Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
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ORIGINAL RESEARCH

Interaction of General or Central Obesity and Hypertension on Diabetes: Sex-Specific Differences in a Rural Population in Northeast China

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Purpose: Some studies have established an association between hypertension or obesity and the risk of diabetes. This study aimed to examine the interaction of hypertension and obesity on diabetes.

Participants and Methods: The data of 11,731 Chinese men and women were analyzed from the 2012–2013 Northeast China Rural Cardiovascular Health Study. The interaction was examined by both additive and multiplicative scales. General obesity was measured by body mass index (BMI); central obesity was defined by waist circumference (WC), waist-to-height ratio (WHtR) and waist-to-hip ratio (WHpR).

Results: After controlling for potential confounders, the odds ratios for diabetes were 3.864 (3.205–4.660), 4.500 (3.673–5.514), 4.932 (3.888–6.255) and 4.701 (3.817–5.788) for the combinations of hypertension and BMI, WC, WHtR or WHpR, respectively, which had the highest risk of diabetes among the four combinations. Notwithstanding the multiplicative interactions showed statistically significant in all analyses, the results of additive interactions were not consistent, suggesting the diabetes risk from female BMI (relative excess risk due to interaction (RERI): 1.136, 95% CI: 0.127–2.146, attributable proportion due to interaction (AP): 0.267, 95% CI: 0.057–0.477, synergy index (S):1.536, 95% CI: 1.017–2.321) or female WHpR (RERI: 1.076, 95% CI: 0.150–2.002, AP:0.205, 95% CI: 0.037–0.374, S:1.340, 95% CI: 1.012–1.775) was additive to the risk from hypertension.

Conclusion: The findings suggest that high BMI and high WHpR have synergistic interactions with hypertension on the risk of diabetes for females. The results of this study also suggest that BMI and WHpR, rather than WC, should be used for the diagnosis of metabolic syndrome in Chinese population.

Keywords: interaction, diabetes, hypertension, general obesity, central obesity

Introduction

The prevalence of diabetes mellitus, as one of the most important chronic non-communicable diseases, is increasing in China and across the world.[1,2] Since 1980, the prevalence of diabetes has been increasing in almost every country in the world;[1] in 2015, 415 million people worldwide had diabetes, and it is estimated to increase to 642 million by 2040.[3] It is estimated that from 1994 to 2013, the total prevalence of diabetes in China rose from 2.5% to 10.9%, which shows that the harm of diabetes to the health of the Chinese population is gradually increasing.[2,4]

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DovePress
http://doi.org/10.2147/DMSO.S295960

Compared with individuals without diabetes, people with diabetes had a 15% increased risk of death from all causes.[5] Accordingly, diabetes has become an important public health issue in China and even the world. Controlling the occurrence and development of diabetes is an inevitable problem in reducing the economic burden on global health.

Hypertension is an important risk factor for diabetes, and because of the overlap of risk factors for diabetes and hypertension, the two diseases often coexist. A large prospective study of the American population showed that patients with hypertension were 2.5 times more likely to develop diabetes than normal people.[6] Similarly, a recent follow-up study in Daqing of China found that the risk of diabetes increased by 9% for every 10 mmHg increase of systolic blood pressure in hypertensive patients.[7] Growing studies have revealed that elevated blood pressure significantly increased the risk of long-term vascular complications in diabetic patients.[8–10]

Along with hypertension, obesity has also been considered as a significant risk factor for diabetes mellitus. Previous studies have demonstrated that the risk of diabetes increased in a dose-dependent manner with an increase of body mass index (BMI); the risk of diabetes increased by 12% for every unit increase of BMI.[11–13] Individuals with a body mass index >35 kg/m^2 were 20 times more likely to develop diabetes than those with a body mass index between 18.5–24.9 kg/m^2.[14] Furthermore, clinical trials supported that obesity was closely related to insulin resistance, prediabetes, and the development of diabetes.[15,16] Besides, accumulating evidence indicated that central obesity, measured by waist circumference, waist-to-height ratio and waist-to-hip ratio, was considered an independent predictor for diabetes.[17–20] Due to the limited number of prospective studies and only covering limited ethnic groups, the evidence based on these studies lacks certainty and the main reason may be that they are confounded by other concurrent diseases, such as dyslipidemia and hypertension.[21]

Considering the potential association between hypertension, obesity and diabetes, as well as their interactions, it is necessary to better understand the relationship between these conditions. Therefore, our study aimed to examine the individual and interactive associations of general obesity (defined by body mass index) or central obesity (defined by waist circumference, waist-to-height ratio and waist-to-hip ratio) and hypertension associated with diabetes, based on the Northeast China Rural Cardiovascular Health Study (NCRCHS) data. We also intended to explore the relative risk of having diabetes according to the presence of obesity, hypertension, or both conditions.

Participants and Methods

Study Population

The present study was performed using the data of NCRCHS, a representative sample of the rural population in Northeast China. We used the cross-sectional epidemiological data of NCRCHS, which was conducted between January 2012 and August 2013. Detailed information about NCRCHS has been extensively described elsewhere.[22] Participants had attended face-to-face interviews and examinations. Of the 11,956 subjects whose data were used in the NCRCHS, individuals under the age of 35 years and those with incomplete biochemical data were excluded from the present study. As a result, 11,734 subjects were enrolled in our work. Written informed consent was obtained from all participants. The Ethics Committee of China Medical University approved the protocol of this study.

Data Collection

Details of data collection were presented in our previous works.[22] Briefly, cardiologists and nurses participated in a training course, passed a uniform exam, and obtained the qualification to collect information through self-administered questionnaires. The information was about demographic data, anthropometric parameters, and health-related behaviors. The quality assurance process of data collection was performed by the central steering committee with a subcommittee.

The questionnaires were designed to gather detail information from subjects. Drinking and smoking status were split into the current status and others according to subjects' self-reports.

After resting for at least five minutes in a completely relaxed and sitting state, each participant was measured blood pressure, taken three times, and performed by two randomly selected staff. The average value of three consecutive readings was used as the result of blood pressure.

After subjects took off heavy clothes and shoes, anthropometric indices of the participants were measured. The body weight of participants was measured by calibrated digital scales and height was measured by calibrated portable stadiometers. The waist circumference

and hip circumference were measured at the umbilicus and maximal gluteal protrusion, respectively, using non-elastic tape. The weight, height, waist circumference and hip circumference were recorded to the nearest 0.1 kg, 0.1 cm, 0.1 cm and 0.1 cm respectively. The body mass index was calculated as follows: BMI = weight/height (kg/m^2). The waist-to-hip ratio (WHpR) and waist-to-height ratio (WHtR) were determined as follows: WHpR = waist circumference (cm)/hip circumference (cm); WHtR = waist circumference (cm)/height (cm).

Blood samples of participants were collected in the morning after fasting for more than 12 hours. For long-term storage, the serum and plasma were subsequently separated by calibrated centrifuge. The fasting blood samples were tested to collect biochemical information, including fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and serum creatine (Scr).

Definition

General obesity was determined as a BMI ≥28 kg/m^2, regardless of gender.[23] Central obesity was defined as a WC ≥90 cm or a WHpR ≥0.9 or a WHtR ≥0.5 for male and a WC ≥80 cm or a WHpR ≥0.85 or a WHtR ≥0.5 for female.[24–26] Hypertension was defined by systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, previous hypertension diagnosis, or being on an anti-hypertensive treatment.[27] Diabetes was defined by either a fasting plasma glucose ≥7.0 mmol/L or self-reported physician-diagnosed diabetes or being on oral hypoglycemic agents.[28]

Statistical Analysis

For categorical variables, the results were shown as frequencies (percentages). Also, the following continuous variables were exhibited as mean values ± standard deviation (SD) or median (interquartile). The chi-square test was taken to compare categorical variables between the two groups. Similarly, Students' *t*-test or Mann–Whitney test was taken to compare continuous variables between the two groups. For ordinal category variables, the rank-sum test was employed to compare between two groups for the sake of making the best of the ordinal information.

Spearman correlation coefficient was applied to evaluate the relationship between fasting plasma glucose levels and variables (age, BMI, WC, WHtR, WHpR, SBP, DBP, TC, TG, HDL-C, LDL-C and eGFR). Multivariate logistic regression analysis was conducted to estimate the correlation of diabetes with hypertension, central obesity in various criteria, and general obesity, which exhibited with adjusted odds ratio (OR) and 95% confidence interval (95% CI). Subgroup analyses were performed after categorizing the participants in accordance with age, sex, and presence of hypertension with or without obesity in four different definitions. Based on the results of correlation coefficients and the established risk factors of hypertension, obesity and diabetes, certain variables (including Sex, age, current smoking, current drinking, TG, HDL-C and eGFR) were adjusted for the present analyses.

Interactions among general obesity, central obesity, and hypertension on the additive and multiplicative measures were used to examine the association with diabetes risk. Additive interaction was evaluated using the relative excess risk due to interaction (RERI) which is calculated as: RERI = OR_{11} - (OR_{10}-OR_{01}) + 1, the attributable proportion due to interaction (AP) which is calculated as: AP = RERI/OR_{11}, and the synergy index (S) which is calculated as: S = (OR_{11} − 1)/[(OR_{10}–1) + (OR_{01}–1)].[29,30] Multiplicative interaction was evaluated using the ratio of ORs: OR_{11}/(OR_{10} × OR_{01}).[30] A two-tailed P value <0.05 was regarded as statistically significant. All analyses were conducted using SPSS 25.0 software (IBM corp).

Results

Characteristics of the Study Population

Of the 11,734 subjects who enrolled in our study, a total of 1219 were divided as having diabetes. Table 1 exhibits the characteristics of this study population. Among the total participants with diabetes, males were less than half and the mean age was 57.6 ± 9.7 years. Subjects with diabetes had higher age, waist circumference, BMI, SBP, DBP, FPG, TC, TG, and LDL-C, with lower HDL-C, and eGFR, compared to those without diabetes. The proportion of participants with current smoking was lower in the diabetes group. General obesity, hypertension and central obesity by WC, WHtR and WHpR presented a higher prevalence among individuals with diabetes. Similarly, there were no differences in above-mentioned covariates between normal and diabetes groups.

Figure 1 presents the prevalence of diabetes mellitus according to the presence of hypertension and general or central obesity in three definitions. The prevalence of diabetes was highest in participants with both conditions among

Table 1 Characteristics of Study Population Divided by Diabetes Mellitus and Sex

	Total			Men			Women		
	Diabetes Mellitus			Diabetes Mellitus			Diabetes Mellitus		
	No (n = 10,515)	Yes (n = 1219)	p value	No (n = 4894)	Yes (n = 538)	p value	No (n = 5621)	Yes (n = 681)	p value
Age (years)	53.4 ± 10.6	57.6 ± 9.7	<0.001	54.1 ± 10.8	56.5 ± 10.3	<0.001	52.8 ± 10.3	58.4 ± 9.1	<0.001
Male (%)	4894 (46.5)	538 (44.1)	0.110						
WC (cm)	81.9 ± 9.7	87.2 ± 9.5	<0.001	83.3 ± 9.6	88.3 ± 9.6	<0.001	80.7 ± 9.6	86.2 ± 9.2	<0.001
WHtR	0.5 ± 0.1	0.5 ± 0.1	<0.001	0.5 ± 0.1	0.5 ± 0.1	<0.001	0.5 ± 0.1	0.6 ± 0.1	<0.001
WHpR	0.9 ± 0.1	0.9 ± 0.1	<0.001	0.9 ± 0.1	0.9 ± 0.1	<0.001	0.8 ± 0.1	0.9 ± 0.1	<0.001
BMI (kg/m^2)	24.6 ± 3.7	26.2 ± 3.7	<0.001	24.6 ± 3.5	26.0 ± 3.5	<0.001	24.7 ± 3.8	26.3 ± 3.8	<0.001
SBP (mmHg)	140.5 ± 23.0	153.3 ± 24.1	<0.001	142.5 ± 22.2	154.3 ± 23.6	<0.001	138.7 ± 23.6	152.6 ± 24.5	<0.001
DBP (mmHg)	81.6 ± 11.6	85.5 ± 12.5	<0.001	83.3 ± 11.6	87.7 ± 12.5	<0.001	80.2 ± 11.4	83.8 ± 12.1	<0.001
FPG (mmol/L)	5.5 (5.1–5.9)	8.2 (7.3–10.3)	<0.001	5.5 (5.2–5.9)	8.2 (7.4–10.5)	<0.001	5.4 (5.1–5.8)	8.2 (7.3–10.1)	<0.001
TC (mmol/L)	5.2 ± 1.1	5.6 ± 1.3	<0.001	5.1 ± 1.0	5.4 ± 1.2	<0.001	5.2 ± 1.1	5.8 ± 1.3	<0.001
TG (mmol/L)	1.2 (0.9–1.8)	1.8 (1.2–2.8)	<0.001	1.2 (0.8–1.8)	1.8 (1.1–2.8)	<0.001	1.2 (0.9–1.8)	1.9 (1.2–2.8)	<0.001
HDL-C (mmol/L)	1.4 ± 0.4	1.3 ± 0.3	<0.001	1.4 ± 0.4	1.3 ± 0.4	<0.001	1.4 ± 0.3	1.3 ± 0.3	<0.001
LDL-C (mmol/L)	2.9 ± 0.8	3.2 ± 0.9	<0.001	2.9 ± 0.8	3.0 ± 0.9	<0.001	2.9 ± 0.8	3.3 ± 0.9	<0.001
eGFR ($mL/min/1.73\ m^2$)	93.5 ± 15.6	89.2 ± 18.0	<0.001	94.4 ± 15.1	92.1 ± 17.3	<0.001	92.7 ± 15.9	87.0 ± 18.2	<0.001
Current smoking (%)	3743 (35.6)	371 (30.4)	<0.001	2800 (57.2)	282 (52.4)	0.033	943 (16.8)	89 (13.1)	0.014
Current drinking (%)	2374 (22.6)	258 (21.2)	0.263	2203 (45.0)	246 (45.7)	0.753	171 (3.0)	12 (1.8)	0.060
General obesity (%)	1727 (16.4)	371 (30.4)	<0.001	766 (15.7)	146 (27.1)	<0.001	961 (17.1)	225 (33.0)	<0.001
High WC (%)	4239 (40.3)	778 (63.8)	<0.001	1259 (25.7)	244 (45.4)	<0.001	2980 (53.0)	534 (78.4)	<0.001
High WHtR (%)	5865 (55.8)	962 (78.9)	<0.001	2409 (49.2)	386 (71.7)	<0.001	3456 (61.5)	576 (84.6)	<0.001
High WHpR (%)	4168 (39.6)	780 (64.0)	<0.001	1519 (31.0)	280 (52.0)	<0.001	2649 (47.1)	500 (73.4)	<0.001
Hypertension (%)	5081 (48.3)	917 (75.2)	<0.001	2531 (51.7)	400 (74.3)	<0.001	2550 (45.4)	517 (75.9)	<0.001

Note: Data are displayed as mean ± standard deviation (SD) or median (interquartile range) and numbers (percentage) as appropriate.

Abbreviations: WC, waist circumference; WHtR, waist-to-height ratio; WHpR, waist-to-hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

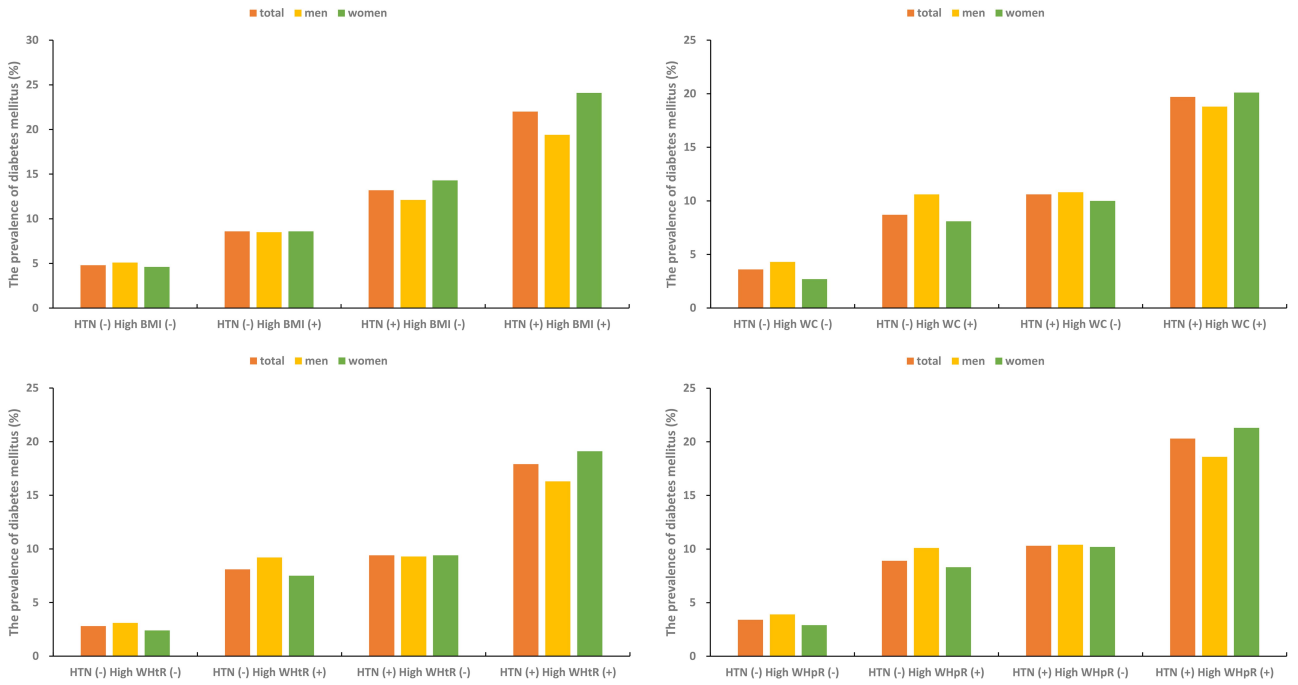

Figure 1 The prevalence of diabetes mellitus according to presence of hypertension and general or central obesity. High BMI status was determined as a BMI ≥28 kg/m^2, regardless of gender. High WC status was determined as a WC ≥90 cm for men and a WC ≥80 cm for women. High WHtR status was determined as a WHtR ≥0.5 for both men and women. High WHpR status was determined as a WHpR ≥0.9 for men and a WHpR ≥0.85 for women.
Abbreviations: HTN, hypertension; WC, waist circumference; WHtR, waist-to-height ratio; WHpR, waist-to-hip ratio.

the four groups and was higher in women than in men. About hypertension and general obesity, the prevalence of diabetes that met both conditions was 19.4% in men and 24.1% in women, compared to 5.1% in men and 4.6% in women of those without any conditions. The prevalence of diabetes with hypertension and central obesity by WC, WHtR or WHpR was respectively 18.8% for men versus 20.1% for women, 16.3% for men versus 19.1% for women and 18.6% for men versus 21.3% for women.

Correlation Between Fasting Plasma Glucose Levels with Variables

Correlation between FPG levels with various anthropometric and biochemical parameters according to gender is shown in Table 2. All correlations were statistically significant at P <0.05. Regardless of gender, FPG levels were positively associated with age, BMI, WC, WHtR, WHpR, SBP, DBP, TC, TG and LDL-C, and negatively associated with HLD-C and eGFR.

Risk Factors for Diabetes Mellitus

Table 3 shows the results of logistic regression analyses, used to confirm the independent risk factors for diabetes mellitus. All general obesity, central obesity by WC, WHtR and WHpR, and hypertension were significant risk factors for diabetes in the total population. After adjusting for sex and age, the ORs for having diabetes were 2.372 (2.073–2.714) among participants with general obesity, 2.756 (2.418–3.140), 2.800 (2.422–3.237), and 2.572 (2.-266–2.919) among subjects with central obesity by WC, WHtR and WHpR respectively, and 2.800 (2.430–3.226) among those with hypertension. These relationships remained significant after further adjustments for confounding variables, including current smoking, current drinking, TG, HDL-C, eGFR. Similarly, general obesity, high WC, high WHtR, high WHpR, and hypertension were significantly correlated with an increased risk of diabetes in men and women.

Subgroup Analysis According to Combination of Hypertension and General or Central Obesity

Table 4 presents the relative risks (ORs, 95% CI) of having diabetes based on the different combinations of hypertension and general or central obesity compared with the reference group (namely, without both hypertension and obesity). Sex, age, current smoking, current drinking, TG, HDL-C and eGFR were adjusted for the present analyses. In the total

Table 2 Correlation Coefficients of Fasting Plasma Glucose Levels with Various Anthropometric and Biochemical Parameters

	Total		Men		Women	
	r	P value	r	P value	r	P value
Age	0.199	<0.001	0.117	<0.001	0.266	<0.001
BMI	0.161	<0.001	0.157	<0.001	0.166	<0.001
WC	0.199	<0.001	0.169	<0.001	0.211	<0.001
WHtR	0.187	<0.001	0.178	<0.001	0.221	<0.001
WHpR	0.183	<0.001	0.153	<0.001	0.193	<0.001
SBP	0.234	<0.001	0.207	<0.001	0.248	<0.001
DBP	0.193	<0.001	0.179	<0.001	0.191	<0.001
TC	0.199	<0.001	0.155	<0.001	0.244	<0.001
TG	0.210	<0.001	0.185	<0.001	0.236	<0.001
HDL-C	−0.090	<0.001	−0.066	<0.001	−0.107	<0.001
LDL-C	0.164	<0.001	0.116	<0.001	0.212	<0.001
eGFR	−0.178	<0.001	−0.138	<0.001	−0.22	<0.001

Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHpR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 3 Multivariate-Adjusted Odds Ratios (ORs) of the Association of Diabetes with General Obesity, Central Obesity, and Hypertension

	Total (n = 11,734)		Men (n = 5432)		Women (n = 6302)	
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
High BMI	2.372 (2.073, 2.714)	1.912 (1.662, 2.200)	2.142 (1.741, 2.636)	1.680 (1.348, 2.094)	2.516 (2.105, 3.006)	2.081 (1.732, 2.502)
High WC	2.756 (2.418, 3.140)	2.161 (1.885, 2.477)	2.467 (2.055, 2.960)	1.962 (1.616, 2.382)	2.989 (2.467, 3.621)	2.339 (1.918, 2.853)
High WHtR	2.800 (2.422, 3.237)	2.166 (1.863, 2.520)	2.590 (2.128, 3.151)	2.064 (1.677, 2.540)	2.977 (2.396, 3.700)	2.280 (1.822, 2.852)
High WHpR	2.572 (2.266, 2.919)	2.040 (1.787, 2.327)	2.383 (1.991, 2.854)	1.891 (1.564, 2.286)	2.690 (2.245, 3.222)	2.168 (1.798, 2.614)
Hypertension	2.800 (2.430, 3.226)	2.545 (2.202, 2.941)	2.562 (2.080, 3.156)	2.389 (1.932, 2.955)	2.928 (2.414, 3.551)	2.616 (2.147, 3.188)

Notes: High BMI status was determined as a BMI ≥28 kg/m^2, regardless of gender. High WC status was determined as a WC ≥90 cm for men and a WC ≥80 cm for women. High WHtR status was determined as a WHtR ≥0.5 for both men and women. High WHpR status was determined as a WHpR ≥0.9 for men and a WHpR ≥0.85 for women. Model 1: adjust for age and sex. Model 2: adjust for age, sex, current smoking, current drinking, TG, HDL-C, eGFR.
Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHpR, waist-to-hip ratio; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

population, the odds ratios for diabetes were 3.864 (3.205–-4.660), 4.500 (3.673–5.514), 4.932 (3.888–6.255) and 4.701 (3.817–5.788) for the combinations of hypertension and BMI, WC, WHtR or WHpR, respectively, which had the highest risk of diabetes among the four combinations. The risk of diabetes in participants with both hypertension and general obesity has increased up to five-fold among the young age group (age <55 years). Among three different combinations of hypertension and high WC, high WHtR or high WHpR, subjects with both conditions were correlated with an increased risk of diabetes regardless of gender, but females showed a slightly higher risk compared to males. Among the younger age groups, subjects with both hypertension and high BMI, high WC, high WHtR or high WHpR had 4.9, 6.7, 7.6 and 6.9 times, respectively, higher risk against the reference groups.

Table 4 The Odds Ratios for the Presence of Diabetes According to Combination of Hypertension and General or Central Obesity

	Total (n = 11,734)	Age		Sex	
		<55 (n = 6431)	≥55 (n = 5303)	Men (n = 5432)	Women (n = 6302)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Combination of HTN and High BMI					
HTN (-) High BMI (-)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
HTN (-) High BMI (+)	2.338 (1.986, 2.754)	3.152 (2.473, 4.016)	1.899 (1.532, 2.353)	1.403 (0.873, 2.255)	1.756 (1.177, 2.621)
HTN (+) High BMI (-)	1.599 (1.178, 2.170)	1.986 (1.366, 2.888)	1.165 (0.668, 2.031)	2.250 (1.775, 2.852)	2.363 (1.885, 2.962)
HTN (+) High BMI (+)	3.864 (3.205, 4.660)	4.933 (3.750, 6.489)	3.065 (2.374, 3.957)	3.289 (2.472, 4.374)	4.255 (3.310, 5.471)
Combination of HTN and High WC					
HTN (-) High WC (-)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
HTN (-) High WC (+)	2.554 (2.058, 3.171)	3.233 (2.320, 4.505)	2.071 (1.559, 2.753)	2.115 (1.455, 3.074)	2.503 (1.765, 3.550)
HTN (+) High WC (-)	2.177 (1.709, 2.774)	2.715 (1.946, 3.787)	1.738 (1.213, 2.491)	2.396 (1.833, 3.131)	2.896 (2.011, 4.171)
HTN (+) High WC (+)	4.500 (3.673, 5.514)	6.672 (4.974, 8.949)	3.211 (2.431, 4.240)	3.805 (2.888, 5.013)	5.324 (3.872, 7.321)
Combination of HTN and High WHtR					
HTN (-) High WHtR (-)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
HTN (-) High WHtR (+)	3.091 (2.354, 4.058)	4.248 (2.803, 6.437)	2.265 (1.581, 3.246)	2.545 (1.760, 3.680)	2.460 (1.691, 3.580)
HTN (+) High WHtR (-)	2.438 (1.878, 3.166)	3.191 (2.208, 4.612)	1.838 (1.262, 2.676)	2.985 (2.085, 4.273)	3.175 (2.091, 4.821)
HTN (+) High WHtR (+)	4.932 (3.888, 6.255)	7.600 (5.383, 10.729)	3.329 (2.410, 4.599)	4.469 (3.230, 6.183)	5.335 (3.755, 7.581)
Combination of HTN and High WHpR					
HTN (-) High WHpR (-)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
HTN (-) High WHpR (+)	2.673 (2.149, 3.326)	3.447 (2.508, 4.738)	2.030 (1.506, 2.735)	2.153 (1.507, 3.075)	2.331 (1.662, 3.269)
HTN (+) High WHpR (-)	2.171 (1.706, 2.763)	2.719 (1.956, 3.779)	1.663 (1.165, 2.376)	2.558 (1.919, 3.409)	2.832 (2.024, 3.961)
HTN (+) High WHpR (+)	4.701 (3.817, 5.788)	6.917 (5.151, 9.289)	3.291 (2.468, 4.388)	4.100 (3.069, 5.477)	5.241 (3.858, 7.118)

Note: Age, sex, current smoking, current drinking, TG, HDL-C and eGFR were adjusted.
Abbreviations: HTN, hypertension; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHpR, waist-to-hip ratio; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Figure 2 shows the ORs of diabetes according to the presence of hypertension and general or central obesity by gender. For males and females, the odds ratios of subjects with both hypertension and obesity were largest among the four groups in all combinations. The results demonstrated the trend that the risks of diabetes in subjects with both conditions were highest among the four different combinations regardless of gender.

Interaction of Hypertension and General or Central Obesity on Diabetes

Interaction analyses of hypertension and general or central obesity on the risk of diabetes are shown in Table 5. Sex, age, current smoking, current drinking, TG, HDL-C and eGFR were adjusted for the present analyses. The multiplicative interactions were statistically significant in all analyses. However, the results of additive interactions were not consistent. In the total population, the additive interaction between hypertension and general obesity was positively significant with RERI (0.928, 95% CI: 0.272–-1.583), AP (0.240, 95% CI: 0.087–0.393) and S (1.479, 95% CI: 1.095–1.997). Similarly, the additive interactions between hypertension and high WC or high WHpR were synergistically significant in the total population. No additive interaction was found between hypertension and central obesity by WHtR on diabetes. When further performing gender analyses, the additive interactions only existed among women with hypertension and general obesity or central obesity measured by WHpR.

Discussion

In this study we explored the individual and interactive associations of hypertension and general or central obesity when estimating the risk of diabetes. After controlling for confounding factors, BMI, WC, WHtR, WHpR and hypertension were independently and positively associated with

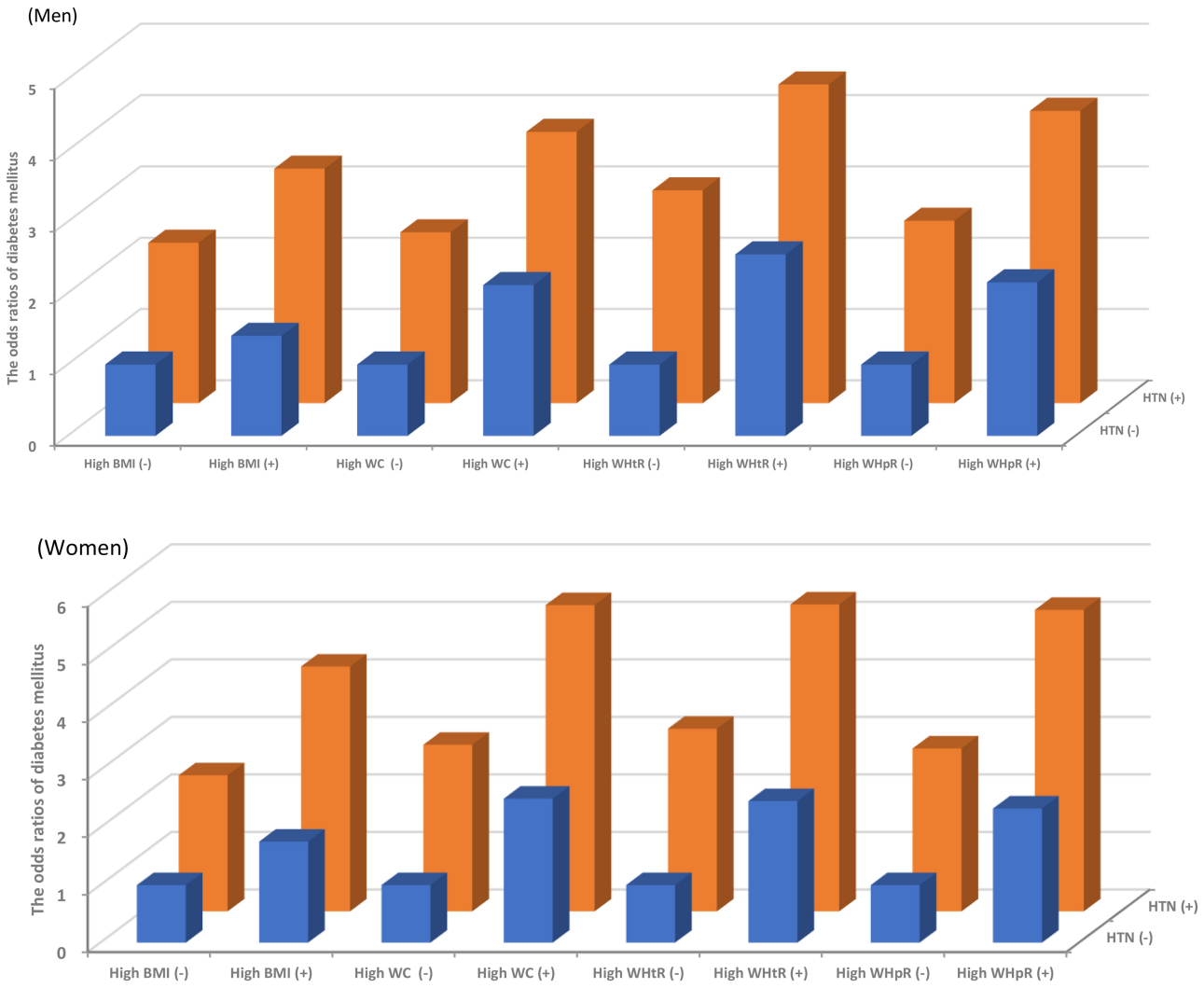

Figure 2 The odds ratios of diabetes mellitus according to presence of hypertension and general or central obesity by gender. High BMI status was determined as a BMI ≥28 kg/m^2, regardless of gender. High WC status was determined as a WC ≥90 cm for men and a WC ≥80 cm for women. High WHtR status was determined as a WHtR ≥0.5 for both men and women. High WHpR status was determined as a WHpR ≥0.9 for men and a WHpR ≥0.85 for women.
Abbreviations: HTN, hypertension; WC, waist circumference; WHtR, waist-to-height ratio; WHpR, waist-to-hip ratio.

an increased risk of diabetes. Our main finding is the combined and interactive associations across four obesity indices for hypertension and diabetes relationship. The results indicated that the combinations of hypertension and high BMI, high WC, high WHtR or high WHpR were correlated with the highest risks of diabetes, which were respectively 3.9-fold, 4.5-fold, 4.9-fold and 4.7-fold higher than that of total population without both conditions, but these factors had synergistic interactions only in women between hypertension and high BMI or high WHpR. Consequently, the results suggested that BMI-defined general obesity or WHpR-defined central obesity may be a susceptible factor for female diabetic individuals with hypertension.

To the best of our knowledge, this is the first study to estimate not only the independent and joint associations of hypertension and obesity indices on the risk of diabetes, but also the potential additive and multiplicative interactions. Further understanding of the interactions of these common modifiable risk factors can help inform preventive measures in susceptible people. Although providing more information on the impact of public health, additive interactions are often not examined.[31,32] Prior studies have documented similar results for hypertension, BMI, WC, WHtR or WHpR in association with diabetes, without exploring their interactions.[6,7,33–37] Our results suggested that the combination of obesity indices (including BMI and WHpR) and hypertension in women was correlated

Table 5 Interaction Analyses of Hypertension and General or Central Obesity Towards Diabetes

	High BMI	High WC	High WHtR	High WHpR
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Total				
Additive scale				
RERI	0.928 (0.272, 1.583)	0.768 (0.087, 1.448)	0.406 (−0.287, 1.100)	0.858 (0.295, 1.421)
AP	0.240 (0.087, 0.393)	0.171 (0.027, 0.314)	0.082 (−0.059, 0.223)	0.182 (0.067, 0.298)
S	1.479 (1.095, 1.997)	1.281 (1.012, 1.622)	1.115 (0.915, 1.359)	1.302 (1.074, 1.578)
Multiplicative scale	2.288 (1.970, 2.658)	2.409 (2.115, 2.743)	2.339 (2.054, 2.664)	2.417 (2.123, 2.751)
Men				
Additive scale				
RERI	0.636 (−0.315, 1.586)	0.292 (−0.658, 1.243)	−0.060 (−1.071, 0.951)	0.389 (−0.596, 1.374)
AP	0.193 (−0.074, 0.461)	0.077 (−0.168, 0.322)	−0.013 (−0.239, 0.213)	0.095 (−0.140, 0.329)
S	1.385 (0.823, 2.328)	1.116 (0.771, 1.616)	0.983 (0.738, 1.309)	1.144 (0.804, 1.628)
Multiplicative scale	2.023 (1.601, 2.556)	2.156 (1.764, 2.635)	2.134 (1.764, 2.580)	2.172 (1.785, 2.642)
Women				
Additive scale				
RERI	1.136 (0.127, 2.146)	0.924 (−0.065, 1.912)	0.700 (−0.360, 1.760)	1.076 (0.150, 2.002)
AP	0.267 (0.057, 0.477)	0.173 (−0.009, 0.356)	0.131 (−0.068, 0.331)	0.205 (0.037, 0.374)
S	1.536 (1.017, 2.321)	1.272 (0.953, 1.696)	1.193 (0.888, 1.602)	1.340 (1.012, 1.775)
Multiplicative scale	2.475 (2.032, 3.013)	2.541 (2.132, 3.029)	2.485 (2.074, 2.979)	2.555 (2.143, 3.046)

Note: Age, sex, current smoking, current drinking, TG, HDL-C and eGFR were adjusted.
Abbreviations: BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; WHpR, waist-to-hip ratio; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

with the highest risk of diabetes, and these factors had positive additive and multiplicative interactions.

The significance of interaction analysis is to evaluate whether the coexistence of two or more risk factors can cause the risk to be different from the sum or product of their individual effects. The interaction analysis can be examined by both additive and multiplicative scales. Additive and multiplicative interactions measure whether the disease risk caused by the joint effect of two or more risk factors is different from the sum or product of the disease risk caused by their individual effects.[29,38] Although there is currently no consensus on which scale is better, the interaction in additive scale may be more clinically meaningful than the multiplicative interaction, because the additive scale directly evaluates the proportion of risks caused by the synergy of two or more risk factors.[29,39] However, the new STROBE statement advocates that the authors should perform the interaction analysis in both additive and multiplicative scales when assessing the combined effects of two or more risk factors.[40] Therefore, our study performed both additive and multiplicative interactions simultaneously. Our study might provide a simple example for the public to understand the risks of coexisting hypertension and obesity to diabetes. The public may gain greater awareness about maintaining appropriate blood pressure and weight after understanding our results.

Results of this study also showed that the presence of hypertension, general obesity or central obesity, defined by WC, WHtR and WHpR, was independently correlated with diabetes in both men and women. Our results suggested that central obesity had a more significant impact on diabetes risk than general obesity, which was consistent with previous studies.[41,42] Furthermore, our findings also indicated that hypertension had a stronger influence than general or central obesity on diabetes risk. However, obesity indices were also strong risk factors among those without hypertension. These findings suggested that better control of general and central obesity early in life may have more long-term health benefits, even for those without hypertension.

In the overall population, the presence of concurrent hypertension and general obesity had the highest risk of diabetes among the four groups. When individuals were

divided into males and females, this trend still existed. Furthermore, the young age participants with both conditions had a stronger association with the risk of diabetes than the elderly age individuals, which may be explained by the fact that ageing is related to significant changes in body composition, that is, a striking increase in fat mass and a decrease in lean body mass.[42] For central obesity measured by WC, WHtR and WHpR, the results were similar to that of general obesity. However, zero additive interaction of hypertension and central obesity defined by WHtR was observed, suggesting that risk from WHtR-defined central obesity was not additive to the risk of hypertension. After further performing gender analyses, the additive interactions only existed in women with general obesity or WHpR-defined central obesity, indicating risk from general obesity and WHpR-defined central obesity was additive to the risk from hypertension. Taken together, the findings may suggest that female individuals with hypertension should pay attention to preventing BMI-defined general obesity and WHpR-defined central obesity to prevent diabetes.

Metabolic syndrome (MetS) is a condition characterized by obesity, high blood pressure, hyperglycemia and dyslipidemia, and is a pivotal risk factor for cardiovascular disease and diabetes.[43] However, at present, there are no universally recognized and unified diagnostic criteria, which will affect the assessment and prevention of metabolic syndrome. The main diagnostic criteria for MetS including the World Health Organization (WHO in 1998), the American Association of Clinical Endocrinologists (AACE in 2003), the National Cholesterol Education Program Adult Treatment Panel III (updated ATP III in 2005), the international diabetes federation (IDF in 2005) and the joint interim statement (JIS in 2009).[43–46] Among them, the most controversial one is the diagnostic criteria of obesity. BMI and WHpR were used as the diagnostic criteria for obesity in WHO criteria, BMI was used as the diagnostic criteria for MetS in AACE criteria, and WC was used as the benchmark for the definition of obesity in other MetS diagnostic criteria. In this study, a novel method of interaction showed that hypertension and obesity as defined by BMI or WHpR had statistical significance for the risk of diabetes, and the results supported the diagnostic criteria of MetS by WHO and AACE.

Therefore, the results of this study suggest that BMI and WHpR, rather than WC, should be used for the diagnosis of MetS in Chinese population.

Several limitations of this study should be overcome in future work. First, the nature of the cross-sectional design limits its interpretation to the causal relationship of diabetes and hypertension as well as various obesity indices. Although the nature of the cross-sectional studies limits the interpretation of causality, we can provide a clue for future longitudinal studies to explore the causative interaction of hypertension and obesity on diabetes. Second, the study sample was from rural areas in northeast China, and accordingly, our conclusions may not be generalized to populations from other regions. Third, the data of obesity only contained anthropometric criteria and lacked measurements of body fat composition. Thus, our study might contain data for bias. Lastly, although a series of confounding factors were taken into account, other potential confounders such as medication information and family history were not considered in the analysis, which may partially influence the validity and accuracy of the findings.

Conclusion

This study examined the individual and interactive associations of general or central obesity and hypertension associated with diabetes, especially evaluating both additive and multiplicative interactions. It indicated that various obesity indices play different roles in the association between hypertension and diabetes, and that high BMI and high WHpR have synergistic interactions with hypertension in females. The findings suggest that BMI and WHpR, rather than WC, should be used for the diagnosis of MetS in Chinese population.

Data Sharing Statement

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Declaration

This study was conducted in accordance with the ethical principle of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of China Medical University (Shenyang, China).

Acknowledgments

This work was supported by the National Key Research and Development Program from the Ministry of Science and Technology of China (grant numbers 2017YFC1307600, 2018YFC1312400); Liaoning science and technology project (grant number 2017107001); and

Science and Technology Program of Shenyang, China (grant number 17-230-9-06).

Disclosure

The authors declare that they have no competing interests in this work.

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