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Metabolically Healthy Obesity and Development of Chronic Kidney Disease

A Cohort Study

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Background: The risk for chronic kidney disease (CKD) among obese persons without obesity-related metabolic abnormalities, called *metabolically healthy obesity*, is largely unexplored.

Objective: To investigate the risk for incident CKD across categories of body mass index in a large cohort of metabolically healthy men and women.

Design: Prospective cohort study.

Setting: Kangbuk Samsung Health Study, Kangbuk Samsung Hospital, Seoul, South Korea.

Participants: 62 249 metabolically healthy, young and middle-aged men and women without CKD or proteinuria at baseline.

Measurements: Metabolic health was defined as a homeostasis model assessment of insulin resistance less than 2.5 and absence of any component of the metabolic syndrome. Underweight, normal weight, overweight, and obesity were defined as a body mass index less than 18.5 kg/m^2, 18.5 to 22.9 kg/m^2, 23 to 24.9 kg/m^2, and 25 kg/m^2 or greater, respectively. The outcome was incident CKD, defined as an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2.

Results: During 369 088 person-years of follow-up, 906 incident CKD cases were identified. The multivariable-adjusted differences in 5-year cumulative incidence of CKD in underweight, overweight, and obese participants compared with normal-weight participants were −4.0 (95% CI, −7.8 to −0.3), 3.5 (CI, 0.9 to 6.1), and 6.7 (CI, 3.0 to 10.4) cases per 1000 persons, respectively. These associations were consistently seen in all clinically relevant subgroups.

Limitation: Chronic kidney disease was identified by a single measurement at each visit.

Conclusion: Overweight and obesity are associated with an increased incidence of CKD in metabolically healthy young and middle-aged participants. These findings show that metabolically healthy obesity is not a harmless condition and that the obese phenotype, regardless of metabolic abnormalities, can adversely affect renal function.

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Chronic kidney disease (CKD) is a major clinical and public health problem (1). It is a precursor for end-stage renal disease and a strong risk factor for cardiovascular morbidity and mortality (2). Its prevalence is increasing worldwide along with the growing prevalence of obesity and metabolic disease (3). Indeed, obesity—mediated by hypertension, insulin resistance, hyperglycemia, dyslipidemia, and other metabolic abnormalities—is a major risk factor for CKD (4).

Although the role of obesity-induced metabolic abnormalities in CKD development is well-established, *metabolically healthy obese* (MHO) persons, seem to have a favorable profile with no metabolic abnormalities (5, 6). The association between MHO and CKD, however, is largely unknown. The only study available found no association (7), but the comparison between MHO and normal-weight participants could be biased because the reference group included overweight participants, and metabolically healthy participants were defined as those with fewer than 2 metabolic components. Therefore, we examined the association between categories of body mass index (BMI) and CKD in a large sample of metabolically healthy men and women who had health screening examinations.

Methods

Study Population

The Kangbuk Samsung Health Study is a cohort study of South Korean men and women aged 18 years or older who had a comprehensive annual or biennial health examination at the clinics of the Kangbuk Samsung Hospital Health Screening Centers in Seoul and Suwon, South Korea (8). More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Act requires all employees to receive annual or biennial health screening examinations, offered free of charge. The remaining participants registered for the screening examinations on their own.

Our analysis included all persons who had comprehensive health examinations from 1 January 2002 to 31 December 2009 and had at least 1 other screening examination before 31 December 2013 (that is, they all had a baseline visit and ≥1 follow-up visit [n = 175 859]) (Figure 1). We excluded persons who had metabolic abnormalities (5, 9, 10) or evidence of kidney disease at baseline (n = 108 263). We excluded those with fasting glucose levels of 100 mg/dL or greater or who used glucose-lowering agents; blood pressure (BP) of

EDITORS' NOTES

Context

The risk for chronic kidney disease (CKD) among obese patients without metabolic abnormalities is unknown.

Contribution

In this cohort study of South Korean men and women, metabolically healthy overweight and obese participants had increased incidence of CKD compared with normal-weight participants.

Caution

Body mass index was a marker of obesity and was assessed only once at baseline.

Implication

Physicians should monitor metabolically healthy obese and overweight patients for CKD and counsel them about maintaining a healthy weight and lifestyle.

130/85 mm Hg or greater or who used BP-lowering agents; triglyceride levels of 150 mg/dL or greater or who used lipid-lowering agents; high-density lipoprotein (HDL) cholesterol levels less than 40 mg/dL in men or less than 50 mg/dL in women; insulin resistance, defined as homeostasis model assessment of insulin resistance (HOMA-IR) scores of 2.5 or greater (11); estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2; proteinuria; history of CKD; or history of cancer. Among eligible participants (n = 67 596), we further excluded those with missing values in any of the study variables (n = 5347 [7.9%]). The final sample size was 62 249 participants (**Figure 1**), all of whom were metabolically healthy and did not have markers of kidney disease at baseline. This study was approved by the Institutional Review Board of the Kangbuk Samsung Hospital, which exempted the requirement for informed consent because we only accessed deidentified data routinely collected as part of health screening examinations.

Measurements

Data on medical history, medication use, family history, physical activity, alcohol intake, smoking habits, and education level were collected by a standardized, self-administered questionnaire. Anthropometry data, BP, and blood samples were obtained by trained staff during the examinations (8, 12). Smoking status was categorized as never, former, or current. Alcohol consumption was categorized as none, moderate (≤20 g per day), or high (>20 g per day). The weekly frequency of moderate- or vigorous-intensity physical activity was also assessed.

Sitting BP, height, and weight were measured by trained nurses. Height was measured to the nearest 1 cm with a stadiometer while the participant stood barefoot. Weight was measured to the nearest 0.1 kg on a bioimpedance analyzer (InBody 3.0 and Inbody 720, Biospace), which was validated for reproducibility and accuracy of body composition measurements (13) and calibrated every morning before testing started. Body mass index was calculated as weight in kilograms divided by height in meters squared and was classified according to Asian-specific criteria (14) (underweight, BMI <18.5 kg/m^2; normal weight, BMI of 18.5 to 22.9 kg/m^2; overweight, BMI of 23 to 24.9 kg/m^2; and obese, BMI ≥25 kg/m^2).

Blood specimens were sampled from the antecubital vein after at least a 10-hour fast. The methods for measuring serum levels of glucose, uric acid, total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, HDL cholesterol, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, insulin, and high-sensitivity C-reactive protein (hsCRP) have been reported elsewhere (8, 12). The Department of Laboratory Medicine of the Kangbuk Samsung Hospital has been accredited by the Korean Society for Laboratory Medicine and the Korean Association of Quality Assurance for Clinical Laboratories and participates in the College of American Pathologists Proficiency Testing survey.

Insulin resistance was assessed with the HOMA-IR equation (fasting insulin [uU/mL] × fasting glucose [mmol/L] ÷ 22.5). An ultrasonographic diagnosis of fatty liver was defined as a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma (15, 16).

During the study period, serum creatinine levels were measured with the kinetic alkaline picrate method (Jaffe method) in an automated chemistry analyzer (from 2002 to 2009, we used the Advia 1650a Autoanalyzer [Bayer Diagnostics]; from 2010 to 2013, we used the Modular D2400 [Roche]). The within-batch and total coefficients of variation were 1.8% to 3.9% for low-level and 1.4% to 1.8% for high-level quality control specimens throughout the study. Because the laboratory method that was used to measure serum creatinine levels from 2002 to 2009 was not traceable to isotope-dilution mass spectrometry, we estimated GFR by using the 4-variable Modification of Diet in Renal Disease Study equation (17). The conclusions did not change if we used the Chronic Kidney Disease Epidemiology Collaboration equation (18) for GFR estimation (data not shown).

Urine protein was measured semiquantitatively by urine dipstick (URiSCAN Urine test strips, YD Diagnostics) tested on fresh, midstream urine samples and was reported in the following 6 grades: absent, trace, 1+, 2+, 3+, and 4+ (corresponding to protein levels of undetectable, 10 mg/dL, 30 mg/dL, 100 mg/dL, 300 mg/dL, and 1000 mg/dL, respectively). Proteinuria was defined as a grade of 1+ or greater.

Statistical Analysis

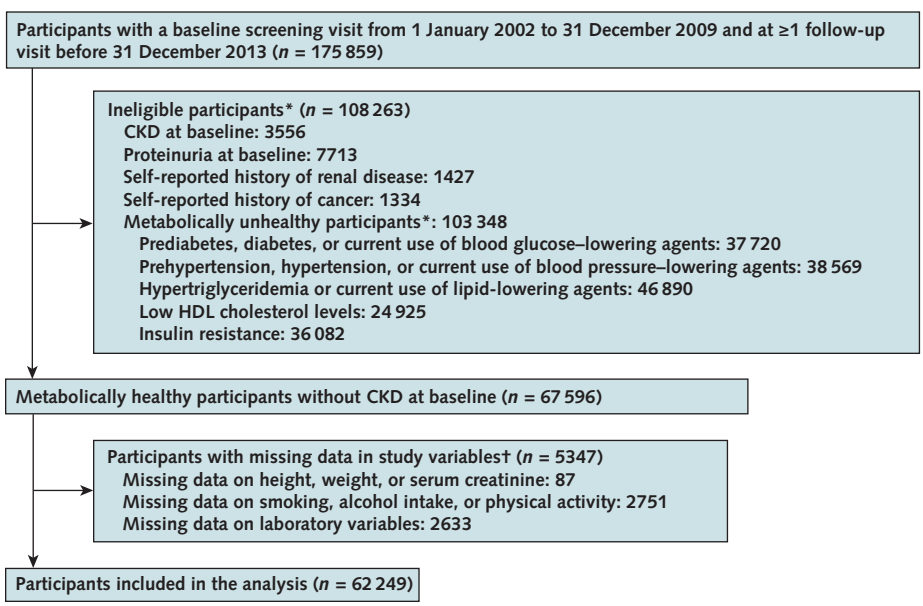
Person-years of follow-up were calculated from the date of the baseline health examination until the date of CKD diagnosis or the last screening examination, whichever came first. The cumulative incidence of CKD for baseline BMI categories (<18.5, 18.5 to 22.9, 23.0 to

24.9, or ≥25.0 kg/m^2) were standardized to the empirical distribution of baseline confounders in the overall study sample with inverse probability weighting (19, 20). We first fitted a multinomial logistic regression to estimate each participant's probability of being in his or her own BMI category given the observed confounders. Stabilized weights were then calculated as the inverse of the estimated conditional probabilities of exposure, further rescaled by the overall proportion of participants in each BMI category to reduce variability of weights across groups and to avoid influential observations involving extremely obese persons (19).

For risk analyses, we fitted a spline-based, parametric survival model (21) according to the stabilized weights and stratified by BMI category to obtain smooth estimates of the CKD cumulative incidence curves that would have been seen in the entire population if every participant had been in each category (20). This survival model parameterized stratum-specific log cumulative hazards as distinct natural cubic splines of log time with 3 internal knots at the 25th, 50th, and 75th percentiles; allowed for interval-censored events (incident CKD occurred at an unknown time point between the visit at which CKD was diagnosed and the previous visit); and used robust SEs for spline parameters that accounted for the correlation induced by weighting (21). For comparison, we also applied weighted Kaplan–Meier methods to estimate nonparametric cumulative incidence curves for each BMI category. We used the previously mentioned weighted, spline-based survival model to calculate adjusted differences in cumulative incidences of CKD at 2, 5, and 10 years of follow-up of normal-weight participants compared with those in the other BMI categories. We calculated 95% CIs by applying delta methods to the robust variance estimates of spline parameters. In addition to risk differences, we estimated adjusted differences in follow-up times to 0.5%, 1.0%, and 1.5% cumulative incidences of CKD and their CIs of normal-weight participants compared with those in the other BMI categories.

For confounder adjustment, we included 4 increasing sets of baseline covariates in the multinomial logistic model for baseline BMI categories. The first exposure model (model 1) included age (<30, 30 to 34, 35 to 39, 40 to 44, 45 to 49, or ≥50 years), sex (female or male), study center (Seoul or Suwon), and year of screening examination (2002 to 2003, 2004 to 2005, 2006 to 2007, or 2008 to 2009). The second model (model 2) further adjusted for potential confounding factors, such as smoking status (never, former, or current), alcohol intake (0, <20, or ≥20 g per day), and regular exercise (<3 or ≥3 times per week). To evaluate the residual association between BMI and CKD risk after adjustment for physiologic variables, the third exposure model (model 3) also included fasting glucose level (<90 or 90 to 99 mg/dL), systolic BP (<120 or 120 to 129 mm Hg), triglyceride level (<100 or 100 to 149 mg/dL), HDL cholesterol level (40/50 to 59 or ≥60 mg/dL), LDL cholesterol level (<100, 100 to 159, or ≥160 mg/dL), HOMA-IR score (<2.00 or 2.00 to 2.49), hsCRP level (<1.0, 1.0 to 2.9, or ≥3.0 mg/L), alanine aminotransferase level (<55 or ≥55 IU/L), aspartate aminotransferase level (<40 or ≥40 IU/L), and γ-glutamyltransferase level (<50 or ≥50 IU/L). The

Figure 1. Study flow diagram.



CKD = chronic kidney disease; HDL = high-density lipoprotein.
* Participants in the screening program could have >1 criterion that made them ineligible for the study.
† Eligible participants could have missing data in >1 study variable.

Table 1. Baseline Characteristics of Metabolically Healthy Participants in the Kangbuk Samsung Health Study, by BMI Category, 2002–2009

Characteristic	Overall	BMI Category				*P* for Trend*
		Underweight (<18.5 kg/m²)	Normal Weight (18.5–22.9 kg/m²)	Overweight (23.0–24.9 kg/m²)	Obese (≥25.0 kg/m²)	
Participants, *n*	62 249	4461	36 490	13 149	8149	
Mean age (SD), *y*	36.1 (6.6)	33.9 (5.5)	35.8 (6.3)	37.1 (7.0)	37.2 (7.1)	<0.001
Sex, *n (%)*						
Women	30 812 (49.5)	3459 (77.5)	21 441 (58.8)	4036 (30.7)	1876 (23.0)	
Men	31 437 (50.5)	1002 (22.5)	15 049 (41.2)	9113 (69.3)	6273 (77.0)	<0.001
Study center, *n (%)*						
Seoul	36 545 (58.7)	2699 (60.5)	21 141 (57.9)	7814 (59.4)	4891 (60.0)	
Suwon	25 704 (41.3)	1762 (39.5)	15 349 (42.1)	5335 (40.6)	3258 (40.0)	0.020
Smoking status, *n (%)*						
Never	38 326 (61.6)	3466 (77.7)	24 598 (67.4)	6707 (51.0)	3555 (43.6)	
Former	8792 (14.1)	276 (6.2)	4201 (11.5)	2499 (19.0)	1816 (22.3)	
Current	15 131 (24.3)	719 (16.1)	7691 (21.1)	3943 (30.0)	2778 (34.1)	<0.001
Alcohol intake, *n (%)*						
0 g/d	26 448 (42.5)	2632 (59.0)	17 301 (47.4)	4266 (32.4)	2249 (27.6)	
1–19 g/d	30 747 (49.4)	1693 (38.0)	16 972 (46.5)	7401 (56.3)	4681 (57.4)	
≥20 g/d	5054 (8.1)	136 (3.0)	2217 (6.1)	1482 (11.3)	1219 (15.0)	<0.001
Physical activity, *n (%)*						
<3 times/wk	52 074 (83.7)	4130 (92.6)	30 935 (84.8)	10 577 (80.4)	6432 (78.9)	
≥3 times/wk	10 175 (16.3)	331 (7.4)	5555 (15.2)	2572 (19.6)	1717 (21.1)	<0.001
Mean fasting glucose level (SD)						<0.001
mmol/L	4.9 (0.3)	4.8 (0.4)	4.9 (0.3)	5.0 (0.3)	5.0 (0.3)	
mg/dL	88.5 (6.3)	86.9 (6.5)	88.1 (6.3)	89.2 (6.1)	89.6 (6.2)	
Mean systolic blood pressure (SD), *mm Hg*	107.8 (9.4)	103.8 (9.7)	106.8 (9.5)	109.7 (8.7)	111.2 (8.2)	<0.001
Mean triglyceride level (SD)						<0.001
mmol/L	1.0 (0.3)	0.8 (0.3)	0.9 (0.3)	1.0 (0.3)	1.1 (0.3)	
mg/dL	84.1 (28.7)	70.7 (23.2)	79.4 (27.3)	92.0 (28.5)	100.0 (28.1)	
Mean HDL cholesterol level (SD)						<0.001
mmol/L	1.6 (0.3)	1.7 (0.3)	1.6 (0.3)	1.5 (0.3)	1.4 (0.3)	
mg/dL	60.4 (11.7)	65.8 (11.6)	62.1 (11.7)	57.3 (10.7)	55.1 (9.9)	
Mean LDL cholesterol level (SD)						<0.001
mmol/L	2.8 (0.7)	2.4 (0.6)	2.7 (0.7)	3.0 (0.7)	3.1 (0.7)	
mg/dL	107.0 (27.5)	92.4 (23.0)	102.8 (25.9)	114.6 (27.2)	121.2 (28.1)	
Mean HOMA-IR index score (SD)	1.53 (0.48)	1.43 (0.49)	1.49 (0.48)	1.58 (0.47)	1.69 (0.46)	<0.001
Mean hsCRP level (SD), *nmol/L*†	3.05 (31.52)	1.90 (28.29)	2.57 (30.38)	4.00 (30.57)	5.62 (29.91)	<0.001
Mean ALT level (SD), *U/L*†	18.9 (1.58)	15.6 (1.44)	17.2 (1.51)	21.5 (1.57)	25.8 (1.64)	<0.001
Mean AST level (SD), *U/L*†	21.7 (1.31)	20.6 (1.28)	21.0 (1.30)	22.5 (1.31)	24.0 (1.35)	<0.001
Mean GGT level (SD), *μkat/L*†	0.3 (0.03)	0.2 (0.03)	0.2 (0.03)	0.3 (0.03)	0.4 (0.03)	<0.001
Mean estimated GFR (SD), *mL/min/1.73 m²*	80.9 (9.6)	82.9 (10.0)	81.3 (9.7)	80.1 (9.3)	79.5 (9.3)	<0.001

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; GFR = glomerular filtration rate; GGT = γ-glutamyltransferase; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.
* *P* value for linear trend in means or proportions across BMI categories.
† Data are geometric means (geometric SDs).

fourth model (model 4) further adjusted for estimated GFR (60 to 89 or ≥90 mL/min/1.73 m²) at baseline. The mean (range) stabilized inverse probability weights derived from these exposure models were 1.00 (0.35 to 9.53), 1.00 (0.24 to 23.12), 1.00 (0.15 to 33.74), and 1.00 (0.15 to 35.87), respectively. Inverse probability weighting provided an effective standardization because the weighted distributions of baseline covariates were nearly identical across BMI categories and closely matched their empirical distributions in the overall study sample (data not shown).

We evaluated heterogeneity in risk differences among BMI categories across prespecified subgroups defined by age (<40 or ≥40 years), sex (female or male), study center (Seoul or Suwon), year of baseline examination (2002 to 2005 or 2006 to 2009), smoking status (noncurrent or current), alcohol intake (no or yes), and regular exercise (<3 or ≥3 times per week) by fitting spline-based survival models weighted by stabilized inverse probability weights and stratified by BMI category and covariate subgroup. We used stratum-specific weights in subgroup analyses to standardize the CKD cumulative incidence curves in each BMI category and covariate subgroup to the empirical distribution of confounders in the entire covariate stratum (19). Adjusted differences in 5-year cumulative incidences of CKD and CIs for each BMI category compared with the normal-weight category were estimated within each covariate stratum and tested for heterogeneity across strata with joint Wald tests. Statistical analyses were performed using the *stpm* command in Stata, version 13 (StataCorp), and graphics were produced in R, version 3 (R Foundation for Statistical Computing).

Role of the Funding Source

This study did not receive external funding.

RESULTS

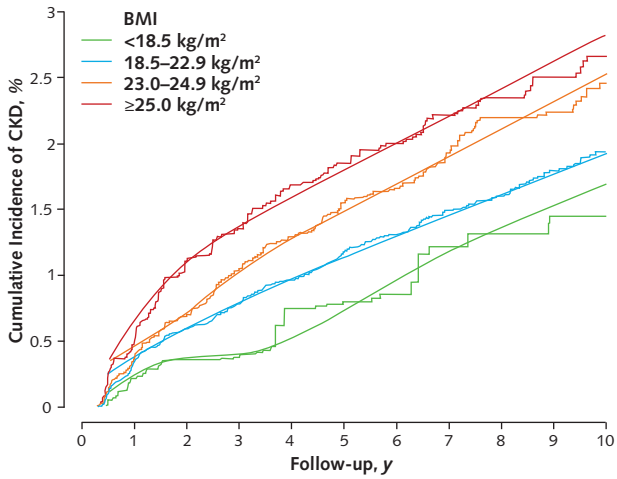
At baseline, the mean (SD) age of the 62 249 participants was 36.1 years (6.6) and mean (SD) BMI was 22.1 kg/m^2 (2.6), with a range of 14.3 to 35.9 kg/m^2. Participants with higher BMI were more likely to be older, men, current smokers, alcohol drinkers, and regular exercisers (**Table 1**). Baseline fasting glucose levels, systolic BP, triglyceride levels, LDL cholesterol levels, HOMA-IR scores, hsCRP levels, and hepatic enzyme (alanine aminotransferase, aspartate aminotransferase, and γ-glutamyltransferase) levels increased gradually across BMI categories, whereas HDL cholesterol levels and estimated GFR decreased with increasing BMI.

During 369 088 person-years of follow-up, 906 participants developed CKD, with an overall incidence rate of 2.5 cases per 1000 person-years. The average (SD) follow-up for participants without CKD was 6.0 years (3.0). After direct standardization to the overall sample distribution of age, sex, study center, year of screening examination, smoking status, alcohol intake, and physical activity at baseline, the cumulative incidence of CKD was consistently higher in persons with higher BMI over the entire follow-up (**Figure 2**). Compared with normal-weight participants, the adjusted differences in 5-year cumulative incidence of CKD for underweight, overweight, and obese participants were −4.0 (95% CI, −7.8 to −0.3), 3.5 (CI, 0.9 to 6.1), and 6.7 (CI, 3.0 to 10.4) cases per 1000 persons, respectively (**Table 2**, model 2). The adjusted differences in the time at which 1.0% of participants developed CKD for underweight, overweight, and obese participants compared with normal-weight participants were 2.0 (CI, −0.5 to 4.4), −1.2 (CI, −2.2 to −0.3), and −2.4 (CI, −3.4 to −1.5) years, respectively (**Appendix Table**, model 2 [available at www.annals.org]).

After further standardization of the overall baseline distribution of metabolic risk factors associated with obesity (fasting glucose level, systolic BP, triglyceride level, LDL cholesterol level, HDL cholesterol level, HOMA-IR score, hsCRP level, and hepatic enzyme levels), the association of BMI categories with CKD risk that was not mediated by these metabolic components was slightly attenuated but remained strong: The respective adjusted 5-year risk differences in cumulative incidence of CKD for underweight, overweight, and obese participants compared with normal-weight participants were −4.6 (CI, −7.7 to −1.4), 2.8 (CI, 0.1 to 5.5), and 3.6 (CI, 0.1 to 7.1) cases per 1000 persons, and the respective adjusted differences in time to 1.0% cumulative incidence were 2.6 (CI, −0.3 to 5.4), −1.1 (CI, −2.0 to −0.1), and −2.0 (CI, −3.3 to −0.8) years (**Table 2** and **Appendix Table**, model 3). The association was virtually unchanged after additional adjustment for estimated GFR at baseline (**Table 2** and **Appendix Table**, model 4).

In subgroup analyses, differences in CKD risk among BMI categories were larger in participants aged 40 years or older at baseline than in younger participants (*P* for heterogeneity = 0.02). The adjusted 5-year risk differences for underweight, overweight, and obese participants compared with normal-weight participants were −3.6 (CI, −5.8 to −1.4), 2.5 (CI, −0.1 to 5.2), and 3.5 (CI, −0.4 to 7.4) cases per 1000 participants younger than 40 years. These differences increased to −7.0 (CI, −19.2 to 5.3), 9.4 (CI, 1.5 to 17.4), and 19.0 (CI, 8.7 to 29.3) cases per 1000 participants aged 40 years or older (**Appendix Figure**). No other risk-difference heterogeneity was evident across subgroups defined by sex, study center, year of baseline examination, smoking status, alcohol intake, or physical activity.

Figure 2. Adjusted cumulative incidence of CKD, by BMI category at baseline, among metabolically healthy participants in the Kangbuk Samsung Health Study, 2002–2009 to 2013.



Parametric cumulative incidence curves (smooth lines) were estimated from a spline-based parametric survival model and nonparametric cumulative incidence curves (step functions) from Kaplan–Meier methods, both weighted by stabilized inverse probability weights and stratified by BMI category. Stabilized weights were used to standardize cumulative incidence curves in each category to the empirical distribution of baseline confounders in the overall study sample, including age (<30, 30-34, 35-39, 40-44, 45-49, or ≥50 y), sex (female or male), study center (Seoul or Suwon), year of screening examination (2002–2003, 2004–2005, 2006–2007, or 2008–2009), smoking status (never, former, or current), alcohol intake (0, <20, or ≥20 g/d), and regular exercise (<3 or ≥3 times/wk). BMI = body mass index; CKD = chronic kidney disease.

DISCUSSION

In this large cohort study of metabolically healthy Korean adults, being overweight or obese was associated with increased CKD risk compared with being normal weight. The association between MHO and CKD was consistently seen in all prespecified clinical subgroups, including participants without low-grade inflammation or fatty liver. Furthermore, the association could not be explained by the residual levels of metabolic factors in MHO participants. Our study demonstrates that MHO was associated with higher incident risk for CKD and adds to an increasing body of evidence that indicates that MHO is not a harmless condition (12, 22).

Table 2. Adjusted Differences in Cumulative Incidence of Chronic Kidney Disease per 1000 Persons at 2, 5, and 10 y of Follow-up, by Baseline BMI Category Among Metabolically Healthy Participants in the Kangbuk Samsung Health Study, 2002–2009 to 2013

Variable	Baseline BMI Category			
	Underweight (<18.5 kg/m²)	Normal Weight (18.5–22.9 kg/m²)	Overweight (23.0–24.9 kg/m²)	Obese (≥25.0 kg/m²)
Person-years, *n*	25 976.7	215 324.5	78 894.7	48 892.2
Incident cases, *n*	41	456	232	177
Incidence rate per 1000 person-years	1.6	2.1	2.9	3.6
2-y follow-up				
Cumulative incidence (95% CI)*	4.6 (3.0 to 7.1)	5.8 (5.0 to 6.6)	6.7 (5.4 to 8.3)	11.8 (9.6 to 14.4)
Adjusted risk difference (95% CI)†				
Model 1‡	−2.1 (−4.1 to −0.2)	0 (reference)	1.3 (−0.5 to 3.2)	5.2 (2.3 to 8.1)
Model 2§	−2.3 (−4.2 to −0.4)	0 (reference)	1.2 (−0.6 to 3.1)	5.0 (2.1 to 7.9)
Model 3‖	−2.0 (−4.2 to 0.2)	0 (reference)	0.9 (−1.1 to 2.8)	3.7 (0.9 to 6.5)
Model 4¶	−2.0 (−4.2 to 0.2)	0 (reference)	0.8 (−1.1 to 2.7)	3.6 (0.8 to 6.4)
5-y follow-up				
Cumulative incidence (95% CI)*	8.3 (5.8 to 11.7)	11.7 (10.5 to 12.9)	15.7 (13.5 to 18.2)	19.9 (16.9 to 23.5)
Adjusted risk difference (95% CI)†				
Model 1‡	−3.2 (−7.4 to 1.1)	0 (reference)	3.7 (1.0 to 6.3)	6.9 (3.2 to 10.6)
Model 2§	−4.0 (−7.8 to −0.3)	0 (reference)	3.5 (0.9 to 6.1)	6.7 (3.0 to 10.4)
Model 3‖	−4.6 (−7.7 to −1.4)	0 (reference)	2.8 (0.1 to 5.5)	3.6 (0.1 to 7.1)
Model 4¶	−4.5 (−7.7 to −1.3)	0 (reference)	2.7 (0 to 5.4)	3.4 (−0.1 to 6.9)
10-y follow-up				
Cumulative incidence (95% CI)*	13.8 (9.6 to 19.9)	18.8 (16.9 to 20.9)	26.6 (22.9 to 30.8)	30.1 (25.5 to 35.6)
Adjusted risk difference (95% CI)†				
Model 1‡	−1.5 (−10.9 to 7.8)	0 (reference)	6.2 (2.0 to 10.4)	9.3 (3.7 to 14.9)
Model 2§	−2.3 (−11.1 to 6.5)	0 (reference)	6.2 (1.9 to 10.4)	9.1 (3.5 to 14.6)
Model 3‖	−4.9 (−12.0 to 2.1)	0 (reference)	5.5 (1.2 to 9.8)	5.9 (0.2 to 11.7)
Model 4¶	−4.6 (−11.9 to 2.7)	0 (reference)	5.3 (1.0 to 9.6)	5.6 (−0.1 to 11.3)

BMI = body mass index.
* Unadjusted cumulative incidences (95% CIs) at the specified follow-up times were obtained from standard Kaplan–Meier and Greenwood methods stratified by BMI category.
† Adjusted differences in cumulative incidences at the specified follow-up times comparing BMI categories with the normal-weight category were obtained from spline-based parametric survival models weighted by stabilized inverse probability-of-exposure weights and stratified by BMI category, with 95% CIs derived from robust SEs of spline parameters by applying delta methods.
‡ Adjusted for baseline age (<30, 30–34, 35–39, 40–44, 45–49, or ≥50 y), sex (female or male), study center (Seoul or Suwon), and year of screening examination (2002–2003, 2004–2005, 2006–2007, or 2008–2009).
§ Further adjusted for baseline smoking status (never, former, or current), alcohol intake (0, 1–19, or ≥20 g/d), and regular exercise (<3 or ≥3 times/wk).
‖ Further adjusted for potential mediators, including baseline fasting glucose level (<90 or 90–99 mg/dL), systolic blood pressure (<120 or 120–129 mm Hg), triglyceride level (<100 or 100–149 mg/dL), high-density lipoprotein cholesterol level (40/50–59 or ≥60 mg/dL), low-density lipoprotein cholesterol level (<100, 100–159, or ≥160 mg/dL), homeostatic model assessment of insulin resistance score (<2.00 or 2.00–2.49), high-sensitivity C-reactive protein level (<1.0, 1.0–2.9, or ≥3.0 mg/L), alanine aminotransferase level (<55 or ≥55 U/L), aspartate aminotransferase level (<40 or ≥40 U/L), and γ-glutamyltransferase level (<50 or ≥50 U/L).
¶ Further adjusted for baseline estimated glomerular filtration rate (60–89 or ≥90 mL/min/1.73 m²).

A previous study in a sample of Japanese men and women found no association between MHO and CKD (7), but this study defined metabolically healthy participants as those with fewer than 2 metabolic abnormalities. In contrast, we defined metabolically healthy participants as those without any abnormality, including no increase in HOMA-IR score. The Japanese study also included overweight persons in the reference group, whereas we compared MHO participants with metabolically healthy, normal-weight participants. The very strict definition of metabolic health plus the restriction to normal-weight participants in the reference category may have allowed us to identify an association between MHO and incident CKD that was missed in the previous study. Our study participants were asymptomatic young and middle-aged men and women who may be less likely to be affected by selection bias, reverse causation, and confounding by comorbidities and medication use than studies based on older populations.

The mechanisms whereby obesity contributed to CKD remain incompletely elucidated. In our study, the association between MHO and CKD was evident even after adjustment for metabolic components, LDL cholesterol level, HOMA-IR score, and hsCRP level, and the association persisted among participants with low hsCRP levels or with no fatty liver. Potential mechanisms directly linking obesity to kidney damage independent of metabolic risk factors include hemodynamic changes, oxidative stress, and hormonal effects (23–26). Adipose tissue functions as an active endocrine organ, and several adipokines, including leptin and adiponectin, may be involved in the pathogenesis of CKD (25). Activation of the renin–angiotensin–aldosterone system is also common in obesity and may contribute to obesity-related CKD via sympathetic stimulation and renal hemodynamic changes (27). Other adipose tissue–derived factors, such as tumor necrosis factor-α, interleukin-6, and plasminogen activator

inhibitor-1, may also compromise renal function (28). Furthermore, excess adiposity may be associated with ectopic lipid accumulation in the kidney, which may be associated with structural and functional changes that mediate obesity-related renal disease (29, 30).

Several limitations of our study need to be considered. First, we used BMI as a marker of obesity, but it is an imperfect measure of adiposity and does not distinguish differences in adipose tissue distribution. If the MHO group had a higher proportion of lean mass than normal-weight participants, the association between MHO and incident CKD in our study could have been attenuated. Second, duration of obesity may be an independent risk factor for adiposity-related health outcomes (31, 32), but this information was not available in our study. We also used a single assessment of BMI at baseline and did not incorporate changes in BMI or other changes in metabolic health status during follow-up. Third, our definition of insulin resistance was based on HOMA-IR scores rather than invasive and time-consuming euglycemic insulin clamp analyses, which are impractical in studies of this size. Data on these 2 variables are strongly correlated (33), but we cannot disregard the possibility that some participants were insulin-resistant. Fourth, CKD was identified by a single measurement at each visit, although diagnostic criteria recommend confirmation by repeated testing. This source of random measurement error may have further attenuated the observed associations. Fifth, information on smoking, alcohol use, physical activity, and medical history was obtained via a self-administered structured questionnaire used in health checkup programs in Korea as part of the National Health Insurance Program, and measurement error in these variables may have resulted in some degree of residual confounding. Finally, our study was conducted in asymptomatic, relatively young Korean men and women, and our findings may not be generalizable to other populations, particularly other age or race/ethnicity groups.

Our study also had several strengths, including the large sample size and the availability of detailed information on multiple laboratory variables, which allowed us to study many participants even after excluding those with metabolic abnormalities or insulin resistance. In addition, the use of carefully standardized and high-quality clinical, imaging, and laboratory procedures and the availability of carefully phenotyped participants are major strengths of our data.

In conclusion, being overweight or obese was associated with increased CKD incidence in metabolically healthy young and middle-aged participants. These findings indicate that MHO is not a harmless condition and that the obese phenotype, regardless of metabolic abnormalities, can adversely affect renal function. Therefore, physicians should address the increased CKD risk in MHO persons and counsel them about healthy weight and lifestyle.

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Appendix Table. Adjusted Differences in Follow-up Times to 0.5%, 1.0%, and 1.5% Cumulative Incidence of Chronic Kidney Disease, by Baseline BMI Category Among Metabolically Healthy Participants in the Kangbuk Samsung Health Study, 2002–2009 to 2013

Variable	Baseline BMI Category			
	Underweight (<18.5 kg/m²)	Normal Weight (18.5–22.9 kg/m²)	Overweight (23.0–24.9 kg/m²)	Obese (≥25.0 kg/m²)
0.5% cumulative incidence				
Follow-up time (95% CI), *y**	2.9 (1.0 to 4.5)	1.6 (1.3 to 1.9)	1.3 (1.0 to 1.7)	0.9 (0.5 to 1.0)
Adjusted difference in time (95% CI), *y*†				
Model 1‡	2.2 (0.9 to 3.5)	0 (reference)	−0.4 (−1.1 to 0.3)	−0.8 (−1.3 to −0.3)
Model 2§	2.4 (1.0 to 3.7)	0 (reference)	−0.4 (−1.1 to 0.3)	−0.8 (−1.3 to −0.2)
Model 3‖	2.3 (0.8 to 3.9)	0 (reference)	−0.2 (−1.0 to 0.5)	−0.7 (−1.4 to −0.1)
Model 4¶	2.3 (0.7 to 3.9)	0 (reference)	−0.2 (−0.9 to 0.5)	−0.7 (−1.4 to −0.1)
1.0% cumulative incidence				
Follow-up time (95% CI), *y**	6.4 (3.9 to 10.8)	4.3 (3.5 to 4.9)	2.9 (2.5 to 3.4)	1.6 (1.4 to 2.3)
Adjusted difference in time (95% CI), *y*†				
Model 1‡	1.4 (−0.6 to 3.5)	0 (reference)	−1.3 (−2.2 to −0.4)	−2.5 (−3.4 to −1.6)
Model 2§	2.0 (−0.5 to 4.4)	0 (reference)	−1.2 (−2.2 to −0.3)	−2.4 (−3.4 to −1.5)
Model 3‖	2.6 (−0.3 to 5.4)	0 (reference)	−1.1 (−2.0 to −0.1)	−2.0 (−3.3 to −0.8)
Model 4¶	2.5 (−0.2 to 5.1)	0 (reference)	−1.0 (−2.0 to −0.1)	−2.0 (−3.3 to −0.7)
1.5% cumulative incidence				
Follow-up time (95% CI), *y**	10.8 (6.6 to NA)	7.3 (6.4 to 8.3)	4.8 (4.1 to 6.1)	3.2 (2.4 to 4.2)
Adjusted difference in time (95% CI), *y*†				
Model 1‡	0.8 (−4.4 to 5.9)	0 (reference)	−2.3 (−3.7 to −0.8)	−3.8 (−5.5 to −2.1)
Model 2§	1.5 (−3.0 to 6.1)	0 (reference)	−2.2 (−3.7 to −0.7)	−3.7 (−5.4 to −2.0)
Model 3‖	3.5 (−3.3 to 10.3)	0 (reference)	−1.8 (−3.4 to −0.2)	−2.2 (−4.4 to 0)
Model 4¶	3.2 (−3.0 to 9.4)	0 (reference)	−1.7 (−3.3 to −0.1)	−2.1 (−4.3 to 0.2)

BMI = body mass index; NA = not available.

* Unadjusted follow-up times to the specified cumulative incidences (95% CIs) were obtained from standard Kaplan–Meier and Greenwood methods stratified by BMI category.

† Adjusted differences in follow-up times to the specified cumulative incidences and their 95% CIs comparing BMI categories with the normal-weight category were obtained from spline-based parametric survival models weighted by stabilized inverse probability-of-exposure weights and stratified by BMI category.

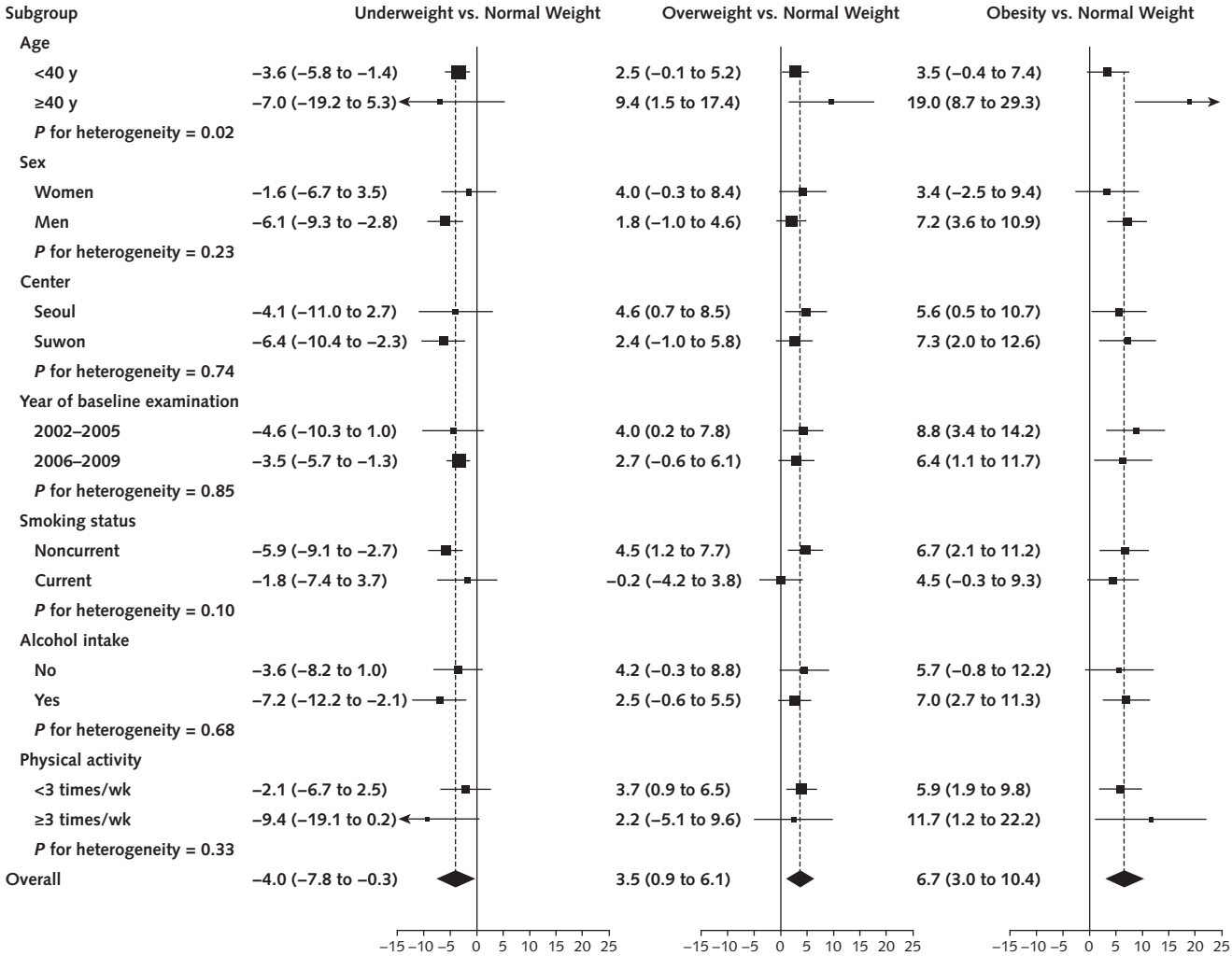
‡ Adjusted for baseline age (<30, 30–34, 35–39, 40–44, 45–49, or ≥50 y), sex (female or male), study center (Seoul or Suwon), and year of screening examination (2002–2003, 2004–2005, 2006–2007, or 2008–2009).

§ Further adjusted for baseline smoking status (never, former, or current), alcohol intake (0, 1–19, or ≥20 g/d), and regular exercise (<3 or ≥3 times/wk).

‖ Further adjusted for potential mediators, including baseline fasting glucose level (<90 or 90–99 mg/dL), systolic blood pressure (<120 or 120–129 mm Hg), triglyceride level (<100 or 100–149 mg/dL), high-density lipoprotein cholesterol level (40/50–59 or ≥60 mg/dL), low-density lipoprotein cholesterol level (<100, 100–159, or ≥160 mg/dL), homeostatic model assessment of insulin resistance score (<2.00 or 2.00–2.49), high-sensitivity C-reactive protein level (<1.0, 1.0–2.9, or ≥3.0 mg/L), alanine aminotransferase level (<55 or ≥55 U/L), aspartate aminotransferase level (<40 or ≥40 U/L), and γ-glutamyltransferase level (<50 or ≥50 U/L).

¶ Further adjusted for baseline estimated glomerular filtration rate (60–89 or ≥90 mL/min/1.73 m^2).

Appendix Figure. Adjusted differences in 5-y cumulative incidence of chronic kidney disease per 1000 persons comparing categories of body mass index at baseline with the normal-weight category in prespecified subgroups of metabolically healthy participants in the Kangbuk Samsung Health Study, 2002–2009 to 2013.



Subgroup-specific risk differences (squares with area inversely proportional to the variance) and their 95% CIs (horizontal lines) were obtained from spline-based parametric survival models weighted by stabilized inverse probability weights and stratified by category of body mass index and covariate subgroup. Subgroup-specific weights were used to standardize cumulative incidences in each category of body mass index and covariate subgroup to the empirical distribution of baseline confounders in the overall covariate subgroup, including age (<30, 30-34, 35-39, 40-44, 45-49, or ≥50 y), sex (female or male), study center (Seoul or Suwon), year of screening examination (2002–2003, 2004–2005, 2006–2007, or 2008–2009), smoking status (never, former, or current), alcohol intake (0, <20, or ≥20 g/d), and regular exercise (<3 or ≥3 times/wk).