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Original Article

Different cutoffs of hypertension, risk of incident diabetes and progression of insulin resistance: A prospective cohort study

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Background/Purpose: Hypertension is a risk factor of incident diabetes. In 2017, the ACC/AHA updated the definition of hypertension to above 130/80 mmHg, while the 2018 ESC/ESH guideline and the JNC7 criteria remained the cutoff of 140/90 mmHg. This study was aimed to investigate how different cutoffs of hypertension affect the association of hypertension to incident diabetes and the progression of insulin resistance.
Methods: A total of 1177 subjects without diabetes at baseline were followed for 4.5 years.

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Diabetes was diagnosed by the results of oral glucose tolerance tests and hemoglobin A1c, or if anti-diabetic agents were used.
Results: Hypertension by both criteria was associated with incident diabetes. Change of HOMA2-IR every 5 years (ΔHOMA2-IR/5 yr) was higher in subjects with hypertension than those without (adjusted $p = 0.044$). Subjects with treated hypertension had the highest risk of diabetes (HR 2.98, $p < 0.001$) and ΔHOMA2-IR/5 yr, compared with subjects with normal blood pressure. However, the associations of hypertension, HR of incident diabetes and ΔHOMA2-IR/5 yr were attenuated by the 2017 ACC/AHA criteria, as compared with that by the JNC7 and 2018 ESC/ESH criteria.
Conclusion: Hypertension by both criteria is associated with incident diabetes and accelerated progression of insulin resistance, and the associations are attenuated by the 2017 ACC/AHA criteria.

Introduction

Hypertension is a risk factor of diabetes and can precede the incidence of diabetes,[1] which has been demonstrated in five studies in the literature, including the Osaka Health Survey, the MONICA study, a report using cohorts from the ARIC, CARDIA and Framingham Heart Study, the KoGES and the Dongfeng Tongji cohort.[2–6] In 2017, the American College of Cardiology (ACC) and American Heart Association (AHA) updated the definition of hypertension,[7] which lowered the threshold for hypertension to 130/80 mmHg. It is the only one which changes the definition of hypertension since 1984 when JNC 3 was published.[8] However, the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) published their guideline of hypertension in 2018. It recommended keeping the definition of hypertension of 140/90 mmHg, as previously suggested in the Seventh Report of the Joint National Committee (JNC7) criteria.[9,10] The different definitions pose a great impact on various aspects of hypertension. For example, whether hypertension remains a risk factor of diabetes when the definitions are changed remains unknown. Therefore, this is an important area to be explored.

Insulin resistance has been proposed to be the underlying cause linking hypertension and diabetes,[11] which has been supported by the results from cross-sectional studies in human[12] and several mechanistic studies.[13,14] Theoretically, these mechanisms may persist over time, which could accelerate the progression of insulin resistance in hypertensive subjects. Furthermore, one recent study disclosed that a more rapid progression of insulin resistance was associated with a higher risk of incident diabetes.[15] However, there is no human study which explores the effect of hypertension on the progression of insulin resistance over time.

Therefore, in this prospective cohort study, we investigated the impact of the different definitions of hypertension, including the 2017 ACC/AHA criteria (130/80 mmHg) and the JNC7 and 2018 ESC/ESH criteria (140/90 mmHg), on the incidence of diabetes and the progression of insulin resistance over time. In addition, to evaluate the impact of different cutoffs of hypertension, we analyzed the relationship of systolic and diastolic blood pressure to the risk of incident diabetes and the progression of insulin resistance.

Materials and methods

Study populations

Since 2006, we conducted a large prospective community-based cohort study, called Taiwan Lifestyle Study.[16–19] Subjects who lived in Yun-Lin county, Taiwan and aged more than 18 years old were included. Clinical characteristics, demographic data, and results of blood tests including oral glucose tolerance tests and hemoglobin A1c (HbA1c) were acquired by physicians and study nurses at the initial visit and every follow-up visit. Those who reported or diagnosed of diabetes mellitus at the first visit were excluded. Participants were followed at least 1 year after the initial visit and every 2 years thereafter. All participants signed informed consent before enrollment, and the institutional review board of National Taiwan University Hospital reviewed and approved the study protocol.

Blood pressure measurements and definitions of hypertension

Standardized blood pressure measurement was performed in this study according to the ACC/AHA guideline for hypertension.[7] Subjects were asked to avoid exercise, caffeine or smoking for at least 30 min with his/her bladder being emptied before measurement. After sitting quietly and casually for at least 10 min, blood pressure was measured by well-trained nurses using automated sphygmomanometer (Omron HEM 76271, Omron Healthcare Co., Ltd., Kyoto, Japan) with three separate readings at 1-min intervals. The average of the last two measurement was used for analysis.

Hypertension was defined using two different cutoffs.[7,9] According to the JNC 7 and 2018 ESC/ESH criteria, subjects with blood pressure greater than 140/90 mmHg, or medications for hypertension were defined as having

hypertension. Pre-hypertension was determined if blood pressure was 120–139/80–89 mmHg in subjects without medications for hypertension. Those without a history of hypertension but diagnosed as having hypertension at enrollment were classified as untreated hypertension group; whereas those who took anti-hypertensive drugs at enrollment were categorized as treated hypertension group. According to the 2017 ACC/AHA hypertension guideline, subjects with blood pressure greater than 130/80 mmHg, or medications for hypertension were defined as having hypertension. Those with systolic blood pressure 120–129 mmHg, diastolic blood pressure <80 mmHg and without medications for hypertension were defined as having elevated blood pressure.

Definition of diabetes mellitus and measurements of pancreatic β cell function and insulin resistance

The definition of diabetes mellitus were according to the American Diabetes Association (ADA) guideline,[1] i.e., fasting plasma glucose ≥126 mg/dL, oral glucose tolerance test (OGTT) 2-h plasma glucose ≥200 mg/dL, HbA1c ≥ 6.5%, or if anti-diabetic medications were used. The classification of diabetes was made by endocrinologists. In the present study, all subjects with diabetes were classified as type 2 diabetes. Updated computerized models of homeostatic model assessment was used to estimate pancreatic β cell function (HOMA2-%B) and insulin resistance (HOMA2-IR).[20] Progression rate of HOMA2-IR every 5 years (ΔHOMA2-IR/5 yr) were calculated as follows: HOMA2-IR at the last visit ($HOMA2\text{-}IR_{lv}$) minus HOMA2-IR at the first visit ($HOMA2\text{-}IR_{first}$), divided by the interval between the first visit and the last visit in years, and then multiplied by 5 (($HOMA2\text{-}IR_{lv}$ - $HOMA2\text{-}IR_{first}$)*5/interval).

Assays for biochemical parameters

Plasma glucose and lipid profiles were examined using an automatic analyzer (Toshiba TBA 120FR, Toshiba Medical Systems Co., Ltd., Tokyo, Japan). Plasma insulin was measured by an automatic analyzer with microparticle enzyme immunoassay (Abbott AxSYM system; Abbott Laboratories, Abbott Park, IL). HbA1c was tested using an automatic analyzer (HLC-723 G7 HPLC system, Tosoh Corporation, Tokyo, Japan), and the HbA1c assay was certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) reference assay.

Statistical analyses

Categorical variables were shown as numbers (percentages), and continuous variables with normal distribution were presented as means ± standard deviation (SD). Continuous variables without normal distribution were reported as medians (inter-quartile ranges). Logarithmic transformation was done to approximate normal for the statistical analyses of these variables. Statistical significance in different groups were analyzed by Student's *t* test, Fisher's exact test or chi-squared test according to the nature of variables. Cox proportional hazards models were utilized to estimate the hazard ratios (HRs) of incident diabetes of various risk factors, adjusted for confounders. Kaplan–Meier failure curve was applied for cumulative incidence of diabetes by the presence of hypertension at baseline. The difference between the two groups were tested by log-rank test. Subgroup analysis for HRs of incident diabetes of subjects without hypertension, with pre-hypertension (pre-HTN), with untreated hypertension (untreated HTN) and with treated hypertension (treated HTN) at baseline was shown as bar chart with standard errors as error bars. Linear regression was utilized to analyze the relationship between hypertension (independent variable) and the progression rate of HOMA2-IR every 5 years (dependent variable), adjusted for confounders in different statistical models. The relationships between different blood pressure categories with the incidence of diabetes, HR of incident diabetes, HOMA2-IR at baseline and ΔHOMA2-IR/5 yr were analyzed in subjects without anti-hypertensive drugs. Analysis of variance (ANOVA) was used to compare HOMA2-IR at baseline and ΔHOMA2-IR/5 yr in different categories of blood pressure. A two-tailed *p*-value below 0.05 was considered significant. Stata/SE 14.0 for Windows (StataCorp LP, College Station, TX) was used for statistical analyses.

Results

A total of 1177 subjects were enrolled with a median follow-up period of 4.54 years (inter-quartile range 2.41–6.51 years), and the baseline characteristics were shown in Table 1. There were 315 subjects with hypertension by the JNC7 and 2018 ESC/ESH criteria (164 subjects (52%) received anti-hypertensive drugs) and 586 subjects with hypertension by the 2017 ACC/AHA criteria (164 subjects (28%) received anti-hypertensive drugs) at baseline. Subjects with hypertension by both criteria were older, male-predominant, and had higher body mass index (BMI) and waist circumference (WC), compared with those without hypertension at baseline. In addition, their fasting and OGTT 2-h plasma glucose, HbA1c, fasting insulin, triglyceride, total cholesterol, low-density lipoprotein cholesterol and urine-microalbumin-to-creatinine ratio were significant higher, and the high-density lipoprotein cholesterol and serum creatinine were lower in the hypertensive subgroup. Moreover, HOMA2-IR at baseline were significantly higher in subjects with hypertension. The ΔHOMA2-IR/5 yr was higher in subjects with hypertension by the JNC7 and 2018 ESC/ESH criteria, but when hypertension was defined by the 2017 ACC/AHA criteria, the statistical significance was only borderline.

In Fig. 1A and C, subjects with hypertension by both criteria had a higher incidence of diabetes during follow-up, compared with subjects without hypertension ($p < 0.001$). In Fig. 1B and D, treated hypertension group had the highest HR of incident diabetes (2.98 by both criteria, $p < 0.05$), followed by subjects with untreated hypertension (HR 2.12 by the JNC7 and 2018 ESC/ESH criteria, HR 1.57 by the 2017 ACC/AHA criteria, both $p < 0.05$), compared with subjects with pre-hypertension/elevated blood pressure or normal blood pressure. The HRs of incident diabetes for subjects with pre-hypertension or

Table 1 Baseline characteristics of subjects with and without hypertension before follow-up. Hypertension was defined by the JNC7 and 2018 ESC/ESH criteria or the 2017 ACC/AHA criteria.

	Hypertension by the JNC7 and 2018 ESC/ESH criteria			Hypertension by the 2017 ACC/AHA criteria		
	Subjects without hypertension	Subjects with hypertension	p	Subjects without hypertension	Subjects with hypertension	p
N (%)	862 (73.2)	315 (26.8)		591 (50.2)	586 (49.8)	
Age (years)	47.9 ± 11.6	55.9 ± 9.8	<0.0001	47.1 ± 11.6	53.0 ± 11.0	<0.0001
Male gender (N, %)	287 (33.3)	157 (50.0)	<0.001	156 (26.4)	288 (49.2)	<0.001
Family history of diabetes	284 (33.0)	95 (30.2)	0.365	202 (34.2)	177 (30.2)	0.145
Smoking (N, %)	171 (19.8)	70 (22.2)	0.369	108 (18.3)	133 (22.7)	0.060
BMI (kg/m^2)	23.5 ± 3.2	25.4 ± 2.9	<0.0001	23.0 ± 3.0	25.0 ± 3.2	<0.0001
WC (cm)	78.8 ± 9.2	85.2 ± 8.9	<0.0001	77.2 ± 8.5	83.9 ± 9.3	<0.0001
SBP (mmHg)	116.2 ± 10.8	141.0 ± 14.6	<0.0001	111.4 ± 8.7	134.3 ± 13.7	<0.0001
DBP (mmHg)	74.7 ± 7.66	88.9 ± 10.3	<0.0001	70.9 ± 5.7	86.2 ± 8.5	<0.0001
Fasting glucose (mg/dL)	89.4 ± 8.1	93.3 ± 8.8	<0.0001	88.9 ± 7.9	92.0 ± 8.8	<0.0001
OGTT 2-h plasma glucose (mg/dL)	110.1 ± 28.4	125.2 ± 29.6	<0.0001	108.2 ± 28.5	120.2 ± 29.3	<0.0001
Fasting insulin (μIU/mL)	6.55 ± 5.35	7.89 ± 5.25	0.0001	6.05 ± 4.56	7.77 ± 5.93	<0.0001
HbA1c			<0.0001			<0.0001
(%)	5.58 ± 0.36	5.69 ± 0.39		5.55 ± 0.36	5.67 ± 0.37	
(mmol/mol)	37 ± 2.46	39 ± 2.67		37 ± 2.38	38 ± 2.47	
HOMA2-IR index	0.69 (0.41–1.02)	0.89 (0.52–1.29)	<0.0001	0.66 (0.39–0.96)	0.84 (0.52–1.23)	<0.0001
HOMA2-%B index	75.4 (58.9–99.7)	82.2 (61.2–105.7)	0.1152	72.7 (57.1–97.1)	81.3 (62.4–105.5)	0.0002
Δ HOMA2-IR per 5 years	0.23 ± 1.77	0.68 ± 2.60	0.0008	0.25 ± 1.93	0.46 ± 2.13	0.0772
Δ HOMA2-%B per 5 years	1.67 ± 89.70	22.31 ± 107.19	0.0010	2.92 ± 98.23	11.48 ± 91.67	0.1230
TG (mg/dL)	86 (63–125)	117 (82–157)	<0.0001	86 (63–125)	117 (82–157)	<0.0001
T-CHO (mg/dL)	191.2 ± 37.3	199.0 ± 34.8	0.0014	190.1 ± 37.3	196.4 ± 36.0	0.0030
LDL-C (mg/dL)	113.8 ± 31.7	123.7 ± 32.6	<0.0001	111.3 ± 30.9	121.8 ± 32.7	<0.0001
HDL-C (mg/dL)	52.2 ± 13.1	49.3 ± 11.3	0.0004	53.6 ± 13.2	49.3 ± 11.8	<0.0001
hsCRP (mg/dL)	0.17 ± 0.51	0.20 ± 0.37	0.4443	0.16 ± 0.41	0.20 ± 0.53	0.1199
Cre (mg/dL)	0.97 ± 0.20	1.03 ± 0.20	0.0001	0.96 ± 0.21	1.02 ± 0.19	<0.0001
UACR (mg/g)	8.7 (5–16)	12.4 (6.8–23.15)	<0.0001	8.3 (4.9–15.05)	10.7 (5.9–20.2)	<0.0001
Statin user (N, %)	15 (1.74)	12 (3.81)	0.036	9 (1.52)	18 (3.07)	0.076

Medians (inter-quartile ranges) were reported for plasma TG, HOMA2-%B and HOMA2-IR. Statistical analyses for these variables were done after logarithmic transformation. A total of 164 subjects received anti-hypertensive drugs, which accounts for 52% and 28% of the hypertensive subjects in the JNC7 and 2018 ESC/ESH group and the 2017 ACC/AHA group respectively.
Data are listed as the mean ± SD. BMI, body mass index; Cre, creatinine; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; TG, triglyceride; T-CHO, total cholesterol; UACR, urine microalbumin-to-creatinine ratio; WC, waist circumference.

elevated blood pressure were not significantly elevated, compared with normotensive group (both $p > 0.05$).

Among hypertensive patients by different criteria, the HRs of incident diabetes were compared, using subjects without hypertension as the reference group. In Table 2, the unadjusted HR of incident diabetes for hypertension by the JNC7 and 2018 ESC/ESH criteria was 2.37 (95% CI 1.66–3.38, $p < 0.001$). After adjustment for confounders, hypertension remained to be significantly associated with incident diabetes (adjusted HRs 1.51–1.63, $p < 0.05$ in model 1–4). Replacing BMI with waist circumference as a confounder in the models resulted in similar findings (adjusted HRs 1.47–1.57, $p < 0.05$ in model 1–4). On the other hand, the unadjusted HR of incident diabetes for hypertension by the 2017 ACC/AHA guideline was 1.96 (95% CI 1.35–2.84, $p < 0.001$), which was lower than the HR for hypertension by the JNC7 and 2018 ESC/ESH criteria. Adjusting for confounders reduced the HR, and the adjusted HRs were not statistically significant (model 1–4).

In addition, we also categorized the study subjects into three groups, including (1) normal blood pressure by both criteria, (2) hypertension by the 2017 ACC/AHA criteria but

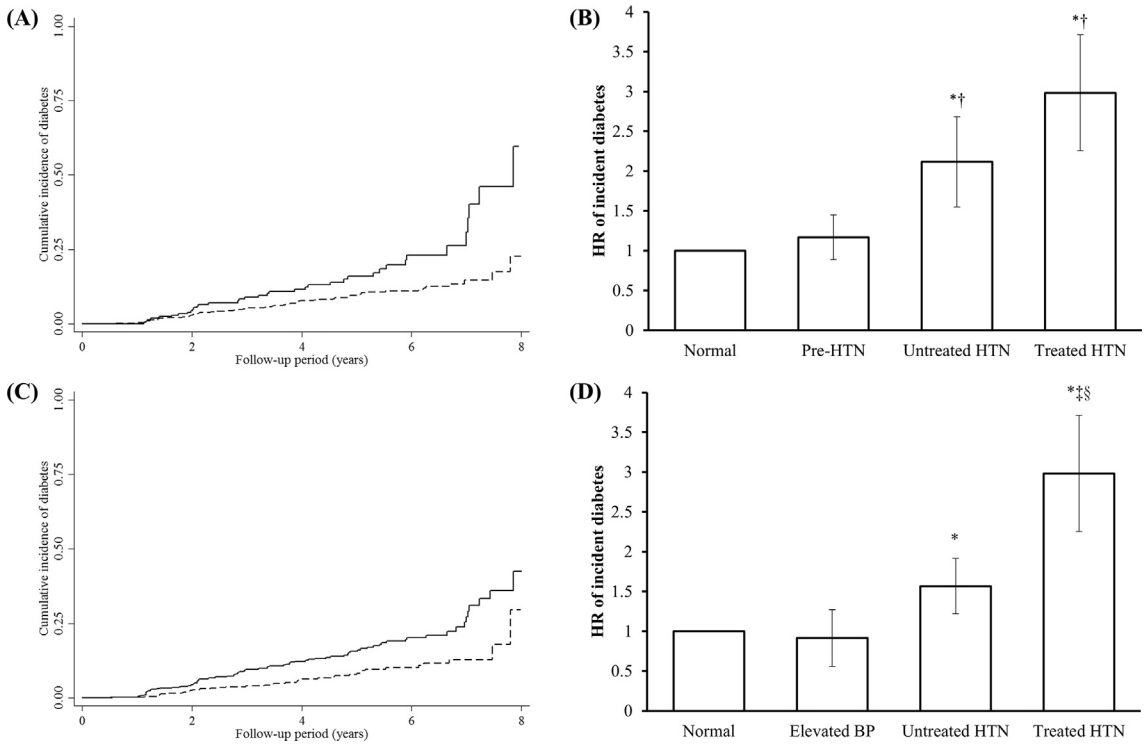

Figure 1 (A) Kaplan–Meier failure curve for the cumulative incidence of diabetes by the presence of hypertension at baseline by the JNC7 and 2018 ESC/ESH criteria. Solid line, subjects with hypertension; dash line, subjects without hypertension. $P < 0.001$ by log-rank test. (B) Hazard ratios (standard errors) of incident diabetes for subjects without hypertension, with pre-hypertension (pre-HTN), with untreated hypertension (untreated HTN) and with treated hypertension (treated HTN) at baseline, using the JNC7 and 2018 ESC/ESH criteria. (C) Kaplan–Meier failure curve for the cumulative incidence of diabetes by the presence of hypertension at baseline using the 2017 ACC/AHA criteria. Solid line, subjects with hypertension; dash line, subjects without hypertension. $P < 0.001$ by log-rank test. (D) Hazard ratios (standard errors) of incident diabetes for subjects without hypertension, with elevated blood pressure (elevated BP), with untreated hypertension (untreated HTN) and with treated hypertension (treated HTN) at baseline, using the 2017 ACC/AHA criteria.*$p < 0.05$ compared with the normal group; †$p < 0.05$ compared with the pre-HTN group. ‡$p < 0.05$ compared with the elevated BP group. §$p < 0.05$ compared with the untreated hypertension group.

not the JNC7 and 2018 ESC/ESH criteria, and (3) hypertension by both criteria. The cumulative incidence of diabetes of the subgroup of HTN defined only by the 2017 ACC/AHA criteria was in between of the other two subgroups ($p < 0.001$, Fig. S1), although the HR of incident diabetes was not statistically significant in this subgroup (Fig. S2, Table S1). Besides, ΔHOMA2-IR every 5 years was highest in subjects with HTN by both criteria, followed by subjects with HTN only by the 2017 ACC/AHA criteria, compared with the normal blood pressure group (Table S2).

The relationship between hypertension and the progression rate of HOMA2-IR was analyzed in Table 3. Interestingly, subjects with hypertension by the JNC7 and 2018 ESC/ESH criteria had a higher progression rate of HOMA2-IR than those without hypertension (0.45 more increase every 5 years, $p = 0.001$, Table 3A). There was a significant trend of increased progression rate of HOMA2-IR in the order of subjects without hypertension, untreated hypertension and treated hypertension (*p* for trend 0.006, Table 3B). These findings remained significant after adjusting for different combination of confounders (Table 3, Model A and B). Replacing BMI with WC as a confounder in the models resulted in similar findings. The results by using the 2017 ACC/AHA criteria were similar to the results using the JNC7 and 2018 ESC/ESH criteria, but the impact of hypertension on the progression rate of HOMA2-IR was attenuated, as demonstrated by the reduced regression coefficients.

The relationships of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with the incidence of diabetes, the HR of incident diabetes, the baseline HOMA2-IR and ΔHOMA-IR/5 yr in subjects without anti-hypertensive drugs were demonstrated in Fig. 2 and 3. There was a positive relationship between SBP categories, the incidence of DM and the HR of diabetes, without a clear threshold for SBP (Fig. 2A–B, p for trend 0.05). In Fig. 2C, as SBP became higher, HOMA2-IR increased significantly ($p < 0.05$ in all SBP categories as compared with subjects with SBP <110 mmHg, p for trend <0.001). On the other hand, ΔHOMA-IR/5 yr was significantly increased only in the subgroup with SBP≥140 mmHg (Fig. 2D, $p < 0.05$). Similarly, there was a positive relationship between DBP categories, the incidence of DM and the HR of diabetes, without a clear threshold for DBP (Fig. 3A-B, p for trend = 0.038). In Fig. 3C-D, HOMA2-IR at baseline rose as DBP elevated ($p < 0.05$ in all DBP categories, compared with subjects with DBP <70 mmHg, p for trend <0.001), and ΔHOMA-IR/

Table 2 The relationship between hypertension at baseline and the incidence of diabetes in unadjusted and adjusted models. Hypertension (HTN) was defined by the JNC7 and 2018 ESC/ESH criteria or by the 2017 ACC/AHA criteria. Hazard ratios (HR) of incident diabetes for hypertension and 95% confidence interval (95% CI) were shown, using subjects without hypertension as the reference group.

	HTN by the JNC7 and 2018 ESC/ESH criteria		HTN by the 2017 ACC/AHA criteria	
	HR (95% CI)	p	HR (95% CI)	p
Unadjusted	2.37 (1.66–3.38)	<0.001	1.96 (1.35–2.84)	<0.001
Model 1	1.63 (1.13–2.34)	0.009	1.34 (0.91–1.96)	0.135
Model 2	1.52 (1.04–2.20)	0.030	1.27 (0.86–1.86)	0.232
Model 3	1.51 (1.04–2.20)	0.030	1.26 (0.86–1.86)	0.238
Model 4	1.51 (1.04–2.20)	0.031	1.26 (0.86–1.86)	0.241

Model 1: adjusted for HOMA2-%B, HOMA2-IR, BMI, HbA1c and plasma triglyceride.
Model 2: adjusted for HOMA2-%B, HOMA2-IR, BMI, HbA1c, plasma triglyceride, age, gender and family history of diabetes.
Model 3: adjusted for HOMA2-%B, HOMA2-IR, BMI, HbA1c, plasma triglyceride, age, gender, family history of diabetes and hsCRP.
Model 4: adjusted for HOMA2-%B, HOMA2-IR, BMI, HbA1c, plasma triglyceride, age, gender, family history of diabetes, hsCRP and use of statin.

Table 3 The association between hypertension (HTN) at baseline and the progression rate of HOMA2-IR every 5 years (ΔHOMA2-IR every 5 years) by linear regression, using ΔHOMA2-IR every 5 years as the dependent variables. Hypertension was defined by the JNC7 criteria and 2018 ESC/ESH and the 2017 ACC/AHA criteria. (A) Regression coefficients (β) and p values for hypertension (vs. without hypertension) were shown. (B) Regression coefficients (β) and p for trend for normal (reference group), untreated hypertension and treated hypertension were shown.

	ΔHOMA2-IR every 5 years			
	HTN by the JNC7 and 2018 ESC/ESH criteria		HTN by the 2017 ACC/AHA criteria	
	β	p	β	p
(A) Hypertension vs. without hypertension				
Unadjusted	0.450	0.001	0.210	0.077
Model A	0.488	<0.001	0.253	0.044
Model B	0.436	0.002	0.207	0.099
(B) Without hypertension, untreated hypertension and treated hypertension				
Unadjusted	0.227	0.006	0.161	0.053
Model A	0.251	0.004	0.197	0.027
Model B	0.218	0.013	0.157	0.077

Model A: adjusted for HOMA2-IR at baseline, age, gender, family history of diabetes and body mass index (BMI).
Model B: adjusted for HOMA2-IR at baseline, age, gender, family history of diabetes, BMI, ΔBMI, HbA1c, plasma TG concentration, plasma hsCRP concentration and use of statin.

5 yr increased significantly only in subjects with DBP≥90 mmHg ($p < 0.05$).

Discussion

In this study, we found positive associations of systolic and diastolic blood pressure to the risk of diabetes, HOMA2-IR at baseline and increase in HOMA2-IR over time. Therefore, it is reasonable that application of the 2017 ACC/AHA criteria to define hypertension attenuated the impact of hypertension on the incidence of diabetes, compared with the JNC7 and the 2018 ESC/ESH criteria. In addition, we showed for the first time that hypertension by both criteria was associated with a more rapid increase in insulin resistance over time, which provide evidence to support this potential pathophysiology.

We reported an attenuated association between hypertension defined by the 2017 ACC/AHA criteria, incident diabetes and progression insulin resistance. The 2017 ACC/AHA guideline lowered the cutoffs for hypertension in order to include more adults who are at risk of cardiovascular diseases and death to facilitate early interventions.[7] Subjects with blood pressure 130–139/80-89 mmHg, defined as having pre-hypertension by the JNC7 and 2018 ESC/ESH criteria, are classified as hypertension by the 2017 ACC/AHA criteria. It is conceivable that the extent of hypertension-induced endothelial dysfunction and insulin resistance may be less severe in these subjects. Supporting this, fasting plasma glucose, OGTT 2-h plasma glucose, plasma insulin levels and HOMA2-IR were lower in hypertensive subjects by the 2017 ACC/AHA criteria than in hypertensive subjects by the JNC7 and 2018 ESC/ESH criteria (Table 1). Therefore, the attenuated association between hypertension by the 2017 ACC/AHA criteria and the development of diabetes could be attributed to the increased number of hypertensive subjects with slightly elevated blood pressure. On the other hand, in the present study, we found a positive relationship between blood pressure, the incidence of diabetes and insulin resistance at baseline, without a clear threshold for blood pressure. In contrast, the progression rate of insulin resistance increased significantly only when systolic blood pressure was above 140 mmHg or diastolic blood pressure was above 90 mmHg. These findings could explain the attenuated associations by the 2017 ACC/AHA criteria. Therefore, the risks of incident diabetes and progression of insulin resistance should also be considered, along with other evidence, in the definition of hypertension to prompt timely treatments.

Several mechanisms have been proposed for the pathogenesis between hypertension and the development of diabetes. Hypertension is known to result in endothelial dysfunction, with the consequences of defective vasodilatation and increased coagulability.[21] As a result of defective vasodilatation and vascular luminal obliteration, insulin delivery is impaired and insulin resistance develops.[22] Besides, endothelial dysfunction may also

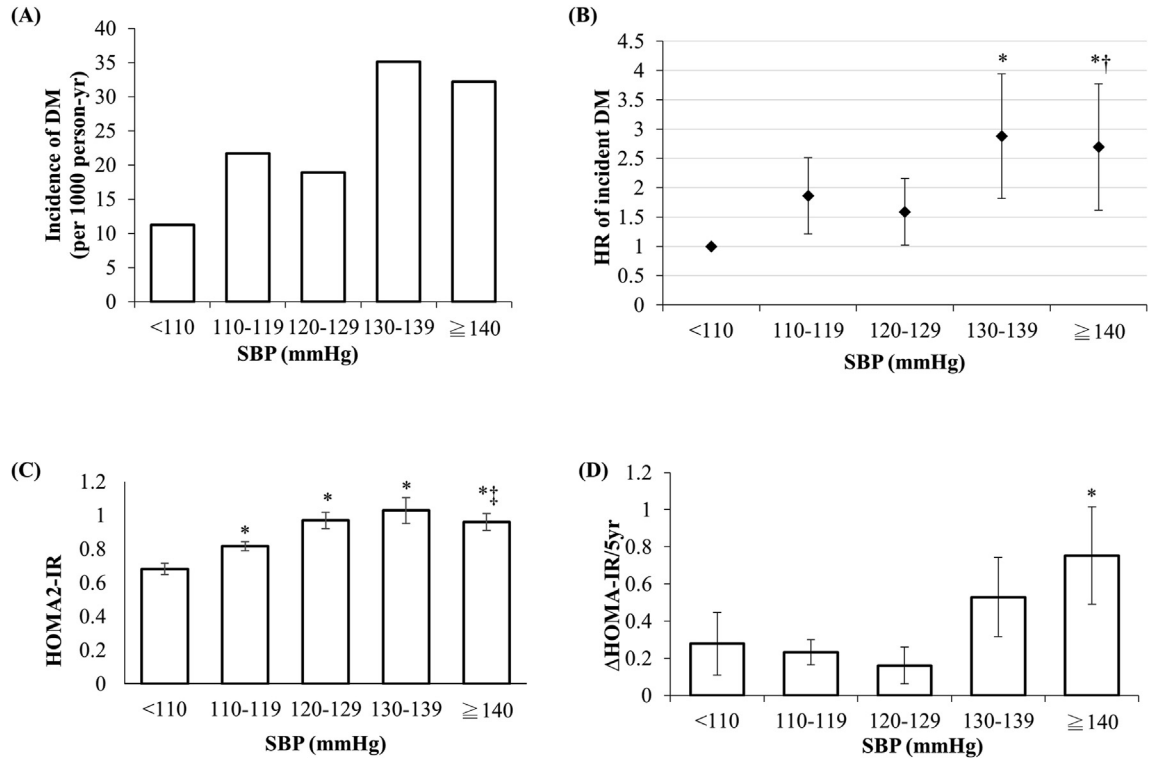

Figure 2 The relationship between systolic blood pressure (SBP) and (A) the incidence of diabetes mellitus (DM), (B) the hazard ratio (HR) of incident DM, (C) HOMA2-IR at baseline, or (D) the change of HOMA2-IR per 5 years (ΔHOMA-IR/5 yr). The HR in each group (from the lowest to the highest tertile of SBP) were 1, 1.86, 1.59, 2.88 and 2.69, respectively. *p $<$ 0.05 compared with the group with SBP $<$110 mmHg. †p for trend = 0.05. ‡p for trend $<$0.001. Only subjects without anti-hypertensive drugs were included in the analyses. HOMA2-IR was logarithmically transformed for statistical analyses.

contribute to adipose tissue inflammation and insulin resistance.[23,24] As blood pressure increases, expression of chemotactic factors and endothelial adhesion molecules are up-regulated, which facilitates leukocytes, especially monocytes, to adhere to and transmigrate across the endothelium and initiate inflammation.[22,24] In adipose tissue, these macrophages are activated to produce proinflammatory cytokines including tumor necrosis factors (TNF)-α and interleukin (IL)-1β, which are responsible of inducing insulin resistance through several molecular mechanisms such as phosphorylation of insulin receptor substrate-1 at serine sites in adipocytes.[25,26] Persistent inflammation in adipose tissue can also impair angiogenesis, promote fibrosis and result in adipocyte dysfunction and insulin resistance.[27] Furthermore, plasma free fatty acids increase in insulin-resistant states, which can further impair insulin signaling through diacylglycerol (DAG)-mediated activation of protein kinase C (PKC) pathway in the liver and muscle.[28] On the other hand, plasma adiponectin concentration is lower in subjects with hypertension and is negatively associated with blood pressure.[29] Since hypo-adiponectinemia is a well-established mechanism for the development of insulin resistance,[30] this could also contribute to the link between hypertension, insulin resistance and the development of diabetes. All these pathophysiologies persist in subjects with hypertension, which supports our findings that subjects with hypertension had a higher progression rate of insulin resistance over time.

To our knowledge, this is the first study exploring the impact of the 2017 ACC/AHA criteria for hypertension on the relationship between hypertension, progression of insulin resistance and incident diabetes. Moreover, this study is also the first one demonstrating a higher progression rate of insulin resistance in hypertensive subjects, which provide human evidence on a novel mechanism linking hypertension and the incidence of diabetes. Last but not least, this study also systemically analyzed the relationships between blood pressure, incidence of diabetes and insulin resistance, which explained the attenuated associations by the 2017 ACC/AHA criteria found in the study and provided more evidence to be considered in the definition of hypertension. The findings of the present study are not surprising that 2017 ACC/AHA criteria would attenuate the association or predictive power of hypertension on diabetes incidence. However, this study does provide the supporting evidence, since without the findings of this study, it would remain unknown if there was a lower threshold between the definition of hypertension and the risk of diabetes incidence. On the other hand, this study is limited in that the enrolled populations were all Han Chinese. Studies on other ethnic groups should be performed to understand if there are ethnic differences. Also, the type and duration

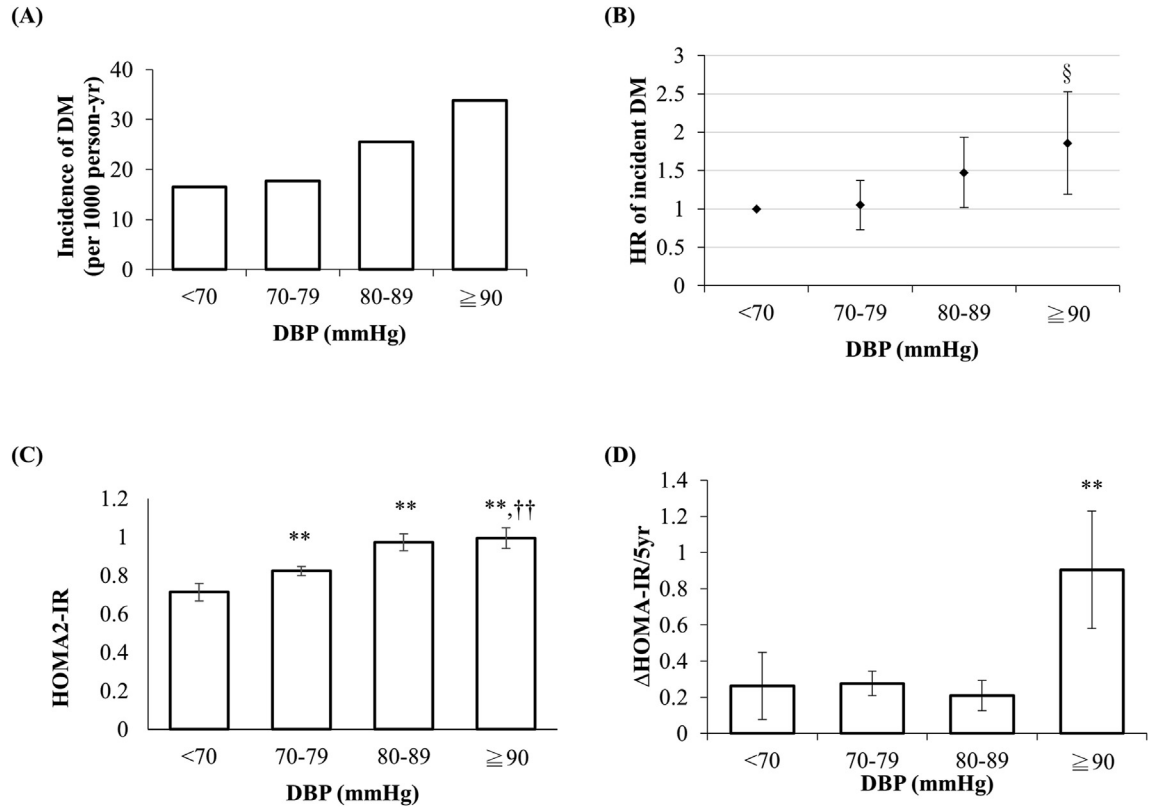

Figure 3 The relationship between diastolic blood pressure (DBP) and (A) the incidence of DM, (B) the HR of incident DM, (C) HOMA2-IR at baseline, or (D) ΔHOMA-IR/5 yr. The HR in each group (from the lowest to the highest tertile of DBP) were 1, 1.05, 1.47 and 1.86, respectively. §p for trend = 0.038. **p < 0.05 compared with the group with DBP <70 mmHg. ††p for trend <0.001. Only subjects without anti-hypertensive drugs were included in the analyses. HOMA2-IR was logarithmically transformed for statistical analyses.

of anti-hypertensives used by subjects could not be specified, which may confound our findings. Besides, since this is an observational study, causal relationship could not be fully established. Further interventional study might be necessary to elucidate if lower blood pressure alleviates the development of diabetes.

In conclusion, hypertension by both criteria is associated with the incidence of diabetes and the progression of insulin resistance. However, different cutoffs of hypertension have impact on the association between hypertension, incident diabetes and the progression of insulin resistance. Therefore, application of the 2017 ACC/AHA criteria for hypertension attenuates the associations as compared with hypertension defined by JNC7 and 2018 ESC/ESH criteria.

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Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2021.02.022.

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