Impact of Transition in Metabolic Health and Obesity on the Incident Chronic Kidney Disease: A Nationwide Cohort Study

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Context. Metabolically healthy obesity (MHO) is a dynamic condition.

Objective. To evaluate the risk of chronic kidney disease (CKD) among people with MHO according to its longitudinal change.

Design. Observational study.

Setting. A nationwide population-based cohort.

Participants. A total of 514,866 people from the Korean National Health Insurance Service-National Sample Cohort.

Intervention. The initial presence and changes of obesity (using body mass index [BMI] and waist circumference [WC]) and metabolic health status.

Main outcome Measure. Incident CKD from 2011 to 2015.

Results. Of the people classified as MHO at baseline (BMI criteria), 47.6% remained as MHO in 2011 and 2012, whereas 12.1%, 5.5%, and 34.8% were classified as metabolically healthy, non-obese (MHNO), metabolically unhealthy, non-obese, and metabolically unhealthy, obese, respectively. The risk of incident CKD in the baseline MHO group was higher than that in the MHNO group (hazard ratio, 1.23; 95% confidence interval, 1.12-1.36). However, when transition was taken into account, people who converted to MHNO were not at increased risk (hazard ratio, 0.98; 95% confidence interval, 0.72-1.32), whereas the stable MHO group and the groups that evolved to metabolically unhealthy status had a higher risk of incident CKD than the stable MHNO group. When the risk was analyzed using WC criteria, it showed a similar pattern to BMI criteria except for the stable MHO group.

Conclusions. MHO was a dynamic condition, and people with MHO constituted a heterogeneous group. Although the MHO phenotype was generally associated with incident CKD, maintenance of metabolic health and weight reduction might alleviate the risk of CKD. (J Clin Endocrinol Metab 105: e148–e157, 2020)

Key Words: Obesity, metabolic syndrome, chronic kidney disease

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; ICD-10, International Classification of Disease; LDL-C, low-density lipoprotein cholesterol; NHS-HEALS, Korean National Health Insurance Service-National Health Screening Cohort; MHO, metabolically healthy, non-obese; MHO, metabolically unhealthy obesity, MUNO, metabolically unhealthy, non-obese, MUO, metabolically unhealthy, obese, TG, triglyceride; WC, waist circumference
The rapidly increasing prevalence of obesity is a huge global health concern (1). Although the effect of obesity on the development of cardio-metabolic disorders, including type 2 diabetes, and cardiovascular disease, or several types of cancer (2, 3) mostly accounts for the global health problem, the rapidly increasing prevalence of obesity is also related to the development of chronic kidney disease (CKD), which increases the risk of cardiovascular disease (4, 5). However, the association of the risk of CKD with obesity or obesity-induced metabolic disturbances remains controversial.

A condition called “metabolically healthy obesity” (MHO) (i.e., obese population with a low burden of adiposity-related metabolic abnormalities compared with “at-risk” obese individuals) has been identified (4, 6–8). Numerous studies have demonstrated that individuals with MHO are not at an increased risk of cardio-metabolic disorders and mortality compared with normal-weight individuals (6, 9–11). However, the prognostic value of MHO is a subject of debate and faces a considerable challenge (12, 13). In addition, the value may depend on the health outcomes being examined (13). With regard to the risk of CKD, recent studies reported that MHO was associated with higher incident risk of CKD, suggesting that MHO is not a harmless condition (4, 14).

MHO is a dynamic condition that changes over time (15, 16). For example, Soriguer et al (16) showed that 30% to 40% of individuals with MHO transitioned to a metabolically unhealthy status after 6 years of follow-up. Other studies have also reported that one-third to one-half of people with MHO transitioned to a metabolically unhealthy state (15–20). This transition may alter the risk of metabolic complications, including CKD, over time, suggesting that MHO determination at the 1 time point is unreliable. Because of the dynamic condition of MHO, the previous association between MHO and incident CKD must be carefully interpreted (4, 14).

Thus, this study was designed to determine the impact of phenotypic transitions on the risk for developing CKD among participants with MHO by using a large study cohort from a national health screening examination.

**Research Design and Methods**

**Study population**

The present study used data from the Korean National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS). Currently, the Korean NHIS maintains and manages databases on the use of all health services throughout Korea (21). This cohort comprises a random sample of 514,866 individuals who represent approximately 10% of the source population who underwent NHIS health screening examinations between 2002 and 2003 and who were followed to disqualification from health services owing to death or emigration or the end of the study period in 2015 (21). Importantly, this cohort contains data of general health examination of people who participated in biannual examinations. The detailed structure and function of Korean NHIS-HEALS have been described elsewhere (21).

We analyzed the demographic and biochemical data of the cohort during the index period, defined as the 2-year period between January 1, 2009, and December 31, 2010. This index period was chosen because the NHIS-HEALS began to measure some biochemical parameters, including triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C), concentrations from 2009 (21), which are necessary for defining the baseline metabolic health of the participants. Furthermore, we collected the data from the next biannual health examinations performed between January 1, 2011, and December 31, 2012, to evaluate the changes in their metabolic health status and obesity over time.

Of the 514,866 people in NHIS-HEALS, those who died or had any history of CKD or low estimated glomerular filtration rate (eGFR) (<60 mL/min/1.73 m²) before the end of the index period were excluded, as were people with missing values for baseline body mass index (BMI), systolic blood pressure (BP), diastolic BP, fasting plasma glucose (FPG), TG, and HDL-C. The final study cohort comprised 319,647 people; of these, 25,548 were categorized as MHO during the baseline examination (2009-2010), and their status on metabolic health and obesity were followed up between 2011 and 2012. Fig. 1 shows the study design and study flow.

This study was approved by the NHIS inquiry commission. Specific informed consent was not obtained from each participant because this study was based on the NHIS-HEALS results, wherein all data were fully anonymized and deidentified for all analyses. This study was approved by the institutional review board of Asan Medical Center.

**Definition of CKD**

CKD was defined using International Classification of Disease (ICD)-10 code indicating CKD and/or eGFRs (mL/min/1.73 m²) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation as follows (22): GFR = 141 × min (Scr/κ, 1)⁶ × max (Scr/κ, 1⁻¹.²⁰⁹ × 0.99³⁺κ × 1.01⁸ (if female), where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, and min

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*References*

1. doi:10.1210/clinem/dgaa033 https://academic.oup.com/jcem
and max indicate the minimum and maximum of Scr/k or 1, respectively.

CKD was defined as follows (4, 23):

1. At least 1 inpatient or 3 outpatient claims of N183 (CKD, stage 3), N184 (CKD, stage 4), or N185 (CKD, stage 5) and/or
2. At least 1 inpatient or 3 outpatient claims of N18* (CKD), N19* (unspecified kidney failure), I12* (hypertensive renal disease), I13* (hypertensive heart and renal disease), E102 (type 1 diabetes mellitus with renal complications), E112 (type 2 diabetes mellitus with renal complications), E132 (other specified diabetes mellitus with renal complications), or E142 (unspecified diabetes mellitus with renal complications) and at least 1 procedure code for hemodialysis (O702* or O9991) or 1 procedure code for peritoneal dialysis (O706* or O707*) or 1 dialysate solution (23, 24) or 1 procedural code for kidney transplantation (R3280) and/or
3. eGFR <60 mL/min/1.73 m² at 2 consecutive examinations.

To define incident CKD, we excluded people who met these criteria before the entry of their baseline examinations (i.e., people with previous CKD). In the case of eGFR criteria, we excluded people with at least 1 eGFR value of <60 mL/min/1.73 m² before the index period. Incident CKD was defined when any of these criteria were met during the follow-up period.

**Definitions of metabolic health and obesity states**

Obesity was defined based on the BMI criteria and waist circumference (WC). For BMI criteria, obesity

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**Figure 1.** Study design and participants. (a) Selection of study participants. (b) Study design. NHIS-HEALS, National Health Insurance Service-Health Screening Cohort.

(a) NHIS-HEALS (2002-2015) N=514,866

**Exclusion criteria**
- Death before the index period (N=24,593)
- Previous CKD or low baseline eGFR (N=57,192)
- Missing values in BMI, FPG, BP, TG and/or HDL (N=113,084)

**Whole Cohort** N=319,647

**Inclusion criteria**
- Baseline MHO status (N=29,597)

**Exclusion criteria**
- Missing data at follow up (N=3,979)

(b) **Exclusion of death, previous CKD, or low eGFR**

**Index period**
- Year 02 03 04 05 06 07 08
- 09 10 11 12 13 14 15

**Follow-up of Incident CKD**
- Baseline assessment of metabolic health and obesity
- Follow-up assessment of metabolic health and obesity

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(BMI ≥25 kg/m²) and non-obesity (BMI <25 kg/m²) were defined according to Asia-Pacific criteria, established by the World Health Organization Western Pacific Region (25) and officially adopted by the Korean Centers for Disease Control and Prevention and the Korean Society for the Study of Obesity (26, 27). For WC criteria, sex-specific cutoff values (i.e., men with WC ≥90 cm and women with WC ≥85 cm) were used to define obesity (27). Metabolic health was defined according to the Adult Treatment Panel III criteria as having none or 1 of the following risk factors (28)(1): systolic BP ≥130 mm Hg and/or diastolic BP ≥85 mm Hg and/or taking antihypertensive treatment (2); TG ≥150 mg/dL and/or taking antidyshlipidemic medications (3); FPG ≥100 mg/dL and/or taking antidiabetic medications; and (4) HDL-C <40 mg/dL in men and <50 mg/dL in women. Based on these criteria, all study participants were categorized into 1 of 4 groups (1): metabolically healthy, non-obese (MHNO), with BMI <25 kg/m² (in case of WC criteria, WC < sex-specific cutoff value) and no or 1 metabolic risk factor (2); metabolically unhealthy, non-obese (MUNO), with BMI <25 kg/m² (in case of WC criteria, WC < sex-specific cutoff value) and ≥2 metabolic risk factors (3); MHO, defined as BMI ≥25 kg/m² (in case of WC criteria, WC ≥ sex-specific cutoff value) and no or 1 metabolic risk factor; and (4) metabolically unhealthy, obese (MUO), with BMI ≥25 kg/m² (in case of WC criteria, WC ≥ sex-specific cutoff value) and ≥2 metabolic risk factors. People with MHO at the baseline examination were categorized into 4 subgroups based on their transition in the metabolic health and obesity status. We applied a multiple imputation procedure using a fully conditional specification method to impute missing values of eGFR, smoking, drinking, and physical activities. The 5 imputed data sets were created with 20 burn-in iterations, were analyzed by the same analytical procedures, and the results from these analyses were combined to obtain an overall estimate.

Covariates from the baseline health examination included age, sex, smoking habits (non-, ex-, or current smoker), drinking habits (none, mild, moderate, or heavy drinking), physical activity (0, 1-2, 3-4, or ≥5 times per week), low-density lipoprotein cholesterol (LDL-C) concentrations, and baseline eGFR level. Heavy drinkers were defined as individuals consuming ≥7 drinks on the same occasion and drinking >5 days per week, whereas mild and moderate drinkers were those consuming <7 drinks on any single day and drank 1 to 2 or 3 to 4 days per week, respectively.

Statistical analysis
Continuous data were expressed as means ± SD, and categorical data as percentages. ANOVA and Scheffe’s test for post hoc analysis or χ² test was used to compare the baseline characteristics of study participants based on their metabolic health and obesity status. We applied a multiple imputation procedure using a fully conditional specification method to impute missing values of eGFR, smoking, drinking, and physical activities. The 5 imputed data sets were created with 20 burn-in iterations, were analyzed by the same analytical procedures, and the results from these analyses were combined to obtain an overall estimate.

Cox proportional-hazard analyses were performed to estimate the hazard ratio (HR) and 95% confidence interval (CI) of incident CKD during the follow-up period. In eGFR criteria of incident CKD, the event was considered to occur during the first eGFR decline of ≤60 mL/min/1.73 m². Multivariate-adjusted models were adjusted for age, sex, smoking, alcohol drinking, physical activities, LDL-C level, and baseline eGFR. The risk of incident CKD was first analyzed according to the baseline metabolic health and obesity without considering their transition in reference to the MHNO group. Next, the risk was further assessed after considering
the transition of metabolic health and obesity in people with MHO at baseline. The stable MHNO group during their follow-up period was considered as the reference group. All statistical analyses were performed using SAS Enterprise Guide software (version 7.1, SAS Institute, Inc., Cary, NC, USA).

**Results**

**Baseline characteristics of the entire cohort**

Table 1 shows the clinical and biochemical characteristics of the people stratified by BMI categories and metabolic health status at baseline. The prevalence of MHNO, MHO, MUNO, and MUO was 30.5% (n = 97,449), 9.2% (n = 29,527), 34.1% (n = 108,926), and 26.2% (n = 83,772), respectively. The people with MHO were characterized by worse lipid profiles, including elevated TG, LDL-C, and total cholesterol concentrations and reduced HDL-C concentrations compared with the healthy and lean population. In contrast, individuals with MHO exhibited more favorable risk profiles than those with MUNO or MUO. FPG and TG levels were lower, and HDL-C level in the MHO group was higher than those in the MUNO group. When stratified by WC categories and metabolic health status at baseline, the clinical and biochemical characteristics of the people exhibited patterns similar as seen when stratified by BMI categories (29). The prevalence of MHNO, MHO, MUNO, and MUO was 34.1% (n = 108,905), 5.7% (n = 18,045), 40.9% (n = 130,719), and 19.4% (n = 61,940), respectively.

**Prognosis relative to baseline metabolic health and obesity state**

Table 2 shows the risk for incident CKD based on baseline metabolic health and obesity defined by BMI criteria without considering their transition over time. The risk of incident CKD in the MHO group was significantly higher than that in the MHNO group (multivariate-adjusted HR, 1.23; 95% CI, 1.12-1.36) after full adjustment. The risks of incident CKD in metabolically unhealthy individuals were also significantly higher than those in the lean healthy population, showing multivariate-adjusted HRs of 1.60 (95% CI, 1.16-2.20) and 1.68 (95% CI, 1.45-1.96) in the MHO to MUNO and MHO to MUO groups, respectively. Notably, the risk of incident CKD was not increased in the MHO to MHNO group, in which people stayed healthy and reduced their body weight compared with those in the stable MHNO group (multivariate-adjusted HR, 0.98; 95% CI, 0.72-1.32).

When the baseline and follow-up status of obesity was defined using WC criteria, the risk of CKD development in the MHO to MHNO people was also similar to that of stable MHNO group (multivariate-adjusted HR, 1.16; 95% CI, 0.90-1.48) (29). In addition, the risk still remained higher in people who progressed to a metabolically unhealthy status irrespective of their obesity status based on WC (29). However, stable MHO group defined by WC criteria did not show statistically higher risk for incident CKD compared with stable MHNO group (multivariate-adjusted HR, 1.17; 95% CI, 0.94-1.45) (29). Fig. 2 summarizes the associations of MHO with incident CKD, focusing on the transitions in metabolic health and obesity state in the MHO group.

**Discussion**

The present study showed that people with MHO were at a higher risk of developing incident CKD than the lean healthy population, which was consistent with the results of previous studies (4, 14, 30). However, this was the only case when an MHO status was maintained or aggravated to an unhealthy status (i.e., MUNO or MUO).
People who remained healthy and reduced their body weight (i.e., MHO to MHNO) showed a favorable prognosis in terms of incident CKD. Our results further addressed that the dynamic status of metabolic health and obesity should always be considered to predict a more precise outcome (CKD in the present study) in people with MHO.

Obesity is an established risk factor of CKD and a major public health problem worldwide (1, 4, 5). Because obesity-induced metabolic derangements, including hypertension, insulin resistance, hyperglycemia, and dyslipidemia, are well-known contributors to CKD development (31), the association of CKD with obesity or obesity-induced metabolic disturbances is unclear (32). Accordingly, the risk for developing CKD in obese people lacking metabolic abnormalities has been a matter of interest. To date, few longitudinal studies have investigated the risk of developing CKD in individuals with MHO (4, 14, 30, 33). In 2015, a Japanese study group reported that the MHO phenotype was not associated with a higher risk of developing CKD (33). On the contrary, more recent studies have consistently shown a significant association between MHO phenotype and incident CKD (4, 14, 30). For example, in a large cohort study of metabolically healthy Korean adults, Chang et al. reported that being overweight or obese was associated with increased CKD risk compared with having normal weight (14). Similarly, baseline MHO status was associated with

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### Table 1. Characteristics of Study Participants According to Baseline Metabolic Health and Obesity Status Defined by BMI Criteria

<table>
<thead>
<tr>
<th>Baseline Category</th>
<th>MHNO</th>
<th>MHO</th>
<th>MUNO</th>
<th>MUO</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;25 kg/m²</td>
<td>≥25 kg/m²</td>
<td>&lt;25 kg/m²</td>
<td>≥25 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic health status 0–1 risk factor</td>
<td>0–1 risk factor</td>
<td>≥2 risk factors</td>
<td>≥2 risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>97,449 (30.5)</td>
<td>29,527 (9.2)</td>
<td>108,926 (34.1)</td>
<td>83,772 (26.2)</td>
<td></td>
</tr>
<tr>
<td>Sex (% men)</td>
<td>48.4</td>
<td>50.5</td>
<td>56.3</td>
<td>59.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>57.1 ± 8.3b</td>
<td>56.9 ± 7.7b</td>
<td>59.5 ± 8.9</td>
<td>58.4 ± 8.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.1 ± 1.9</td>
<td>26.8 ± 1.6</td>
<td>22.7 ± 1.7</td>
<td>27.2 ± 1.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>77.2 ± 6.7</td>
<td>87.0 ± 6.4</td>
<td>80.5 ± 6.4</td>
<td>89.5 ± 6.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>119.1 ± 13.5</td>
<td>123.1 ± 13.5</td>
<td>130.4 ± 14.8</td>
<td>132.7 ± 14.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>77.0 ± 6.4</td>
<td>86.4 ± 6.4</td>
<td>80.3 ± 6.4</td>
<td>89.4 ± 6.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking (%)a</td>
<td>16.2</td>
<td>13.4</td>
<td>20.8</td>
<td>18.6</td>
<td></td>
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<tr>
<td>Current smoker</td>
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<td>18.2</td>
<td>18.5</td>
<td>22.2</td>
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</tr>
<tr>
<td>Ex-smoker</td>
<td>67.3</td>
<td>67.0</td>
<td>59.5</td>
<td>57.9</td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>16.4</td>
<td>13.9</td>
<td>56.4</td>
<td>53.3</td>
<td></td>
</tr>
<tr>
<td>Drinking (%)a</td>
<td>18.9</td>
<td>18.1</td>
<td>16.6</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>18.9</td>
<td>18.1</td>
<td>16.6</td>
<td>16.4</td>
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<tr>
<td>Mild</td>
<td>4.0</td>
<td>4.0</td>
<td>4.9</td>
<td>4.4</td>
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</tr>
<tr>
<td>Moderate</td>
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<td>18.1</td>
<td>21.6</td>
<td>25.3</td>
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<tr>
<td>Heavy</td>
<td>3.6</td>
<td>3.9</td>
<td>29.3</td>
<td>21.7</td>
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<tr>
<td>Physical activity (%)a</td>
<td>27.0</td>
<td>27.9</td>
<td>30.0</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>27.0</td>
<td>27.9</td>
<td>30.0</td>
<td>29.7</td>
<td></td>
</tr>
<tr>
<td>1–2 times/wk</td>
<td>22.7</td>
<td>23.3</td>
<td>22.4</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td>3–4 times/wk</td>
<td>21.9</td>
<td>21.5</td>
<td>21.1</td>
<td>21.2</td>
<td></td>
</tr>
<tr>
<td>≥5 times/wk</td>
<td>28.1</td>
<td>27.1</td>
<td>26.3</td>
<td>24.5</td>
<td></td>
</tr>
<tr>
<td>Medical history (%)</td>
<td>1.2</td>
<td>1.2</td>
<td>15.2</td>
<td>17.6</td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>12.4</td>
<td>21.3</td>
<td>42.8</td>
<td>53.7</td>
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</tr>
<tr>
<td>HTN</td>
<td>12.4</td>
<td>21.3</td>
<td>42.8</td>
<td>53.7</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4.0</td>
<td>4.3</td>
<td>28.9</td>
<td>34.3</td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>91.5 ± 12.8</td>
<td>92.3 ± 12.2</td>
<td>108.4 ± 29.7</td>
<td>110.4 ± 29.5</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>97.3 ± 44.9</td>
<td>108.8 ± 49.2</td>
<td>166.2 ± 102.0</td>
<td>189.0 ± 112.2</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>119.8 ± 34.0</td>
<td>125.7 ± 34.2</td>
<td>121.1 ± 41.3</td>
<td>122.5 ± 43.1</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>59.2 ± 21.7</td>
<td>56.8 ± 23.3</td>
<td>51.2 ± 23.2</td>
<td>49.0 ± 20.5</td>
<td></td>
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<tr>
<td>TC (mg/dL)</td>
<td>198.1 ± 33.2</td>
<td>203.5 ± 33.7b</td>
<td>203.7 ± 39.8b</td>
<td>207.0 ± 39.8</td>
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<tr>
<td>eGFR (mL/min/1.73 m²a)</td>
<td>85.5 ± 13.6</td>
<td>84.4 ± 13.4</td>
<td>83.2 ± 13.2</td>
<td>82.5 ± 13.4</td>
<td></td>
</tr>
</tbody>
</table>

Results reported as means ± SD, unless otherwise indicated. All variables were statistically different among the 4 groups, unless otherwise indicated. Abbreviations: BMI; body mass index, BP; blood pressure, eGFR; estimated glomerular filtration rate, FPG; fasting plasma glucose, HDL-C; high-density lipoprotein cholesterol, HTN; hypertension, LDL-C; low-density lipoprotein cholesterol, MHO, metabolically healthy, non-obese; MHO, metabolically healthy obesity, MUNO, metabolically unhealthy, non-obese; MUO, metabolically unhealthy, obese; TC; total cholesterol, TG; triglyceride, WC; waist circumference

aData on smoking were missing in 4053 (1.27%), 1215 (1.25%), 404 (1.37%), 1370 (1.26%), and 1063 (1.26%) people in total, MHNO, MHO, MUNO, and MUO groups, respectively. Data on drinking were missing in 2109 (0.66%), 694 (0.71%), 226 (0.77%), 674 (0.62%), and 515 (0.61) people in total, MHNO, MHO, MUNO, and MUO groups, respectively. Data on physical activity were missing in 962 (0.30%), 314 (0.32%), 99 (0.34%), 302 (0.28%), and 247 (0.29%) people in total, MHNO, MHO, MUNO, and MUO groups, respectively. Data on eGFR were missing in 9 (0.003%), 3 (0.003%), 0 (0.000%), 2 (0.002%), and 4 (0.005) people in total, MHNO, MHO, MUNO, and MUO groups, respectively.

bNo statistical difference was observed.
a high incidence of CKD (Table 2 and Fig. 2A) (29), suggesting that MHO is not a benign condition in the context of renal outcome. However, all of these results were derived from the static condition of MHO.

More evidence suggests that MHO is not a permanent state (16, 34–36). Approximately one-third to one-half of people originally identified as MHO was found to change to a metabolically unhealthy state over time (15–20). Based on BMI criteria, our data also showed that 40.3% of the initial MHO cohort progressed to a metabolically unhealthy phenotype (i.e., MUNO and MUO). By contrast, 12.1% of people with MHO initially reduced their body weight while maintaining their metabolic health, supporting the concept that MHO is not a static condition.

By following up the metabolic health status, BMI, and WC 2 years after the baseline study, we found that the risk of CKD incidence of the MHO group was highly variable. The risk of incident CKD was particularly high in people who had progressed to a metabolically unhealthy phenotype (i.e., MUNO and MUO) compared with the stable MHNO group (Table 3) (29). These results showed that MHO status was a hazardous condition of CKD, particularly for those who later transitioned to a metabolically unhealthy phenotype. In contrast, the people who reduced their body weight and maintained metabolic health (MHO to MHNO group) were not at a higher risk for developing CKD than the stable MHNO group (Table 3) (29). These data suggest that although people with MHO are at a high risk of CKD development, the risk for developing CKD could be mitigated if their body weight is controlled while maintaining metabolic health. Taken together, our results have important clinical implications that obesity is a modifiable risk factor in preventing CKD development.

### Table 2. Risk of Incident CKD According to Baseline Metabolic Health and Obesity Status Defined by BMI Criteria

<table>
<thead>
<tr>
<th>Baseline Category</th>
<th>MHNO</th>
<th>MHO</th>
<th>MUNO</th>
<th>MUO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI</strong></td>
<td>&lt;25 kg/m²</td>
<td>≥25 kg/m²</td>
<td>&lt;25 kg/m²</td>
<td>≥25 kg/m²</td>
</tr>
<tr>
<td><strong>Metabolic health status</strong></td>
<td>0–1 risk factor</td>
<td>0–1 risk factor</td>
<td>≥2 risk factors</td>
<td>≥2 risk factors</td>
</tr>
<tr>
<td><strong>N (% of total)</strong></td>
<td>97 449 (30.5)</td>
<td>29 527 (9.2)</td>
<td>108 926 (34.1)</td>
<td>83 772 (26.2)</td>
</tr>
<tr>
<td><strong>CKD event incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of events (%)</strong></td>
<td>1417 (1.5)</td>
<td>531 (1.8)</td>
<td>3329 (3.1)</td>
<td>2988 (3.6)</td>
</tr>
<tr>
<td><strong>Incidence/1000 person-years (95% CI)</strong></td>
<td>2.49 (2.36–2.62)</td>
<td>3.07 (2.81–3.34)</td>
<td>5.24 (5.07–5.42)</td>
<td>6.10 (5.89–6.33)</td>
</tr>
<tr>
<td><strong>Crude HR (95% CI)</strong></td>
<td>1 (ref)</td>
<td>1.23 (1.11–1.36)</td>
<td>2.09 (1.96–2.22)</td>
<td>2.44 (2.29–2.60)</td>
</tr>
<tr>
<td><strong>Multivariate-adjusted HR (95% CI)</strong></td>
<td>1 (ref)</td>
<td>1.23 (1.12–1.36)</td>
<td>1.61 (1.52–1.72)</td>
<td>1.98 (1.85–2.10)</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MHO, metabolically healthy obesity; MUNO, metabolically unhealthy, non-obese; MUO, metabolically unhealthy, obese.

aEgFR criteria/claims of CKD/procedure code for dialysis.

<table>
<thead>
<tr>
<th>Follow-up Category</th>
<th>Stable MHNO</th>
<th>MHO</th>
<th>MUNO</th>
<th>MUO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Follow-up BMI</strong></td>
<td>&lt;25 kg/m²</td>
<td>≥25 kg/m²</td>
<td>&lt;25 kg/m²</td>
<td>≥25 kg/m²</td>
</tr>
<tr>
<td><strong>Follow-up metabolic health status</strong></td>
<td>0–1 risk factor</td>
<td>0–1 risk factor</td>
<td>≥2 risk factors</td>
<td>≥2 risk factors</td>
</tr>
<tr>
<td><strong>N (% of baseline MHO)</strong></td>
<td>58 727</td>
<td>3092 (12.1)</td>
<td>12 159 (47.6)</td>
<td>1409 (5.5)</td>
</tr>
<tr>
<td><strong>CKD event incidence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of events (%)</strong></td>
<td>755 (1.29)</td>
<td>44 (1.42)</td>
<td>184 (1.51)</td>
<td>40 (2.84)</td>
</tr>
<tr>
<td><strong>Incidence/1000 person-years (95% CI)</strong></td>
<td>2.19 (2.03–2.35)</td>
<td>2.41 (1.75–3.24)</td>
<td>2.57 (2.22–2.97)</td>
<td>4.82 (3.44–6.57)</td>
</tr>
<tr>
<td><strong>Crude HR (95% CI)</strong></td>
<td>1 (ref)</td>
<td>1.09 (0.80–1.47)</td>
<td>1.18 (1.00–1.39)</td>
<td>2.17 (1.58–2.99)</td>
</tr>
<tr>
<td><strong>Multivariate-adjusted HR (95% CI)</strong></td>
<td>1 (ref)</td>
<td>0.98 (0.72–1.32)</td>
<td>1.23 (1.04–1.44)</td>
<td>1.60 (1.16–2.20)</td>
</tr>
</tbody>
</table>

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MHO, metabolically healthy obesity.

aEgFR criteria/claims of CKD/procedure code for dialysis.

bAdjusted for baseline age, sex, smoking, alcohol drinking, physical activities, LDL-cholesterol, and baseline eGFR level.
in people with MHO, as well as emphasize the significance of metabolic health in CKD development.

We performed additional analysis to examine the risk for incident CKD in the possible remaining 12 transitions of metabolic health and obesity status using BMI criteria (29). The results demonstrated that the transition to metabolically unhealthy status from MHNO or MHO conferred higher risks of incident CKD. In metabolically unhealthy groups at baseline (i.e. MUNO and MUO group), staying in a metabolically unhealthy phenotype was predictive of higher risks of CKD compared with groups in which people changed to a healthy phenotype. These expanded results further support the crucial role of phenotypic transitions in metabolic health in the risk of incident CKD.

In our current analysis, the stable MHO group defined by BMI criteria exhibited a statistically higher risk for incident CKD compared with the stable MHNO group (Table 3), whereas the stable MHO defined by WC criteria did not reach statistical significance ($P = .1685$) (29). This might be owing to the limited number of people in the stable MHO group ($n = 4885$ for WC criteria vs. $n = 12,159$ for BMI criteria). However, considering the several reports that demonstrated that central obesity index including WC were potentially better indicators to assess CKD risk in individuals regardless of BMI (37, 38), we could not exclude the possibility that stable MHO defined by WC criteria might provide us with more accurate prognostic information in terms of incident CKD risk.

The mechanisms whereby obesity contributes to CKD remain unclear. Metabolic syndrome, a constellation of various metabolic abnormalities, is associated with the development of CKD (4, 39–42). Because obese individuals commonly have several components of metabolic syndrome, clearly defining whether the impact of obesity per se on CKD is independent of these metabolic derangements is difficult. In this study, the stable MHO people had a higher risk for developing CKD than the stable MHNO people (Table 3), supporting the role of obesity per se in CKD development. Therefore, although the association between obesity and CKD is largely dependent on components of metabolic syndrome, other mechanisms directly linking obesity to kidney damage independent of metabolic risk factors could exist. Possible mechanisms include hemodynamic changes, oxidative stress, and hormonal factors (43–46). Renal hemodynamic changes, including hyperfiltration, increased glomerular capillary wall tension, and podocyte stress, have been suggested to play a significant role in obesity-induced renal dysfunction (1, 44). Several adipokines, including leptin and adiponectin, and other adipose tissue-derived factors, such as TNF-α, interleukin-6 (IL-6), and plasminogen activator inhibitor-1, have been reported to compromise renal function (45, 47). Although whether these factors were altered in people with MHO remains controversial (48–52), these mechanisms may contribute to the development of incident CKD in obese individuals, particularly in MHO people. In this study, MHO people who reduced their body weight over time were not at high risk for developing CKD compared with the lean healthy people, suggesting that kidney injury from these factors is, at least in part, reversible.

Our study has several limitations to be acknowledged. First, generalizability to other ethnic groups is...
limited because our study population mainly consisted of Koreans. Second, as the age- and sex- distribution of NHIS-HEALs was not similar to the general Korean population (21), selection bias cannot be excluded. Third, although this cohort was constructed with populations who participated in biannual health screening programs and followed up thoroughly, the interval of follow-up visits within a 2-year window period was not predetermined. Therefore, the timing of detection of incident CKD by two consecutive eGFR tests could be inaccurate. Fourth, GFR was not directly measured but was estimated by a serum creatinine-based equation that might have overestimated or underestimated the actual GFR (53). In addition, we could not consider albumin to creatinine ratio when defining CKD because the albumin to creatinine ratio was not routinely performed in NHIS health screening examinations. Last, this study may not be powered to fully assess interactions because of a relatively short follow-up duration. Because CKD could occur after long-term exposure to risk factors, further long-term follow-up study is needed to evaluate the long-term impact of MHO on the risk for developing CKD.

Despite these limitations, this study had strengths in that we have analyzed data from a very large number of people using a national cohort sample in Korea and elucidated the implications of phenotypic transitions on incident CKD among people with MHO. This approach showed that transition to metabolically unhealthy status was a predictor of poor prognosis, and control of body weight might be a feasible therapeutic strategy to protect CKD in people with MHO.

In conclusion, our data showed that MHO was a dynamic condition, and people with MHO constituted a heterogeneous group. Although the MHO phenotype was generally associated with incident CKD, maintenance of metabolic health and weight reduction could alleviate the risk of CKD. Hence, clinicians should consider the risk of incident CKD in people with MHO and counsel them about metabolic fitness and weight control.

Acknowledgments

The authors thank Editage (https://www.editage.co.kr) for the English language review.

Additional Information

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Disclosure Summary: The authors declare that they have no conflict of interest.

Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

References


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