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Original Article

The association and interaction analysis of hypertension and diabetes mellitus on diastolic heart failure in a high-risk population

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Abstract: Objective: The purpose of this study was to evaluate the extent to which hypertension (HT) interacts with diabetes mellitus (DM) to affect diastolic heart failure (DHF) in a high-risk population. Methods: We conducted a hospital-based case-control study to investigate the relationship between HT or DM and DHF in 251 patients (case: 133 patients with DHF; control: 118 patients without DHF). Echocardiography was used to assess left ventricular (LV) diastolic function. The association between HT or DM and DHF was assessed by multivariate logistic regression (MLR) analysis controlling for confounders. The effect of the interaction between HT and DM on DHF was assessed in MLR models. Interaction on an additive scale can be calculated by using the relative excess risk due to interaction (RERI), the proportion attributable to interaction (AP), and the synergy index (S). Results: The MLR analyses showed that HT and DM were independent predictors of DHF after adjustment for potential confounders (OR = 2.35-3.14, P<0.05 for all models). DHF was affected by the interaction between HT and DM (OR_{Int} = 3.11-4.31, P_{Int}<0.1, RETI = 2.13-2.69, AP = 0.38-0.49 and S = 4.11-6.80). Conclusion: The findings provide evidence that HT and DM are independent predictors of DHF and that both risk factors act synergistically to influence DHF in a Chinese high-risk population.

Keywords: Hypertension, diabetes mellitus, diastolic heart failure, synergy effect

Introduction

Diastolic heart failure (DHF) refers to a decline in the performance of one or both ventricles of the heart during the time phase of diastole. It is characterized by elevated diastolic pressure in the left ventricle (LV), despite an essentially normal end diastolic volume [1]. Previous studies have suggested that the morbidity and mortality of DHF are similar to those of systolic HF [2, 3]. DHF has been attributed to multiple factors that are mainly linked to metabolic disturbances and high blood pressure [3]. Diabetes mellitus (DM) is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Untreated diabetes can cause many serious long-term complications, including cardiovascular disease, chronic renal failure, and diabetic retinopathy [4]. Studies have indicated that DM is strongly associated with DHF, which leads to LV stiffening, resulting in diastolic dysfunction [5]. Hypertension (HT) is a chronic medical condition in which blood pressure in the arteries is elevated [6]. HT is the most important preventable risk factor for premature death worldwide, and it increases the risk of systolic HF and DHF [7].

In general, physicians pay more attention to the associations of risk factors and outcomes. However, the interaction of risk factors on outcomes was often neglected. The term of interaction refers to the situation where the effect of one risk factor on a certain disease outcome is different across strata of another risk factor, or vice versa. It is important to clarify the relationship between risk factors for DHF. The effect modification refers to the size of an effect or to the difference in an association compared to another factor. This information can be of ben-

efit to clinicians in the prediction, prevention, and treatment of DHF. Our previous study indicated that the interaction between metabolic syndrome (MetS) and uric acid (UA) influenced DHF [8]. In addition, our previous studies reported that metabolic syndrome was associated with diastolic and/or systolic heart failure [9, 10]. A biomedicine study demonstrated that the combination of DM and HT on determinants of endothelial adhesiveness was differed according to the additive effects of separate risk factors [11]. The association between DHF and DM or HT has been well documented [1-6]. However, the extent to which the interaction between DM and HT affect DHF is unknown. The purpose of this study focused on elucidating whether both risk factors act synergistically to influence the outcome.

Methods and materials

Study population

One hundred-thirty three patients with DHF (cases) were recruited from those who attended the department of cardiology of Hua Shan Hospital affiliated to Fudan University or who were treated in the department between July 2008 and July 2011. Patients were selected if they were 35-70 years and had been diagnosed with DHF. One hundred-eighteen age- and sex-matched patients without DHF from the same cohort were recruited as controls. Patients with potential confounding factors that may have influenced diastolic heart function were excluded from the study. The exclusion criteria were as follows: (1) history or findings of cardiovascular disease, including systolic HF (left ventricular ejection fraction [LVEF] <50%), significant valvular heart disease (i.e., more than a mild valvular insufficiency or stenosis), hyperthyroidism or hypothyroidism and dilated or hypertrophic cardiomyopathy; (2) pregnancy or lactating; and/or (3) a major systemic illness or serious liver or renal disease. Written consent was obtained from all the patients before the study. The present study was approved by the Ethics Committee of the Huashan Hospital, Shanghai, China. The study was a case-control study performed in patients.

The patients' medical histories and medication and history of smoking habits, were documented, and they underwent a laboratory assessment of cardiovascular disease risk factors and standardized echocardiographic examination. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the patient's height in meters. The systolic and diastolic blood pressure (SBP and DBP) values were based on the means of two physician-obtained measurements on the left arm of the seated participant. HT was defined according to a BP reading of 140/90 mmHg or current antihypertensive therapy. DM was defined by the oral glucose tolerance test (OGTT) and either glycosylated hemoglobin (HbAlc) ≥6.5% or the use of insulin or hypoglycemic medications.

Laboratory assays

Peripheral venous blood samples were collected in tubes in the fasting state in all subjects. Fasting plasma glucose (FPG) was quantified by the glucose oxidase procedure; HbA1c was measured by ion-exchange high-performance liquid chromatography (Bio-Rad, Hercules, CA, USA). The homeostasis model assessment insulin resistance estimate (HOMA-IR) was calculated as the serum glucose (mmol/L) multiplied by the plasma insulin (mU/mL) divided by 22.5. The serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, triglyceride (TG) levels, creatinine (Cr), and uric acid UA levels were measured by an enzymatic method with a chemical analyzer (Hitachi 7600-020, Tokyo, Japan). The day-to-day and inter-assay coefficients of variation at the central laboratory in our hospital for all analyses were between 1% and 3%.

Echocardiography

Echocardiography examinations were performed with a Vingmed System 5 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway). Conventional echocardiography measurements were performed according to American Society of Echocardiography guidelines. The left ventricular mass (LVM) was calculated using the Devereux formula. The LVM was corrected for the body surface area (BSA) to obtain the LVM index (LVMI). The left atrial diameter (LAD) and the aortic root dimension (AOD) were also measured. The LV systolic function was assessed by calculation of the LVEF. The diastolic function was assessed by determining the E-to-A ratio (E/A) and the deceleration time (DT), where E and A represent the

Table 1. Baseline characteristics of subjects

	DHF (*N* = 133)	Control (*N* = 118)	*P* value
Gender M/F (M, %)	53/80 (39.85%)	50/68 (42.37%)	0.685
Age	57.75±16.05	54.82±16.2	0.152
Height	165.51±7.04	166.71±9.23	0.245
Weight	65.08±10.98	65.11±13.65	0.981
BMI	23.71±3.78	23.23±3.93	0.323
HR	72.67±13.46	71.1±10.76	0.325
SBP	126.16±15.93	127.51±21.1	0.566
DBP	77.26±9.8	76.61±13.09	0.655
Past medical history, %			
MetS (yes, %)	34 (25.56%)	17 (14.41%)	0.011
HT (yes, %)	91 (68.42%)	45 (38.46%)	<0.001
DM (yes, %)	42 (31.58%)	24 (20.51%)	0.048
Smoking (yes, %)	31 (23.31%)	35 (29.91%)	0.237
Laboratory test			
FPG	5.81±2.47	6.11±2.55	0.347
PBG	7.76±3.52	8.81±4.85	0.158
FINS	12.90±11.86	9.81±13.99	0.272
HbAlc	6.47±1.84	6.93±2.57	0.285
TC	4.47±1.02	4.4±1.19	0.595
TG	1.59±1.18	1.5±1.12	0.532
HDL	1.14±0.3	1.15±0.3	0.817
LDL	2.58±0.84	2.50±0.94	0.465
Ccr	83.98±30.15	84.5±31.27	0.080
UA	0.36±0.11	0.32±0.08	0.003
Echocardiography measurement			
EF	65.00±7.08	65.05±5.95	0.951
LAD	37.20±5.28	34.4±4.7	<0.001
DT	218.34±76.59	198.22±22.73	0.002
LVMI	118.77±40.47	102.33±31.4	<0.001
Medical therapy, %			
Anti-hypertension drug	54 (40.6%)	45 (38.46%)	0.73
Hypoglycemia drug	36 (27.07%)	26 (22.22%)	0.376
Anti-lipidemia drug	31 (23.31%)	29 (24.58%)	0.814

Note: BMI-Body mass index, SBP-systolic blood pressure, DBP-diastolic blood pressure, MetS-metabolic syndrome, HT-Hypertension, DM-Diabetes mellitus, FPG-fasting plasma glucose, PBG-plasma blood glucose, HbA1c-glycated hemoglobin, TC-serum total cholesterol, HDL-high-density lipoprotein cholesterol, TG-triglyceride, UA-uric acid, LDL-low density lipoprotein cholesterol, Ccr-creatinine clearance rate, LVMI-left ventricular mass index, LAD-left atrial diameter, DT-deceleration time, LVEF-left ventricular ejection fraction, HR-heart rate.

early and late velocities, respectively. We used the definition of DHF recommended by the European Society of Cardiology guidelines in 2008 [12]. The diagnosis of DHF was based on the following three conditions: (1) presence of signs and/or symptoms of chronic heart failure, (2) presence of normal or only mildly abnormal LV systolic function (LVEF ≥50%), and (3) evidence of diastolic dysfunction (abnormal LV relaxation or diastolic stiffness). The diastolic function of the LV was evaluated on the basis of the ventricular filling pattern in patients with HF. A Normal LV diastolic function was defined as an E/A ratio >1 and 160 ms <DT <240 ms. The LV diastolic dysfunction was defined as an E/A ratio <1 and a DT ≥260 ms or an E/A ratio >2 and a DT <150 ms.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine whether continuous variables followed a normal distribution. Variables that were not normally distributed were log-transformed to an approximate normal distribution for analysis. The results are expressed as the mean ± SD or the median, unless otherwise stated. The characteristics of the subjects according to DHF groups were assessed using a one-way analysis of variance (ANOVA) for continuous variables and the χ^2 test for categorical variables.

Univariate linear regression was performed to determine the variables associated with DHF and to estimate confounding factors possibly disturbing the relationship between HT or DM and DHF. Multivariable logistic linear regression (MLR) was carried out to determine the independent contribution of the variables to DHF. To better investigate the effect of the interaction of HT and DM on DHF, stratification analysis was performed. To identify the interaction term after controlling for confounding factors, MLR was conducted, with two variables and its interaction item included. Potential confounding variables, including age, gender, smoking, lipid profiles, UA, LAD, and LVMI, were controlled in the regression model. Three parameters of the relative excess risk due to interaction (RERI), the proportion attrib-

Table 2. Univariable association analysis of diastolic heart failure

Variable	*β*	S.E.	*P* value	*OR*
Age	-0.004	0.008	0.611	0.99
Gender	-0.038	0.257	0.882	0.96
Height	-0.002	0.016	0.888	0.99
Weight	-0.007	0.01	0.496	0.99
Smoking	0.340	0.288	0.238	1.40
BMI	0.018	0.033	0.583	1.01
SBP	1.086	0.908	0.232	2.96
DBP	0.273	0.961	0.776	1.31
FPG	0.064	0.054	0.237	1.06
HDL	0.183	0.439	0.677	1.20
TG	0.167	0.242	0.490	1.18
LAD	0.114	0.028	<0.001	1.12
LVMI	0.013	0.004	0.001	1.01
UA	0.004	1.396	0.005	1.00
HT	1.243	0.266	<0.001	3.16
DM	0.581	0.295	0.0170	2.00
MetS	0.801	0.213	<0.001	2.22

Note: BMI-Body mass index, SBP-systolic blood pressure, DBP-diastolic blood pressure, MetS-metabolic syndrome, HT-Hypertension, DM-Diabetes mellitus, FPG-fasting plasma glucose, PBG-plasma blood glucose, HbA1c-glycated hemoglobin, TC-serum total cholesterol, HDL-high-density lipoprotein cholesterol, TG-triglyceride, UA-uric acid, LDL-low density lipoprotein cholesterol, Ccr-creatinine clearance rate, LVMI-left ventricular mass index, LAD-left atrial diameter, DT-deceleration time, LVEF-left ventricular ejection fraction.

utable to interaction (AP), and the synergy index (S) were used to estimate measures of interaction on an additive scale. The first bootstrap percentile method was adopted to calculate the CI around the estimate of interaction. From the original data set, 10,000 bootstrap samples (with replacement) were taken, each of which was the same size as the original sample. The three parameters of RERI, AP, and S were then estimated in each of these new samples and the 95% CI for the three parameters were estimated as the 2.5th and 97.5th percentiles of the resulting bootstrap sampling distribution.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the relative risk of HT and/or DM with DHF. Tests were two-sided, and a *P* value of <0.05 was considered significant. The level of significance for the interaction term was a two-sided *P* value <0.1. The results were analyzed using the Statistical Package for Social Sciences for Windows version 16.0 (SPSS, Chicago, IL, USA).

Results

The baseline clinical characteristics of the 251 subjects were grouped into DHF groups and a control (**Table 1**). There were 53 males and 80 females (mean age, 57.75 ± 16.05 years) in the case group and 50 males and 68 females (mean age, 54.82 ± 16.2 years) in the control. The BMI, SBP, DBP, and lipid and lipoprotein profile were similar between the case and the control group (*P*>0.05), but the serum UA was significantly different (*P*<0.001). The LVEF was not significantly different between the two groups, but the LAD, DT, and LVMI were significantly different (*P*<0.05). MetS, HT, and DM were more prevalent in the cases, and oral medications for medical therapy were significantly different (*P*<0.05).

Association analysis for DHF

To estimate the association of DM or HT and other risk factors with DHF, univariate logistic regression models were developed to include gender, age, height, weight, BMI, SBP, DBP, FPG, TG, HDL, other lipid profiles, UA, echocardiography parameters of LVEF, past medical history, and medical therapy (**Table 2**). The univariate analyses indicated that the variables of LAD, LVMI, and UA were significantly associated with DHF (*P*<0.05 for all). MLRs analyses controlling for confounding factors were carried out to determine the extent to which DHF was governed by DM and HT. After adjusting for age, gender, BMI, and smoking, Model 1 indicated that HT and DM was significantly and independently associated with DHF, respectively (*P*<0.001 for two variables, **Table 3**). Similarly, significant results were reported in Model 2 and Model 3 controlling for relevant confounding factors, respectively (*P*<0.05 for two variables in both models, **Table 3**).

Interaction analysis of DM and HT on DHF

Patients with DHF accounted for 37.26% of the non-HT group and 65.25% of the HT group. In patients with HT, the OR for DHF was 3.16 (*P*<0.01). Patients with DHF accounted for 48.35% and 65.22% of the patients without DM and with DM, respectively. The OR for DHF was 2.00 (*P* = 0.017) in patients with DM.

Table 3. Multivariable logistic regression analysis of diastolic heart failure, including hypertension and diabetes

Model	Variable	β	S.E.	*P* value	OR (95% CI)
Model 1	Hypertension	1.102	0.272	<0.001	3.01 (1.76-5.13)
	Diabetes	0.502	0.314	0.031	1.65 (1.09-3.05)
Model 2	Hypertension	1.147	0.277	<0.001	3.14 (1.82-5.41)
	Diabetes	0.454	0.319	0.035	1.57 (1.04-2.94)
Model 3	Hypertension	0.855	0.308	0.005	2.35 (1.28-4.29)
	Diabetes	0.652	0.358	0.047	1.91 (1.05-3.87)

Note: Model 1: adjusted for age, gender, BMI; Model 2: adjusted for age, gender, BMI, TG, HDL, LDL and UA; Model 3: adjusted for age, gender, BMI, TG, HDL, LDL, UA, LA and LVMI.

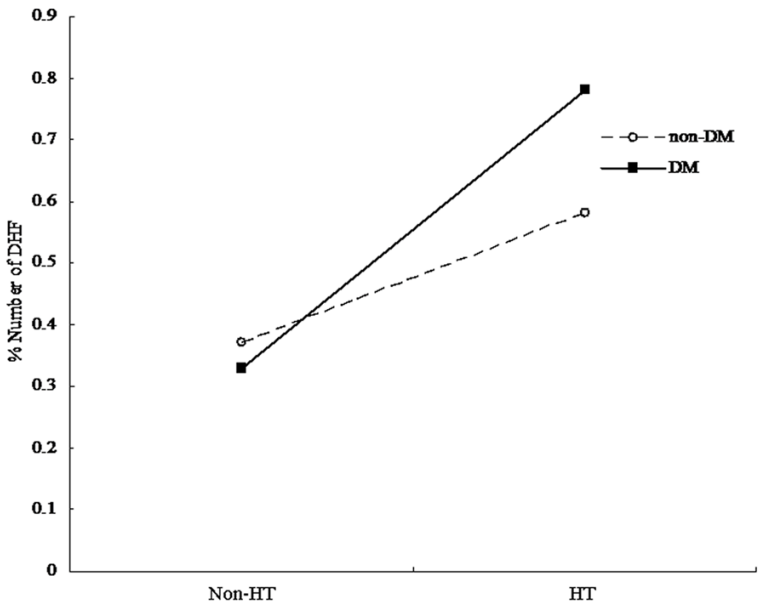

Figure 1. Proportion of diastolic heart failure (DHF) in the case group according to diabetes mellitus (DM) and hypertension (HT). A solid line represents patients with DM; a dash line represents patients without DM.

Moreover, the proportion of patients with DHF was 78.00% of diabetic patients with HT (**Figure 1**). Stratification analysis indicated that the OR for DHF was 2.13 (*P* = 0.007, **Table 4**) in nondiabetic patients and that the OR was 8.67 (*P*<0.001) in diabetic patients. Effect modification between HT and DM on DHF was detected (*P* value for interaction = 0.036). To assess the interaction between HT and DM on DHF after controlling for confounding factors, three MLR models were developed that included the main effect variables of DM and HT and their interaction item. All the models suggested that the interactions detected were significant (*OR* = 3.11-3.45, *P*<0.10, **Table 5**). The interaction on an additive scale was also estimated (RETI = 2.13-2.69, AP = 0.38-0.49 and S = 4.11-6.80, **Table 5**). Stratification analysis and MLR analysis demonstrated that HT and DM acted synergistically to affect DHF.

Discussion

We carried out a case-control study to evaluate the association between HT or DM and DHF in Chinese patients in the hospital and to estimate the effect modification of both risk factors on the outcome. We recruited 251 patients in our hospital (133 cases and 118 age- and gender-matched controls). The demographic measurements and the results of the laboratory assay were similar between the case and the control group. Doppler echocardiography has become a well-accepted, reliable noninvasive tool to measure the LV diastolic function to diagnose DHF. Stratification analysis and MLR analysis were performed to evaluate the effect modification of both risk factors on DHF.

The findings from the present study showed that HT and DM were strongly and independently associated with DHF. Univariate association analysis showed that HT and DM exhibited a strong and significant association with DHF. After adjustments for potential confounding factors, both risk factors remained significantly associated with DHF independently in three MLR models. Similar results were reported in previous studies [13-20]. These showed that 60% of patients with DHF were hypertensive. Our results are consistent with this finding. The underlying pathophysiological abnormality in diastolic dysfunction is impaired relaxation of the left ventricle, resulting in reduced LV compliance. HT plays a vital role in the development of diastolic

Table 4. Interaction of hypertension and diabetes mellitus in diastolic heart failure

	Case (*n* = 133)	Control (*n* = 118)	*OR*	*P* value
Entire sample				
Without hypertension	41	69		
Hypertension	92	49	3.16	<0.001
Patients without diabetes mellitus				
Without hypertension	35	56		
Hypertension	52	39	2.13	0.007
Patients with diabetes mellitus				
Without hypertension	6	13		
Hypertension	40	10	8.67	<0.001

P for interaction = 0.036.

Table 5. Multiple logistic regression analysis of the effect of the interaction of hypertension and diabetes on diastolic heart failure

Variable	β	S.E.	*P* value	OR	95% CI
Model 0					
Hypertension	0.937	0.309	0.002	2.55	1.39-4.68
Diabetes	-0.274	0.541	0.524	0.76	0.26-2.20
Hypertension by diabetes	1.15	0.602	0.073	3.16	0.97-10.28
RERI		3.21			0.32-6.10
AP		0.52			-0.10-1.15
S		3.91			0.31-7.50
Hypertension	0.839	0.307	0.006	2.31	1.26-4.22
Diabetes	-0.262	0.551	0.634	0.76	0.26-2.26
Hypertension by diabetes	1.18	0.678	0.082	3.25	0.96-12.29
RERI		2.69			0.27-5.12
AP		0.47			-0.09-1.04
S		4.39			0.35-8.44
Model 2					
Hypertension	0.869	0.311	0.005	2.38	1.29-4.38
Diabetes	-0.24	0.552	0.663	0.78	0.26-2.32
Hypertension by diabetes	1.136	0.682	0.096	3.11	0.95-11.84
RERI		2.88			0.29-5.48
AP		0.49			-0.1-1.1
S		4.11			0.33-7.9
Model 3					
Hypertension	0.56	0.351	0.011	1.75	1.08-3.48
Diabetes	-0.093	0.58	0.873	0.91	0.29-2.84
Hypertension by diabetes	1.239	0.737	0.043	3.45	1.01-14.63
RERI		2.13			0.21-4.05
AP		0.38			-0.08-0.85
S		6.80			0.54-13.07

Note: Model 0-unadjusted for confounding factors; Model 1-adjusted for age, gender and BMI; Model 2-adjusted for age, gender, BMI, TG, HDL, LDL and UA; Model 3-adjusted for age, gender, BMI, TG, HDL, LDL, UA, LA, and LVMI; RERI-the relative excess risk due to interaction, AP-the proportion attributable to interaction, and S-the synergy index.

dysfunction. Elevations of BP alter LV diastolic function via several mechanisms. One of these involves the development of LV hypertrophy. This is a short-term adaptive response, which reduces local LV wall stress, leading to poor LV compliance and a vicious cycle of ever greater LV filling pressures and cardiac hypertrophy [13-20]. DM involves multiple complex metabolic reactions, such as glycotoxicity, altered insulin signaling, increased cytokine activity, and interstitial deposition of triacylglycerol, which may all directly or indirectlyimpact on myocardial function [16-21]. Thus, HT and DM are strong independent predictors of DHF, and this finding was confirmed by our study and other previous studies [1-6].

Another important finding in the present study was that DM and HT synergistically affected the development of DHF. The univariate and multiple association analysis suggested that DM and HT are significantly associated with DHF (**Table 2**). The stratification analysis and the MLR models detected an interaction effect between DM and HT on DHF. The additive model and the multiplication model showed that HT and DM acted synergistically to influence the development of LV diastolic dysfunction. The positive interaction effect was estimated by using parameters of RETI >0, AP >0 and S >1, suggesting that the combined effect of DM and HT on DHF is greater by more than two times than the sum of the individual effects of the two factors. As mentioned above, HT alters LV diastolic function,

and DM leads to reduced energy availability. Furthermore, both factors lead to endothelial dysfunction via additive and synergistic effects [22]. Thus, diabetic patients with HT are susceptible to DHF progression. In this study, we did not propose to delineate the mechanisms underlying the modification of DM by HT and the development of DHF. A large-scale case-control study or a cohort study will be conducted to confirm this finding, with resulting benefits for clinical practice in term of the prediction, prevention, and treatment of DHF.

Several limitations of this study deserve comment. First, it used a hospital-based design, which is susceptible to selection bias. Second, the sample size was moderate, limiting its ability to detect significant association and interaction results. Third, the MLR models pointed to a moderate influence of DM and HT and interaction effects on DHF. Other environmental factors may contribute to the unexplained variation in DHF prevalence. Finally, it is important to mention that our study was conducted in Chinese individuals, and our findings may not be relevant to people of other ethnicities.

In conclusion, our findings indicated that HT and DM are independently associated with DHF and that both risk factors act synergistically to affect DHF. The findings support the hypothesis that HT and DM interactions are involved in the regulation of DHF progression. The present observations provide evidence that improving metabolic control and reducing BP may coordinately and synergistically inhibit the progression of DHF.

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Disclosure of conflict of interest

None.

Abbreviations

AOD, Aortic root dimension; AP, Proportion attributable to interaction; BMI, Body mass index; BSA, Body surface area; Ccr, Creatinine clearance rate; CI, Confidence interval; Cr, Creatinine; DBP, Diastolic blood pressure; DHF, Diastolic heart failure; DM, Diabetes mellitus; DT, Deceleration time; E/A, E-to-A ratio; FPG, Fasting plasma glucose; HbAlc, Glycosylated hemoglobin; HDL, High-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment insulin resistance estimate; HT, Hypertension; LDL, Low-density lipoprotein cholesterol; LV, Left ventricle; LVEF, Left ventricular ejection fraction; LVM, Left ventricular mass; LVMI, Left ventricular mass index; MetS, Metabolic syndrome; MLR, Multivariable logistic linear regression; OGTT, Oral glucose tolerance test; OR, Odds ratios; PBG, Postprandial blood glucose; RERI, Relative excess risk due to interaction; S, Synergy index; SBP, Synergy index; TC, Serum total cholesterol; TG, Triglyceride; UA, Uric acid.

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