmol/L	5.00 (0.79)	5.03 (0.91)	5.02 (0.80)	4.94 (0.85)	0.42
Systolic blood pressure, mm Hg	123.7 (15.0)	123.2 (14.2)	124.0 (15.4)	124.5 (15.1)	0.61
Diastolic blood pressure, mm Hg	75.9 (10.1)	75.0 (9.4)	74.2 (9.7)	73.4 (10.1)	<0.0001
Heart rate, beats per minute	68.0 (7.6)	68.0 (7.3)	67.2 (7.9)	66.8 (8.0)	0.0012
Mean (SD) of variability index					
SD, mm Hg	5.3 (1.3)	7.4 (1.2)†	9.2 (1.5)†	12.4 (2.9)†	<0.0001
Coefficient of variation, %	4.3 (0.9)	6.0 (0.5)†	7.4 (0.6)†	9.9 (1.8)†	<0.0001
Maximum-minimum difference, mm Hg	20.7 (6.1)	29.2 (6.3)†	35.9 (7.8)†	46.8 (12.6)†	<0.0001
Average real variability, mm Hg	5.6 (1.6)	7.7 (1.7)†	9.5 (2.1)†	12.6 (3.5)†	<0.0001

Values are number of participants (%) or arithmetic mean (SD). Blood pressure variability is based on self-measurement in the morning on 5 days within 1 hour after awakening and before taking antihypertensive medications in treated participants. Drinking status was unavailable in 608 participants. *P* denotes the significance of the linear trend across categories of systolic blood pressure level.

*$P<0.05$, significance of the difference with the adjacent lower fourth.

†$P<0.0001$, significance of the difference with the adjacent lower fourth.

(Table S2). Although heart rate in women was similar to that in men ($P=0.15$), women had a significantly lower heart rate than men did in the evening ($P<0.0001$; Table S2). Coefficient of variation, VIM, and MMD were higher in women than in men in the morning ($P\leq0.0039$), whereas in the evening these indices were similar in both sexes ($P\geq0.089$; Table S2).

Incidence of Mortality and Morbidity

Over a median follow-up of 12.0 years (interquartile range, 9.9–15.4; maximum, 16.9 years), 412 participants died, 139 of cardiovascular causes (33.7%), and 223 stroke events occurred. All of the end points occurred at higher rates ($P<0.0001$) in treated compared with untreated participants (Table S3). Figure 1 shows the sex- and age-standardized rates across quartiles of the mean level and VIM of the morning systolic blood pressure. Total and cardiovascular mortality and stroke increased ($P\leq0.0004$) with higher levels of mean blood pressure in the morning and evening. Total and cardiovascular mortality ($P\leq0.014$) but not stroke ($P=0.15$) increased with higher morning VIM, whereas none of the studied end points was associated with evening VIM ($P\geq0.069$). As shown by Kaplan-Meier survival estimates across quartiles of systolic blood pressure in the morning or evening, the mean level and VIM were consistent and significant ($P<0.0001$) predictors of cardiovascular mortality for all of the participants (Figure 2).

Multivariable-Adjusted Analyses

Morning Blood Pressure

In multivariable-adjusted models (Table 2), the morning systolic blood pressure predicted total and cardiovascular mortality and stroke in all ($P\leq0.021$) and untreated ($P\leq0.018$) participants and stroke in patients on antihypertensive treatment ($P=0.0008$). In models including mean systolic blood pressure, VIM and ARV predicted total and cardiovascular mortality in all of the participants ($P\leq0.044$). VIM also predicted total mortality in untreated participants ($P=0.019$) and cardiovascular mortality in treated patients ($P=0.014$). However, these indices did not predict any cardiovascular end point in untreated participants ($P\geq0.11$). The R^2 statistics for adding morning VIM or ARV to models including mean blood pressure (Table 2) ranged from 0.08% to 0.88%. MMD added to models including the morning systolic blood pressure did not predict future events (Table 2; $P\geq0.085$).

Figure 3 shows the multivariable-adjusted 10-year risk of a cardiovascular death in relation to the mean level and VIM

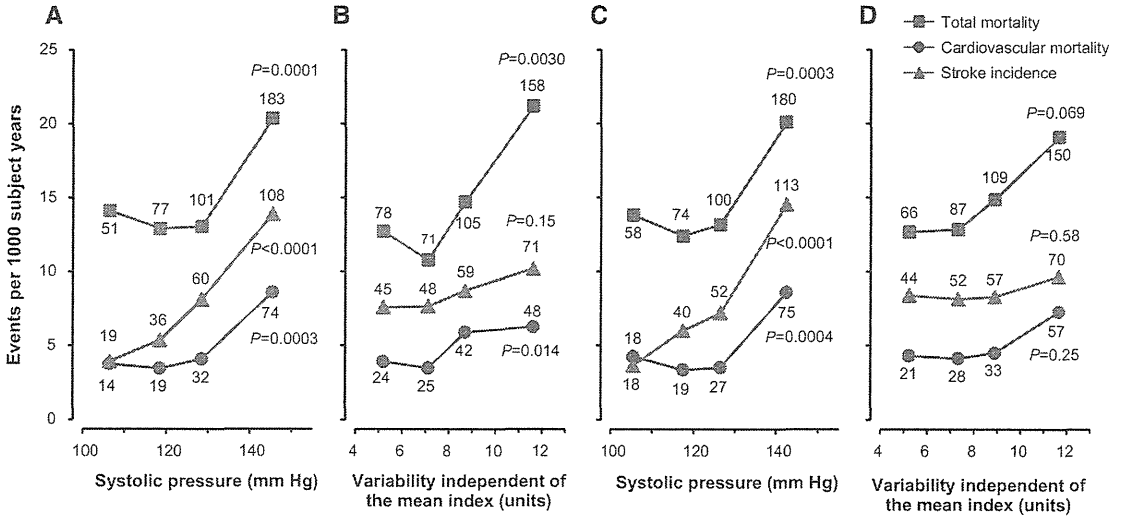

Figure 1. Incidence of total and cardiovascular mortality and stroke by quartiles of the mean level (**A** and **C**) and variability independent of the mean (**B** and **D**) of systolic blood pressure measured at home in the morning (**A** and **B**) or evening (**C** and **D**) in 2421 participants. Rates given as end points per 1000 person-years were standardized for sex and age by the direct method. The number of end points contributing to the rates is presented. The *P* values refer to the significance for linear trend across the quartiles.

of morning and evening systolic blood pressures in all of the participants. Figures S1 and S2 show similar information by treatment status. Morning systolic blood pressure was a consistent predictor of stroke and cardiovascular mortality ($P \leq 0.0049$) with the exception of cardiovascular mortality in treated participants ($P=0.082$).

Evening Blood Pressure

The evening systolic blood pressure predicted all of the end points ($P \leq 0.044$). In models already including the evening systolic blood pressure, VIM predicted cardiovascular mortality in all ($P=0.014$) and untreated ($P=0.46$) participants, whereas MMD and ARV did not significantly ($P \geq 0.057$) refine risk stratification (Table 3). The R^2 statistics for adding evening VIM, MMD, or ARV to models including mean blood pressure ranged from <0.01% to 0.27% (Table 3).

Additional Analyses

The interaction terms between treatment status and the indices of variability were all not significant ($P \geq 0.06$). Results based on 5 home readings were confirmatory for morning (Table S4) and evening (Table S5) blood pressures.

Discussion

Our study addressed the incremental value of newly proposed indices[11] in the prediction of mortality and cardiovascular events over and beyond the blood pressure level. The key findings were as follows: (1) morning VIM and ARV, independent of blood pressure level, predicted total and cardiovascular mortality in all of the participants; (2) being treated with blood pressure–lowering drugs underlayed the predictive value of morning VIM; (3) in untreated participants, these indices of variability did not predict cardiovascular mortality; (4) none of the variability indices predicted stroke incidence; and (5) for all or cause-specific fatal combined with nonfatal outcomes, the incremental predictive value of VIM, MMD, and ARV over and beyond blood pressure level was tiny based on the viewpoint of R^2 statistics. These findings must be interpreted within the context of the overall available evidence.

To our knowledge, only 2 previous population studies[10,21] reported on the refinement of prognosis by considering variability of the self-measured blood pressure in addition to blood pressure level and other risk factors. In 2008, we assessed blood pressure variability from the self-measured blood pressure in the Ohasama population, using the within-subject SD of the morning systolic blood pressure over 26 days (median) of self-measurement.[10] Over 11.9 years of follow-up, 462 participants died, the underlying cause being cardiovascular in 168, noncardiovascular in 294, stroke in 83, and cardiac in 85 participants.[10] In multivariable-adjusted Cox models also including blood pressure level, a 1-SD increase in the between-subject variability was associated with higher risk of any death (hazard ratio, 1.18 [95% CI, 1.07–1.31]), cardiovascular death (hazard ratio, 1.20 [95% CI, 1.02–1.40]), noncardiovascular mortality (hazard ratio, 1.18 [95% CI, 1.04–1.34]), and stroke mortality (hazard ratio, 1.38 [95% CI, 1.12–1.72]) but not cardiac mortality hazard ratio (hazard ratio, 1.02 [95% CI, 0.89–1.29]). The association of blood pressure variability with noncardiovascular mortality was difficult to interpret but might reflect reverse causality, subclinical disease leading to greater variability. More recently, the Finn-Home investigators noticed 130 deaths and 179 cardiovascular events among 1866 Finns followed up for 7.8 years. In multivariable-adjusted Cox models, day-to-day variability of the self-measured systolic blood pressure in the morning, estimated from the within-participant SD over 7 days, predicted total mortality and cardiovascular events. The hazard ratios expressing incremental risk for a 1-SD between-subject increment in variability (3.93 mm Hg) were ≈1.17 (95% CI, 1.00–1.30; $P=0.03$) and 1.21 (95% CI, 1.08–1.40; $P=0.006$), respectively.[21] Day-to-day variability in the evening systolic blood pressure was not predictive ($P \geq 0.11$).[21]

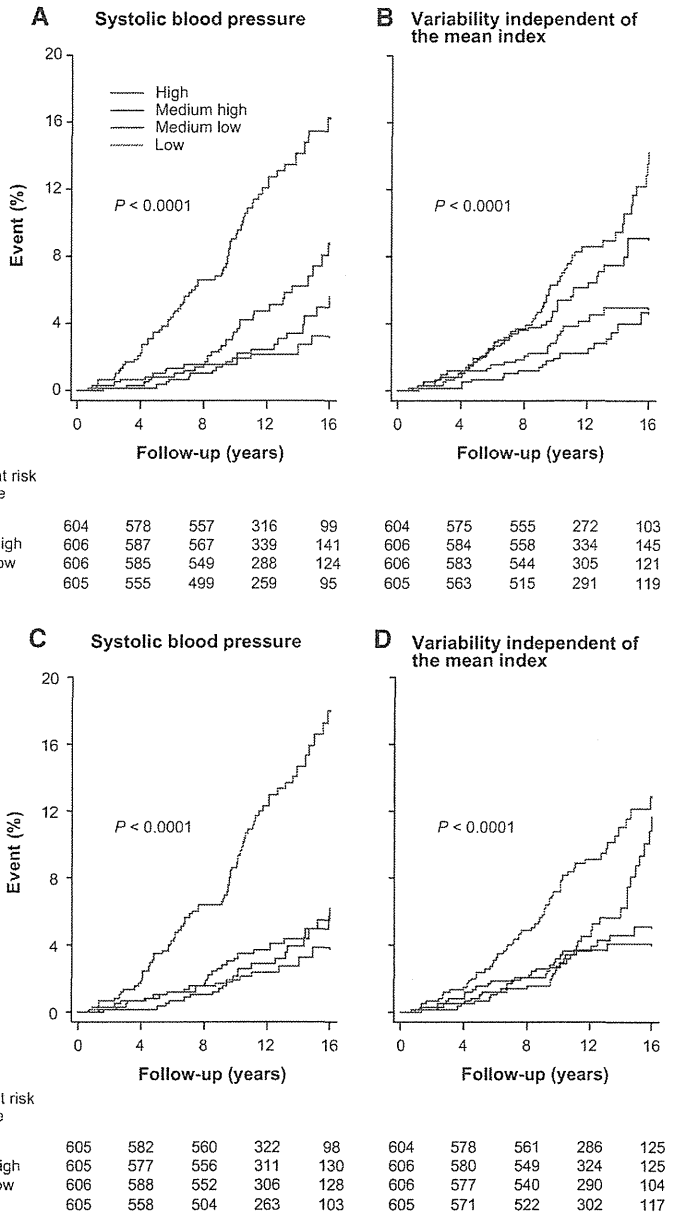

Figure 2. Kaplan-Meier survival function estimates for cardiovascular mortality by quartiles of the mean level (**A** and **C**) and variability independent of the mean (**B** and **D**) of systolic blood pressure measured at home in the morning (**A** and **B**) or evening (**C** and **D**) in 2421 participants. The *P* values refer to the significance of the log-rank test across quartiles.

Our current findings confirm that variability of the self-measured systolic blood pressure in the morning predicts total[10] and cardiovascular[10,21] mortality. In addition to being based on novel indices of blood pressure variability relatively independent of the mean,[7,11] our current report breaks new grounds in various ways. First, the previous Ohasama report[10] evaluated only fatal outcomes. In our current report, we demonstrated that neither morning nor evening blood pressure variability refined the risk stratification for fatal combined with nonfatal outcomes based on blood pressure level. In the Finn-Home study,[21] evening variability of systolic blood pressure (SD, 3.94 mm Hg) neither predicted total mortality (hazard ratio, 1.17 [95% CI, 0.96–1.35]; P=0.11) nor cardiovascular events (hazard ratio, 1.08 [95% CI, 0.92–1.26]; P=0.27). Second, as in previous studies,[10,21] we adjusted for antihypertensive treatment in the whole study population. In addition, we also ran analyses stratified by treatment status, which showed that the association between cardiovascular mortality and morning blood pressure variability was in fact confined to patients on antihypertensive drug treatment. Third, cerebrovascular disease causes increased blood pressure variability by impairing baroreflexes[22] and interfering with the central regulation of blood pressure by the autonomous nervous system. To avoid confounding by reverse causality, we excluded patients with a history of stroke at enrollment.[23] Fourth, although the morning systolic blood pressure was an independent predictor of cardiovascular mortality, the incremental prognostic value over and beyond blood pressure level was small with R^2 statistics in the whole study population of ≤0.31% and ≤0.88% in the patients on antihypertensive drug treatment. Previous population studies[10,21] did not report R^2 statistics. Finally, Muntner et al[24] selected a subsample (n=2174) of the participants in the

Table 2. Adjusted Standardized Hazard Ratios for End Points in Relation to the Mean and Overall Variability of Systolic Pressure in the Morning

			Full Model					
	Basic Model, Mean SBP		VIM		MMD		ARV	
End Point (n)	RH (95% CI)	R^2 (%)	RH (95% CI)	R^2 (%)	RH (95% CI)	R^2 (%)	RH (95% CI)	R^2 (%)
All participants								
Total mortality (412)	1.14 (1.02–1.27)*	22.9	1.15 (1.04–1.26)†	0.30	1.06 (0.96–1.17)	0.06	1.10 (1.00–1.21)*	0.16
CV mortality (139)	1.30 (1.09–1.56)†	10.7	1.26 (1.07–1.49)†	0.31	1.14 (0.97–1.34)	0.10	1.22 (1.04–1.42)*	0.25
Stroke (223)	1.43 (1.23–1.66)§	8.3	1.14 (1.00–1.30)	0.15	1.12 (0.98–1.28)	0.12	1.13 (1.00–1.27)	0.14
Untreated participants								
Total mortality (231)	1.17 (1.03–1.34)*	20.1	1.17 (1.03–1.33)*	0.30	1.11 (0.98–1.27)	0.15	1.12 (0.99–1.26)	0.17
CV mortality (68)	1.38 (1.09–1.74)†	7.9	1.16 (0.92–1.46)	0.08	1.10 (0.88–1.39)	0.04	1.19 (0.96–1.46)	0.14
Stroke (113)	1.35 (1.12–1.63)†	6.8	1.11 (0.91–1.34)	0.06	1.08 (0.90–1.31)	0.04	1.12 (0.94–1.35)	0.09
Treated participants								
Total mortality (181)	1.06 (0.91–1.23)	23.9	1.12 (0.97–1.30)	0.33	1.01 (0.87–1.17)	<0.01	1.09 (0.94–1.27)	0.20
CV mortality (71)	1.20 (0.95–1.52)	13.5	1.34 (1.06–1.69)*	0.88	1.15 (0.91–1.45)	0.21	1.24 (0.99–1.55)	0.50
Stroke (110)	1.39 (1.15–1.68)‡	5.7	1.17 (0.97–1.41)	0.39	1.15 (0.95–1.38)	0.31	1.14 (0.96–1.36)	0.32

Systolic blood pressure (SBP) level and variability are based on self-measurement in the morning for median 26 days (interquartile range, 21–28) within 1 hour after awakening and before taking antihypertensive medications in treated participants. VIM, MMD, and ARV indicate variability independent of the mean, the difference between maximum and minimum blood pressure, and average real variability. CV indicates cardiovascular. The basic model accounts for sex, age, body mass index, heart rate, smoking and drinking, serum cholesterol, and diabetes mellitus, and history of CV disease. Full models include the aforementioned covariables and both mean SBP and an index of SBP variability. Hazard ratios (HRs) given with 95% confidence intervals (CIs) express the risk associated with a 1-SD increase in the explanatory variables: in all participants, 14.9 mm Hg for level of blood pressure and 2.9 units, 12.8 mm Hg, and 3.5 mm Hg for VIM, MMD, and ARV, respectively. The R^2 statistic is a measure for the risk prediction provided by the basic model including mean SBP and the additive contribution of the indexes of variability.

*$P<0.05$, significance of the hazard ratios.

†$P<0.01$, significance of the hazard ratios.

‡$P<0.001$, significance of the hazard ratios.

§$P<0.0001$, significance of the hazard ratios..

Third National Health and Examination Survey, who took part in 3 consecutive study visits, at which the office blood pressure was measured. For various reasons, they excluded 1218 participants from analysis. Among the remaining 956 subjects (44.0%), 240 died. In multivariable-adjusted analyses, hazard ratios for all-cause mortality associated with an SD of systolic blood pressure of 4.80 to 8.34 mm Hg and ≥8.35 mm Hg versus <4.80 mm Hg were 1.57 (95% CI, 1.07–2.18) and 1.50 (95% CI, 1.03–2.18), respectively.[24] However, the *P* value for trend across these tertiles was marginal (0.064). Modeled as a continuous variable, blood pressure variability did not predict mortality.[24] Thus, although large epidemiologic studies might pick up incremental prognostic accuracy provided by blood pressure variability, this presumed risk factor remains weak and is unlikely to be clinically meaningful in individual subjects.

A key finding in our current study was that morning blood pressure variability was a predictor of cardiovascular mortality in patients on antihypertensive drug treatment but was not prognostically informative in untreated participants. Redon et al[25] enrolled 15 618 hypertensive patients in an observational study. Patients recorded their blood pressure at home for 2 weeks. Blood pressure control was a self-measured blood pressure <135 mm Hg systolic and 85 mm Hg diastolic. At baseline (day 1 of the first week), control rates of the home blood pressure were 8.5%, 11.3%, and 9.9% in the morning, at lunchtime, and in the evening, respectively; at follow-up (day 4 of the second week), these rates were 31.8%, 42.2%, and 36.4%, respectively. In our current study, the systolic difference between morning and evening blood pressure averaged 2.15 mm Hg in the whole study population and 3.55 mm Hg in patients on antihypertensive drug treatment. Patients on treatment had to measure their blood pressure before taking their medication in the morning. In 1992, 21.3% of the Ohasama patients were on a once-daily treatment regimen, and 70.9% were taking nifedipine, nicardipine, or diltiazem in sustained-release formulations,[26] which have a duration of action of <12 hours.[27] To what extent these findings and the observations of Redon et al[25] explain why blood pressure variability was predictive in the morning, but not in the evening, remains to be elucidated. Rothwell et al[11] reported that amlodipine reduced visit-to-visit blood pressure variability partly by its long half-life. On the other hand, a meta-analysis by the same group, using interindividual variance as a surrogate for within-individual variability, put forward that calcium channel blockers reduced blood pressure variability independent of drug half-life.[12]

The present study must be interpreted within the context of its potential limitations. First, our study population consisted of residents from a specific Japanese rural district. Although our results are in partial agreement with the Finn-Home study,[21] our current might not be generalizable to Western populations, in whom not stroke but myocardial infarction is the overriding cardiovascular complication associated with blood

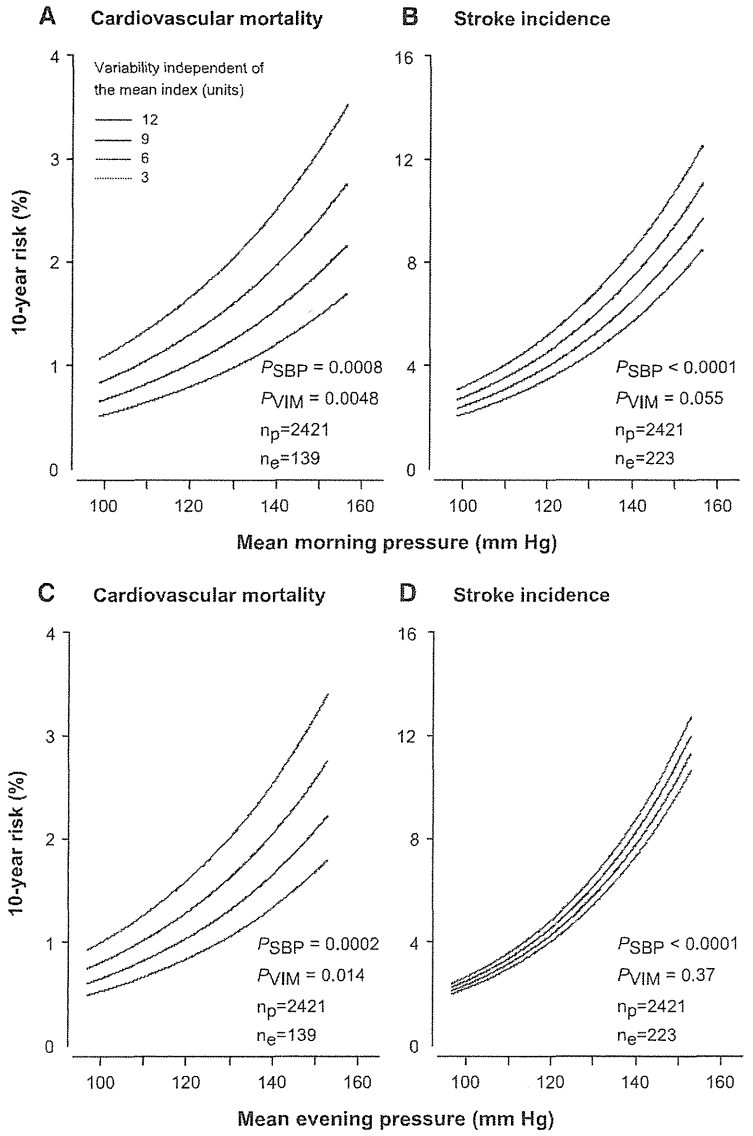

Figure 3. Absolute 10-year risk of cardiovascular mortality (**A** and **C**) and stroke incidence (**B** and **D**) in relation to the mean level of systolic blood pressure measured at home in the morning (**A** and **B**) or evening (**C** and **D**) in 2421 participants. The analyses were standardized to the distributions (mean or ratio) of sex, age, body mass index, heart rate, smoking and drinking, total cholesterol, diabetes mellitus, history of cardiovascular diseases, and treatment with antihypertensive drugs. In each panel, mean systolic blood pressure along the horizontal axis (SBP) covers the 2.5th to 97.5th percentile interval. Four continuous lines represent the risk independently associated with variability independent of the mean (VIM) equal to 3, 6, 9, and 12 units. *P* values are for the independent effect of SBP (P_{SBP}) and VIM (P_{VIM}). n_p and n_e indicate the number of participants at risk and the number of events.

pressure. In the Ohasama study, stroke caused 18.0% of total mortality, whereas in Finn-Home[21] this proportion was only 6.2%. Ischemic heart disease accounted for 7.1% and 22.3%, respectively. Second, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),[11] within-patient visit-to-visit variability was lower in the amlodipine than in the atenolol group among 19 257 randomized patients. The lower stroke risk in the amlodipine group (0.78 [95% CI, 0.67–0.90]) was partly attenuated by adjusting for mean systolic blood pressure during follow-up (0.84 [95% CI, 0.72–0.98]) and was diminished by also adjusting for VIM of clinic systolic blood pressure (0.96 [95% CI, 0.82–1.12]).[11] For coronary events, the ASCOT findings were similar.[11] In the current study, we only obtained detailed information on antihypertensive drug class in 366 treated patients, of whom 48.7% were taking calcium channel blockers and 17.5% β-blockers. In view of the incomplete information on drug class and the smaller sample size and observational nature of our current study, we could not stratify our analyses of 656 treated participants by drug class. Third, we based our main analyses on all of the available home blood pressure readings and only involved a single blood pressure reading in the morning and evening over a period of median 26 days. This is more than other European studies; for example, 5 consecutive home blood pressure readings in a European population study[16] and 7 days in the Finn-Home study.[6] Little information is currently available on how many days are required to capture blood pressure variability in a reliable way. However, sensitivity analyses making use of the home blood pressure over 5 days produced confirmatory results (Tables S3 and S4). Finally, the R^2 statistic is not a perfect measure of the variation explained by Cox models. R^2 values can be compared within but not across studies because of the dependence on censoring. Nevertheless, a measure of explained variance is crucial for the correct interpretation of the prognostic vale of a risk factor. *P* values of hazard ratios do not suffice to compare indicators of risk.

Table 3. Adjusted Standardized Hazard Ratios for End Points in Relation to the Mean and Overall Variability of Systolic Pressure in the Evening

			Full Model					
	Basic Model Mean SBP		VIM		MMD		ARV	
End Point (n)	RH (95% CI)	R^2 (%)	RH (95% CI)	R^2 (%)	RH (95% CI)	R^2 (%)	RH (95% CI)	R^2 (%)
All participants								
Total mortality (412)	1.16 (1.05–1.29)†	23.0	1.08 (0.98–1.19)	0.09	1.00 (0.91–1.10)	<0.01	1.05 (0.95–1.16)	0.04
CV mortality (139)	1.37 (1.15–1.63)‡	10.9	1.23 (1.04–1.44)*	0.24	1.15 (0.98–1.34)	0.12	1.15 (0.98–1.35)	0.12
Stroke (223)	1.54 (1.34–1.78)§	8.9	1.06 (0.93–1.21)	0.03	1.04 (0.91–1.18)	0.01	1.05 (0.92–1.19)	0.02
Untreated participants								
Total mortality (231)	1.14 (1.01–1.30)*	20.0	1.09 (0.96–1.25)	0.10	1.01 (0.89–1.15)	<0.01	1.10 (0.96–1.25)	0.11
CV mortality (68)	1.40 (1.12–1.76)†	7.9	1.26 (1.01–1.59)*	0.22	1.12 (0.90–1.40)	0.06	1.24 (0.99–1.55)	0.19
Stroke (113)	1.49 (1.25–1.79)§	7.2	1.03 (0.86–1.24)	0.01	1.00 (0.84–1.20)	<0.01	1.03 (0.86–1.24)	<0.01
Treated participants								
Total mortality (181)	1.17 (1.00–1.36)*	24.3	1.05 (0.91–1.21)	0.07	1.00 (0.87–1.14)	<0.01	0.99 (0.86–1.14)	<0.01
CV mortality (71)	1.31 (1.03–1.67)*	13.9	1.16 (0.93–1.47)	0.25	1.16 (0.93–1.43)	0.27	1.04 (0.83–1.30)	0.01
Stroke (110)	1.46 (1.20–1.76)‡	6.2	1.09 (0.91–1.31)	0.13	1.08 (0.90–1.29)	0.10	1.07 (0.90–1.28)	0.09

Systolic blood pressure (SBP) level and variability are based on self-measurement for median 26 days (interquartile range, 22–28) before going to bed. VIM, MMD, and ARV indicate variability independent of the mean, the difference between maximum and minimum blood pressure, and average real variability. CV indicates cardiovascular. The basic model accounts for sex, age, body mass index, heart rate, smoking and drinking, serum cholesterol, and diabetes mellitus, and history of CV disease. Full models include the aforementioned covariables and both mean SBP and an index of SBP variability. Hazard ratios (HRs) given with 95% confidence interval (CIs) express the risk associated with a 1-SD increase in the explanatory variables: in all participants, 14.5 mm Hg for level of blood pressure and 2.8 units, 12.6 mm Hg, and 3.5 mm Hg for VIM, MMD, and ARV, respectively. The R^2 statistic is a measure for the risk prediction provided by the basic model including mean SBP and the additive contribution of the indices of variability.

*$P<0.05$, significance of the hazard ratios.

†$P<0.01$, significance of the hazard ratios.

‡$P<0.001$, significance of the hazard ratios.

§$P<0.0001$, significance of the hazard ratios.

Perspectives

In the general population, blood pressure variability derived from home blood pressure does not substantially refine risk profiling over and beyond the blood pressure level. Being on antihypertensive drug treatment seems to be the main driver of the significant associations between cardiovascular mortality and blood pressure variability. Our findings also suggest, at variance with current guidelines,[1,3] that blood pressure variability, although showing up for selected fatal end points, might be too weak a predictor to be clinically meaningful. In risk stratification, clinicians should concentrate on what really matters, that is, blood pressure level, the predominant modifiable risk factor, which is reversible by adequate medical treatment.

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Disclosures

None.

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Novelty and Significance

What Is New?

- In multivariable Cox models, home morning variability independent of the mean and average real variability predicted total and cardiovascular mortality in all participants independent of home morning blood pressure level.
- In untreated participants, these indices of variability did not predict cardiovascular mortality.
- None of the variability indices predicted stroke incidence.
- The R^2 statistics showed the incremental risk explained by adding blood pressure variability to models already including systolic blood pressure and covariables ranged from <0.01% to 0.88%.

What Is Relevant?

- In risk stratification, clinicians should concentrate on what really matters, that is, blood pressure level, the predominant modifiable risk factor, which is reversible by adequate medical treatment.

Summary

In a general population, new indices of blood pressure variability derived from home blood pressure did not incrementally predict outcome over and beyond the blood pressure level. Being on antihypertensive drug treatment seems to be the main driver of the significant associations between cardiovascular mortality and blood pressure variability.

Original Article

Night-time blood pressure is associated with the development of chronic kidney disease in a general population: the Ohasama Study

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Objective: Ambulatory blood pressure (BP) is reportedly associated with target organ damage. However, whether ambulatory BP carries prognostic significance for the development of chronic kidney disease (CKD) has not been confirmed.

Method: We measured ambulatory BP in 843 participants without CKD at baseline from a general Japanese population and examined the incidence of CKD defined as positive proteinuria or an estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m^2 at health checks. The association between baseline ambulatory BP and CKD incidence was examined using the Cox proportional hazard regression model adjusted for sex, age, BMI, habitual smoking, habitual alcohol consumption, diabetes mellitus, hypercholesterolemia, a history of cardiovascular disease, antihypertensive medication, eGFR at baseline, the number of follow-up examinations, and the year of the baseline examination.

Results: The mean age of the participants averaged 62.9±8.1 years, 71.3% were women and 23.7% were under antihypertensive medication. During a median follow-up of 8.3 years, 220 participants developed CKD events. The adjusted hazard ratios for CKD in a 1-standard deviation increase in daytime and night-time SBP were 1.13 [95% confidence interval (CI) 0.97–1.30] and 1.21 (95% CI 1.04–1.39), respectively. When night-time and daytime BP was mutually adjusted into the same model, only night-time BP persisted as an independent predictor of CKD.

Conclusion: Night-time BP is a better predictor of CKD development than daytime BP in the general population. Ambulatory BP measurement is considered useful for evaluating the risk of progression to CKD.

Keywords: ambulatory blood pressure measurement, chronic kidney disease, dipping status, hypertension, night-time blood pressure

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; SD, standard deviation; VIF, variance inflation factor

INTRODUCTION

Ambulatory blood pressure (BP) provides valuable clinical information that is more effective than casual BP in predicting cardiovascular disease (CVD) [1,2]. We analyzed evidence from various reports indicating that ambulatory BP is associated with target organ damage among the general population [3–5], as well as cohorts with hypertension [6,7], diabetes [8,9], and chronic kidney disease (CKD) [10,11]. However, a population-based study has not yet examined whether or not ambulatory BP is directly linked to kidney damage or to a decline in renal function before reaching end-stage renal disease (ESRD). Furthermore, night-time BP is a more reliable predictor of CVD and cardiovascular mortality than daytime BP [12–14]. However, whether either daytime or night-time BP has prognostic importance for kidney disease has not been fully elucidated.

Contrarily, CKD is an established risk factor for independent cardiovascular disease risk [15,16], for which risk increases with worsening renal function [17,18]. Therefore, risk factors for developing CKD should be identified and a

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further decline in glomerular filtration rate (GFR) must be prevented because it is closely associated with ESRD and the prevalence of CVD.

The present study examines whether ambulatory BP is a significant prognostic determinant of CKD, clarifies its benefit for the general Japanese population, and analyzes the components of ambulatory BP, namely daytime BP, night-time BP, and their ratios relative to outcomes.

MATERIALS AND METHODS

Design

The present study was based on a longitudinal analysis of individuals who had participated in a community-based project to determine ambulatory BP in Ohasama, Iwate Prefecture, Japan. This study (the Ohasama study) was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. The socioeconomic and demographic characteristics of this region and the details of this project have been described [19].

Study cohort

Farmers, self-employed individuals, pensioners, and dependents aged at least 40 years are eligible for free annual health checks in Japan. Ohasama is a rural community with a population of 7496, of whom 3076 were eligible for annual health checks in 1992. Among them, 2528 participated in at least one health check-up between 1992 and 1997 (baseline values), and another between 2002 and 2010 (follow-up values). For those who were examined more than once at baseline, the findings at the first health check-up were considered as baseline values. We excluded individuals who did not provide written informed consent to participate in the study ($n=55$) and those who were diagnosed with CKD at baseline based on findings of either proteinuria ($n=91$) or estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m^2 ($n=231$). Of the 2150 remaining individuals, we further excluded 1307 because ambulatory BP baseline values had not been determined ($n=1293$) or because fewer than 12 and six daytime and night-time BP values, respectively, had been measured ($n=14$). Thus, data from 843 individuals were statistically analyzed.

Ambulatory blood pressure

Ambulatory BP was monitored at 30-min intervals using the fully automated and validated ABPM-630 (Nippon Colin, Komaki, Japan) instrument [20]. This device uses cuff-oscillometry to measure BP and meets the criteria of the Association for the Advancement of Medical Instrumentation [21]. The device was attached to each participant by public health nurses on weekday mornings and detached on the following morning. Participants reported their daily activities, including the times at which they went to bed at night and awoke in the morning. The rate of nocturnal decline in BP was defined as follows: rate of nocturnal decline in BP = (daytime SBP − night-time SBP)/daytime SBP × 100 (%). Nondipper was defined as having a dipping rate of less than 10 (%), and all other participants were defined as dippers [22].

Casual blood pressure

Seated participants rested for at least 2 min and then casual BP was measured twice by nurses at local medical centers using a semiautomated and validated BP measuring device (USM-700F; UEDA Electronic Works, Tokyo, Japan) based on the microphone method [20]. The average of two readings was analyzed. The device meets the criteria of the Association for the Advancement of Medical Instrumentation [21].

Data collection

Smoking status, habitual alcohol consumption, use of antihypertensive medications at baseline, as well as a history of CVD, diabetes mellitus and hypercholesterolemia were verified from medical charts at Ohasama Hospital and a questionnaire administered during the annual health checks [23]. We defined habitual alcohol drinker as intake of 3 days or more per week, and habitual smoker as currently smoking cigarettes. Individuals under medication with lipid-lowering drugs or having serum cholesterol levels at least 220 mg/dl were considered to have hypercholesterolemia. Individuals with fasting serum glucose levels at least 126 mg/dl or nonfasting glucose levels at least 200 mg/dl, or who used insulin or oral antihyperglycemic agents were defined as having diabetes mellitus. BMI was calculated as weight (kg) divided by height squared (m^2). CVD was defined as a history of disease associated with the circulatory system (ICD-10: I00–I99) or transient ischemic attack. Hypertension was diagnosed on a threshold of 140/90 and 130/80 mmHg for casual and 24-h ambulatory BP, respectively [24]. Participants under treatment for hypertension were included in the group with hypertension.

Serum creatinine (Scr) was measured at annual health checks using the Jaffé method before 2002 and the enzymatic method thereafter. Renal function was determined from the eGFR calculated using a modified Japanese equation based on inulin clearance as follows: eGFR (ml/min per 1.73 m^2) = 194 × (Scr in enzymatic method)$^{-1.094}$ × age$^{-0.287}$ (× 0.739, if woman) [25]. We subtracted 0.2 from the Scr value determined using the Jaffé method (mg/dl) for conversion to the enzymatically determined value [26]. We quantified proteinuria using a dipstick test for spot-urine (Urohemabonbix 5G08C: Bayer Medical, Tokyo, Japan) and the results were manually determined by qualified laboratory technicians. Test outcomes were considered positive if proteinuria exceeded 30 mg/dl that is comparable to macroalbuminuria. We defined CKD as a composite of eGFR less than 60 ml/min per 1.73 m^2 or proteinuria.

Follow-up and outcomes

Primary outcomes were defined as CKD determined during an annual health check between 2002 and 2010. If more than one CKD event occurred during follow-up, only the first event contributed to the outcome analysis. The date of CKD onset was defined as the midpoint between the most recent date when the individual did not have CKD and the date of the first diagnosis of CKD. The follow-up period was defined as the number of days from the baseline

examination to the onset of CKD or to the final health check. Secondary outcomes were defined as a composite of CKD or all-cause death.

Statistical analysis

All data were statistically analyzed using SAS software version 9.1 (SAS Institute, Cary, North Carolina, USA). Statistical differences between means and categories were compared using Student's *t*-test and categories by χ^2-test, respectively. Associations between ambulatory BP and the incidence of CKD and its components, including proteinuria, eGFR less than 60 ml/min per 1.73 m^2, were examined using the Cox proportional hazard regression model adjusted for sex, age, BMI, habitual smoking and habitual alcohol consumption, diabetes mellitus, hypercholesterolemia, a history of CVD, antihypertensive medication, eGFR at baseline, the number of follow-up examinations, and the year of the baseline examination. When mortality was included as an outcome in any analysis, participants who died or who were lost to follow-up were treated as censored. We performed the likelihood ratio test between one model that included a single BP with each confounding factor and another that included two BP values. A significant likelihood ratio χ^2 means that the BP was significantly more closely associated with CKD. We also analyzed collinearity and calculated collinearity statistics (variance inflation factor, VIF) for night-time and daytime BP values. The independent effect of the rate of nocturnal decline in BP was further tested including 24-h SBP in the model; similarly, hazard ratios of outcomes were compared between nondippers and dippers using the Cox hazard model. We also conducted stratified analyses according to age, sex, and antihypertensive medication, and tested interactions by introducing a multiplicative term into main effect models.

We conducted sensitivity analyses as follows. First, we applied a correction coefficient used in a study that recommended subtracting 0.234 mg/dl from the Jaffé method [27]. In that case, total number of participants increased from 843 to 857. We also calculated eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [28] multiplied by a Japanese coefficient of 0.813 [29] instead of the modified Japanese equation. In this analysis, we excluded those who were diagnosed with CKD at baseline and the number of participants totaled 900. The value of creatinine determined using the Jaffé method was corrected to an isotope dilution mass spectrometry method when applying the CKD-EPI equation. Therefore, we corrected the values determined using the Jaffé method to isotope dilution mass spectrometry method by subtracting 18 μmol/l (0.2 mg/dl) [30]. We also tested likelihood ratios when using the CKD-EPI equation.

RESULTS

Baseline characteristics of the participants

Our 843 study participants were significantly older (62.9 ± 8.1 vs. 58.6 ± 10.2 years) and had significantly more complications than the 1307 individuals, who were excluded from the present study on the basis of entry criteria (Table 1). The mean age of the 843 study participants was 62.9 ± 8.1 years and 601 (71.3%) of them were women. Among the total, 200 (23.7%) were under antihypertensive medication, 241 (28.6%) had hypercholesterolemia, 109 (12.9%) had diabetes mellitus, and 36 (4.3%) had a history of CVD. The baseline Scr from the Jaffé method converted to that for the enzymatic method was 0.64 ± 0.12 mg/dl and eGFR was 81.1 ± 15.0 ml/min per 1.73 m^2. Table 2 shows the characteristics of the participants categorized according to the development of CKD.

Follow-up and outcome

Median follow-up was 8.3 (interquartile range 3.2–13.7) years. Among the 843 participants, 220 developed CKD events, including only eGFR less than 60 ml/min per 1.73 m^2 in 151 (69%), isolated positive proteinuria in 42 (19%), and both in 27 (12%). During the follow-up period, 152 individuals died and 339 reached a composite outcome of CKD or death.

We examined the hazard ratios for outcomes over a 1-standard deviation (SD) increase in ambulatory BP (Table 3). Night-time BP was significantly associated with

TABLE 1. Comparison of baseline clinical characteristics[a] between included and excluded participants

Variable	Study participants ($N = 843$)	Excluded participants[b] ($N = 1307$)	P[c]
Woman (%)	71.3	58.4	<0.001
Age (years)	62.9 ± 8.1	58.6 ± 10.2	<0.001
BMI (kg/m^2)	22.5 ± 3.0	23.7 ± 3.3	<0.001
Current smoker (%)	12.9	8.8	0.003
Current drinker (%)	21.6	13.5	<0.001
Diabetes mellitus (%)	12.9	2.9	<0.001
Hypercholesterolemia (%)	28.6	26.5	0.28
History of CVD (%)	4.3	1.1	<0.001
Antihypertensive medication (%)	23.7	11.2	<0.001
Scr (mg/dl)	0.64 ± 0.12	0.66 ± 0.12	<0.001
eGFR[d] (ml/min per 1.73 m^2)	81.1 ± 15.0	83.0 ± 14.5	<0.001

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; SD, standard deviation.
[a]Values are expressed as percentage or mean ± SD.
[b]We excluded the 1307 participants because their ambulatory BPs had not been measured at baseline ($n = 1293$) or because their daytime or night-time BPs were the averages of fewer than 12 or six readings ($n = 14$).
[c]Student's *t*-test was used to compare continuous variables and χ^2-test was performed to analyze categorical variables between two groups.
[d]eGFR was calculated with the use of a modified Japanese equation as follows: eGFR (ml/min per 1.73 m^2) = 194 × (Scr in enzymatic method)$^{-1.094}$ × Age$^{-0.287}$ (× 0.739, if woman) [25].

TABLE 2. Clinical characteristics of participants at baseline[a]

Variable	Overall ($N=843$)	CKD events ($N=220$)	Non-CKD events ($N=623$)	P^b
Woman (%)	71.3	73.2	70.6	0.47
Age (years)	62.9±8.1	64.5±8.5	62.4±7.8	0.001
BMI (kg/m^2)	22.5±3.0	23.3±2.7	22.9±2.9	0.13
Habitual smoker (%)	12.9	13.2	12.8	0.89
Habitual drinker (%)	21.6	19.1	22.5	0.29
Diabetes mellitus (%)	12.9	12.3	13.2	0.74
Hypercholesterolemia (%)	28.6	31.4	27.6	0.29
History of CVD (%)	4.3	5.0	4.0	0.53
Antihypertensive medication (%)	23.7	28.2	22.2	0.071
Hypertension based on casual BP[c] (%)	37.9	44.1	35.8	0.029
Hypertension based on 24-h BP[c] (%)	39.4	47.7	36.4	0.003
Scr (mg/dl)	0.64±0.12	0.67±0.11	0.62±0.12	<0.001
eGFR[d] (ml/min per 1.73 m^2)	81.1±15.0	74.5±12.7	83.5±15.1	<0.001
Number of follow-up examinations	4.4±2.0	4.9±1.8	4.3±2.0	<0.001
Follow-up period (years)	8.0±5.1	4.8±4.2	9.2±4.9	<0.001
Casual SBP (mmHg)	127.8±16.2	128.6±15.9	127.6±16.3	0.43
Casual DBP (mmHg)	70.7±10.6	70.9±11.0	70.6±10.4	0.76
24-h SBP (mmHg)	122.4±12.5	124.3±13.1	121.7±12.3	0.008
24-h DBP (mmHg)	71.7±7.5	72.6±7.5	71.4±7.4	0.035
Daytime SBP (mmHg)	128.3±13.5	130.0±14.1	127.7±13.3	0.031
Daytime DBP (mmHg)	75.9±8.2	76.7±8.2	75.6±8.2	0.094
Night-time SBP (mmHg)	110.9±13.3	113.4±13.7	110.0±13.1	0.001
Night-time DBP (mmHg)	63.4±7.6	64.6±7.7	63.0±7.5	0.005
Rate of nocturnal decline in BP[e] (%)	13.4±7.2	12.6±6.9	13.7±7.4	0.059
Nondipper[f] (%)	29.3	32.7	28.1	0.19

BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; SD, standard deviation.
[a]Values are expressed as percentages or mean±SD.
[b]Student's *t*-test was used to compare continuous variables and χ^2-test was performed to analyze categorical variables between CKD event and non-CKD event groups.
[c]Diagnosis of hypertension was based on the thresholds of 140/90 mmHg for casual BP, 130/80 mmHg for 24-h BP, respectively. Treated participants were also included into hypertension groups.
[d]eGFR was calculated with the use of a modified Japanese equation as follows; eGFR (ml/min per 1.73 m^2) = 194 × (Scr in enzymatic method)$^{-1.094}$ × Age$^{-0.287}$ (× 0.739, if woman) [25].
[e]Rate of nocturnal decline in BP was defined as follows: rate of nocturnal decline in BP = (daytime SBP − night-time SBP)/daytime SBP × 100 (%).
[f]Nondipper was defined as rate of nocturnal decline in BP <10 (%) [22].

risk of CKD and a composite outcome of CKD or all-cause mortality, whereas 24-h, daytime, and casual BP were not significantly related. The rates of a nocturnal decline in BP and nondipping did not significantly differ in relation to CKD or a composite outcome of CKD or death from all causes (Table 3). Table 4 shows adjusted hazard ratios after including daytime and night-time BP into the same models. Night-time BP remained a significant predictor of CKD and

TABLE 3. Adjusted hazard ratios[a] for chronic kidney disease[b], components of chronic kidney disease and composite outcomes of chronic kidney disease or all-cause death

	CKD	Proteinuria	eGFR <60 ml/min per 1.73 m^2	CKD or death[c]
Number of events	220	69	178	339
Event rate per 100 person years[d]	3.25	0.90	2.51	3.28
1-SD increase in SBP				
24-h, 12.5 mmHg	1.16 (1.00–1.34)[h]	1.31 (1.02–1.69)[h]	1.13 (0.96–1.33)	1.09 (0.97–1.23)
Daytime, 13.5 mmHg	1.13 (0.97–1.30)	1.29 (1.01–1.66)[h]	1.09 (0.93–1.28)	1.06 (0.95–1.20)
Night-time, 13.3 mmHg	1.21 (1.04–1.39)[g]	1.30 (1.01–1.66)[h]	1.18 (1.01–1.39)[h]	1.14 (1.02–1.27)[g]
Casual, 16.3 mmHg	1.12 (0.97–1.29)	1.27 (0.99–1.63)	1.08 (0.92–1.27)	1.10 (0.98–1.23)
1-SD increase in DBP				
24-h, 7.5 mmHg	1.15 (0.99–1.33)	1.25 (0.97–1.62)	1.13 (0.96–1.33)	1.09 (0.98–1.24)
Daytime, 8.2 mmHg	1.11 (0.96–1.29)	1.23 (0.95–1.59)	1.10 (0.93–1.29)	1.07 (0.95–1.20)
Night-time, 7.6 mmHg	1.20 (1.04–1.39)[g]	1.25 (0.97–1.61)	1.19 (1.01–1.39)[h]	1.16 (1.03–1.29)[g]
Casual, 10.6 mmHg	1.09 (0.95–1.25)	1.33 (1.05–1.70)[g]	1.03 (0.88–1.19)	1.07 (0.96–1.19)
Rate of nocturnal decline in BP[e] (%)	0.27 (0.04–1.63)	0.62 (0.02–16.14)	0.23 (0.03–1.73)	0.27 (0.06–1.12)
Nondipper[f]	1.08 (0.81–1.45)	0.91 (0.54–1.55)	1.18 (0.86–1.63)	1.10 (0.87–1.39)

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Scr, serum creatinine.
[a]Hazard ratios and 95% confidence intervals were adjusted for sex, age, BMI, habitual smoking and habitual alcohol consumption, diabetes mellitus, hypercholesterolemia, a history of cardiovascular disease, antihypertensive medication, eGFR at baseline, the number of follow-up examinations, and the year of the baseline examination.
[b]CKD is defined as positive proteinuria or eGFR < 60 ml/min per 1.73 m^2, and eGFR was calculated with the use of a modified Japanese equation as follows; eGFR (ml/min per 1.73 m^2) = 194 × (Scr in enzymatic method)$^{-1.094}$ × Age$^{-0.287}$ (× 0.739, if woman) [25].
[c]CKD or Death means a composite outcome of CKD or all-cause death.
[d]Event rates were calculated as 100 × Number of events / (Number of participants × study duration).
[e]Rate of nocturnal decline in BP was defined as follows; rate of nocturnal decline in BP = (daytime SBP − night-time SBP)/daytime SBP × 100 (%); additionally, hazard ratios for outcomes were calculated in a 1-percentage increase of rate of nocturnal decline in BP.
[f]Nondipper was defined as rate of nocturnal decline in BP <10 (%) [22]. Hazard ratios for outcomes in nondipper were further adjusted for 24-h SBP.
[g]$P<0.03$.
[h]$P<0.05$.

TABLE 4. Adjusted hazard ratios[a] for chronic kidney disease[b], components of chronic kidney disease and composite outcomes of chronic kidney disease or all-cause death in 1-standard deviation increase of ambulatory blood pressure when model included daytime and night-time blood pressure

	CKD	Proteinuria	eGFR < 60 ml/min per 1.73 m^2	CKD or death[c]
Number of events	220	69	178	339
Event rate per 100 person-years[d]	3.25	0.90	2.51	3.28
1-SD increase in SBP				
Daytime, 13.5 mmHg	0.99 (0.81–1.20)	1.16 (0.83–1.63)	0.96 (0.77–1.19)	0.95 (0.81–1.11)
Night-time, 13.3 mmHg	1.21 (1.00–1.47)[f]	1.17 (0.84–1.65)	1.22 (0.98–1.51)	1.18 (1.01–1.37)[f]
1-SD increase in DBP				
Daytime, 8.2 mmHg	0.98 (0.81–1.18)	1.11 (0.79–1.55)	0.96 (0.81–1.19)	0.95 (0.81–1.11)
Night-time, 7.6 mmHg	1.22 (1.01–1.48)[f]	1.17 (0.84–1.64)	1.22 (0.99–1.41)[g]	1.20 (1.03–1.39)[e]

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; SD, standard deviation.
[a]Hazard ratios and 95% confidence intervals were adjusted for sex, age, BMI, habitual smoking and habitual alcohol consumption, diabetes mellitus, hypercholesterolemia, a history of cardiovascular disease, antihypertensive medication, eGFR at baseline, the number of follow-up examinations, and the year of the baseline examination with entering daytime and night-time BP into the model simultaneously.
[b]CKD is defined as a positive proteinuria or eGFR < 60 ml/min per 1.73 m^2, and eGFR was calculated with the use of a modified Japanese equation as follows; eGFR (ml/min per 1.73 m^2) = 194 × (Scr in enzymatic method)$^{-1.094}$ × Age$^{-0.287}$ (× 0.739, if woman) [25].
[c]CKD or death means a composite outcome of CKD or all-cause death.
[d]Event rates were calculated as 100 × number of events/(number of participants × study duration).
[e]$P < 0.03$.
[f]$P < 0.05$.
[g]$P < 0.07$.

a composite outcome of CKD or all-cause mortality, whereas daytime BP did not predict risk for these outcomes (Table 4). We also analyzed collinearity and calculated collinearity statistics (VIF) of night-time and daytime BP values. All VIFs were small enough to indicate that collinearity was absent (all VIFs <2.4). We then divided the participants into tertiles based on night-time SBP and analyzed the hazard ratios for outcomes (Fig. 1). The adjusted hazard ratio of CKD was significantly higher in the third, than the first tertile of night-time SBP (Fig. 1a). The tendency of the adjusted hazard ratio of a composite outcome of CKD or death from all-causes in night-time BP (Fig. 1b) was similar. The results showed that the likelihood ratio was significantly larger for night-time, than for daytime BP (Supplemental Table S1, http://links.lww.com/HJH/A274). Stratified analyses according to sex, age, and antihypertensive medication confirmed these findings (Supplemental Tables S2, S3, http://links.lww.com/HJH/A274). None of the interaction terms reached significance ($P \geq 0.29$). The results of the different correction coefficient equation in which 0.234 mg/dl was subtracted from the values obtained in the Jaffé method were similar to those in our present study (Supplemental Table S4, http://links.lww.com/HJH/A274). The result of sensitivity analysis using the CKD-EPI equation basically provided similar results to the present study, although daytime BP was also significantly related to some CKD outcomes (Supplemental Table S5, http://links.lww.com/HJH/A274). Likelihood ratio was larger for night-time BP than for daytime BP, although some of the difference was not statistically significant (Supplemental Table S6, http://links.lww.com/HJH/A274).

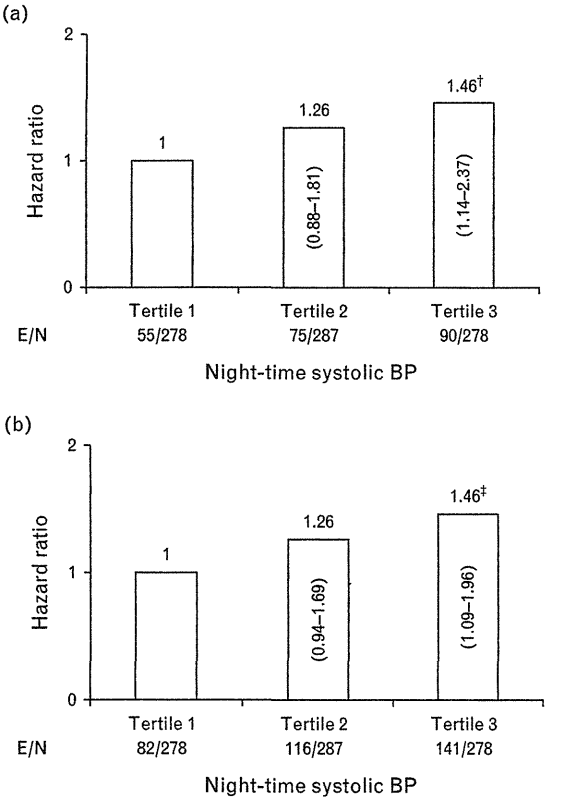

FIGURE 1 Adjusted hazard ratios and 95% confidence intervals for chronic kidney disease (CKD) and composite outcome of CKD or all-cause death stratified by tertiles of night-time SBP. Adjusted hazard ratios for CKD (a) and for composite outcomes of CKD or death from all-causes death (b) determined from tertiles of night-time SBP were determined using Cox proportional hazard regression model adjusted for sex, age, BMI, habitual smoking, habitual alcohol consumption, diabetes mellitus, hypercholesterolemia, a history of CVD, antihypertensive treatment, eGFR at baseline, the number of follow-up examinations, and the year of the baseline examination. Night-time SBP was divided into tertiles 1, 2, and 3 based on values of <102, 103–115, and ≥116 mmHg. Event rates were calculated as 100 × number of events/(number of participants × study duration). Trend for *P* indicates linearity of the trend. BP, blood pressure; CVD, cardiovascular disease; *E/N*, number of events/number of participants; eGFR, estimated glomerular filtration. †$P < 0.01$ vs. tertile 1, ‡$P < 0.02$ vs. tertile 1.

DISCUSSION

The present study found that 24-h ambulatory BP was significantly associated with the development of CKD and that night-time BP in particular predicted CKD and death from all causes. An association between ambulatory BP and CVD events, as well as ambulatory BP and all-cause

mortality in a general population has been demonstrated [3,4]. However, the association between ambulatory BP and renal prognosis has only been determined among patients with CKD [10,11], hypertension [6,7], or diabetes mellitus [8,9]. Night-time BP is a significant determinant of albuminuria among hypertensive or diabetic cohorts [31,32] and a predictor of progression to ESRD or death among cohorts with CKD [10,33], but not always after adjustment for other risk factors involved in CKD progression [11]. Therefore, whether night-time BP is an independent determinant of CKD development requires confirmation, especially in population-based cohorts. The present study demonstrated that night-time BP is associated with a risk for CKD among the general population.

Night-time BP reflects intrinsic systemic BP without modifying factors including physical and mental activities compared with daytime BP and thus night-time BP would reflect hemodynamic effects on target organs more accurately. Night-time BP might affect renal function because the afferent arteriolar tone in the glomerular capillary tuft is the lowest during this period of the day. High night-time systemic BP would be directly transmitted to the glomerulus, which would lead to intraglomerular hyperfiltration and result in hypertension-induced kidney damage [34]. Furthermore, the pathogenesis of a higher night-time BP might result from disordered natriuresis during the daytime or volume overload [35,36], impaired baroreflex sensitivity [37], damaged sympathetic modulation of night-time BP [38], or sleep apnea syndrome [39], some of which might be based on latently decreased renal function and easily facilitate progression to a later stage of CKD.

Disturbed dipping status has been significantly associated with ESRD or CVD mortality among patients with CKD [12] and with a further decline in renal function [40], whereas other studies have found that this is not always true [11,41]. Nevertheless, disturbed dipping status might have been associated with hard outcomes in previous studies of high-risk populations, such as those complicated with several risk factors for CVD. The present study confirmed that absolute night-time BP itself predicts the development of early stage of CKD whereas impaired dipping status does not. A future study should clarify whether either absolute night-time BP or impaired nocturnal dipping would have more renal prognostic significance in a different population.

We discovered that night-time BP predicts progression to CKD in the general population. The strengths of the present study are the large cohort in which ambulatory BP was monitored, the definition of CKD as decreased eGFR together with positive proteinuria, and the application of a modified Japanese equation for the diagnosis of CKD. However, the results obtained using the CKD-EPI equation were basically similar to the original analysis, although daytime BP was also significantly related to some CKD outcomes. In addition, we simultaneously adjusted the hazard ratios of outcomes associated with night-time BP using daytime BP, which was not necessarily a feature of previous studies.

A limitation of the present study was that the definition of CKD depended on the value of creatinine or positive proteinuria on only one occasion. In 2002, the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation guidelines included a clear CKD definition and classification. It defines CKD as the presence of kidney damage or GFR less than 60 ml/min per 1.73 m^2 for at least 3 months [42]. However, CKD has been similarly diagnosed in an epidemiological study [43,44] and the method has achieved consensus. We did not consider the timing of daily dosing with antihypertensive medication and thus we could not address any potential effects. The possibility of selection bias should be considered because the participation rate amounted to only 27.4% of the total population. Most our study population comprised woman and elderly participants whose renal functions in particular were likely to be affected by several insults. Our study participants also had more risk factors than the excluded individuals whose ambulatory BP was not measured. Because we analyzed only Japanese residents, our findings might not be representative of other ethnicities. Thus, the generalizability of the present results requires further verification. Scr determined by the Jaffé method was corrected using a validated modified equation to obtain an equivalent value in the enzymatic method [24]. However, the possibility that this conversion affected the results cannot be ruled out. Finally, proteinuria was defined as a positive result of a semiquantitative assessment using a dipstick test for spot-urine. This approach did not enable us to distinguish microalbuminuria from macroalbuminuria.

In conclusion, this is the first population-based study demonstrated that night-time BP significantly predicted progression to CKD in a general Japanese population irrespective of daytime BP. Ambulatory BP measurement might provide useful information about BP control and progression to CKD.

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Material in this manuscript has not been published and is not being considered for publication elsewhere in whole or in part in any language.

Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

Night-time blood pressure is known to provide important information on the cardiovascular risk of hypertensive patients. The level of BP at night has also been associated with a worst prognosis in patients with renal diseases. In this study, authors have investigated the prognostic role of night-time and daytime BP on the risk of developing CKD defined as a GFR<60 ml/min per 1.73 m^2 or the presence of proteinuria in a large group of patients followed for 8 years. Their results clearly demonstrate that night-time BP but not the dipping pattern is a good predictive factor of the future development of CKD. However, it has to be mentioned that the studied population was at relatively high risk of CKD and whether this applies to the general unselected population remains to be confirmed.

Reviewer 2

The predictive power of 24-h, as well as night-time and daytime, blood pressure values with respect to renal risk is of great interest and one that has been the object of several studies in the past. This work confirms previous observations and extend them by demonstrating that blood pressure load, especially night-time BP, is related to an increased risk of de novo incidence of renal damage in a general population, even after adjustments for several confounding variables. A well conceived and well written study. Results are appropriately reported and commented upon.

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Original Article

Effect of Age on the Association Between Waist-to-Height Ratio and Incidence of Cardiovascular Disease: The Suita Study

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ABSTRACT

Background: Waist-to-height ratio (WHtR) has been shown to be a useful screening tool for metabolic syndrome and cardiovascular disease (CVD). We investigated the association of WHtR with CVD incidence by age group.
Methods: We conducted a 13.0-year cohort study of Japanese adults (2600 men and 2888 women) with no history of CVD. WHtR was calculated as waist circumference (cm) (WC) divided by height (cm). We stratified participants by sex and age group (30–49, 50–69, ≥70 years). Using the Cox proportional hazards model, we calculated hazard ratios (HRs) and 95% CIs for CVD in relation to WHtR quartile for participants aged 50 to 69 years and 70 years or older.
Results: Men aged 50 to 69 years in the highest quartile had significantly increased risks of CVD and coronary heart disease as compared with the lowest quartile; the HRs (95% CI) were 1.82 (1.13–2.92) and 2.42 (1.15–5.12), respectively. Women aged 50 to 69 years in the highest quartile had a significantly increased risk of stroke (HR, 2.43; 95% CI, 1.01–5.85). No significant results were observed in men or women aged 70 years or older. The likelihood ratio test showed that the predictive value of WHtR was greater than that of WC among men aged 50 to 69 years.
Conclusions: The association between WHtR and CVD risk differed among age groups. WHtR was useful in identifying middle-aged Japanese at higher risk of CVD and was a better predictor than WC of CVD, especially in men.

Key words: waist-to-height ratio; age difference; cardiovascular disease

INTRODUCTION

Obesity and central obesity are closely tied to metabolic risks.[1,2] Waist circumference (WC) is an index of central obesity[3] and is an important component in the diagnostic criteria for metabolic syndrome.[4] Several meta-analyses have reported an association of WC with cardiovascular disease (CVD) and mortality.[5,6] Recently, waist-to-height ratio (WHtR) was shown to be a useful global clinical screening tool for cardiometabolic risk and CVD.[7,8]

WHtR is easy to measure, and the cut-off point for WHtR is subject to less ethnic variation.[7,8] However, WHtR could differ among age groups because whole-body fat distribution and WC change considerably with age[9,10] and because height differs among generations.[11] It is thus important to consider age in assessing the association between WHtR and CVD risk, but few previous studies have done so.[12,13] Therefore, in this long-term prospective cohort study of a Japanese urban population, we investigated the effect of WHtR on CVD risk among participants classified by age group.

METHODS

Study population

The Suita Study is a prospective population-based cohort study of an urban area of Japan and was established in 1989. The details of this study have been described elsewhere.[14–16] Briefly, 6407 men and women aged 30 to 83 years underwent

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a baseline survey at the National Cerebral and Cardiovascular Center between September 1989 and March 1994. Among them, a total of 919 were excluded due to past history of CVD ($n = 208$), loss to follow-up ($n = 535$), and missing data ($n = 176$). The remaining 5488 participants (2600 men and 2888 women) were included in the analysis. This cohort study was approved by the Institutional Review Board of the National Cerebral and Cardiovascular Center.

Baseline examination

Blood samples were centrifuged immediately after collection, and a routine blood examination was performed, including measurement of serum levels of total cholesterol and glucose. About 96% of participants had fasted for at least 8 hours before the blood test. Well-trained physicians used a standard mercury sphygmomanometer to measure blood pressure in triplicate on the right arm after 5 minutes of rest. Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or use of antihypertensive agents. Diabetes was defined as a fasting plasma glucose level of at least 7.0 mmol/L (126 mg/dL), a non-fasting plasma glucose level of at least 11.1 mmol/L (200 mg/dL), or use of antidiabetic agents. Hypercholesterolemia was defined as a total cholesterol level of at least 5.7 mmol/L (220 mg/dL) or use of antihyperlipidemic agents. Participants were wearing light clothing during height and weight measurement. WC was measured at the umbilical level, with the participant in a standing position. WHtR was defined as WC (cm) divided by height (cm). Body mass index (BMI) was defined as weight (kg) divided by the height (m) squared. Public-health nurses obtained information on participants' smoking, drinking, and medical histories.

Endpoint determination

The endpoint determination has been previously reported.[14–16] The endpoints of the present study were (1) date of first coronary heart disease (CHD) or stroke event; (2) date of death; (3) date of departure from Suita city; or (4) December 31, 2007. The first step in the survey of CHD and stroke was checking the health status of all participants by means of clinical visits every 2 years and a yearly questionnaire (by mail or telephone). For the second step, in-hospital medical records of participants suspected of having CHD or stroke were reviewed by registered hospital physicians, who were blinded to the baseline information. In addition, to complete the survey, we also conducted a systematic search of death certificates to identify cases of fatal CHD and stroke. In Japan, all death certificates are forwarded to the Ministry of Health, Welfare, and Labour and coded for the National Vital Statistics. The criteria for myocardial infarction were based on the World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease projects.[17] In addition to myocardial infarction, we also evaluated coronary angioplasty, coronary artery bypass grafting, and sudden cardiac death, all of which were included in the definition of CHD. Stroke was defined according to criteria from the US National Survey of Stroke and was confirmed by computed tomography.[18] Classification of stroke was based on examination of computed tomography scans, magnetic resonance images, and autopsy findings.

Statistical analysis

To assess the association between age and WHtR, we analyzed mean WC, height, and WHtR according to age in men and women. Pearson product-moment correlation coefficients between height and waist were calculated by sex and age group (30–49, 50–69, ≥70 years). Participants were categorized based on quartiles of WHtR by sex and age group. To compare baseline characteristics among WHtR quartiles, analysis of variance was used for continuous variables and the χ^2 test was used for dichotomous and categorical variables.

The Cox proportional hazards model was used to investigate the association between WHtR and CVD risk only among participants aged 50 to 69 years and 70 years or older, because there were too few CVD cases (men: 17, women: 11) for statistical analysis among those aged 30 to 49 years. Interaction terms were added to the models to assess the interaction between age and WHtR quartile for the risk of CVD. Hazard ratios (HRs) and 95% CIs were computed, and the lowest quartile of WHtR was defined as the reference group. To adjust for confounding factors, we included age, smoking status (current, quit, or never), and drinking status (current, quit, or never) in the model. Cardiometabolic risk factors such as hypertension, diabetes, and hypercholesterolemia were not included in the model because central obesity is upstream in the "metabolic domino".[19] However, in sensitivity analysis, we adjusted for hypertension, diabetes, and hypercholesterolemia to confirm that WHtR was an independent risk factor. The same analysis was performed for WC. In addition, to further assess cut-off points for WHtR, the highest quartile was dichotomized by median WHtR (ie, upper Q4 and lower Q4), and HRs and 95% CIs were estimated. The likelihood ratio test was used to compare the predictive values of WHtR with WC, as follows. First, we calculated the −2 logarithm likelihood for the model including the confounding factors, age, smoking, and drinking status ($-2\,ln[L_c]$). Second, we calculated the −2 logarithm likelihood for the model including the confounding factors plus WHtR ($-2\,ln[L_{c+WHtR}]$). The difference, ie, $(-2\,ln[L_c] - (-2\,ln[L_{c+WHtR}]))$, had an approximate χ^2 distribution with 1 degree-of-freedom. The same analysis was performed for WC.

All P values were 2-tailed, and a P value less than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS (Version 20.0J; Japan IBM, Tokyo, Japan).

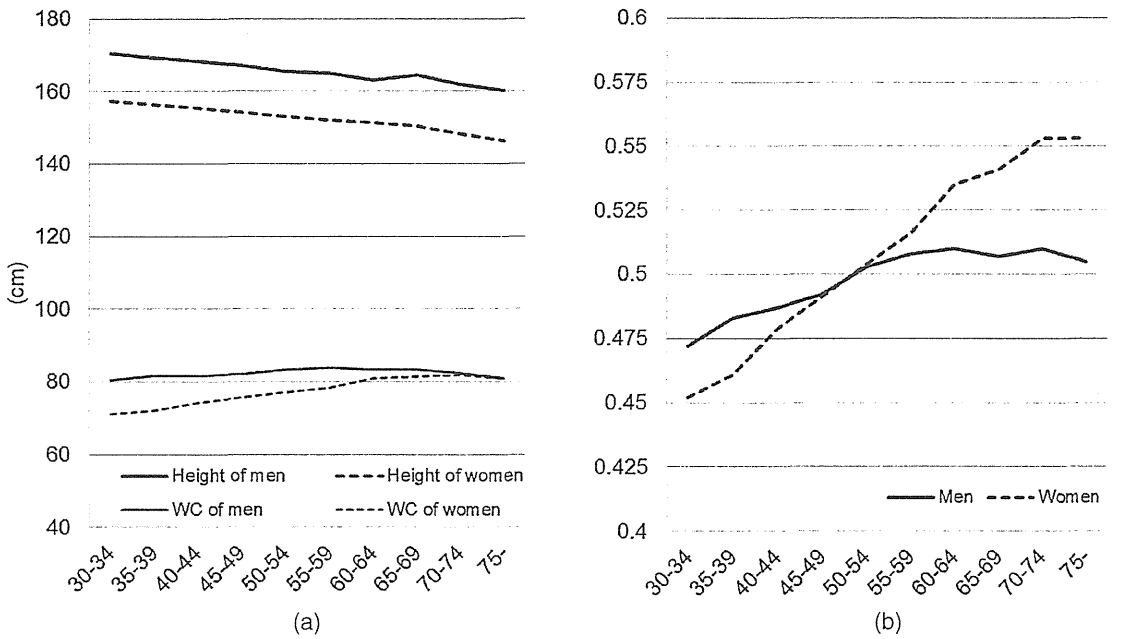

Figure. (a) Average WC (waist circumference), height, and (b) waist-to-height ratio according to age (The Suita Study, Japan)

RESULTS

During the follow-up period (mean, 13.0 years), 428 CVD events (184 CHD and 244 strokes) were observed. The Figure shows average WC, height, and WHtR by sex and age. WC in men increased up to age 50 years, remained almost unchanged from age 50 to 69 years, and decreased at age 70 years or older. WC in women younger than 75 years increased with advancing age and decreased in women aged 75 years or older, as compared with women aged 70 to 74 years. Height decreased with advancing age in both sexes. WHtR in men increased until approximately age 60 years. WHtR in women younger than 75 years increased with advancing age. The Pearson product-moment correlation coefficients (95% CI) between height and WC were 0.16 (0.09–0.22), 0.24 (0.19–0.30), and 0.13 (0.04–0.22) among men aged 30 to 49, 50 to 69, and 70 years or older, respectively, and 0.07 (0.01–0.13), 0.07 (0.02–0.13), 0.09 (−0.003–0.19) among women in the respective age groups.

Tables 1 and 2 summarize the baseline characteristics according to WHtR quartile (results among men and women aged 30–49 years are shown in eTable 1.) The prevalence of hypertension significantly differed by WHtR quartile, except among men aged 70 years or older. The prevalence of hypercholesterolemia and diabetes significantly differed by WHtR quartile among men and women aged 50 to 69 years.

Table 3 shows multivariable-adjusted HRs and 95% CIs for CVD and its subtypes according to WHtR quartile. A significant interaction was observed between age and WHtR for CVD among men (P for interaction = 0.02). Men aged 50 to 69 years in the highest quartile had significantly higher risks of CVD and CHD as compared with men in the lowest quartile; the HRs (95% CI) were 1.82 (1.13–2.92) and 2.42 (1.15–5.12), respectively. There were significant linear increases in the HRs for CVD, CHD, and ischemic stroke in men aged 50 to 69 years. After further adjustment for hypertension, diabetes, and hypercholesterolemia, the HRs (95% CI) were 1.46 (0.90–2.36) and 1.89 (0.89–4.03), respectively (eTable 3). Women aged 50 to 69 years in the highest quartile had a significantly higher risk of stroke than did those in the lowest quartile; the HR (95% CI) was 2.43 (1.01–5.85). There were significant linear increases in the HRs of CVD and stroke in women aged 50 to 69 years. After further adjustment for hypertension, diabetes, and hypercholesterolemia, the HR (95% CIs) was 2.06 (0.84–5.04) (eTable 3).

When men aged 50 to 69 years in the highest quartile were dichotomized by median WHtR (0.56), the HR (95% CI) for CVD was 1.37 (0.76–2.46) for those in the lower WHtR group and 2.34 (1.38–3.97) for those in the upper WHtR group (eTable 2). When women aged 70 years or older in the highest quartile were dichotomized by median WHtR (0.65), the HR for CVD was 1.42 (0.63–3.18) for those in the lower WHtR group and 2.33 (1.10–4.94) for those in the upper WHtR group. After adjustment for hypertension, diabetes, and hypercholesterolemia, the HRs in the upper WHtR decreased but remained significant, ie, 1.78 (1.04–3.05) among men aged 50 to 69 years and 2.16 (1.02–4.61) among women aged 70 years or older.

Table 4 shows the HRs and 95% CIs for CVD in relation to WC quartile. Among men aged 50 to 69 years in the highest quartile, the HR for CVD was 1.63 (1.03–2.59), although the HRs of CVD did not show a significant linear increase in this group. Among women aged 50 to 69 years, a significant linear