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CLINICAL STUDY

# Associations of resistin with inflammatory and fibrinolytic markers, insulin resistance, and metabolic syndrome in middle-aged and older Chinese

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## Abstract

*Objective*: Resistin increases insulin resistance (IR) in mice. However, the role of resistin in human disease remains controversial. We aimed to assess plasma resistin levels and their associations with inflammatory and fibrinolytic markers, IR and metabolic syndrome (MetS) among Chinese.
*Design and methods*: Plasma resistin was measured in a population-based cross-sectional survey of 3193 Chinese aged from 50 to 70 years in Beijing and Shanghai.
*Results*: The median resistin concentration was 8.60 ng/ml (interquartile range, 5.78–14.00) among all participants, and it was higher in women than in men ($P=0.008$). Resistin was correlated weakly with body mass index, waist circumference, high-density lipoprotein (HDL) cholesterol (negatively), homeostatic model assessment of IR and tumor necrosis factor-α receptor 2 (TNFR2; $r=0.04$, 0.07, –0.09 and 0.06 respectively, all $P<0.05$), and more highly with C-reactive protein (CRP), interleukin (IL)6 and plasminogen activator inhibitor (PAI)1 ($r=0.12$, 0.12 and 0.21 respectively, all $P<0.001$), but only HDL cholesterol, CRP, IL6, TNFR2, and PAI1 remained significantly associated with resistin in multiple regression analysis (all $P<0.05$). Furthermore, elevated resistin levels were associated with the higher prevalence of IR and MetS. However, the significant relationships disappeared after adjustment for inflammatory and fibrinolytic markers especially PAI1.
*Conclusions*: This study suggests that resistin is more strongly associated with inflammatory and fibrinolytic markers than with obesity or IR status. The associations of resistin with IR and MetS could largely be explained by inflammatory and fibrinolytic markers especially PAI1 levels.

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## Introduction

Resistin was originally reported to link obesity to insulin resistance (IR) and diabetes as an adipokine in mice (1). Subsequent studies indicated that hyperresistinemia induced hepatic IR in rodents (2), and that resistin played a role in the regulation of glucose metabolism in mice (3). However, studies on the association between resistin and chronic diseases in humans have yielded controversial results. Several studies showed that circulating resistin levels were associated with obesity (4–6), but this association was not found in others (7–10). Although some studies have reported that resistin levels were higher in type 2 diabetic subjects than controls (8, 11), other studies did not find any association between resistin and IR or fasting glucose levels (4, 7, 9, 10, 12).

Unlike the clear function of resistin in mice, it is difficult to confirm the association between resistin and obesity-related disease in humans, which may be due to the different sources of circulating resistin in humans and rodents. Resistin is produced mostly in adipocytes in mice (1), while it was expressed less in adipocytes, but strongly in monocytes and macrophages among humans (13, 14). Moreover, proinflammatory cytokines (interleukin (IL)1, IL6, and tumor necrosis factor-α (TNF)) could increase resistin expression in human peripheral blood mononuclear cells (PBMCs) (15), and meanwhile recombinant resistin also triggers the release of these proinflammatory cytokines in human PBMCs (16). Human population studies also showed that resistin levels were associated positively with leukocytes (10, 17), C-reactive protein (CRP) (10, 18–20), IL6, and tumor necrosis factor-α receptor 2 (TNFR2) (21). In addition, resistin was found to



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upregulate the expression of cytokines and adhesion molecules in human endothelial cells (22, 23). Subsequent studies in human subjects revealed that elevated resistin levels were associated with increasing coronary artery calcification (21) and the presence and severity of coronary artery disease (19). Moreover, Pischon *et al.* reported that the association between resistin and coronary heart disease in women could be largely explained by CRP levels (24). Thus, it is possible that the inflammatory process may play a crucial role in the relationship of resistin with cardiovascular disease (CVD). However, it is still unclear whether CRP or other inflammatory and fibrinolytic markers (such as IL6, TNFR2, and PAI1) are also important in the determination of the relationships of resistin with IR and metabolic syndrome (MetS), the two well-known risk factors of CVD and type 2 diabetes. Furthermore, it remains unknown the profile of resistin levels and their associations with obesity, inflammation, IR, and related diseases in large Chinese populations. Additionally, few studies have investigated the association of resistin with retinol-binding protein 4 (RBP4), a newly identified adipokine that was reported to be associated with IR and MetS in previous studies (25, 26).

Therefore, we aimed to evaluate plasma resistin levels and their associations with various inflammatory and fibrinolytic factors (CRP, IL6, soluble TNFR2, and PAI1) and adipokines (adiponectin and RBP4), as well as with obesity, IR, diabetes, and MetS in 3193 middle-aged and older Chinese men and women.

## Subjects and methods

### Study population

The design and recruitment of the population-based cross-sectional study has been described in detail elsewhere (27). In brief, a total of 3289 eligible participants (1458 men and 1831 women) aged 50–70 years from urban and rural areas of the north (Beijing) and the south (Shanghai) were recruited in 2005 for the 'Nutrition and Health of Aging Population in China' study. Data on demographic variables, health status, medication use, health behavior, and physical activity were collected using a standardized questionnaire. All participants were required to fast overnight ($\geq$7 h) before physical examination by trained staff and physicians using standard protocols. Measurements of body weight and height, waist and hip circumference, and blood pressure have been described previously (27). The study was approved by the Institutional Review Board of the Institute for Nutritional Sciences, with written informed consent from all participants.

A total of 96 individuals were excluded from resistin analysis due to gross hemolysis or lipemia, 3193 subjects (1419 men and 1774 women) remaining for the present analysis.

### Laboratory measurements

Overnight fasting blood samples were collected in tubes containing liquid EDTA, centrifuged at 4 °C, and stored at −80 °C until analysis. The measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, insulin, CRP, IL6, PAI1, RBP4, and adiponectin were as previously described (26–29). Plasma resistin was measured by Luminex xMAP Technology (Linco Research, St Charles, MO, USA) on a Bio-Rad Multiplex Suspension Array System. The sensitivity of the assay was 6.7 pg/ml for resistin, with an intra-assay coefficient variation (CV) of 1.4–7.9% and an inter-assay CV of $<$21% according to the manufacturer's instruction. Soluble fraction of TNFR2 was detected with Human Death Receptor 3-Plex kit (Biosource International Inc., Camarillo, CA, USA), through the Multiplex Suspension Array System (Bio-Plex System) with Bio-Plex Manager 4.0 (Bio-Rad Laboratories Inc). The average intra-assay and inter-assay CVs for TNFR2 were 7.9 and 10.1% respectively.

***Definition of obesity, hypertension, dyslipidemia, IR, diabetes, and MetS*** Overweight and obesity were defined as a participant with body mass index (BMI) $\geq$24 and $<$28 kg/m$^2$, and BMI $\geq$28 kg/m$^2$ respectively, according to the cut-off point for Chinese adults (30). Another cut-off point for overweight ($25 \leq$BMI$<30$ kg/m$^2$) and obesity (BMI $\geq$30 kg/m$^2$) proposed by the World Health Organization was also used in the analyses. Hypertension was defined as a participant with blood pressure $\geq$140/90 mmHg, or the current use of anti-hypertensive medications (31). Dyslipidemia was defined according to the National Cholesterol Education Program (NCEP) ATP III on Detection, Evaluation, and Treatment of High Blood Cholesterol (32) as a participant with total cholesterol $\geq$ 6.21 mmol/l, or LDL cholesterol $\geq$4.14 mmol/l, or HDL cholesterol $<$1.03 mmol/l, or triglycerides $\geq$2.26 mmol/l, or current use of lipid-lowering medications. IR was calculated using homeostasis model assessment (HOMA) of IR (HOMA-IR = fasting glucose (mmol/l) $\times$ fasting insulin (μU/ml)/22.5) (33), and participants in the top quartile of HOMA-IR were defined as IR. Diabetes was defined as a participant with previous diagnosis or use of hypoglycemic agents including insulin, or with a fasting glucose $\geq$7.0 mmol/l (34).

MetS was defined based upon the updated NCEP ATP III criteria (AHA/NHLBI Scientific Statement) for Asian Americans (35) as presenting at least three of the following components, and the International Diabetes Federation (IDF) criteria for Chinese (36) as presenting the first of the following components and at least two of others:

(i) Waist circumferences $\geq 90$ cm in men or $\geq 80$ cm in women;
(ii) Triglycerides $\geq 1.7$ mmol/l;
(iii) HDL cholesterol $< 1.03$ mmol/l in men or $< 1.30$ mmol/l in women;
(iv) Blood pressure $\geq 130/85$ mmHg, or current use of anti-hypertensive medications;
(v) Fasting plasma glucose $\geq 5.6$ mmol/l, or previously diagnosed type 2 diabetes, or on oral anti-diabetic agents or insulin.

### *Statistical analysis*

Normally distributed variables were expressed as means $\pm$ S.D., whereas variables with a skewed distribution were reported as median (interquartile range) and log transformed to approximate normality before analysis. Categorical variables were represented by frequency and percentage. The gender and geographic differences of resistin levels were compared by analysis of covariance respectively. Analysis of covariance for continuous variables and multivariate logistic regression analysis for categorical variables were applied for the comparison according to resistin quartiles. Correlation coefficients between resistin, inflammatory, and metabolic features were calculated by partial correlation analysis on ranks (Spearman correlation). The effects of independent variables such as obesity BMI, IR status HOMA-IR, MetS components (waist circumference, triglycerides, HDL cholesterol, systolic/diastolic blood pressure, and glucose), inflammatory and fibrinolytic markers (CRP, IL6, TNFR2, and PAI1) on plasma resistin concentrations (dependent variables) were tested in multivariate linear regression models after controlling for potential confounding factors. Meanwhile, the standardized linear regression coefficients of each independent variable were also evaluated after controlling for age, gender, geographic locations, smoking, alcohol drinking, physical activity, educational levels, family history of chronic disease (diabetes, CVD, and hypertension), and uses of medications (lipid-lowering, anti-hypertensive and anti-diabetic agents or insulin, aspirin, and anti-thrombotic medications) in model 1, and further controlling for all other independent variables except for waist circumference and glucose in model 2. The relationships of resistin quartiles with the crude prevalence of obesity, diabetes, IR, and MetS were evaluated using $\chi^2$ tests for trend. Multivariate logistic regression models were used to estimate the adjusted odds ratios (ORs) for IR and MetS according to resistin quartiles. Also, potential confounding variables described above, as well as HOMA-IR, BMI, CRP, IL6, TNFR2, and PAI1 were selectively controlled in the logistic regression models. Data management and statistical analysis were performed with Stata version 9.2 (College Station, TX, USA). $P < 0.05$ was considered statistically significant.

## Results

### *Plasma resistin levels*

The median plasma resistin concentration was 8.60 ng/ml (interquartile range, 5.78–14.00) in the study population. Women had a significantly higher median level of resistin than men (8.81 ng/ml (5.78–14.00) vs 8.28 ng/ml (5.49–13.49), $P=0.009$) after adjustment for age and geographic locations. The median plasma resistin was significantly higher in rural residents than in urban residents (8.91 ng/ml (5.99–14.16) vs 8.28 ng/ml (5.54–13.80), $P=0.049$) but was not different between Beijing and Shanghai participants (8.65 ng/ml (5.77–14.55) vs 8.57 ng/ml (5.80–13.57), $P=0.16$) after adjustment for age, sex, region, and residence (where appropriate). However, the gender and rural–urban differences of resistin levels became insignificant after further adjustment for alcohol drinking, smoking, education levels, physical activity, family history of chronic diseases, and uses of medications.

When analyzed by quartiles of resistin levels, as shown in Table 1, more female and rural residents (both $P<0.05$), and more participants having lower levels of physical activity were in higher resistin quartiles ($P<0.001$). The percentages of participants currently using anti-hypertensive medications and anti-diabetic agents including insulin were different among resistin quartiles ($P=0.005$ and $P=0.02$ respectively). Moreover, the subjects in higher resistin quartiles were more likely to be with dyslipidemia ($P=0.003$), IR ($P=0.002$), ATP III and IDF defined MetS (both $P<0.001$), and also exhibited higher waist circumference, waist-to-hip ratio, triglycerides, insulin, HOMA-IR and RBP4 (all $P<0.05$), lower HDL cholesterol levels ($P<0.001$) and elevated levels of CRP, IL6, TNFR2, PAI1, and adiponectin (all $P<0.001$).

### *Associations of resistin with metabolic features, and inflammatory and fibrinolytic markers*

Partial Spearman correlation analysis showed that resistin was correlated weakly but significantly with BMI, waist circumference, hip circumference, waist-to-hip ratio, HDL cholesterol (negatively), triglycerides, insulin, HOMA-IR, TNFR2, and RBP4 (all $P<0.05$), while more highly correlated with CRP, IL6, PAI1, and adiponectin (all $P<0.001$; Table 2). Further analysis in multivariate linear regression, as presented in Table 3, showed that waist circumference, triglycerides, HDL cholesterol (negatively), CRP, IL6, TNFR2, and PAI1 were associated with resistin after adjustment for age, gender, region, residence, alcohol drinking, smoking, education, physical activity, family history of chronic disease, and uses of medications (all $P<0.05$). However, after further adjustment for all other parameters in Table 3 except

**Table 1** Characteristics of study participants according to resistin quartiles[a].

| Characteristics | Q1 ($n$=798) <5.78 | Q2 ($n$=796) 5.78–8.59 | Q3 ($n$=800) 8.60–13.98 | Q4 ($n$=799)≥13.99 | *P* value |
|---|---|---|---|---|---|
| Resistin (ng/ml)[b] | 4.43 (3.46–5.13) | 6.98 (6.37–7.77) | 10.87 (9.68–12.23) | 19.46 (16.15–26.75) | <0.001 |
| Age (year)[c] | 58.5±6.0 | 58.5±5.8 | 58.5±6.0 | 58.9±6.1 | 0.37 |
| Female ($n$, %)[c] | 411 (51.5) | 449 (56.4) | 445 (55.6) | 469 (58.7) | 0.03 |
| Rural residents ($n$, %)[c] | 369 (46.2) | 400 (50.2) | 420 (52.5) | 415 (51.9) | 0.04 |
| Residents of Beijing ($n$, %)[c] | 395 (49.5) | 388 (48.7) | 374 (46.8) | 420 (52.6) | 0.11 |
| Smoking (yes, $n$, %) | 335 (42.0) | 285 (35.8) | 302 (37.8) | 290 (46.3) | 0.38 |
| Alcohol drinking (yes, $n$, %) | 260 (32.6) | 222 (27.9) | 210 (26.20) | 213 (26.7) | 0.31 |
| Education (year, $n$, %) | | | | | 0.42 |
| 0–6 | 330 (41.4) | 334 (42.0) | 330(41.3) | 327 (40.9) | |
| 7–9 | 286 (35.8) | 275 (34.5) | 289 (36.1) | 288 (36.1) | |
| ≥10 | 182 (22.8) | 187 (23.5) | 181 (22.6) | 184 (23.0) | |
| Physical activity ($n$, %) | | | | | <0.001 |
| Low | 53 (6.6) | 59 (7.4) | 58 (7.2) | 65 (8.1) | |
| Moderate | 295 (37.0) | 324 (40.7) | 342 (42.8) | 379 (47.4) | |
| High | 450 (56.4) | 413 (51.9) | 400 (50.0) | 355 (44.4) | |
| Family history of chronic disease ($n$, %)[d] | | | | | |
| Diabetes | 106 (13.3) | 115 (14.5) | 110 (13.8) | 103 (12.9) | 0.64 |
| Hypertension | 339 (42.5) | 351 (44.1) | 348 (43.5) | 373 (46.7) | 0.14 |
| Cardiovascular disease | 183 (22.9) | 180 (22.6) | 160 (20.0) | 191 (23.9) | 0.33 |
| Uses of medications ($n$, %) | | | | | |
| Lipid-lowering medications | 54 (6.8) | 55 (6.9) | 46 (5.8) | 72 (9.0) | 0.08 |
| Anti-hypertensive medications | 193 (24.2) | 220 (24.2) | 229 (28.6) | 258 (32.3) | 0.005 |
| Anti-diabetic agents or insulin | 51 (6.4) | 54 (6.8) | 76 (9.5) | 57 (7.1) | 0.02 |
| Aspirin | 72 (9.0) | 63 (7.9) | 72 (9.0) | 72 (9.0) | 0.70 |
| Anti-thrombotic medications | 14 (1.8) | 16 (2.0) | 24 (3.0) | 21 (2.6) | 0.44 |
| Metabolic disorders ($n$, %) | | | | | |
| Overweight (24≤BMI<28 kg/m$^2$) | 307 (38.5) | 309 (38.8) | 304 (38.0) | 314 (39.3) | 0.30 |
| Obesity (BMI≥28 kg/m$^2$) | 112 (14.0) | 102 (12.8) | 127 (15.9) | 134 (16.8) | 0.10 |
| Overweight (25≤BMI <30 kg/m$^2$) | 285 (35.7) | 270 (33.9) | 297 (37.1) | 294(36.8) | 0.18 |
| Obesity (BMI≥30 kg/m$^2$) | 51 (6.4) | 43 (5.4) | 54 (6.8) | 66 (8.3) | 0.23 |
| Diabetes | 102 (12.8) | 102 (12.8) | 126 (15.8) | 104 (13.0) | 0.09 |
| Hypertension | 416 (52.1) | 424 (53.3) | 438 (54.8) | 466 (58.3) | 0.23 |
| Dyslipidemia | 324 (40.6) | 326 (41.0) | 370 (46.3) | 370 (46.3) | 0.003 |
| Insulin resistance | 168 (21.1) | 186 (23.4) | 223 (27.9) | 221 (27.7) | 0.002 |
| MetS (ATP III defined) | 298 (37.3) | 313 (39.3) | 364 (45.5) | 375 (46.9) | <0.001 |
| MetS (IDF defined) | 248 (31.1) | 260 (32.7) | 305 (38.1) | 317 (39.7) | <0.001 |
| SBP (mmHg) | 139.37±22.23 | 139.92±22.31 | 140.09±22.11 | 141.11±22.97 | 0.93 |
| DBP (mmHg) | 79.77±10.34 | 79.94±10.66 | 80.50±10.89 | 80.49±10.78 | 0.31 |
| BMI (kg/m$^2$) | 24.42±3.51 | 24.25±3.44 | 24.48±3.66 | 24.70±3.68 | 0.12 |
| Waist circumference (cm) | 83.25±10.36 | 83.02±10.40 | 84.12±10.60 | 84.55±10.74 | 0.002 |
| Hip circumference (cm) | 93.58±6.67 | 93.17±6.88 | 93.54±6.86 | 94.08±6.91 | 0.07 |
| Waist-to-hip ratio | 0.89±0.07 | 0.89±0.07 | 0.90±0.08 | 0.90±0.07 | 0.001 |
| Glucose (mmol/l) | 5.82±1.72 | 5.83±1.65 | 5.91±1.91 | 5.81±1.67 | 0.43 |
| Total cholesterol (mmol/l) | 4.71±0.96 | 4.67±0.95 | 4.65±0.99 | 4.70±0.99 | 0.78 |
| LDL cholesterol (mmol/l) | 3.27±0.97 | 3.25±0.97 | 3.24±0.96 | 3.21±0.97 | 0.98 |
| HDL cholesterol (mmol/l) | 1.31±0.34 | 1.28±0.32 | 1.25±0.33 | 1.25±0.34 | <0.001 |
| Triglycerides (mmol/l)[b] | 1.02 (0.72–1.54) | 1.08 (0.73–1.66) | 1.11 (0.77–1.73) | 1.13 (0.79–1.72) | 0.02 |
| Insulin (μU/ml)[b] | 13.45 (9.65–17.35) | 13.09 (9.55–18.05) | 14.09 (10.22–19.50) | 14.36 (10.38–20.06) | <0.001 |
| HOMA-IR[b] | 3.28 (2.35–4.49) | 3.26 (2.26–4.66) | 3.55 (2.46–4.82) | 3.52 (2.50–5.12) | 0.002 |
| CRP (mg/l)[b] | 0.56 (0.29–1.24) | 0.65 (0.31–1.37) | 0.66 (0.37–1.58) | 0.84 (0.39–1.97) | <0.001 |
| Interleukin 6 (pg/ml)[b] | 0.93 (0.56–1.46) | 1.03 (0.68–1.52) | 1.05 (0.69–1.63) | 1.18 (0.76–1.75) | <0.001 |
| TNFR2 (ng/ml) | 1.63±0.57 | 1.64±0.59 | 1.65±0.60 | 1.77±0.70 | <0.001 |
| PAI1 (ng/ml)[b] | 6.81 (2.27–15.13) | 7.77 (3.23–16.01) | 8.19 (2.71–19.42) | 13.27 (4.11–28.67) | <0.001 |
| Adiponectin (μg/ml)[b] | 11.18 (6.68–17.67) | 14.02 (8.44–21.74) | 14.51 (8.52–22.39) | 15.58 (8.87–25.46) | <0.001 |
| RBP4 (μg/ml) | 39.32±11.53 | 39.72±11.44 | 40.51±11.49 | 40.50±12.42 | 0.02 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; CRP, C-reactive protein; TNFR2, tumor necrosis factor-α receptor 2; PAI1, plasminogen activator inhibitor 1; RBP4, retinol-binding protein 4.

[a]Data are means±S.D., median (interquartile range), or $n$ (%); $P$ value was calculated after adjustment for age, gender, region (Beijing/Shanghai), and residence (urban/rural).

[b]These variables were log transformed before analysis.

[c]Not adjusted for itself.

[d]Parents or siblings had a history of diabetes, cardiovascular disease, or hypertension.

**Table 2** Partial Spearman correlation coefficients of resistin with metabolic features, and inflammatory and fibrinolytic markers[a].

| | **All** ($n=3193$) | | **Women** ($n=1774$) | | **Men** ($n=1419$) | |
|---|---|---|---|---|---|---|
| | *r* | *P* | *r* | *P* | *r* | *P* |
| BMI | 0.04 | 0.03 | 0.05 | 0.05 | 0.02 | 0.47 |
| Waist circumference | 0.07 | <0.001 | 0.09 | <0.001 | 0.05 | 0.06 |
| Hip circumference | 0.04 | 0.02 | 0.05 | 0.04 | 0.02 | 0.35 |
| Waist-to-hip ratio | 0.07 | <0.001 | 0.09 | <0.001 | 0.05 | 0.04 |
| SBP | 0.01 | 0.62 | 0.01 | 0.72 | 0.01 | 0.75 |
| DBP | 0.02 | 0.17 | 0.05 | 0.05 | −0.02 | 0.41 |
| Total cholesterol | −0.01 | 0.62 | −0.02 | 0.42 | 0.04 | 0.12 |
| LDL cholesterol | 0.00 | 0.86 | −0.03 | 0.29 | 0.03 | 0.15 |
| HDL cholesterol | −0.09 | <0.001 | −0.06 | 0.016 | −0.11 | <0.001 |
| Triglycerides | 0.07 | <0.001 | 0.07 | 0.007 | 0.06 | 0.02 |
| Glucose | 0.02 | 0.25 | 0.04 | 0.10 | −0.02 | 0.52 |
| Insulin | 0.07 | <0.001 | 0.08 | <0.001 | 0.04 | 0.12 |
| HOMA-IR | 0.06 | <0.001 | 0.09 | <0.001 | 0.03 | 0.23 |
| CRP | 0.12 | <0.001 | 0.11 | <0.001 | 0.14 | <0.001 |
| IL6 | 0.12 | <0.001 | 0.12 | <0.001 | 0.12 | <0.001 |
| TNFR2 | 0.08 | <0.001 | 0.06 | 0.017 | 0.10 | 0.017 |
| PAI1 | 0.21 | <0.001 | 0.23 | <0.001 | 0.18 | <0.001 |
| Adiponectin | 0.14 | <0.001 | 0.13 | <0.001 | 0.16 | <0.001 |
| RBP4 | 0.06 | 0.001 | 0.08 | 0.001 | 0.04 | 0.18 |

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; CRP, C-reactive protein; IL6, interleukin 6; TNFR2, tumor necrosis factor-α receptor 2; PAI1, plasminogen activator inhibitor 1; RBP4, retinol-binding protein 4.
[a]All correlation coefficients were calculated after adjustment for age, gender (where appropriate), region, and residence.

for waist circumference and glucose, only CRP, IL6, TNFR2 and PAI1, and HDL cholesterol (all $P<0.05$) remained significantly associated with resistin, and PAI1 (standardized $\beta=0.240$, $P<0.001$) had the strongest association with plasma resistin levels.

## *Associations of resistin with IR and MetS*

As shown in Table 1, the prevalence of IR and MetS (both ATP III and IDF defined) progressively increased across resistin quartiles (all $P<0.003$ ($\chi^2$ tests)), while the

**Table 3** Multivariate regression analyses of obesity status, insulin resistance, components of metabolic syndrome (MetS), and inflammatory and fibrinolytic markers on plasma resistin[a] levels.

| | **Multivariate standardized linear regression coefficients** | | | |
|---|---|---|---|---|
| | Model 1[b] | | Model 2[c] | |
| **Parameters** | β1 (S.E.M.) | *P* | β2 (S.E.M.) | *P* |
| Obesity status | | | | |
| BMI (kg/m$^2$) | 0.026 (0.020) | 0.19 | −0.040 (0.023) | 0.11 |
| Insulin resistance | | | | |
| HOMA-IR[a] | 0.032 (0.020) | 0.11 | 0.001 (0.021) | 0.70 |
| Components of MetS | | | | |
| Waist circumference (cm) | 0.059 (0.020) | 0.003 | −0.036 (0.023) | 0.12 |
| Triglycerides (mmol/l)[a] | 0.042 (0.019) | 0.03 | −0.023 (0.022) | 0.28 |
| HDL cholesterol (mmol/l) | −0.081 (0.019) | <0.001 | −0.050 (0.021) | 0.02 |
| SBP (mmHg) | −0.021 (0.021) | 0.34 | −0.031 (0.028) | 0.08 |
| DBP (mmHg) | 0.002 (0.020) | 0.91 | −0.002 (0.026) | 0.99 |
| Glucose (mmol/l) | −0.023 (0.022) | 0.28 | −0.020 (0.020) | 0.25 |
| Inflammatory and fibrinolytic markers | | | | |
| CRP (mg/l)[a] | 0.111 (0.020) | <0.001 | 0.050 (0.021) | 0.02 |
| IL6 (pg/ml)[a] | 0.120 (0.019) | <0.001 | 0.065 (0.021) | 0.002 |
| TNFR2 (ng/ml) | 0.107 (0.019) | <0.001 | 0.089 (0.019) | <0.001 |
| PAI1 (ng/ml)[a] | 0.239 (0.020) | <0.001 | 0.240 (0.021) | <0.001 |

HOMA-IR, homeostatic model assessment of insulin resistance; BMI, body mass index; HDL, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure; CRP, C-reactive protein; IL6, interleukin 6; TNFR2, tumor necrosis factor-α receptor 2; PAI1, plasminogen activator inhibitor 1. Data are β (S.E.M.) and reflect per S.D. changed.
[a]These variables were log transformed before analysis.
[b]Adjusted for age, gender, region, and residence, alcohol drinking, smoking, education, physical activity, family history of chronic disease, and uses of medications.
[c]Further adjusted for all other parameters in the table except for waist circumference and glucose, while β2 of waist circumference and glucose did not adjust for BMI and HOMA-IR respectively.

prevalence of obesity (both BMI $\geq 28\ kg/m^2$ and $\geq 30\ kg/m^2$) and diabetes did not vary significantly with resistin levels (all $P > 0.11$ ($\chi^2$ tests)). After adjusting for age, gender, region, residence, alcohol drinking, smoking, education, physical activity, family history of chronic disease, and uses of medications, presented in Table 4, higher ORs for IR were observed in the 3rd and 4th resistin quartiles compared with that in the lowest resistin quartile ($P=0.01$ for trend, model 1). Moreover, the ORs for IR in the 3rd and 4th resistin quartiles changed slightly after additional adjustment for BMI based on model 1, and the association between resistin and IR remained significant ($P=0.02$ for trend, model 2). However, the association between resistin and IR became insignificant after additional adjustment for CRP, IL6, and TNFR2 based on model 1 ($P=0.13$ for trend, model 3), and particularly after additional adjustment for PAI1 based on model 1 ($P=0.89$ for trend, model 4). Similarly, the association between resistin and ATP III defined MetS was significant in model 1 ($P=0.002$ for trend) and model 2 (additional adjustment for BMI and HOMA-IR, $P=0.01$ for trend). After additional adjustment for CRP, IL6, and TNFR2 based on model 1, the ORs for ATP III defined MetS in the 4th resistin quartiles were attenuated substantially, and the association became marginally significant ($P=0.09$ for trend, model 3). Moreover, the significant association between resistin and MetS disappeared after additional adjustment for PAI1 based on model 1 ($P=0.82$ for trend, model 4). Also, when MetS was defined by IDF criteria, similar results were observed. In addition, gender did not modify the associations between resistin and IR and MetS in all of these models (all $P > 0.29$ for interaction).

## Discussion

This study shows that plasma resistin levels are associated significantly with inflammatory and fibrinolytic markers, including CRP, IL6, TNFR2, and PAI1, as well as with the prevalence of IR and MetS among 3193 middle-aged and older Chinese. Furthermore, inflammatory and fibrinolytic markers, particularly PAI1, may play an important role in determining the plasma resistin levels and their associations with IR and MetS.

Consistent with some previous reports in Western (10, 21) and Japanese populations (20) we found that women had higher resistin concentrations than men. However, this difference disappeared after adjustment for age, lifestyle factors, education status, geographic locations, family history of chronic disease, and uses of medications, suggesting that the gender difference of resistin levels could be explained by these factors. In addition, we found that subjects using anti-hypertensive medications and anti-diabetic agents including insulin were different among resistin quartiles. However, when we controlled the uses of medications as potential confounding factors in linear and logistic regression models, there was little effect of these factors on the relationship of resistin with inflammatory and fibrinolytic markers, IR and MetS.

Since resistin is largely expressed in monocytes and macrophages and has a close relation with inflammatory markers in humans, resistin *per se* was considered as an inflammatory marker with potent proinflammatory properties (16, 21). Consistently, previous studies have reported that resistin levels were associated independently with CRP levels in Finnish

**Table 4** Adjusted odds ratios of insulin resistance and metabolic syndrome according to resistin quartiles.

| | Quartile of resistin | | | | |
|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | ***P* for trend** |
| Adjusted odds ratios (95% CI) of IR | | | | | |
| Model 1[a] | 1.0 | 1.11 (0.86–1.42) | 1.36 (1.07–1.74) | 1.31 (1.03–1.69) | 0.01 |
| Model 2[b] | 1.0 | 1.16 (0.90–1.50) | 1.37 (1.06–1.76) | 1.30 (1.01–1.68) | 0.02 |
| Model 3[c] | 1.0 | 1.07 (0.83–1.37) | 1.30 (1.01–1.66) | 1.15 (0.90–1.48) | 0.13 |
| Model 4[d] | 1.0 | 1.04 (0.78–1.31) | 1.18 (0.91–1.52) | 0.97 (0.75–1.26) | 0.89 |
| Adjusted odds ratios (95% CI) of MetS (ATP III defined) | | | | | |
| Model 1[a] | 1.0 | 1.03 (0.82–1.28) | 1.37 (1.10–1.71) | 1.31 (1.05–1.63) | 0.002 |
| Model 2[e] | 1.0 | 1.13 (0.87–1.47) | 1.43 (1.10–1.85) | 1.33 (1.02–1.72) | 0.01 |
| Model 3[c] | 1.0 | 0.98 (0.78–1.23) | 1.30 (1.03–1.63) | 1.12 (0.89–1.41) | 0.09 |
| Model 4[d] | 1.0 | 0.94 (0.74–1.19) | 1.21 (0.95–1.54) | 0.94 (0.74–1.20) | 0.82 |
| Adjusted odds ratios (95% CI) of MetS (IDF defined) | | | | | |
| Model 1[a] | 1.0 | 1.02 (0.81–1.28) | 1.34 (1.07–1.67) | 1.27 (1.01–1.59) | 0.007 |
| Model 2[e] | 1.0 | 1.14 (0.86–1.52) | 1.40 (1.05–1.86) | 1.29 (0.97–1.70) | 0.04 |
| Model 3[c] | 1.0 | 0.97 (0.76–1.22) | 1.25 (0.99–1.58) | 1.07 (0.85–1.36) | 0.22 |
| Model 4[d] | 1.0 | 0.92 (0.72–1.17) | 1.16 (0.91–1.48) | 0.90 (0.70–1.16) | 0.84 |

IR, insulin resistance; MetS, metabolic syndrome; HOMA-IR, homeostatic model assessment of insulin resistance; BMI, body mass index; CRP, C-reactive protein; IL6, interleukin 6; TNFR2, tumor necrosis factor-$\alpha$ receptor 2; PAI1, plasminogen activator inhibitor 1.
[a]Adjusted for age, gender, region, residence, alcohol drinking, smoking, education, physical activity, family history of chronic disease, and uses of medications.
[b]Additional adjusted for BMI based on model 1.
[c]Additional adjusted for CRP (log transformed), IL6 (log transformed) and TNFR2 based on model 1.
[d]Additional adjusted for PAI1 (log transformed) based on model 1.
[e]Additional adjusted for BMI and HOMA-IR (log transformed) based on model 1.

middle-aged subjects (10), in Japanese participants (20), and in other subjects with diabetes or coronary heart disease (18, 24). We also found that plasma resistin was associated with CRP independently, even after adjustment for BMI, HOMA-IR, and other inflammatory markers. In line with the findings that resistin could induce the release of IL6 and TNF, and vice versa in human PBMCs (16), and resistin levels were associated with levels of TNFR2 and IL6 in 879 asymptomatic and nondiabetic subjects (21), we confirmed that IL6 and TNFR2 were independently correlated with resistin levels in this Chinese population. Admittedly, although the correlation coefficients of resistin with CRP ($r=0.12$) and IL6 ($r=0.12$) were similar to those reported from previous studies (CRP: $r=0.14$–$0.25$; IL6: $r=0.16$) (10, 18, 20, 21, 24), the correlation coefficients of resistin with TNFR2 ($r=0.08$) in our study were relatively lower than that previously reported ($r=0.36$) (21). The discrepancies in coefficients may be due to variations in the characteristics of the participants or the measurement methods. In addition, interestingly, we observed that resistin was positively associated with adiponectin, while two previous studies did not find any correlation between resistin and adiponectin (18, 37). Although this positive correlation seemed to be inconsistent with the protective role of adiponectin in metabolic disease, some previous studies have reported that increased adiponectin (38, 39) and resistin (39, 40) were associated with impaired renal function. Thus, the unexpected correlation observed in our study might be attributed to the altered renal function. However, due to limited funds and plasma samples, we were unable to measure creatinine and glomerular filtration rate in the present study and certainly the hypothesis will be verified in our further study.

Consistent with the previous finding that resistin was positively correlated with PAI1 in 177 non-diabetic subjects (37), our study found the strongest relationship between resistin and PAI1 among evaluated inflammatory markers in large samples of Chinese population, while Shetty *et al.* (18) and Burnett *et al.* (41) did not detect any correlation between resistin and PAI1 in 77 subjects with diabetes or at high risk for diabetes and in the case-control study of coronary heart disease with 191 subjects respectively. PAI1 is known to be expressed by many cell types and has a close relation with inflammation (42), but whether resistin could induce the expression and production of PAI1 is unclear. Previous studies have reported that the inactivation of TNF receptors could reduce plasma PAI1 levels in mice (43), and TNF and IL6 could increase the expression of resistin *in vitro* (15), suggesting that TNF or its receptors may be the link between resistin and PAI1. However, our results showed that the association between resistin and PAI1 was independent of these proinflammatory cytokines including CRP, IL6, and TNFR2. Thus, further studies are needed to clarify the possible pathways between resistin and PAI1.

The relationships of resistin with obesity, IR, and diabetes remain controversial in humans. Our results suggested that resistin levels were associated with the prevalence of IR, but not with obesity or diabetes. Although obesity has been thought to be one of the major causes of IR (44), BMI could not explain the association of resistin with IR in our study, which may be due to relatively low expression of resistin in adipocytes in humans (14). However, interestingly, this association between IR and resistin became insignificant after additional adjustment for CRP, IL6, and TNFR2, and especially PAI1. Considering the close relationship between resistin and inflammatory markers in our study and other studies (10, 15, 16, 21), the positive association between resistin and PAI1 in this study, and the evidence of epidemiological associations and molecular pathways linking inflammatory and fibrinolytic markers to IR (45), it is not surprising that the association of resistin and IR was explained by inflammatory and fibrinolytic markers. Thus, it is possible that resistin may contribute to IR via inflammatory and fibrinolytic markers.

MetS, a constellation of metabolic abnormalities (35), is one of the risk factors for type 2 diabetes and CVD, and its pathogenesis is closely linked to IR and inflammation (46). Inflammatory and fibrinolytic markers CRP, IL6, TNF, and PAI1 have been well documented to be associated with MetS (46, 47), while the association of resistin and MetS remains inconsistent. In recent studies, Norata *et al.* (48) found that resistin was correlated with MetS and its components in women, and Aquilante *et al.* (17) reported that resistin concentrations were 1.21 times higher in subjects with MetS compared with those without MetS. On the other hand, no association between resistin and MetS was also indicated by Utzschneider *et al.* (37). In the present study, resistin was found to be associated with the prevalence of MetS in Chinese population, and this relationship was not accounted for by obesity and IR, but was largely explained by inflammatory markers and especially PAI1 levels. As a well-established marker, PAI1 was shown to be correlated closely with MetS and predicted the risk for type 2 diabetes and CVD (42). In our study, it was found that resistin was more strongly associated with PAI1 than with MetS and its components, suggesting that PAI1 could be an important player in the resistin–MetS association.

To our knowledge, this is the first study to investigate the association of circulating resistin levels with inflammatory and fibrinolytic markers, as well as with obesity, diabetes, IR, and MetS, controlling for most potential confounders in a large sample of Chinese participants. Admittedly, there are some limitations of our study that need to be acknowledged. Due to the cross-sectional study design, we could not establish the

causal relationship of resistin with PAI1. IR was assessed by using HOMA-IR rather than by using euglycemic glucose clamp technique, the gold standard of measuring IR, since it was not feasible to apply such a technique in a large population study. In the analysis of associations between resistin and IR and MetS in logistic regression models, we tested only an overall *P* for trend, rather than controlled for multiple comparisons among resistin quartiles. Although some of our results were confirmatory, it is yet to be seen whether the associations of resistin with IR and MetS could be explained by PAI1 levels in other ethnic groups.

In summary, we found that plasma resistin levels are more strongly associated with inflammatory and fibrinolytic markers including CRP, IL6, TNFR2, and PAI1, than obesity or IR status in middle-aged and older Chinese. Our results suggest a close relationship between resistin and inflammatory and fibrinolytic markers, especially with PAI1, and this relationship may mediate the association of resistin with IR and MetS.

## Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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