Association between metabolically unhealthy overweight/obesity and chronic kidney disease: The role of inflammation


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Abstract

Aim. – Our study explored the association between subtypes of increased fat mass (with or without associated metabolic alterations) and the presence of chronic kidney disease (CKD).

Methods. – In this cross-sectional survey in China, body mass index (BMI) was used to assess fat mass. Metabolically healthy was defined as no insulin resistance or any metabolic syndrome components except abdominal obesity. We also used two previous definitions of metabolically healthy. Multiple logistic regression models were used. Normal weight with metabolic health was designated the reference group. Three other subgroups included normal weight with metabolic unhealthiness, overweight/obesity with metabolic health and overweight/obesity with metabolic unhealthiness.

Results. – Of the 2324 subjects, 11.77% overweight/obese subjects were metabolically healthy. Compared with normal-weight subjects who were metabolically healthy, overweight/obese subjects who were metabolically healthy did not have an increased risk of CKD (OR: 0.79, 95% CI: 0.29–2.14; P = 0.64), whereas overweight/obese subjects who were metabolically unhealthy had a significantly higher risk of CKD (OR: 2.47, 95% CI: 1.5–3.95; P < 0.001). Normal-weight subjects who were metabolically unhealthy also had a higher risk of CKD, but the P value was of borderline significance. On further adjusting for C-reactive protein (CRP) levels, ORs were much attenuated, but did not alter the associations observed. Using two other definitions of metabolically healthy resulted in similar results.

Conclusion. – Metabolically unhealthy overweight/obesity, but not metabolically healthy overweight/obesity, is associated with an increased risk of CKD. Inflammation might mediate at least part of the association between metabolic changes and CKD prevalence.

Keywords: Chronic kidney disease; Metabolically healthy; Overweight; Obesity

1. Introduction

It is well recognized that increased fat mass is associated with mortality, cardiovascular diseases and chronic kidney disease (CKD) [1–3]. However, a meta-analysis indicated that obesity, but not overweight, was associated with higher mortality risk than normal weight [4,5]. This paradox suggests the complexity of the relationship between body weight and adverse outcomes [5]. One potential explanation is that it is not fat mass per se, but the metabolic disorders induced by excess fat mass that contribute to adverse outcomes. Despite having excess body fat, the subtype of metabolically healthy obesity might display a favourable metabolic profile including insulin sensitivity, normotension, and lower triglyceride with higher high-density lipoprotein (HDL) levels. Metabolically healthy obese individuals might also have a lower incidence of type 2 diabetes and cardiovascular diseases [6–8]. Recently, however, a meta-analysis indicated that metabolically healthy obesity should not be considered a benign condition, as it was associated with a higher risk of all-cause mortality and cardiovascular events, and the metabolically healthy overweight and metabolically

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unhealthy subgroups (normal weight, overweight and obese) all had similarly elevated risks of mortality and cardiovascular events [5].

Although previous studies supported an association between excess fat mass and an increased incidence of CKD [1], there is a paucity of data on the association between metabolically healthy overweight/obesity and CKD. One previous study suggested that only insulin-resistant obesity is associated with kidney damage [9]. One longitudinal study comparing metabolically healthy normal-weight individuals with CKD with metabolically healthy overweight/obese individuals with CKD found that mortality was not increased [10].

To the best of our knowledge, no such study has been conducted in Chinese populations. For this reason, the aim of the present study was to explore the association between subtypes of increased fat mass (with and without associated metabolic alterations) and the presence of CKD in China.

2. Methods

2.1. Study population

Data were drawn from a cross-sectional survey conducted in the cities of Zhuhai and Guangzhou between June 2012 and May 2013. Both Guangzhou and Zhuhai are located on the southern coast of China. One district or town was selected from each city. Tianhe District and Wanzhai Town were selected for the survey. Three communities in each district/town were then randomly selected, and all residents aged 18 years or older were invited to participate through the post and home visits. A total of 2855 subjects (mean age 52 ± 15 years, 947 men) participated in the epidemiological survey, but 360 subjects were excluded because of missing data. In addition, 171 people with a history of diabetes were excluded. Ultimately, 2324 subjects (mean age 52 ± 15 years, 756 men) were included in the present analysis. Of these, 20 were taking a traditional Chinese patent medicine on prescription. No subjects had used either contrast agents or antibiotics in the past 3 months, or had history of recurrent urinary tract infections or obstructive uropathy. The epidemiological survey has been described in detail in a previous report [11].

The present survey protocol was approved by the ethics committee of the Third Affiliated Hospital of Southern Medical University, and all subjects gave their written informed consent.

2.2. Data collection

All medical staff received intensive training before carrying out the survey. Data on age, gender, education level, current or past cigarette smoking, alcohol consumption, physical activity, personal/family history and medication history were obtained through questionnaires [11].

Blood pressure was determined using a calibrated mercury sphygmomanometer in a seated position after at least 5 min of rest. Blood pressure was measured three times, and the average of the three readings calculated and used in the analysis [11].

2.3. Determination of different BMI categories

Anthropometric indices were collected at community clinics and measured according to recommendations of the World Health Organization (WHO) [12]. A calibrated scale was used to measure weight in the morning after an overnight fast and emptying of the bladder. All subjects wore light clothing and were barefoot. Weight was accurate to the nearest 0.1 kg. A calibrated height-measuring instrument was used to determine height. Subjects stood up as straight as possible while barefoot and anything on their head were removed. Measurements were accurate to the nearest 0.1 cm.

Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m) [12], and was used to define normal weight and overweight/obesity. Based on the results of a previous meta-analysis in the Chinese population, normal weight was a BMI score < 24 kg/m² and obesity a score ≥ 28 kg/m². Overweight was defined as a BMI score ≥ 24 kg/m² but < 28 kg/m² [13]. All subjects were divided into one of two BMI categories: normal weight or overweight/obesity.

2.4. Determination of CKD

CKD was defined as a glomerular filtration rate (GFR) < 60 mL/min/1.73 m² and/or a urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g [14]. GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation: 175 × (Scr) – 1.234 × (Age) – 0.179 × (0.79 if female), where Scr (serum creatinine) is in mg/dL and age is in years [15]. ACR was calculated as urinary albumin/urinary creatinine (mg/g).

All blood samples were collected after an overnight fast, and only the first morning urine samples were collected, excluding those who were actively menstruating or with symptoms of urinary tract infection. All specimens were transported to the central laboratory of the Third Affiliated Hospital of Southern Medical University within 3 h of being taken [11].

Urinary and serum creatinine was measured by a colorimetric method. Urinary albumin was measured by an immune nephelometric method.

2.5. Other laboratory variables

In the present study, homoeostasis model assessment of insulin resistance (HOMA–IR) was used to determine insulin resistance. HOMA–IR was calculated as fasting plasma glucose (mmol/L) × fasting insulin (μU/L)/22.5 [16]. Fasting glucose was measured by colorimetric methods, while serum insulin was measured using electrochemiluminescence immunoassay [11].

Other variables included serum total cholesterol, serum triglycerides, and serum HDL cholesterol and C-reactive protein (CRP) [11].
2.6. Determination of metabolic status

One major challenge is to define metabolic health and various definitions have been used in previous studies [5,17,18]. The classification of individuals as metabolically healthy was based on the presence or absence of components of the metabolic syndrome (MetS) as defined by criteria proposed by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) and the International Diabetes Federation (IDF) [5,17,18]. In two previous studies [19,20], insulin resistance and inflammatory markers were included as part of the definition of metabolic status. In our study, metabolically healthy was defined as the absence of insulin resistance and of all MetS components except abdominal obesity.

The present study’s proposed definition of metabolically unhealthy was also based on the MetS as defined by ATP III [21]. However, because reduced insulin sensitivity and metabolic abnormalities are not necessarily one and the same, our survey combined insulin resistance with other metabolic abnormalities to define metabolic health [22]. According to one large-scale epidemiological survey in a Chinese population, a HOMA–IR score > 2.69 was considered insulin resistance (based on the top 25% of HOMA–IR scores) [23]. Thus, metabolically unhealthy was defined as having at least one of the following metabolic disorders: elevated triglyceride levels (≥ 150 mg/dL); low HDL cholesterol levels (< 40 mg/dL in men, < 50 mg/dL in women); elevated blood pressure (≥ 130/85 mmHg); elevated fasting glucose (≥ 110 mg/dL or 6.1 mmol/L) [21]; and a HOMA–IR score > 2.69 [23]. Inflammatory markers were not considered a metabolic disorder.

Nevertheless, there is no standardized means to identify metabolically healthy obese individuals in either clinical practice or research protocols [5,17,18]. For this reason, the present survey used two previously recommended definitions to also determine metabolic health. In the Karelis [24] study, metabolically healthy was defined as meeting four out of five metabolic factors: HOMA < 2.7; triglycerides (TG) ≤ 1.7 mmol/L; HDL cholesterol ≥ 1.3 mmol/L; low-density lipoprotein (LDL) cholesterol ≤ 2.6 mmol/L; and high-sensitivity CRP (hsCRP) ≤ 3.0 mg/L. The other definition used is from Wildman et al. [19], who proposed that metabolically healthy was having 0–1 cardiometabolic disorders (blood pressure ≥ 130/85 mmHg, TG ≥ 1.7 mmol/L, glucose ≥ 5.6 mmol/L, HOMA > 5.13, hsCRP > 0.1 mg/L and HDL cholesterol < 1.3 mmol/L).

2.7. Data analysis

Statistical analysis was performed using Stata statistical software, version 11 (StataCorp, College Station, TX, USA), was used for data analysis, means ± standard deviation (SD) was used for continuous variables having a normal distribution, and medians and interquartile range (IQR) for continuous variables having a skewed distribution. Absolute and relative (%) values were used to express categorical variables. A two-tailed P value < 0.05 was considered significant [11].

According to BMI categories, all subjects were in one of two subpopulations (normal weight and overweight/obese). Both of these subpopulations were further divided into two subgroups (metabolically healthy and metabolically unhealthy). The characteristics of these two subgroups in both the normal-weight and overweight/obese subpopulations were examined. Student’s t test or the Wilcoxon rank-sum test was used for continuous variables and the Chi² test or Fisher’s exact test for categorical variables.

We also investigated the prevalence of metabolically healthy and metabolically unhealthy according to BMI categories. Three definitions of metabolically healthy were used in our analysis.

To examine the association between metabolically healthy or metabolically unhealthy overweight/obesity and CKD, multiple logistic regression models were applied. All subjects were divided into four subgroups:

- group 1, normal weight and metabolically healthy;
- group 2, normal weight and metabolically unhealthy;
- group 3, overweight/obese and metabolically healthy;
- group 4, overweight/obese and metabolically unhealthy.

The normal-weight and metabolically healthy subgroup was designated the reference group. Potential confounders were added to the adjusted models. These variables included sociodemographic data (gender, age and education level), lifestyle factors (current smoking, current alcohol consumption, physical activity), comorbidities (history of coronary heart disease, history of stroke), use of traditional Chinese medicine and residence in Zhuhai. To avoid the impact of geography, geographical location was also added to the models.

In some previous studies, inflammatory markers were included as part of the definition of metabolically healthy [19,20]. However, our present study did not include inflammatory markers in the definition of metabolically healthy. Inflammation might be a potentially adverse downstream consequence of increased fat mass, and might also be part of the causal pathway between obesity and CKD [1,25]. Our previous study indicated that obesity is associated with inflammation and that inflammation modifies the links between obesity and CKD [25]. To examine the effects of modifications due to inflammation on the relationships between obesity, metabolic subtypes and CKD, the inflammatory marker CRP was additionally included in the adjusted models.

3. Results

Based on BMI categories, 1449 (62.35%) subjects were normal weight, 690 (29.69%) were overweight and 185 (7.96%) were obese. In both the normal-weight and overweight/obese subpopulations, the metabolically unhealthy subgroups had significantly higher BMI scores, larger waist circumferences, and higher levels of blood pressure, fasting glucose, triglycerides, CRP and HOMA–IR scores, and lower levels of serum HDL cholesterol (Table 1).
Table 1 Characteristics of metabolically healthy/unhealthy subjects according to weight categories based on body mass index (BMI).

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Overweight/obese</th>
<th>P value</th>
<th>Metabolically healthy (n = 432)</th>
<th>Metabolically unhealthy (n = 1017)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.24 ± 14.06</td>
<td>&lt;0.001</td>
<td>52.53 ± 15.29</td>
<td></td>
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</tr>
<tr>
<td>Male (%)</td>
<td>125 (28.94)</td>
<td>0.86</td>
<td>299 (29.40)</td>
<td>33 (32.04)</td>
<td>0.19</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.64 ± 1.97</td>
<td>&lt;0.001</td>
<td>21.25 ± 1.92</td>
<td>25.81 ± 2.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>74.73 ± 7.05</td>
<td>&lt;0.001</td>
<td>78.50 ± 7.53</td>
<td>86.13 ± 7.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>43 (9.95)</td>
<td>0.83</td>
<td>105 (10.32)</td>
<td>12 (11.65)</td>
<td>0.79</td>
</tr>
<tr>
<td>Current alcohol use (%)</td>
<td>21 (4.86)</td>
<td>0.14</td>
<td>33 (3.24)</td>
<td>4 (3.88)</td>
<td>0.81</td>
</tr>
<tr>
<td>Education level: high school or above (%)</td>
<td>221 (51.16)</td>
<td>&lt;0.001</td>
<td>389 (38.25)</td>
<td>53 (51.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical inactivity (%)</td>
<td>279 (64.58)</td>
<td>0.04</td>
<td>598 (58.8)</td>
<td>53 (51.46)</td>
<td>0.16</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>111.48 ± 9.53</td>
<td>&lt;0.001</td>
<td>129.32 ± 19.88</td>
<td>115.76 ± 9.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>69.80 ± 7.45</td>
<td>&lt;0.001</td>
<td>78.29 ± 10.81</td>
<td>72.25 ± 6.11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Laboratory

<table>
<thead>
<tr>
<th>Test</th>
<th>Overweight/obese</th>
<th>P value</th>
<th>Metabolically healthy (n = 432)</th>
<th>Metabolically unhealthy (n = 1017)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (μmol/L)</td>
<td>68.72 ± 14.09</td>
<td>0.007</td>
<td>71.12 ± 16.19</td>
<td>69.19 ± 14.21</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>108.36 ± 22.35</td>
<td>&lt;0.001</td>
<td>101.53 ± 22.55</td>
<td>105.82 ± 20.39</td>
<td>0.001</td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>7.20 (5.22–11.09)</td>
<td>&lt;0.001</td>
<td>8.93 (6.10–15.03)</td>
<td>8.04 (5.39–12.11)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>4.54 ± 0.37</td>
<td>&lt;0.001</td>
<td>4.75 ± 0.95</td>
<td>4.64 ± 0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum CRP (mg/L)</td>
<td>0.51 (0.28–1.11)</td>
<td>&lt;0.001</td>
<td>0.75 (0.33–1.81)</td>
<td>1.34 (0.66–3.12)</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum triglyceride (mmol/L)</td>
<td>0.89 (0.67–1.13)</td>
<td>&lt;0.001</td>
<td>1.13 (0.81–1.67)</td>
<td>1.09 (0.83–1.34)</td>
<td>0.02</td>
</tr>
<tr>
<td>Serum LDL (mmol/L)</td>
<td>2.97 ± 0.82</td>
<td>0.01</td>
<td>3.10 ± 0.91</td>
<td>3.33 ± 0.86</td>
<td>0.54</td>
</tr>
<tr>
<td>Serum HDL (mmol/L)</td>
<td>1.66 ± 0.30</td>
<td>&lt;0.001</td>
<td>1.15 ± 0.61</td>
<td>1.57 ± 0.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA–IR (μU/mL, mmol/mL)</td>
<td>1.27 (0.94–1.66)</td>
<td>&lt;0.001</td>
<td>1.49 (1.09–2.24)</td>
<td>1.61 (1.22–1.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>24 (5.56)</td>
<td>&lt;0.001</td>
<td>149 (14.65)</td>
<td>5 (4.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD or medians (25th–75th percentiles) for continuous variables, and as absolute and relative (%) values for categorical variables. BMI: body mass index; BP: blood pressure; eGFR: estimated glomerular filtration rate; ACR: urinary albumin-to-creatinine ratio; CRP: C-reactive protein; LDL/HDL: low-density/high-density lipoprotein; HOMA–IR: homeostatic model assessment of insulin resistance.

The prevalence of metabolically healthy subjects in the different weight categories according to the three definitions is shown in Fig. S1 (see supplementary material associated with this article online). Only 29.81% of the normal-weight subjects and 11.77% of the overweight/obese were metabolically healthy. Also, the overweight/obese subjects had a significantly higher prevalence of metabolic unhealthyness than normal-weight subjects (data not shown). However, using Wildman’s definition of metabolically healthy, the prevalence was similar, with 31.95% in normal-weight subjects and 11.89% in overweight/obese subjects. Using the Karellis definition of metabolically healthy, 43.62% of normal-weight subjects and 24.22% of overweight/obese subjects were metabolically healthy. Based on all three definitions, obese subjects had a higher prevalence of metabolic unhealthyness than overweight and normal-weight subjects (P < 0.001; data not shown).

The prevalence of CKD in four subgroups according to the current definition of metabolically healthy and unhealthy is presented in Fig. 1. By all three definitions, metabolically unhealthy subgroups had significantly higher prevalence of CKD than the metabolically healthy subgroups.

In both unadjusted and adjusted models, overweight/obese subjects who were metabolically healthy did not have a higher risk of CKD. In the unadjusted models, being metabolically unhealthy was significantly associated with an increased risk of CKD. The odds ratios (ORs) of CKD were 2.92 (95% CI: 1.87–4.56; P < 0.001) in the metabolically unhealthy normal-weight subjects, and 4.31 (95% CI: 2.75–6.74; P < 0.001) in the metabolically unhealthy overweight/obese subjects. After adjusting for potential confounders, only the metabolically unhealthy overweight/obese subjects had a significantly higher risk of CKD (OR: 2.47, 95% CI: 1.54–3.95; P < 0.001). Those who were overweight/obese but metabolically healthy did not have a higher risk of CKD (OR: 0.79, 95% CI: 0.29–2.14; P = 0.64). Also, normal-weight but metabolically unhealthy subjects had a higher risk of CKD (OR: 1.56,
95% CI: 0.97–2.52; \( P = 0.07 \), but the \( P \) value was of borderline significance (Table 2).

Further adjustment for CRP had an impact on the OR. In overweight/obese subjects who were metabolically unhealthy, the OR for CKD was 2.10 (95% CI: 1.30–3.40; \( P = 0.002 \)) (Table 2). However, CRP levels did not alter the associations observed.

When only the association of elevated microalbuminuria with increased fat mass and metabolic profile were examined, the results were similar. In both the unadjusted and adjusted models, overweight/obese subjects who were metabolically healthy were not at higher risk according to ACR. After adjusting for potential confounders, only metabolically unhealthy overweight/obese subjects were significantly associated with elevated microalbuminuria (OR: 2.55, 95% CI: 1.56–4.17; \( P < 0.001 \)). Normal-weight but metabolically unhealthy subjects had an increased risk according to ACR (OR: 1.59, 95% CI: 0.97–2.61; \( P = 0.07 \)), although the difference was not significant. When CRP was added to the adjusted model, overweight/obese subjects who were metabolically unhealthy were still associated with the ACR (OR: 2.14, 95% CI: 1.29–3.52; \( P = 0.003 \)).

When the Karelis and Wildman definitions of metabolically healthy were applied, similar results were obtained. Compared with normal-weight subjects who were metabolically healthy, only overweight/obese subjects who were metabolically unhealthy had a significantly increased risk of CKD. In adjusted models and using the Karelis and Wildman definitions, the ORs for CKD were 1.94 (95% CI: 1.40–2.68; \( P < 0.001 \)) and 2.12 (95% CI: 1.37–3.28; \( P < 0.001 \)), respectively. Normal-weight subjects who were metabolically unhealthy had a higher risk of CKD than normal-weight subjects who were metabolically healthy, although the differences were not significant: OR: 1.24, 95% CI: 0.88–1.77 (\( P = 0.22 \)) and OR: 1.33, 95% CI: 0.86–2.07 (\( P = 0.20 \)), respectively. After adding CRP to the adjusted models, the ORs for overweight/obese and metabolically unhealthy subjects were attenuated to 1.66 (95% CI: 1.16–2.38; \( P = 0.006 \)) and 1.79 (95% CI: 1.13–2.84; \( P = 0.01 \)), respectively, although \( P \) values were still <0.05.

4. Discussion

The results of the present study indicate that metabolically healthy overweight/obesity is not associated with a higher risk of CKD, whereas metabolically unhealthy overweight/obesity was at increased risk of CKD. Metabolic unhealthiness in normal-weight subjects also had a higher risk of CKD, although the difference was not significant. When CRP was added to the models, the association was much attenuated, but not altered. Inflammation modified the association between metabolically unhealthy overweight/obesity and CKD.

It is well established that obesity is linked to chronic diseases such as cardiovascular disease, CKD and diabetes [1–3]. Obese individuals are at increased risk of cardiovascular events and all-cause mortality [2,3]. However, in most previously reported studies, only obesity was evaluated, and the presence of metabolic factors in obese individuals was not considered. Indeed, it has still not been determined whether it is obesity itself or the metabolic disorders initiated by obesity, or being both obese and metabolically unhealthy, that is associated with adverse events and mortality [5].

In 2001, Sims [26] first proposed a special obese phenotype, metabolically healthy obesity. Despite having higher levels of body fat, metabolically healthy obese individuals are nonetheless insulin-sensitive and normotensive, with lower triglyceride, higher HDL [7,8] and lower CRP levels [24]. Previous studies showed that such metabolically healthy but obese individuals might account for as much as 30–40% of the obese population [17,27,28]. Wildman et al. [19] reported, in a sample of 5440 participants from the 1999–2004 US National Health and Nutrition Examination Survey (NHANES) that 29.2% of obese men and 35.4% of obese women were metabolically healthy. This high prevalence of the metabolically healthy obese phenotype was also observed among the African American [29] and Asian [30] populations. However, the present study is the first time that the prevalence of metabolically healthy overweight/obesity has been reported in a Chinese population. According to our findings, 11.78% of overweight/obese subjects and only 3.26% of the obese were metabolically healthy.

The prevalence of metabolic health reported in our present study is lower than in previous studies. However, its prevalence has often shown a wide variance. Also, definitions of metabolically healthy are highly variable, and this may be a plausible explanation for the disparity [5,17,18]. The use of non-MetS features to define metabolically healthy could also lead to mixed results. In most of the previous studies, having fewer than three components of the MetS together with the absence of diabetes was used as a diagnostic criterion of metabolically healthy obesity [18]. However, this definition could be controversial because individuals with established cardiovascular risk (such as hypertension) could be included in the metabolically healthy group. In addition, in some of the previous studies [18,27,31–33], insulin

Table 2

<table>
<thead>
<tr>
<th>Association between metabolically healthy and metabolically unhealthy overweight/obesity and chronic kidney disease.</th>
<th>Model 1 (unadjusted)</th>
<th>Model 2 (adjusted)(^a)</th>
<th>Model 3 (adjusted)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (95% CI)</td>
<td>( P ) value</td>
<td>OR (95% CI)</td>
<td>( P ) value</td>
</tr>
<tr>
<td>Normal weight and metabolically healthy (( n = 432 ))</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>Normal weight and metabolically unhealthy (( n = 1017 ))</td>
<td>2.92 (1.87–4.56)</td>
<td>&lt;0.001</td>
<td>1.56 (0.97–2.52)</td>
</tr>
<tr>
<td>Overweight/obese and metabolically healthy (( n = 103 ))</td>
<td>0.87 (0.32–2.33)</td>
<td>0.78</td>
<td>0.79 (0.29–2.14)</td>
</tr>
<tr>
<td>Overweight/obese and metabolically unhealthy (( n = 772 ))</td>
<td>4.31 (2.75–6.74)</td>
<td>&lt;0.001</td>
<td>2.47 (1.54–3.95)</td>
</tr>
</tbody>
</table>

\( a \) For age, gender, current smoker, current alcohol use, physical inactivity, education level, use of traditional Chinese medicine and residing in Zhuhai.

\( b \) Model 2 plus C-reactive protein.
resistance was assessed and included as part of the definition of metabolic status whereas, in others [34,35], a more stringent definition of metabolically healthy obesity was to have no components of the MetS. Our present study definition was to have no components of the MetS except for abdominal obesity in combination with insulin sensitivity as the diagnostic criteria. This definition of metabolic health is, in fact, more stringent. In most of the previous studies, only obese individuals were defined as having metabolically healthy obesity [18] although, in the study by Bobbioni-Harch et al. [34], overweight subjects were also included in the definition. Our present study used BMI to assess fat mass and, which was also used in most of the previous studies to define obesity. Only one earlier study combined BMI and waist circumference to assess obesity [36], while another study used the body fat percentage to define obesity [37].

It is well established that obesity is associated with cardiovascular diseases and mortality [1–3]. However, in metabolically healthy obese individuals, the results are inconsistent. Some studies have reported that metabolically healthy obesity was significantly associated with all-cause mortality and cardiovascular death, whereas other studies did not [5,17,18]. One possible explanation for these conflicting results is that the control group included normal-weight individuals who may have been metabolically healthy or unhealthy [5]. In contrast, one meta-analysis has shown that obese individuals have an increased risk of death and cardiovascular events over the long-term regardless of metabolic status [5]. Metabolically unhealthy overweight has also been associated with these adverse outcomes [5], while metabolically healthy overweight/obesity is an important subtype with risks lying somewhere between those associated with fat mass and metabolic status [18]. Given the significant variations in the definition of metabolically healthy obesity, a universal, standardized definition should be devised to clarify future study findings and further strengthen between-study comparisons [5,18].

Previous studies have shown that obesity is associated with incident CKD [1]. A large prospective longitudinal study [38] using data from the Atherosclerosis Risk in Communities (ARIC) cohort indicated that the MetS and insulin resistance are associated with the incidence of CKD in non-diabetic adults, with each MetS component contributing to the incident CKD. The results also indicated that not only obesity itself, but also the metabolic disorders induced by obesity are associated with CKD. Yet, in the analyses, potential confounders such as physical activity, lifestyle, education level and comorbidities were not included [38]. Our previous study showed that the association of obesity with CKD is independent of other MetS components in women [39]. Another recent study [40] indicated that the presence of the MetS was associated with decreased GFR and proteinuria, and that individual MetS components were associated with an increased risk of CKD. Indeed, the strength of the association of MetS with CKD increased with the number of MetS components, a result that suggests that both obesity and metabolic disorders contribute to CKD [40].

In one previous study [9], the association between metabolically healthy obesity and CKD was examined, and the results showed that only obese subjects with insulin resistance had impaired kidney function. No differences in estimated GFR were observed between non-obese and metabolically healthy obese individuals. In that study, metabolically healthy was defined as insulin sensitivity, and overweight individuals were not included [9]. In our present study, the results also support that metabolically healthy overweight/obese individuals are not at increased risk of CKD. Also, being metabolically unhealthy, regardless of overweight/obesity or normal weight, was associated with a higher prevalence of CKD, although the difference was only significant between metabolically unhealthy overweight/obese individuals and metabolically healthy normal-weight individuals. Previous studies do not support the concept of ‘benign obesity’ and instead show that there is no ‘healthy’ pattern of obesity [5]. For this reason, the association between metabolically healthy overweight/obesity and CKD needs to be further explored in a longitudinal study.

Another often-discussed point in metabolic disorders is inflammation, and CRP is thought to be the best biomarker of vascular inflammation [18]. In the obese state, adipose tissue might be releasing excess proinflammatory adipokines such as tumour necrosis factor (TNF)-alpha and interleukin (IL)-6. Beneficial adipokines, including leptin and adiponectin, might also be decreased [1]. Four previous studies included CRP in their definition of metabolically healthy obesity, but none of them assessed the association of inflammation with adverse events [18]. As it is difficult to assess the inclusion of inflammation in the definition of metabolically healthy [18], the present study also did not include CRP in the definition of metabolically healthy obesity. Yet, when CRP was added as a covariate to the analysis, the association between metabolically unhealthy overweight/obesity and CKD was much attenuated. The results indicate that inflammation could have an important role in obesity-related adverse events. Our previous study also supported such a view [25].

Although the mechanisms behind metabolically healthy obesity have not been clarified, behavioural and lifestyle factors may be playing a key role [18].

Several advantages of the present study should be mentioned. First, this was the first study to analyse the association between obesity with different metabolic states and CKD in a Chinese population. Second, a relatively large population was included to perform our study analysis and it also used a more stringent definition of metabolically healthy.

Our present study also had several limitations. First, it is not possible to infer causality from our findings, as this was a cross-sectional survey. Second, the gold-standard method for measuring GFR was not used in our study, although the modified MDRD equation is an acceptable method for estimating GFR in Chinese populations [15]. In addition, most of our study subjects with CKD were diagnosed on the basis of ACR, which was obtained from a single measurement with no repeated tests. Third, the prevalence of obesity in our population was only 7.96%, and most of the participants with increased fat mass were included in the overweight phenotype. Finally, our population sample was biased by a male-to-female ratio of 1:2 in the present analysis. As the employment rate is higher among men,
and employers offer free physical examinations, this might have been one reason for the lower participation rate among men [11].

5. Conclusion

Metabolically unhealthy overweight/obesity, but not metabolically healthy overweight/obesity, is associated with an increased risk of CKD. When CRP was added as a covariate, the association was considerably attenuated, but not altered. Inflammation might be a mediator of at least part of the association between metabolic disorders and the prevalence of CKD.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Supplementary data

Supplementary data (French abstract and Fig. S1) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2014.08.005.

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