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Predictive power of isolated high home systolic blood pressure for cardiovascular outcomes in individuals with type 2 diabetes mellitus: KAMOGAWA-HBP study

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Abstract

Aims/Introduction: Isolated high home systolic blood pressure (IHHSBP) is a risk for cardiovascular disease (CVD). However, no study has shown an association between IHHSBP and CVD in diabetes. We examined the association between IHHSBP and CVD in type 2 diabetes.

Materials and Methods: This retrospective cohort study included 1082 individuals with type 2 diabetes, aged 20 to 90 years, without a history of macrovascular complications. Home blood pressure (HBP) was measured three times every morning and evening for 14 days. Cox proportional hazards models were used to examine the relationship between IHHSBP and CVD incidence.

Results: With the normal HBP group as the reference, the adjusted hazard ratio (HR) (95% confidence interval [CI]) for CVD was 1.58 (1.02–2.43) in the IHHSBP group. Correcting for antihypertensive medication use did not change HR. Based on sex, the adjusted HR (95% CI) for CVD was 1.25 (0.74–2.13) in males and 2.28 (1.01–5.15) in females.

Conclusions: In individuals with type 2 diabetes, those with IHHSBP had a higher HR for cardiovascular disease than those with normal HBP. But, Isolated high home diastolic blood pressure and high HBP were not. The association between IHHSBP and CVD was stronger in females than in males.

Keywords

Cardiovascular diseases, diabetes mellitus, type 2, home blood pressure measurement, isolated high home systolic blood pressure, KAMOGAWA-HBP study, multicenter study

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Key messages

- IHHSBP is associated with a higher CVD risk
- Age and sex play a role in this increased risk
- The association between IHHSBP and CVD was stronger in females than in males
- Future work evaluating the effects of reducing systolic blood pressure in patients with IHHSBP and type 2 diabetes is warranted.

Introduction

According to the International Diabetes Federation, one in 10 adults worldwide has diabetes, and the global diabetes population is estimated to reach 643 million by 2030.[1] Diabetes caused 6.7 million deaths in 2021,[1] most likely owing to diabetic vascular complications. Diabetes is a leading cause of atherosclerosis, and the progression of vascular complications increases mortality and decreases quality of life.[2]

Persons with diabetes mellitus have more advanced atherosclerosis, higher systolic blood pressure (SBP), lower diastolic blood pressure DBP, and higher isolated high systolic blood pressure (IHSBP) than people without diabetes.[3] Additionally, IHSBP is a risk factor for cardiovascular disease (CVD).[4]

Home blood pressure (HBP) monitoring is more reproducible than clinic blood pressure (BP) monitoring and can capture small intraday changes in BP.[5] The usefulness of HBP monitoring has been recognized because of its strong association with the prevention of organ damage.[6]

We have reported the association between IHSBP assessed from isolated high home systolic blood pressure (IHHSBP) and nephropathy in persons with diabetes mellitus using the KAMOGAWA-HBP cohort.[7] A previous report has indicated that IHHSBP is a risk factor for CVD.[8] However, no study has reported an association between IHHSBP and CVD in persons with diabetes mellitus. We examined the association between IHHSBP and CVD using the same cohort.

Materials and Methods

Study design

This study used the database registered from March 2008 in the KAMOGAWA-HBP study, a cohort study of HBP monitoring in persons with diabetes mellitus.[9] We included persons with type 2 diabetes, aged 20 to 90 years, who visited the outpatient diabetic clinic of Kyoto Prefectural University of Medicine and four other general hospitals. Follow-up data were obtained until December 2018.

The inclusion criteria did not include specific BP levels. We excluded individuals who failed to take HBP measurements or had a clinical history of CVD, cerebrovascular disease, or arteriosclerosis obliterans. Type 2 diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association.[10] Informed consent was obtained from eligible people. The study was approved by the Research Ethics Review Committee (RBMR-E-349) and conducted according to the Declaration of Helsinki.

Blood pressure measurement

Individuals were lent an automatic brachial sphygmomanometer (HEM-7080IC; Omron Healthcare Co. Ltd, Kyoto, Japan) and instructed to measure their BP three times every morning (within 1 h after waking, after urinating, and before taking medications) and evening (at least 1 h after dinner) for 14 days. The measurements must be taken after at least 2 min of rest and at least 1 min apart in a sitting position. The average of three morning and three evening measurements was calculated per day, and the level of HBP was calculated from the average of 14 daily averages. HEM-70801C had the same components and BP determination algorithm as HEM-705IT, which was previously used for accuracy verification. Additionally, HEM-70801C satisfied the British Hypertension Society Protocol.[11] Clinic BP was calculated as the mean from three readings using the HEM-70801C device, when we rent the device. Electronic readouts from this device were used for analysis.

According to the hypertension diagnostic criteria in JSH 2019, the individuals were divided into four groups[12]: normal HBP group with good HBP, including both SBP and DBP (SBP < 135 mmHg and DBP < 85 mmHg); IHHSBP group with high SBP only (SBP ≥ 135 mmHg and DBP < 85 mmHg); isolated high home DBP (IHHDBP) group with high DBP only (SBP < 135 mmHg and DBP ≥ 85 mmHg); and high HBP group with both high SBP and DBP (SBP ≥ 135 mmHg and DBP ≥ 85 mmHg).

Data collection

Biochemical data for blood glucose, total cholesterol, triglycerides (TG), and creatinine were obtained from peripheral blood at study entry. Data on sex, age, duration of diabetes, body mass index (BMI), smoking, alcohol consumption, diabetes medications, antihypertensive medications, and incidence of cardiovascular events were collected from medical records and questionnaires. The primary endpoint was coded according to the ICD10, International Classification of Diseases, 10th edition.

The composite cardiovascular endpoint was defined based on patient history and physical examination and included cardiovascular death (ICD-10 codes I00 to I99),

angina pectoris (I20), non-fatal myocardial infarction (I21), transient ischemic attack (G45), heart failure (I50), non-fatal stroke (I60, I61, and I63), and occlusive atherosclerosis (I73). Outcome assessment was determined to be the first event in an individual only.

For diabetic nephropathy, albuminuria was defined as a urinary albumin-creatinine ratio ≥30 mg/gCr on two out of three occasions, obtained from urine samples taken in the morning. For diabetic retinopathy, we referred the patient to an ophthalmologist, who diagnosed the patient with retinopathy based on fundus examination findings. For diabetic neuropathy, we used the simplified diagnostic criteria for diabetic neuropathy.[13] PWV (pulse wave velocity) is a test to determine the degree of arteriosclerosis. Blood pressure cuffs were placed around both upper arms and ankles, and the higher PWV value of the left and right was used in the present study.

Statistical analysis

The patient background is presented as medians (interquartile ranges; IQRs) or numerical values (proportions). ANOVA and χ^2 were used for comparison among the four subgroups. Using Cox proportional hazards models and with the normal HBP group as the reference, we examined the relationship among IHHSBP, IHHDBP, and high HBP and incidence of cardiovascular events in type 2 diabetes mellitus. Model 2 was adjusted for factors that may influence cardiovascular events (sex, duration of diabetes, BMI, HbA1c, TG, serum creatinine, and smoking status). Model 3 was adjusted for the variables in model 2 and intake of antihypertensive medications. Statistical analyses were performed using JMP 14.2 (SAS Institute Inc., Cary, NC, USA).

Results

In total, 1526 persons with type 2 diabetes mellitus were included in this study. Owing to insufficient home and clinic BP data, 21 and 3 individuals were excluded, respectively. Additionally, 391 individuals with a history of cardiovascular events and 29 individuals lost to follow-up were excluded (Figure 1). The individuals were followed up for a median of 7.0 (interquartile 4.0–9.0) years, with a maximum follow-up of 10.0 years. In total, 119 patients developed new cardiovascular disease; five patients died of cardiovascular-related diseases (4.2%); as a detail, 42 patients developed angina pectoris (35.3%); 17 developed non-fatal myocardial infarction (14.3%); two developed transient ischemic attack (1.7%); two developed heart failure (1.7%); 37 developed non-fatal stroke (31.1%); and 11 developed occlusive atherosclerosis (9.2%).

Overall, we included 1082 individuals (574 males (53.0%) and 508 females (47.0%)). The mean age, duration of diabetes, BMI, and HbA1c level were 65.0 years, 9.0 years, 23.4 kg/m^2, and 6.7%, respectively. Moreover, the mean BP measurements in the morning and evening were 133.7/74.4 and 128.8/69.3 mmHg, respectively. The median number of days of morning and evening BP measurements per patient during the 14 consecutive days was 13.0 (IQR: 12.0–14.0) and 12.0 (IQR: 12.0–14.0), respectively. Age and duration of diabetes were significantly higher in the IHHSBP group than in the normal HBP group. BMI was significantly higher in the isolated high HDBP and high HBP groups than in the normal HBP group. HbA1c, triglycerides, logarithm of urinary albumin excretion, and clinical systolic BP were significantly higher in the IHHSBP and HBP groups than in the normal HBP group. Clinical

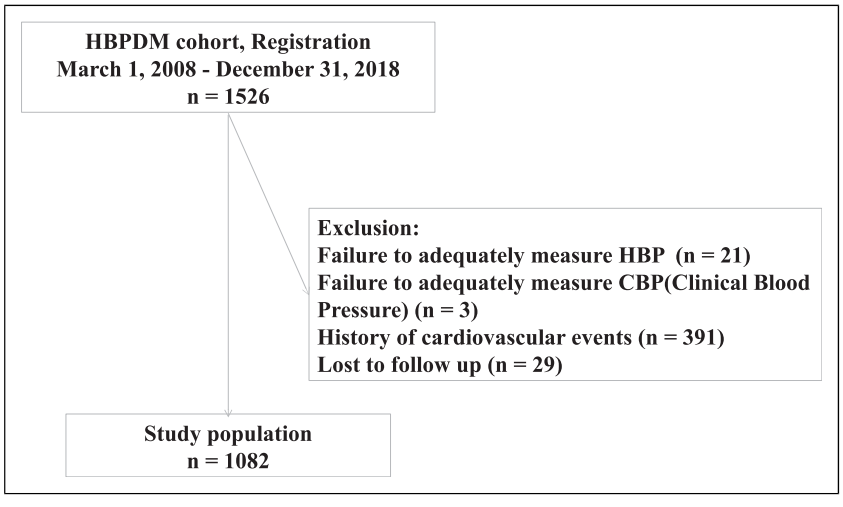

Figure 1. Flow diagram for the KAMOGAWA-HBP cohort.

diastolic BP and morning and evening systolic and diastolic BP were significantly higher in the IHHSBP, isolated high HDBP, and high HBP groups than in the normal HBP group. First onset of cardiovascular events was significantly higher in the IHHSBP group than in the normal HBP group (Table 1).

In Model 1, with the normal HBP group as the reference, the hazard ratio (HR) (95% confidence interval [CI]) for cardiovascular events was 1.77 (1.19–2.63) in the IHHSBP, 0.42 (0.06–3.02) in the IHHDBP group, and 1.50 (0.89–2.54) in the high HBP group (Table 2). In Model 2, with the normal HBP group as the reference, the HR (95% CI) for cardiovascular events was 1.58 (1.02–2.43) in the IHHSBP group, 0.37 (0.05–2.95) in the IHHDBP group, and 1.17 (0.63–2.15) in the high HBP group. In Model 3, with the normal HBP group as the reference, the HR (95% CI) for cardiovascular events was 1.49 (0.96–2.31) in the IHHSBP group, 0.44 (0.06–3.24) in the IHHDBP group, and 1.10 (0.60–2.03) in the high HBP group.

According to age, the individuals were redivided into two groups: the 65 years and older group and the younger than 65 years group. The HRs for cardiovascular events were compared between the groups. A multivariate cox proportional hazards analysis was performed. In the 65 years and older group, the HR (95% CI) for cardiovascular events was 1.46 (0.91–2.35) in the IHHSBP group compared with the normal HBP group. After adjustment for sex, duration of diabetes, BMI, HbA1c, TG, serum creatinine, and smoking status, the HR (95% CI) was 1.25 (0.75–2.08). After further adjustment for intake of antihypertensive medications, the HR (95% CI) was 1.23 (0.74–2.05). In contrast, in the younger than 65 years group, the HR (95% CI) for cardiovascular events was 1.61 (0.73–3.58) in the IHHSBP group compared with the normal HBP group. After the first and second adjustments, the HRs (95% CI) were 1.49 (0.61–3.69) and 1.36 (0.55–3.37), respectively (Supplementary Table 1).

The HRs for cardiovascular events were also examined according to sex. The HR (95% CI) for cardiovascular events was 1.64 (1.02–2.63) in males from the IHHSBP group compared with males from the normal HBP group. After adjustment for duration of diabetes, BMI, HbA1c, TG, serum creatinine, and smoking status, the HR (95% CI) was 1.30 (0.77–2.20). After further adjustment for intake of antihypertensive medications, the HR (95% CI) was 1.25 (0.74–2.13). The HR (95% CI) for cardiovascular events was 2.30 (1.10–4.81) in females from the IHHSBP group compared with females from the normal HBP group. After adjustment for duration of diabetes, BMI, HbA1c, TG, serum creatinine, and smoking status, the HR (95% CI) was 2.43 (1.07–5.50). After further adjustment for intake of antihypertensive medications, the HR (95% CI) was 2.28 (1.01–5.15) (Supplementary Table 2).

Discussion

IHHSBP strongly influenced cardiovascular events in persons with type 2 diabetes mellitus but without CVD. Our most significant finding was that the IHHSBP group had an HR (95% CI) of 1.77 (1.19–2.63) for cardiovascular events compared with the normal HBP group. The IHHSBP group was more likely to have a cardiovascular event than the high HBP group. Further adjustment for factors that may influence cardiovascular events (sex, duration of diabetes, BMI, HbA1c, TG, smoking status, and intake of antihypertensive medication) did not change the results. The HRs of the IHHSBP group against the normal HBP group for individuals without and with antihypertensive medication were 1.15 (0.52–2.53) and 1.75 (1.02–3.03), respectively. The group taking antihypertensive medication had higher BP than the group not taking antihypertensive medication. The group taking antihypertensive medication had more advanced arterial stiffness and higher risk than the group not taking antihypertensive medication, and we consider the IHHSBP group to be at stronger risk for cardiovascular events. So BP should be especially well controlled. In this study, mean age and PWV were higher in the IHHSBP group than in the normal HBP group, and PWV was also significantly higher in the IHHSBP group than in the normal HBP group, suggesting that IHHSBP reflects the state of advanced atherosclerosis.

In the 2020 International Society of Hypertension Global Hypertension Practice Guidelines, IHSBP is defined as SBP ≥ 140 mmHg and DBP < 90 mmHg.[14] In other words, IHSBP is diagnosed when the SBP is elevated but the DBP is normal.[15] Accelerated atherosclerosis increases fibrosis of elastic fibers and increases SBP.[16] Additionally, with aging, SBP and pulse pressure continue to increase while DBP decreases,[17] and according to the Framingham Heart Study, SBP and pulse pressure are the greatest risk factors for arterial stiffness and coronary heart disease, especially in those older than 60 years.[18] In a 1991 study of the Systolic Hypertension in the Elderly Program, lowering SBP in older individuals with systolic hypertension significantly reduced cardiovascular events.[19] Reducing the SBP by 10 mmHg reduces cardiovascular events by 20%, coronary artery disease by 17%, stroke by 17%, and all-cause mortality by 13%.[20] A previous report has indicated that IHHSBP significantly increases the risk of cardiovascular mortality by 135% (95% CI: 41%–290%) compared with normotension; with every 10 mmHg increase in HBP, the risk of cardiovascular mortality increases by 37% (95% CI: 14%–65%).[4] Another study has examined CVD mortality per 100 person-years and found that individuals with IHSBP are 6.2 and 7.8 times more likely to experience cardiovascular mortality than individuals with normotension and isolated high diastolic blood pressure (IHDBP), respectively (IHSBP: 2.04, normotension: 0.33,

Table 1. Clinical characteristics of participants.

	All (n = 1082)	Normal HBP group (n = 557)	Isolated high HSBP group (n = 334)	Isolated high HDBP group (n = 28)	High HBP group (n = 163)
Male	574 (53.0)	287 (51.5)	165 (49.4)	20 (71.4)	102 (62.6)
Age (years)	65.0 (58.0–72.0)	64.0 (58.0–70.0)	70.0 (64.0–75.0)*	50.5 (44.5–56.0)	61.0 (56.0–67.0)
Duration of diabetes (years)	9.0 (5.0–16.8)	9.0 (4.0–16.0)	10.0 (6.0–20.0) †	4.5 (2.0–9.8)	8.0 (4.0–13.0)
Body mass index (kg/m^2)	23.4 (21.4–25.7)	22.9 (21.1–25.0)	23.2 (21.4–25.6)	25.7 (21.9–28.6) †	25.1 (22.8–27.5)*
Hemoglobin A1c (%)	6.7 (6.2–7.4)	6.6 (6.1–7.2)	6.8 (6.3–7.4) †	6.8 (6.1–7.4)	6.8 (6.3–7.5) †
Hemoglobin A1c (mmol/mol)	49.7 (44.2–57.4)	48.6 (42.2–55.2)	50.8 (45.3–57.4)	50.8 (43.2–57.4)	50.8 (45.3–58.5)
Total cholesterol (mg/dL)	191.0 (171.0–214.0)	190.0 (170.0–213.0)	193.0 (173.0–214.0)	178.5 (164.0–204.3)	192.0 (170.0–216.5)
Triglycerides (mg/dL)	116.0 (81.0–173.0)	108.0 (76.0–157.5)	119.0 (87.8–179.0) †	115.5 (69.0–182.8)	147.0 (93.8–206.3)*
Creatinine (mg/dL)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.7 (0.6–0.9) †	0.8 (0.6–0.9)	0.7 (0.6–0.9)
Logarithm of urinary albumin excretion	1.3 (1.0–1.7)	1.1 (0.9–1.5)	1.5 (1.2–2.0)*	1.2 (1.0–1.5)	1.5 (1.1–2.0)*
Clinical systolic BP (mmHg)	138.7 (126.3–150.0)	130.3 (120.0–141.0)	146.3* (136.3–157.3)	129.0 (123.2–131.3)	148.8* (140.2-165.3)
Clinical diastolic BP (mmHg)	77.7 (70.3–85.0)	74.3 (69.0–82.0)	76.5‡ (69.3–83.0)	86.3* (81.2–90.3)	90.0* (85.0–97.3)
Morning systolic BP (mmHg)	133.7 (122.3–144.5)	122.6 (115.1–129.1)	143.0* (138.8–150.9)	131.4* (129.8–132.6)	153.5* (144.6–165.1)
Morning diastolic BP (mmHg)	74.4 (67.8–81.1)	69.9 (65.1–75.5)	75.7* (70.4–79.7)	87.2* (85.9–89.9)	91.6* (87.9–95.1)
Evening systolic BP (mmHg)	128.8 (117.6–139.8)	119.0 (112.5–126.6)	137.6* (130.8–145.2)	126.3 ‡ (121.2–131.3)	144.7* (136.0–154.7)
Evening diastolic BP (mmHg)	69.3 (63.3–76.1)	66.2 (61.0–71.6)	68.9* (64.3–73.9)	82.8* (77.4–85.9)	83.9* (79.0–89.9)
PWV (cm/s)	1760.5 (1529–2011)	1692 (1456.8–1935.5)	1900 (1665.8–2143.3)*	1396 (1310.5–1497)	1773 (1598–2022)
Smoking status					
Current smoker	202 (18.7)	91 (16.3)	52 (15.6)	7 (25.0)	45 (27.6)
Past smoker	274 (25.4)	129 (23.2)	92 (27.5)	9 (32.1)	37 (22.7)
Alcohol consumption status					
daily	250 (23.1)	109 (19.6)	74 (22.2)	8 (28.6)	51 (31.3)
social	238 (22.1)	124 (22.3)	61 (18.3)	9 (32.1)	35 (21.5)
Diabetes complication					
Nephropathy	393 (38.1)	146 (27.2)	161 (50.9)	8 (30.8)	78 (51.3)
Retinopathy	271 (26.6)	133 (23.9)	103 (32.7)	2 (7.4)	33 (21.7)
Neuropathy	333 (30.8)	160 (28.7)	119 (35.6)	4 (14.3)	51 (31.3)
Hypoglycemic treatment (diet/OHA/insulin/GLP-1)	175/787/237/23	95/404/128/13	52/243/80/2	8/21/2/3	27/119/27/5
RASinhibitors/CCB/Diuretics/Others	452/331/69/68	195/130/30/24	164/139/29/32	10/4/1/0	78/56/7/8
First onset of cardiovascular events	119 (11.0)	21 (3.8)	50 (15.0) ‡	1 (3.6)	20 (12.3)

For categorical variables, n (%) is presented. For continuous variables, median (interquartile range) is presented.

Abbreviations: BP, blood pressure; OHA, oral hypoglycemic agent; GLP-1, glucagon-like peptide-1; RAS, renin angiotensin system; CCB, calcium channel blockers.

*p < .0001, †p < .01, ‡p < .05 for difference versus Controlled BP group; ANOVA or $\chi 2$ test for comparison among the 4 subgroups.

Table 2. Unadjusted and adjusted hazard ratios for cardiovascular events in individuals with type 2 diabetes mellitus.

	Model 1		* Model 2		* Model 3	
	Unadjusted HR (95%CI)	*p* value	Adjusted HR (95%CI)	*p* value	Adjusted HR (95%CI)	*p* value
Normal HBP group	1		1		1	
Isolated high HSBP group	1.77 (1.19–2.63)	0.005	1.58 (1.02–2.43)	0.041	1.49 (0.96–2.31)	0.072
Isolated high HDBP group	0.42 (0.06–3.02)	0.387	0.37 (0.05–2.95)	0.371	0.44 (0.06–3.24)	0.422
High HBP group	1.50 (0.89–2.54)	0.125	1.17 (0.63–2.15)	0.617	1.10 (0.60–2.03)	0.762

Abbreviations: HR, hazard ratio; CI, confidence interval; HBP, home blood pressure; HSBP, home systolic blood pressure; HDBP, home diastolic blood pressure. * Model 2: Hazard ratios were adjusted for sex, duration of diabetes, body mass index, hemoglobin A_{1C}, triglyceride, serum creatinine, and smoking status. * Model 3: Hazard ratios were adjusted for the variables in Model 2 with additional adjustment for antihypertensive medication use.

IHDBP: 0.26).[21] In other words, IHSBP and CVD are strongly related.[22] According to an Iranian study, the percentage of IHSBP in persons without diabetes mellitus is 13.31%, whereas that in persons with diabetes mellitus is 23.63%, indicating that IHSBP is more common in persons with diabetes mellitus.[23] Another study has shown an association between type 2 diabetes mellitus and IHSBP.[24] Nocturnal isolated systolic and office hypertension are associated with elevated blood glucose and increased insulin resistance compared with normotension.[25] In persons with type 2 diabetes mellitus, untreated IHSBP is associated with approximately twice the risk of cerebrovascular disease as normotension.[26]

Although the association between IHSBP and cardiovascular events in diabetes has already been shown,[26] this was the first study to show the relationship between IHHSBP and CVD hazard ratios in persons with type 2 diabetes mellitus. Aging reduces arterial compliance and contributes to the development of atherosclerosis,[27] and in this study, analysis by age showed no difference in the hazard ratios for CVD in the IHHSBP group between those aged 65 years and older and those younger than 65 years. IHSBP is 2.4 times higher in males than in females with type 2 diabetes mellitus according to a study by Baye et al.[28] Another study has reported differences in CVD incidence between genders[29]; thus, we analyzed the data by gender as well. IHHSBP was associated with CVD development compared with Normal HBP and High HBP in both males and females, but the risk of CVD tended to be higher in females than in males, suggesting that IHHSBP and CVD development were stronger in females. In our present study, one reason why IHHSBP and CVD risk differed between males and females was that the association between CVD and diabetes duration was stronger in males than in females. In addition, although a decrease in estrogen contributes to the development of atherosclerosis,[30] most of the females in this study were postmenopausal, the effect of estrogen on atherosclerosis cannot be assessed.

This study had several limitations. First, the study was solely based on BP measurements taken at study entry and failed to scrutinize the relationship between HBP during and after the follow-up period, as well as at the onset of cardiovascular events. Second, the external validity of the study is unclear. This study was conducted on Japanese subjects, and it is unclear whether it would be applicable to different ethnic groups. Finally, exercise habits and salt intake can influence BP, but data on these were not available in this study and their influence could not be taken into account.

In summary, our study revealed that IHHSBP is associated with a higher CVD risk in persons with type 2 diabetes mellitus. The subanalysis showed that IHHSBP and CVD had a stronger association in females than in males. Thus, in clinical practice, females with both type 2 diabetes mellitus and IHHSBP might strive to achieve normotension through HBP reduction, especially those who require special attention for CVD.

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Ethical Statements

Ethical Approval

Approval of the research protocol: The study was approved by the Research Ethics Review Committee (RBMR-E-349).

Informed Consent

Informed consent was obtained from eligible people.

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Supplemental Material

Supplemental material for this article is available online.

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Appendix

Abbreviations and Acronyms

IHHSBP	Isolated high home systolic blood pressure
CDV	Cardiovascular disease
HBP	Home blood pressure
HR	Hazard ratio
CI	Confidence interval
SBP	Systolic blood pressure
BP	Blood pressure
IHSBP	Isolated high systolic blood pressure
IHHDBP	Isolated high home DBP
TG	Triglycerides
BMI	Body mass index
HR	Hazard ratio
IHDBP	Isolated high diastolic blood pressure
JSH	The Japanese Society of Hypertension
PWV	Pulse Wave Velocity.