Metabolically Healthy Obesity and Risk of Incident CKD

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Abstract
Background and objectives Metabolically healthy obesity (MHO) is a unique obesity phenotype that apparently protects people from the metabolic complications of obesity. The association between MHO phenotype and incident CKD is unclear. Thus, this study investigated the association between MHO phenotype and incident CKD.

Design, setting, participants, & measurements A total of 3136 Japanese participants were enrolled in an 8-year follow-up cohort study in 2001. Metabolically healthy status was assessed by common clinical markers: BP, triglycerides, HDL cholesterol, and fasting plasma glucose concentrations. Body mass index (BMI) was defined as obesity. CKD was defined by proteinuria or eGFR of <60 ml/min per 1.73 m². To calculate the odds ratio for incident CKD, logistic regression analyses were performed.

Results The crude incidence proportions of CKD were 2.6% (56 of 2122 participants) in participants with the metabolically healthy nonobesity phenotype, 2.6% (8 of 302) in those with the MHO phenotype, 6.7% (30 of 445) in those with the metabolically abnormal nonobesity phenotype, and 10.9% (29 of 267) in those with the metabolically healthy nonobesity phenotype, 2.6% (8 of 302) in those with the MHO phenotype, 6.7% (30 of 445) in those with the metabolically abnormal nonobesity phenotype, and 2.80 (95% CI, 1.45 to 5.35; P = 0.02) for metabolically abnormal obesity phenotype after adjustment for confounders, including age, sex, smoking status, alcohol use, creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes.

Conclusion MHO phenotype was not associated with higher risk of incident CKD. Clin J Am Soc Nephrol 10: 578–583, 2015. doi: 10.2215/CJN.08980914

Introduction
Obesity (1) and metabolic syndrome (2) are major public health problems worldwide that frequently coexist and define obese people who are at risk for adverse health outcomes. Recent studies have identified a subset of obese people who have a low burden of adiposity-related metabolic abnormalities compared with at-risk obese people, the so-called metabolically healthy obesity (MHO) phenotype (3–5). MHO phenotype is characterized by high levels of insulin sensitivity, low prevalence of hypertension, and a favorable fasting glucose, lipid, and inflammation profile (6,7).

CKD is an important and increasingly prevalent health concern worldwide (8,9). It is associated with ESRD, as well as cardiovascular morbidity and mortality (10–12).

Recent studies reported that metabolic syndrome (13,14) and obesity (15–18) were risk factors for incident CKD, but the association between MHO phenotype and incident CKD remains to be elucidated. Therefore, we aimed to investigate whether MHO phenotype was associated with higher risk of incident CKD in this cohort study.

Materials and Methods
Study Participants and Study Design
The Oike Health Survey is an ongoing cohort investigation of risk factors for chronic diseases, including hypertension, diabetes, and CKD. The Oike Clinic (Kyoto, Japan) provides regular health checkups for the employees of various companies. In Japan, yearly routine examination for employees is legally mandated, and all or most of the costs for the health checkup are usually paid by their employers.

In this retrospective cohort study, we enrolled 4127 participants without malignant disease, liver cirrhosis, or hematologic disease who had health checkup examinations at the Oike Clinic in 2001 and 2009. We excluded 709 participants who had CKD at the baseline examination, which was performed in 2001. Furthermore, we excluded 282 participants with missing data on covariates. Thus, 3136 participants were eligible for this analysis.

The Ethical Committee of the Oike Clinic approved this study, and the study was conducted in accordance with the Declaration of Helsinki. Each participant provided informed consent.

Date Collection and Measurements
All participants provided demographic details. Smoking was defined as current tobacco use. Alcohol use was defined as daily alcohol consumption. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. After a brief period of rest, sitting BP was measured in either arm. BP was...
measured once in most participants, but up to three measurements at 1- to 2-minute intervals were made in participants who had hypertensive or prehypertensive BP values. The lowest reading was used in the analysis that assessed the incidence of hypertension. After an overnight fast, venous blood was collected for the measurement of the levels of various factors, including fasting plasma glucose, total cholesterol, triglycerides, HDL cholesterol, creatinine, and uric acid. Serum creatinine was measured using an enzymatic assay (Akyurasuto-auto; Shino-test Corp., Kanagawa, Japan) in an autoanalyzer; the coefficient of variation was 2.0%.

**Definition of CKD**

GFR was estimated using the Japanese Society of Nephrology equation (19):

\[
(eGFR) = 194 \times \text{Cre}^{-1.094} \times \text{age}^{-0.287} \text{ (ml/min per 1.73 m}^2)\]

For women, the eGFR was multiplied by a correction factor of 0.739. Proteinuria was determined using dipstick testing (Yurifuret-S, Arkray, Kyoto, Japan) in fasting morning urine (positive: $\geq 1+ $) (20). CKD was defined as proteinuria or an eGFR $<60$ ml/min per 1.73 m$^2$.

**Definitions of Metabolic Phenotypes**

BMI $\geq 25.0$ kg/m$^2$, which has been proposed as a cutoff for the diagnosis of obesity in Asian people (21), was defined as obesity; BMI $<25.0$ kg/m$^2$ was defined as non-obesity. The validity of this definition was confirmed previously (22,23). We used four metabolic factors (impaired fasting glucose or diabetes, hypertension, hypertriglyceridemia, and low HDL cholesterol concentration), defined by International Diabetes Federation (24), to determine whether the participant was metabolically healthy or metabolically abnormal. Data on waist circumference, visceral fat, fasting insulin, and C-reactive protein concentrations were not available for study participants, although we acknowledge that these markers can be used to define metabolic phenotypes (7,25). Participants with a systolic BP $\geq 130$ mmHg and/or a diastolic BP $\geq 85$ mmHg or who were under medical treatment were considered to have hypertension. Elevated triglyceride level was indicated by $\geq 150$ mg/dl or treatment of hyperlipidemia, and reduced HDL cholesterol level was indicated by $<40$ mg/dl in men and $<50$ mg/dl in women. Participants with fasting plasma glucose $\geq 100$ mg/dl or who were under medical treatment were considered to have impaired fasting glucose or diabetes. A metabolically healthy state was considered if none or one of the metabolic factors based on the International Diabetes Federation definition was present, and a metabolically abnormal state was declared if two or more metabolic factors were present (24). Then, participants were categorized at the baseline examination into four phenotypes: (1) metabolically healthy nonobesity (MHNO), (2) MHO, (3) metabolically abnormal nonobesity (MANO), or (4) metabolically abnormal obesity (MAO). This definition of metabolic phenotypes has often been used in a Japanese population (26). We also analyzed data with obesity defined as BMI $\geq 27.5$ kg/m$^2$, which has also been proposed as a cutoff for the diagnosis of obesity in Asian people (27).

**Statistical Analyses**

Continuous variables were expressed as mean $\pm$ SD, and categorical variables were expressed as percentage (number). The analyses of continuous and categorical variables to assess differences among four phenotypes were determined by one-way ANOVA or the chi-squared test. We performed logistic regression analyses to assess the association of metabolic phenotypes with incident CKD, adjusting for covariates that included age, sex, smoking statuses, alcohol use, creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes. In addition, we performed logistic regression analyses to assess the association of metabolic phenotypes with incident proteinuria adjusting for covariates, including age, sex, smoking statuses, alcohol use, creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes. The variance inflation factor was used for detecting the co-linearity; a variance inflation factor $\geq 10$ indicates a colinearity problem. In addition, we conducted a second analysis when we defined obesity as a BMI $\geq 27.5$ kg/m$^2$. The statistical analyses were performed using JMP software, version 10.0 (SAS Institute Inc., Cary, NC). A $P$ value $<0.05$ was considered to represent a statistically significant difference.

**Results**

The baseline characteristics are shown in Table 1. The prevalence of MHNO, MHO, MANO, and MAO was 67.7% ($n=2122$), 9.6% ($n=302$), 14.2% ($n=445$), and 8.5% ($n=267$), respectively. At the follow-up examination, which was performed 8 years after baseline examination, 123 participants had developed CKD. The crude incidence proportions of CKD were 2.6% (56 of 2122) for the MHNO phenotype, 2.6% (eight of 302) for the MHO phenotype, 6.7% (30 of 445) for the MANO phenotype, and 10.9% (29 of 267) for the MAO phenotype. The crude incidence proportions of proteinuria were 0.5% (11 of 2122) for the MHNO phenotype, 1.0% (three of 302) for the MHO phenotype, 1.6% (seven of 445) for the MANO phenotype, and 5.6% (15 of 267) for the MAO phenotype.

Logistic regression analyses were performed to investigate the association between each metabolic phenotype and incident CKD (Table 2). No colinearity was found between variables. The MHO phenotype was not associated with higher risk of incident CKD. On the other hand, MAO phenotype was associated with significantly higher risk of incident CKD (multivariate-adjusted odds ratio [OR], 2.80; 95% confidence interval [95% CI], 1.45 to 5.35; $P=0.02$).

Logistic regression analyses were also performed to investigate the association between each metabolic phenotype and incident proteinuria (Table 3). The MHO phenotype was not associated with higher risk of incident proteinuria. On the other hand, MAO phenotype was associated with a significantly higher risk of incident proteinuria (multivariate-adjusted OR, 6.29; 95% CI, 2.05 to 19.6; $P<0.01$).

**Results of the Second Analyses**

The prevalence of MHO, MANO, or MAO in the analysis that defined obesity as a BMI $\geq 27.5$ kg/m$^2$ (and in
which participants were considered as being in a metabolically healthy or abnormal state) was 74.7% (n=2344), 2.6% (n=80), 19.8% (n=622), and 2.9% (n=90). Crude incidence proportions of proteinuria were 0.5% (12 of 2344) for the MHNO phenotype, 7.2% (45 of 622) for the MANO phenotype, and 15.6% (14 of 90) for the MAO phenotype. Crude incidence proportions of CKD were 2.6% (61 of 2344) for the MHNO phenotype, 2.1% (13 of 622) for the MANO phenotype, 7.2% (45 of 622) for the MANO phenotype, and 15.6% (14 of 90) for the MAO phenotype. The major finding of our study is that MHNO phenotype was not associated with higher risk of incident CKD. On the other hand, MAO phenotype was associated with significantly higher risk of incident proteinuria (multivariate-adjusted OR, 14.0; 95% CI, 4.01 to 48.5; P<0.001).

### Discussion

The major finding of our study is that MHNO phenotype was not associated with higher risk of incident CKD. On the other hand, MAO phenotype was associated with significantly higher risk of incident CKD. In addition, we also showed that MHNO phenotype was not associated with higher risk of incident proteinuria. On the other hand, MAO phenotype was associated with significantly higher risk of incident proteinuria.

People with the MHNO phenotype are apparently protected from the metabolic complications of obesity; at least, the risk appears to be considerably lower than expected for the given level of obesity (4,5). To our knowledge, ours is

| Table 2. Odds ratios for incident CKD at 8 years after the baseline examination according to metabolic phenotypes |
|------------------------------------------------------|---------|---------|---------|---------|
| Variable                                             | MHNO   | MHO    | MANO   | MAO    |
| Incidence of CKD (n/n)                               | 56/2122| 8/302  | 30/445 | 29/267 |
| Model 1<sup>a</sup>                                   | 1.00   | 1.00 (0.44 to 2.01) | 2.67 (1.67 to 4.18)<sup>b</sup> | 4.50 (2.78 to 7.12)<sup>b</sup> |
| Model 2<sup>c</sup>                                   | 1.00   | 0.97 (0.42 to 1.95) | 1.83 (1.12 to 2.93)<sup>d</sup> | 3.52 (2.14 to 5.69)<sup>b</sup> |
| Model 3<sup>e</sup>                                   | 1.00   | 0.97 (0.42 to 1.95) | 1.83 (1.12 to 2.93)<sup>d</sup> | 3.51 (2.13 to 5.68)<sup>b</sup> |
| Model 4<sup>f</sup>                                   | 1.00   | 0.83 (0.36 to 1.72) | 1.44 (0.80 to 2.57) | 2.80 (1.45 to 5.35)<sup>f</sup> |

Unless otherwise noted, values are expressed as odds ratio (95% confidence interval).

<sup>a</sup>Model 1 was unadjusted.

<sup>b</sup>P<0.01 versus MHNO phenotype.

<sup>c</sup>Model 2 adjusted for age and sex.

<sup>d</sup>P<0.05 versus MHNO phenotype.

<sup>e</sup>Model 3 adjusted for model 2 plus smoking status and alcohol use.

<sup>f</sup>Model 4 adjusted for model 3 plus creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes.
some metabolically healthy participants might have
circumference, insulin resistance, or insulin secretion,
ation. First, because we could not assess changes in waist
participants both at baseline and at follow-up. However,
the kidney as well (36). On this point, studies of obese
people suggested that the MHO phenotype had a more
favorable distribution of low visceral fat, although the to-
anyone with higher risk of incident CKD in the obese people.
Thus, we demonstrated that the association between obe-
sity and CKD may be mediated by metabolic abnormal-
ties. The association between obesity and CKD might be
mediated through multiple biologic mechanisms, includ-
ing hormonal factors, inflammation, oxidative stress, and
endothelial dysfunction (30,31). The expansion of visceral
adipose tissue (i.e., a target for infiltration by immune
cells) is involved in these mechanisms (32). Excess visceral
adipose tissue can lead to the activation of the sympa-
thetic nervous and renin-angiotensin systems, as well as
lipid deposition, hyperfiltration, and increased sodium
absorption in the kidneys, resulting in a feedback loop
where obesity-induced declines in kidney function lead
to the development of hypertension, which results in fur-
ther damage to the kidneys (33). Previous studies have
demonstrated that hypertension mediates the association
between obesity and incident CKD (34,35). Moreover, the
decline in adiponectin concentration is relevant: It is as-
associated with reduced whole body insulin sensitivity and
possibly causes increased proinflammatory signaling in
the kidney as well (36). On this point, studies of obese
people suggested that the MHO phenotype had a more
favorable distribution of low visceral fat, although the to-
total fat mass was similar between MHO phenotype and
MAO phenotype (3,37). Taking these findings together,
not MHO phenotype but MAO phenotype is associated
with higher risk of incident CKD.

Strengths of our study include the large number of
participants both at baseline and at follow-up. However,
this study has some limitations that require consider-
ation. First, because we could not assess changes in waist
circumference, insulin resistance, or insulin secretion,
some metabolically healthy participants might have
isolated insulin resistance or visceral adiposity without
the major common metabolic abnormalities. Thus, we
cannot deny the possibility of misclassification of par-
ticipants. However, the four metabolic factors (impaired
fasting glucose or diabetes, hypertension, hypertrigly-
ceridemia, and low HDL cholesterol concentration) used
in this study are commonly available in clinical settings,
and the validity of this definition was confirmed previously
(26,38).

Second, this is a relatively long follow-up study, but
duration of follow-up may have been insufficient to
allow us to evaluate the risk of incident CKD. Recent
studies revealed the possibility that MHO phenotype
was also a risk factor for different clinical characteristics,
including diabetes (26,38,39), cardiovascular diseases
(40–42), and hypertension (43). On this point, some clin-
ical outcomes occurred only after a long-term follow-up
(40,43). Thus, further long-term follow-up study is
needed.

Third, the study population consisted of Japanese men
and women; therefore, it is uncertain whether these find-
ings can be generalized to other ethnic groups.

Fourth, we defined proteinuria by dipstick testing and
thus did not quantitate the proteinuria. However, a dip-
stick test is a useful tool. Most patients with a 1+ or 2+
dipstick test result have microalbuminuria instead of
macroalbuminuria, whereas patients with 3+ proteinuria
mostly have macroalbuminuria (20). In addition, protein-
uria by dipstick testing was also useful to determine de-
velopment of ESRD (44,45).

Finally, our study participants underwent a health
examination; thus, some participants might have made
lifestyle changes based on results of the health examination
to prevent the development of metabolic abnormalities.
In conclusion, our study showed that MAO phenotype,
not MHO phenotype, was associated with higher risk of
incident CKD.

Acknowledgments
We thank all of the staff members of the Oike Clinic.

Disclosures
None.

Table 3. Odds ratios for incident proteinuria at 8 years after the baseline examination according to metabolic phenotypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>MHNO</th>
<th>MHO</th>
<th>MANO</th>
<th>MAO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of proteinuria (n/n)</td>
<td>11/2122</td>
<td>3/302</td>
<td>7/445</td>
<td>15/267</td>
</tr>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.00 (Reference)</td>
<td>1.93 (0.43 to 6.21)</td>
<td>3.07 (1.12 to 7.83)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.4 (5.22 to 25.8)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.00 (Reference)</td>
<td>1.84 (0.41 to 5.99)</td>
<td>2.05 (0.73 to 5.43)</td>
<td>8.68 (3.83 to 20.3)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.00 (Reference)</td>
<td>1.88 (0.42 to 6.13)</td>
<td>2.06 (0.73 to 5.47)</td>
<td>8.85 (3.89 to 20.8)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Model 4&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.00 (Reference)</td>
<td>1.65 (0.36 to 5.57)</td>
<td>1.62 (0.50 to 5.00)</td>
<td>6.29 (2.05 to 19.6)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Unless otherwise noted, values are expressed as odds ratio (95% confidence interval).
<sup>a</sup>Model 1 was unadjusted.
<sup>b</sup><i>P</i>&lt;0.05 versus MHNO phenotype.
<sup>c</sup><i>P</i>&lt;0.001 versus MHNO phenotype.
<sup>d</sup>Model 2 adjusted for age and sex.
<sup>e</sup>Model 3 adjusted for model 2 plus smoking status and alcohol use.
<sup>f</sup>Model 4 adjusted for model 3 plus creatinine, uric acid, systolic BP, HDL cholesterol, and impaired fasting glucose or diabetes.


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