Morning and Evening Blood Pressures Are Associated With Intima-Media Thickness in a General Population  
— The Hisayama Study —

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Background: The association of morning and evening home blood pressures (HBPs) with carotid atherosclerosis has been uncertain in general populations, so we aimed to investigate it in a general Japanese population.

Methods and Results: We performed a cross-sectional survey of 2,856 community-dwelling individuals aged ≥40 years to examine the association of morning and evening HBPs with carotid mean intima-media thickness (IMT). The age- and sex-adjusted geometric averages of carotid mean IMT increased significantly with increasing morning HBP (optimal: 0.67 mm; normal: 0.69 mm; high normal: 0.72 mm; grade 1 hypertension: 0.74 mm; and grade 2+3 hypertension: 0.76 mm) and with increasing evening HBP (0.68 mm, 0.71 mm, 0.73 mm, 0.76 mm, and 0.78 mm, respectively) (both P for trend <0.001). These associations remained significant even after adjusting for potential confounding factors. Likewise, both isolated morning hypertension (morning HBP ≥135/85 mmHg and evening HBP <135/85 mmHg) and isolated evening hypertension (evening HBP ≥135/85 mmHg and morning HBP <135/85 mmHg) as well as sustained hypertension (both morning and evening HBP ≥135/85 mmHg) were significantly associated with thicker mean IMT.

Conclusions: Our findings suggested that both morning and evening HBPs were significantly associated with carotid atherosclerosis in this general Japanese population.

Key Words: Atherosclerosis; Epidemiology; Home blood pressure; Intima-media thickness

Measuring home blood pressure (HBP) is becoming common for hypertensive patients in clinical practice. HBP measurement can reduce observer biases and white-coat effects, and is useful to assess the duration of the effectiveness of antihypertensive medication and to improve adherence to antihypertensive treatment.1-5 In addition, HBP has been reported to be more sensitive for risk assessment of target organ damage than casual blood pressure (BP) measured at the clinic or health examination.6-9 BP has a circadian rhythm caused by neuroendocrine factors.10,11 Circadian rhythm is also affected by antihypertensive medication, and lifestyle factors.12-14 Therefore, it is important to measure HBP on different occasions. Several recent guidelines or scientific statements for hypertension management have recommended measuring HBP at least twice daily, namely, in the morning and in the evening.3-5,15 Most clinical studies have evaluated the association of HBP with target organ damage using average values of either morning and evening HBPs16-18 or only morning HBP.19,20 Meanwhile, there are limited numbers of studies addressing the influence of morning HBP and evening HBP separately on atherosclerotic disease in general populations, as the clinical significance of morning HBP and evening HBP may be different.

The purpose of the present study was to investigate the association of HBP levels in the morning and evening with carotid atherosclerosis in a general Japanese population.

Methods

Study Population
The Hisayama Study is a population-based observational study for cardiovascular disease, which was established in 1961 in the town of Hisayama, a suburb of the Fukuoka
metropolitan area on Kyushu Island, Japan. In 2007 and 2008, a total of 3,384 residents of Hisayama aged 40 years or older participated in health examinations (participation rate among the total population of this age group: 78.2%). After the exclusion of 8 participants who refused to participate in the epidemiological study, 453 subjects without HBP measurements for more than 3 days, and 67 without information on carotid ultrasonography, a total of 2,856 subjects (1,234 men and 1,622 women) were enrolled in the present study.

**Home and Clinical BP Measurements**
The procedure for the measurement of HBP was described in detail in our previous report and followed the Japanese guidelines for self-monitoring of BP at home. HBP was measured using an automatic device (HEM-7080IC; Omron Healthcare Co., Ltd.) based on the validated cuff oscillometric method. This method uses the identical components and BP-determining algorithm as another device, HEM-705IT, which was previously validated and satisfied the criteria of the British Hypertension Society protocol.
The subjects were instructed to measure their HBP 3 times every morning before breakfast within 1 h of wakening and 3 times every evening before going to bed after more than 5 min of rest while seated, for 4 weeks. Subjects on antihypertensive medication were instructed to measure their HBP before taking their medication. Morning and evening HBPs were defined as the mean value of daily averages of HBP in the morning and in the evening, respectively. In addition, clinical BP was measured 3 times at the health examination using an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare Co., Ltd.), and the mean of 3 measurements was used for the analysis.

**Classification of Groups Based on HBP**
HBP was categorized by the measured values, regardless of antihypertensive medication. In the present analysis, we defined HBP from the European Society of Hypertension and European Society of Cardiology (ESH-ESC) criteria minus 5 mmHg, because HBP of 135/85 mmHg is considered to be equivalent to clinical BP of 140/90 mmHg. For each morning and evening HBP, values were classified into 5 categories as follows: optimal (HBP <115/75 mmHg); normal (HBP 115–124/75–79 mmHg); high normal (HBP 125–134/80–84 mmHg); grade 1 hypertension (HBP 135–145/85–94 mmHg); grade 2+3 hypertension (HBP ≥155/95 mmHg). The subjects were also divided into 4 groups according to the combination of morning and evening HBP: normotension (morning HBP <135/85 mmHg and evening HBP <135/85 mmHg), isolated morning hypertension (morning HBP ≥135/85 mmHg and evening HBP <135/85 mmHg), isolated evening hypertension (morning HBP <135/85 mmHg and evening HBP ≥135/85 mmHg), and sustained hypertension (morning HBP ≥135/85 mmHg and evening HBP ≥135/85 mmHg). Furthermore, for the sensitivity analysis, the subjects were re-categorized into 4 groups using a different cutoff value of 126/76 mmHg for evening HBP, which corresponded to morning HBP of 135/85 mmHg in a linear regression analysis between morning and evening HBP ([Figure S1](#)), in order to correct for the imbalance in the number of subjects with isolated evening hypertension.

**Carotid Ultrasonography**
Carotid ultrasonography was performed using a real-time, B-mode ultrasound imaging unit (Toshiba Sonolayer SSA-250A; Toshiba, Tokyo, Japan) with a 7.5-MHz annular array probe as described previously. Mean intima-media thickness (IMT) was measured using the long-axis views of the right and left common carotid arteries. We examined the far wall of each common carotid artery in the region that was 20 mm proximal to the origin of the bulb, and automatically calculated the average IMT as the mean value of IMT measurements on each side using a computer-assisted measurement system (Intimascoppe; Media Cross Co., Ltd, Tokyo, Japan). Mean IMT was defined as the mean of the average IMT of the left and right sides. Maximum IMT in the observation-possible areas of the left and right common carotid arteries, bulbs, and internal carotid arteries was measured manually. Carotid wall thickening was defined as a maximum IMT >1.0 mm. Moreover, advanced carotid wall thickening was determined as a maximum IMT >1.5 mm.

**Other Risk Factors**
At the health examination, each participant completed a self-administered questionnaire covering medical history, antihypertensive medication, lipid-lowering medication, smoking habit, alcohol intake, and regular exercise. Smoking habit and alcohol intake were classified as either current use or not. Subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up the regular exercise group. Body height and weight were measured in light clothing without shoes, and the body mass index (BMI: kg/m²) was calculated. Serum total and high-density lipoprotein (HDL) cholesterol levels were determined enzymatically. Blood glucose levels were measured by the hexokinase method. Diabetes mellitus was determined as fasting glucose level ≥7.0 mmol/L, postprandial or 2-h postload glucose level ≥11.1 mmol/L, or use of antidiabetic medication.

**Statistical Analysis**
The correlation between morning or evening HBP and clinical BP was evaluated using Pearson's correlation coefficient. The differences in the mean values of continuous variables or frequencies of categorical variables across the morning or evening HBP categories were examined using an analysis of variance or a logistic regression model. Mean and maximum IMT were transformed into logarithm to improve skewness, and geometrical means were reported by back transformation. The adjusted geometric averages of the mean and maximum IMT across the morning or evening HBP categories were assessed using an analysis of covariance. The age- and sex-adjusted prevalence of carotid wall thickening was calculated using the direct method, using the distributions of age and sex in the study population as a reference population. The age- and sex-adjusted or multivariable-adjusted odds ratio and its 95% confidence interval (CI) for the presence of carotid wall thickening were estimated using a multivariable logistic regression model. The subgroup analyses by antihypertensive medication status and by drinking status were conducted, and the heterogeneity in the effects of BP levels on outcomes between the subgroups was estimated by adding interaction terms to the relevant statistical model. The heterogeneity in the association with carotid atherosclerosis between morning and evening HBPs was tested by adding an interaction term in the relevant statistical model with generalized estimating equations in order to account for
repeated measurements of morning and evening HBP for each individual. All statistical analyses were performed using the SAS program package version 9.3 (SAS Institute Inc., Cary, NC, USA). P values <0.05 were considered statistically significant.

Ethical Considerations
The study protocol was approved by Kyushu University Institutional Review Board for Clinical Research, and the procedures followed were in accordance with national guidelines. Written informed consent was given by all the subjects.

Results
For the total subjects, the mean value ± standard deviation of morning HBP, evening HBP, and clinical BP at the health examination was 132±18/77±10 mmHg, 124±16/70±9 mmHg, and 131±19/79±11 mmHg, respectively. The mean values of morning HBP were significantly higher than those of evening HBP (both P<0.001). Both morning and evening HBP were significantly correlated with clinical BP (Pearson’s correlation coefficient: 0.64 between morning systolic HBP and clinical systolic BP; 0.62 for evening systolic HBP and clinical systolic BP; both P<0.001).

Table 1. Clinical Characteristics of Participants According to Morning HBP Levels

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Men, %</th>
<th>Morning home systolic BP, mmHg</th>
<th>Morning home diastolic BP, mmHg</th>
<th>Evening home systolic BP, mmHg</th>
<th>Evening home diastolic BP, mmHg</th>
<th>Antihypertensive medication, %</th>
<th>Diabetes mellitus, %</th>
<th>Total cholesterol, mmol/L</th>
<th>HDL-cholesterol, mmol/L</th>
<th>Lipid-lowering medication, %</th>
<th>Body mass index, kg/m²</th>
<th>Current smoking, %</th>
<th>Current drinking, %</th>
<th>Regular exercise, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>55±10</td>
<td>25.0</td>
<td>107±3</td>
<td>66±5</td>
<td>105±7</td>
<td>62±6</td>
<td>4.1</td>
<td>4.5</td>
<td>5.4±0.9</td>
<td>1.9±0.5</td>
<td>7.6</td>
<td>21.3±2.7</td>
<td>18.5</td>
<td>44.1</td>
<td>9.2</td>
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<tr>
<td>61±11</td>
<td>39.5</td>
<td>119±3</td>
<td>72±5</td>
<td>115±8</td>
<td>67±6</td>
<td>12.7</td>
<td>12.0</td>
<td>5.5±1.0</td>
<td>1.8±0.4</td>
<td>9.8</td>
<td>22.5±3.2</td>
<td>16.6</td>
<td>46.3</td>
<td>13.3</td>
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<tr>
<td>63±11</td>
<td>45.8</td>
<td>129±4</td>
<td>77±6</td>
<td>123±8</td>
<td>70±7</td>
<td>29.5</td>
<td>16.9</td>
<td>5.5±0.9</td>
<td>1.7±0.4</td>
<td>17.4</td>
<td>17.4±3.4</td>
<td>18.6</td>
<td>48.4</td>
<td>11.6</td>
</tr>
<tr>
<td>66±11</td>
<td>49.8</td>
<td>142±7</td>
<td>82±7</td>
<td>131±11</td>
<td>73±8</td>
<td>45.1</td>
<td>22.6</td>
<td>5.4±0.9</td>
<td>1.7±0.4</td>
<td>20.9</td>
<td>23.3±3.4</td>
<td>18.9</td>
<td>51.2</td>
<td>14.9</td>
</tr>
<tr>
<td>69±12</td>
<td>52.1</td>
<td>162±11</td>
<td>89±11</td>
<td>147±15</td>
<td>78±11</td>
<td>57.3</td>
<td>25.3</td>
<td>5.4±0.9</td>
<td>1.7±0.5</td>
<td>18.9</td>
<td>23.8±3.5</td>
<td>22.6</td>
<td>54.1</td>
<td>12.0</td>
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</table>

All values are given as the mean ± SD or as a percentage. HBP, home blood pressure; HDL, high-density lipoprotein.

Table 2 demonstrates geometric averages of mean and maximum IMT according to the levels of morning or evening HBP. The age- and sex-adjusted geometric average of mean IMT increased significantly and progressively with increasing morning HBP levels (optimal: 0.67 mm; normal: 0.69 mm; high normal: 0.72 mm; grade 1 hypertension: 0.74 mm; grade 2+3 hypertension: 0.76 mm; P<0.001 for trend) or evening HBP levels (optimal: 0.68 mm; normal: 0.71 mm; high normal: 0.73 mm; grade 1 hypertension: 0.76 mm; grade 2+3 hypertension: 0.78 mm; P<0.001 for trend). These associations were substantially unchanged even after adjustment for other cardiovascular risk factors, namely, antihypertensive medication, diabetes, total and HDL cholesterol, lipid-lowering medication, BMI, current smoking, current drinking, and regular exercise. When we examined the association of each morning and evening HBP with the geometric average of maximum IMT, a significant linear relation was observed between morning or evening HBP and maximum IMT. The associations of evening HBP with mean and maximum IMT were stronger than those of morning HBP (both P for heterogeneity <0.05).

We also estimated the prevalence and odds ratios for carotid wall thickening (defined as maximum IMT >1.0 mm) according to each HBP level (Table 3). The age- and sex-adjusted prevalence of carotid wall thickening was significantly increased in subjects with higher HBP levels compared with those with optimal HBP levels in the morning. The multivariable-adjusted odds ratios (95% CIs) for carotid wall thickening were 0.92 (0.69–1.23) for normal, 1.33 (1.00–1.76) for high normal, 1.46 (1.11–1.92) for grade 1 hypertension, and 1.67 (1.19–2.35) for grade 2+3 hypertension, compared with the optimal level as a reference (P for trend <0.001). A significant association was also observed for evening HBP levels (multivariable-adjusted odds ratio [95% CI]: 1.37 [1.09–1.72], 1.46 [1.13–1.87], 1.79 [1.37–2.35], and 3.14 [1.92–5.33], respectively; P<0.001 for trend), indicating that both morning and evening HBP levels were significantly associated with carotid wall thickening independent of other cardiovascular risk factors.
Carotid wall thickening was defined as maximum IMT >1.0 mm. *P<0.05 vs optimal level. †Adjusted for age, sex, antihypertensive medication, diabetes, total cholesterol, HDL cholesterol, lipid-lowering medication, body mass index, current smoking, current drinking, and regular exercise. ‡Heterogeneity for multivariable-adjusted geometric averages. CI, confidence interval; IMT, intima-media thickness. Other abbreviations as in Table 1.

### Table 2. Geometric Averages of Mean and Maximum IMT According to Morning or Evening HBP Levels

<table>
<thead>
<tr>
<th>HBP level</th>
<th>Optimal</th>
<th>Normal</th>
<th>High normal</th>
<th>Grade 1 hypertension</th>
<th>Grade 2+3 hypertension</th>
<th>P for trend</th>
<th>P for heterogeneity ‡</th>
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<tbody>
<tr>
<td><strong>Mean IMT</strong></td>
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<td>Morning HBP</td>
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<tr>
<td>No. of participants</td>
<td>518</td>
<td>458</td>
<td>587</td>
<td>891</td>
<td>407</td>
<td></td>
<td></td>
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<tr>
<td>Age- and sex-adjusted geometric average (95% CI)</td>
<td>0.67 (0.66–0.68)</td>
<td>0.69 (0.69–0.70)</td>
<td>0.72 (0.71–0.73)</td>
<td>0.74 (0.73–0.74)</td>
<td>0.76 (0.75–0.77)</td>
<td>&lt;0.001</td>
<td>0.005</td>
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<tr>
<td>Multivariable-adjusted geometric average (95% CI)†</td>
<td>0.68 (0.67–0.69)</td>
<td>0.70 (0.69–0.71)</td>
<td>0.72 (0.71–0.73)</td>
<td>0.74 (0.73–0.74)</td>
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<td><strong>Evening HBP</strong></td>
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<tr>
<td>No. of participants</td>
<td>845</td>
<td>725</td>
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<td>Multivariable-adjusted geometric average (95% CI)†</td>
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<td><strong>Maximum IMT</strong></td>
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<tr>
<td>Age- and sex-adjusted geometric average (95% CI)</td>
<td>1.14 (1.11–1.18)</td>
<td>1.13 (1.09–1.16)</td>
<td>1.20 (1.17–1.24)</td>
<td>1.25 (1.22–1.28)</td>
<td>1.31 (1.26–1.35)</td>
<td>&lt;0.001</td>
<td>0.04</td>
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<td>Multivariable-adjusted geometric average (95% CI)†</td>
<td>1.15 (1.11–1.19)</td>
<td>1.14 (1.10–1.18)</td>
<td>1.20 (1.17–1.23)</td>
<td>1.25 (1.22–1.28)</td>
<td>1.29 (1.25–1.34)</td>
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<td>1.22 (1.18–1.25)</td>
<td>1.30 (1.26–1.34)</td>
<td>1.40 (1.32–1.49)</td>
<td>&lt;0.001</td>
<td>0.001</td>
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<td>1.19 (1.16–1.22)</td>
<td>1.22 (1.19–1.26)</td>
<td>1.28 (1.25–1.32)</td>
<td>1.38 (1.30–1.47)</td>
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Evening HBP was more strongly associated with carotid wall thickening than was morning HBP (P for heterogeneity=0.02). Increased morning and evening HBP levels were also significantly associated with advanced carotid wall thickening defined as maximum IMT >1.5 mm (both P for trend <0.001), but no evidence of heterogeneity between morning and evening HBPs was observed (P for heterogeneity=0.55) (Table S2).
We conducted subgroup analyses stratified by the status of antihypertensive medication (Tables S3-S4). The multivariable-adjusted geometric averages of the mean and maximum IMT were higher in subjects with antihypertensive medication than in those without, but increased significantly and linearly with increasing morning or evening HBP levels both in the subgroups with and without antihypertensive medication (all P for heterogeneity >0.10). We also performed subgroup analyses stratified by drinking status (Tables S5-S6). Regardless of drinking status, there were significant associations of morning and evening HBP levels with the geometric averages of mean and maximum IMT, without any evidence of heterogeneity between subgroups (all P for heterogeneity >0.05).

Next, we examined geometric averages of mean and maximum IMT according to 4 BP groups: normotension, isolated morning hypertension, isolated evening hypertension, and sustained hypertension (Figure, Table S7). The multivariable-adjusted geometric average of the mean IMT increased significantly in subjects with isolated morning hypertension, isolated evening hypertension, and sustained hypertension compared with normotensive subjects. For maximum IMT, similar associations were observed; however, there was no significant increase in isolated evening hypertension, probably because of the relative small number of subjects with isolated evening hypertension. In the subgroup analyses stratified by antihypertensive medication status, there was no evidence of heterogeneity in the association of the 4 BP groups with the mean and maximum IMT (Table S8). When we combined the subjects with isolated morning hypertension and isolated evening hypertension, subjects with either isolated morning or evening hypertension had a significantly higher mean and maximum IMT than those with normotension (Table S9).

In addition, we performed a sensitivity analysis after changing the cutoff value of evening HBP from 135/75 to 126/76 mmHg to correct for the imbalance in the number of subjects with isolated evening hypertension. As a consequence, the average mean IMT and maximum IMT in subjects with isolated evening hypertension became lower, but the findings were not altered substantially (Table S10). There was also no significant heterogeneity in the association between antihypertensive medication status after changing the cutoff value for evening HBP (both P for heterogeneity >0.05) (Table S11).

**Discussion**

The present study demonstrated that increased morning and evening HBP was significantly associated with the presence of carotid atherosclerosis in a general Japanese population. It is noteworthy that these associations were unchanged by the use of antihypertensive medication or drinking status. The findings from this study are expected to show the importance of BP control in both the morning and the evening.

A few epidemiological studies in Japan and Finland have provided consistent findings that higher HBP is significantly associated with greater IMT despite differences in study populations. This suggests that mean HBP is closely related to carotid atherosclerosis. However, there are limited studies addressing the association of morning and evening HBP separately with clinical or subclinical cardiovascular disease, especially in general populations. The J-HOP Study, which evaluated outpatients with at least 1 cardiovascular risk factor, showed that higher morning and evening HBP levels were significantly linked with greater IMT, but the significant association remained only for morning HBP after adjusting for confounding factors. In the present study, evening HBP as well as morning HBP was clearly associated with carotid wall thickening. The discrepancy in the findings between the studies may be attributable to the difference in study populations. Patients with cardiovascular risk factors are more likely to have increased variability in evening BP, which tends towards a non-significant association, caused by insufficient duration of the action of antihypertensive medications and impair...
ment of baroreflex or autonomic dysfunction than general populations. With regard to clinical cardiovascular events, 2 population-based prospective cohort studies have shown that both morning HBP and evening HBP have significant and equal predictive abilities for future stroke or cardiovascular events. All this evidence indicates the importance of assessing both morning and evening BP to prevent future risks of cardiovascular disease.

The present study demonstrated that morning hypertension, which was hypertension observed in the morning only, was significantly linked with greater IMT in this general population. Several studies conducted in hypertensive patients have reported that morning hypertension has a strong association with target organ damage and cardiovascular events. However, there are few previous studies that have examined this issue in general populations. Morning hypertension is considered to reflect inadequate BP control during night (e.g., via insufficient duration of action of antihypertensive drugs) and increased activities of neurohumoral factors, such as the sympathetic nervous system and the renin-angiotensin system in the morning, which promotes progression of arterial damage. Therefore, controlling morning BP is important for the prevention of atherosclerotic disease.

Evening BP has greater variability, affected more by antihypertensive medications, daily customs (e.g., bathing and evening drink) and activities than morning BP. Therefore, morning BP may be considered as a more useful indicator of target organ disease than evening BP in clinical practice. In the current analysis, however, evening hypertension, defined as hypertension in the evening only, was clearly associated with mean IMT, just as with morning hypertension. No prior population-based investigation has evaluated this issue for carotid atherosclerosis to date. A prospective study of a general Japanese population supportively demonstrated that subjects with evening hypertension tended towards having a higher risk of stroke compared with normotensive subjects, though this association was not statistically significant. This finding, together with ours, suggests that higher evening BP itself contributes to the atherosclerotic process. Moreover, in the present study, evening HBP showed a significantly greater association with carotid atherosclerosis than morning HBP, a finding that was probably attributable to the fact that the morning and evening HBP levels were higher in each of the high normal and hypertension categories determined on evening HBP than in the corresponding categories defined on morning HBP (Table 1.S1). This may suggest that evening HBP is a better predictor of atherosclerosis than morning HBP, but the clinical significance of evening hypertension remains to be investigated.

Study Limitations

First, we were not able to determine a causal association of morning and evening HBP with IMT because of the cross-sectional study design. Second, several laboratory technicians measured maximum IMT manually, therefore there is the possibility that the association between HBP and maximum IMT observed in the present study was weaker than the true association. However, this limitation is unlikely to alter the conclusions of the present analysis, because similar results were obtained for mean IMT, which was estimated automatically using a computer-assisted measurement system. Finally, we could not exclude the possibility that residual confoundings still exist in the association.

Conclusions

To the best of our knowledge, this is the first report to demonstrate the association of both morning and evening HBP with IMT in a general population. Both morning and evening HBP provided equally valuable information for target organ damage, therefore physicians should use both HBP measurements as indicators in the management of hypertension. Further longitudinal study addressing the influence of morning and evening HBPs on cardiovascular risk is warranted to elucidate this issue.

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Conflict of Interest / Disclosures

None.

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