

Changes in Body Weight Predict CKD in Healthy Men

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ABSTRACT

Several recent prospective studies have reported that obesity is associated with an increased risk for chronic kidney disease (CKD), but it is unknown whether weight gain increases the risk for CKD if one remains within the "normal" category of body mass index (BMI). We prospectively followed a cohort of 8792 healthy men who had no known risk factors for CKD and participated in a comprehensive health evaluation program at a large worksite. During 35,927 person-years of follow-up, 427 new incident cases of CKD (estimated GFR <64 ml/min per 1.73 m²) developed. Cox proportional hazards modeling revealed that in both the normal-weight and overweight groups, a U-shaped association between weight change categories and development of CKD was observed after adjustment for age, baseline GFR, baseline BMI, HDL, fasting blood glucose, uric acid, and exercise habits. The lowest risk for CKD was observed among those whose weight changed -0.25 to <0.25 kg/yr ($P < 0.001$ for quadratic term). Weight change as a time-dependent variable was significantly related to CKD incidence. These relationships remained significant even after further adjustment for Homeostasis Model Assessment of Insulin Resistance, high-sensitivity C-reactive protein, systolic BP, diastolic BP, metabolic syndrome, incident hypertension, or incident diabetes. In summary, increases in body weight are independently associated with an increased risk for CKD, even when the BMI remains within the normal range.

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The number of patients with ESRD is increasing worldwide.^{1,2} Chronic kidney disease (CKD) is also an increasingly common and important condition³; however, at present, prospective data on risk factors for CKD are limited. Early identification and treatment of CKD is necessary to delay progression from CKD to ESRD.

Obesity is a major public health problem whose prevalence has been rising in developing countries as well as in developed countries.⁴ Overweight and obesity are well-established risk factors for cardiovascular disease, diabetes, and hypertension.^{5–10} Recently, several prospective studies have reported that obesity was associated with an increased risk for CKD or ESRD^{11–15}; however, little research has been done to examine the effect of weight change within normal weight range and risk for CKD. The World Health Organization classification for healthy weight for Asians is a body mass index

(BMI) of 18.5 to 23 kg/m², for overweight as BMI of 23 to 25 kg/m², and for obese as BMI ≥ 25 kg/m².¹⁶ The healthy weight category spans a large range. Individuals at the lower end of healthy weight may, thus, believe that it is permissible to gain some weight as they age, as long as they remain within the healthy weight range; however, weight gain during adult life has been associated with adverse health outcomes.^{17,18} Previous studies have clearly shown

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a positive association between obesity and kidney disease^{11–15} and reported the role of obesity as a causative factor in glomerulomegaly and FSGS^{19–21}; however, there is a paucity of data concerning the influence of the weight gain on CKD, especially in the normal-weight population without hypertension and diabetes. This prospective study examined the effect of weight change within the normal BMI on CKD in Korean male workers without hypertension and diabetes.

RESULTS

During 35,927.4 person-years of follow-up, 427 incident cases of CKD developed. At baseline, the mean age and BMI of the 8792 participants in the analytic cohort were 36.9 yr (SD 4.7; range 30 to 59 yr) and 23.8 kg/m² (SD 2.7; range 15.1 to 37.3 kg/m²), respectively. Participants who were not included in the analytic cohort ($n = 2927$) were on average 0.5 yr older and were more likely to be current smokers and current drinkers than those in the analytic cohort. During the follow-up, seven men died from non-renal diseases; six of them were not included in the analytic cohort. None of the other variables differed between two groups (data not shown).

Baseline characteristics of the study participants in relation to the weight change category are illustrated in Table 1. There were clear dosage-response relationships among all of the listed variables except high-sensitivity C-reactive protein (hsCRP), drinker, and regular exerciser with the weight change. Age, BMI, fasting blood glucose (FBG), systolic BP (SBP), diastolic BP (DBP), total cholesterol, triglyceride (TG), LDL cholesterol, γ -glutamyltransferase (GGT), insulin, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), uric acid, and creatinine were associated inversely with weight change, whereas HDL cholesterol, GFR, and current smoker were associated positively. The proportions of metabolic syndrome (MetS) and obesity (BMI ≥ 25 kg/m²) were also inversely associated with weight change. The overall prevalence of obesity was 33.4%.

Table 2 shows the risk for CKD incidence according to the baseline BMI categories. After adjustment for age, baseline GFR, HDL cholesterol, FBG, uric acid, regular exercise, and weight change over time, the baseline BMI categories were not significantly associated with the development of CKD.

Table 3 shows the risk for CKD incidence according to weight change over time. After adjustment for age, baseline GFR, baseline BMI, HDL cholesterol, FBG, uric acid, and regular exercise, weight change as a time-dependent variable was significantly related to CKD incidence. Non-time-dependent Cox regression models were also performed by using the weight change calculated from the slope of the regression model for each individual. CKD risk was significantly increased in the weight loss category of < -0.75 kg/yr and in the weight gain category of ≥ 0.75 kg/yr. A U-shaped association between weight change categories and development of CKD was observed with the lowest risk in the weight change category of -0.25 to < 0.25 kg/yr ($P < 0.001$ for quadratic term).

We further examined the association between weight change and incident CKD, stratified by BMI at baseline (Figure 1). In both the normal-weight and overweight groups, after adjustment for age, baseline GFR, baseline BMI, HDL cholesterol, FBG, uric acid, and regular exercise, a U-shaped association between weight change categories and development of CKD was observed with the lowest risk in the weight change category of -0.25 to < 0.25 kg/yr ($P < 0.001$ for quadratic term). Weight change as a time-dependent variable was significantly related to CKD incidence. The relationship between weight change and incident CKD remained significant even after further adjustment for HOMA-IR, hsCRP, SBP, DBP, MetS, incident hypertension, and incident diabetes.

In sensitivity analysis, we also examined the association of weight change with incident CKD when the definition of incident CKD was limited to persistent CKD on follow-up or when we reclassified CKD as a GFR < 60 ml/min per 1.73 m². Neither of these analyses qualitatively changed any of the observed associations (data not shown).

Linear mixed-effect models were used to analyze the effect of weight change over time on longitudinal changes in GFR across the weight change groups. In all groups, after adjustment for age and baseline BMI, weight change over time was negatively associated with the longitudinal changes in GFR ($P < 0.001$; data not shown).

DISCUSSION

In this prospective study of Korean men without hypertension and diabetes, weight gain was associated with the development of CKD, and this relationship was observed even in the normal-weight participants. The effect of weight change on incident CKD was maintained irrespective of various potential confounders, including age, baseline GFR, BMI, uric acid, HDL cholesterol, and regular exercise. Moreover, this relationship remained even after adjustment for incident hypertension or incident diabetes.

A recent finding from the Physicians' Health Study (PHS) also showed that men with a BMI increase $> 10\%$ had a significantly increased risk for CKD compared with those who maintained their BMI within 5% of their BMI at baseline.¹¹ To our knowledge, however, this is the first study to demonstrate a relationship between weight change, even within normal-weight range, and CKD.

Few prospective studies have evaluated BMI as a potential risk factor in the development of CKD and subsequent ESRD. In longitudinal data from the PHS, the baseline BMI predicted subsequent CKD after a mean follow-up of 14.0 yr.¹¹ The data from the Framingham Offspring Study showed that higher BMI was a risk factor for the development of new-onset kidney disease after a mean follow-up of 18.5 yr.¹² Similarly, studies have demonstrated a significant positive relationship between BMI and ESRD risk^{13,14}; however, no independent association between BMI and incident CKD was found in our study. Sev-

Table 1. Baseline characteristics of study participants by weight change over time^a

Characteristic	Weight Change Category				P for Trend
	< -0.75	-0.75 to < -0.25	-0.25 to < 0.25	0.25 to < 0.75	
n	854	1274	2193	2153	2318
Age (yr; mean [SD])	37.3 (4.8)	37.4 (4.8)	37.4 (4.8)	36.7 (4.5)	36.1 (4.7)
BMI (kg/m ² ; mean [SD])	25.5 (2.6)	24.4 (2.6)	23.9 (2.6)	23.4 (2.6)	23.2 (2.7)
FBG (mg/dl; mean [SD])	93.7 (9.7)	91.7 (9.4)	90.9 (8.9)	90.0 (8.6)	89.6 (8.6)
SBP (mmHg; mean [SD])	113.0 (9.3)	112.8 (9.5)	112.3 (9.3)	111.7 (9.3)	111.6 (9.5)
DBP (mmHg; mean [SD])	72.8 (7.2)	72.5 (7.2)	72.4 (7.3)	71.8 (7.3)	71.6 (7.6)
Total cholesterol (mg/dl; mean [SD])	208.8 (37.2)	205.4 (34.7)	202.1 (33.8)	197.8 (33.5)	196.7 (34.3)
HDL cholesterol (mg/dl; mean [SD])	50.1 (11.3)	51.0 (11.4)	52.0 (11.4)	52.3 (11.6)	53.1 (11.6)
LDL cholesterol (mg/dl; mean [SD])	125.1 (30.2)	123.0 (29.3)	120.7 (29.1)	117.9 (28.8)	117.8 (29.0)
Triglyceride (mg/dl; median [IQR])	142 (102 to 209)	136 (95 to 190)	129 (94 to 178)	119 (88 to 169)	113 (84 to 157)
GGT (U/L; median [IQR])	30 (20 to 46)	28 (19 to 42)	26 (18 to 39)	24 (17 to 36)	23 (16 to 35)
hsCRP (mg/L; median [IQR])	0.60 (0.30 to 1.10)	0.50 (0.30 to 1.10)	0.50 (0.30 to 1.00)	0.50 (0.20 to 0.90)	0.50 (0.20 to 1.00)
Insulin (μU/dl; median [IQR])	8.39 (6.23 to 10.30)	7.47 (5.76 to 9.83)	7.14 (5.54 to 9.53)	6.88 (5.41 to 9.31)	6.63 (5.22 to 9.07)
HOMA-IR (median [IQR])	1.92 (1.42 to 2.43)	1.70 (1.26 to 2.25)	1.62 (1.22 to 2.13)	1.52 (1.18 to 2.05)	1.48 (1.13 to 2.00)
Uric acid (mg/dl; mean [SD])	6.18 (1.20)	6.06 (1.20)	6.02 (1.13)	5.95 (1.10)	5.96 (1.12)
Creatinine (mg/dl; mean [SD])	1.13 (0.11)	1.12 (0.10)	1.12 (0.10)	1.12 (0.10)	1.12 (0.10)
GFR (ml/min per 1.73 m ²)	78.0 (71.4 to 82.9)	78.5 (72.3 to 83.0)	78.8 (73.1 to 83.1)	79.2 (73.4 to 83.1)	80.0 (73.9 to 86.4)
Current smoker (%)	42.8	40.5	45.2	47.5	52.7
Drinks alcohol (%) ^b	17.4	14.3	16.3	15.7	17.7
Regular exerciser (%) ^c	48.9	50.4	50.2	49.0	48.6
MetS (%)	13.2	10.7	7.1	4.7	4.8
Incident diabetes (%)	5.7	4.3	3.0	2.8	2.0
Incident hypertension (%)	16.5	18.0	16.6	17.0	17.2
BMI categories (kg/m ²)					
<18.5 (%)	0.4	1.4	2.1	2.3	2.5
18.5 to 22.9 (%)	16.4	27.2	33.5	42.1	48.2
23.0 to 24.9 (%)	28.7	31.6	33.6	30.1	26.7
≥25.0 (%)	57.3	42.0	33.4	28.0	24.8

^aIQR, interquartile range.^b≥20 g/d ethanol.^c≥1 time/wk.

Table 2. Association between the development of CKD and baseline BMI^a

BMI (kg/m ²)	Person-Years	Case	Age-Adjusted HR (95% CI)	Multivariate HR (95% CI)		
				Model 1	Model 2	Model 3
<18.5	664.5	2	0.54 (0.13 to 2.19)	1.16 (0.29 to 4.71)	1.21 (0.30 to 4.92)	1.19 (0.29 to 4.86)
18.5 to 22.9	12,837.1	109	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
23.0 to 24.9	5341.4	52	1.01 (0.72 to 1.42)	0.79 (0.56 to 1.10)	0.81 (0.58 to 1.14)	0.81 (0.57 to 1.14)
25.0 to 27.9	14,773.1	225	1.63 (1.30 to 2.04)	1.12 (0.88 to 1.41)	1.17 (0.93 to 1.48)	1.16 (0.91 to 1.47)
≥28.0	2311.3	39	1.97 (1.37 to 2.82)	1.08 (0.74 to 1.57)	1.21 (0.82 to 1.77)	1.18 (0.80 to 1.73)
P for trend			<0.001	0.381	0.135	0.190

^aModel 1 adjusted for age, baseline GFR, HDL, FBG, uric acid, and regular exercise; model 2 adjusted for model 1 plus weight change as time-dependent variable; model 3 adjusted for model 2 plus incident hypertension.

Table 3. Association between the development of CKD and weight change over time^a

Weight Change per Year	Person-Years	Case	Age-Adjusted HR (95% CI)	Multivariate HR (95% CI)		
				Model 1	Model 2	Model 3
Regression slope (β)						
<−0.75	3274.3	85	4.38 (3.16 to 6.08)	3.29 (2.36 to 4.58)	3.33 (2.39 to 4.64)	3.40 (2.44 to 4.75)
−0.75 to −0.251	5292.0	50	1.35 (0.93 to 1.96)	1.20 (0.83 to 1.75)	1.22 (0.84 to 1.77)	1.22 (0.84 to 1.78)
−0.25 to 0.249	9268.9	62	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.25 to 0.749	9046.3	61	1.18 (0.83 to 1.67)	1.23 (0.86 to 1.75)	1.23 (0.87 to 1.76)	1.24 (0.87 to 1.77)
≥0.75	9045.9	169	4.06 (3.03 to 5.44)	4.21 (3.14 to 5.64)	4.32 (3.22 to 5.79)	4.29 (3.20 to 5.76)
P for trend			0.013	<0.001	<0.001	<0.001
P for quadratic term			<0.001	<0.001	<0.001	<0.001
Time-dependent variable			1.05 (1.01 to 1.10)	1.09 (1.05 to 1.14)	1.10 (1.05 to 1.14)	1.10 (1.05 to 1.14)

^aModel 1 adjusted for age, baseline GFR, and baseline BMI; model 2 adjusted for model 1 plus HDL, FBG, uric acid, and regular exercise; model 3 adjusted for model 2 plus incident hypertension.

eral possibilities may underlie this lack of relation. In a cross-sectional analysis of data from the National Health and Nutrition Examination Survey, only morbid obesity (defined as BMI ≥35 kg/m²) was related to CKD,²² whereas only three individuals had BMI of ≥35 kg/m² in our study. Another possibility is that the 4.1-yr follow-up period in this study may have been insufficient to establish any relationship between these factors. Iseki *et al.*²³ suggested that BMI was not a major risk factor for the development of ESRD after their 10-yr follow-up period. After extending this follow-up period to 17 yr, however, they found that BMI was associated with an increased risk for the development of ESRD in men.¹⁴ Finally, the difference may have arisen as a result of the restriction of our study to individuals without diabetes and hypertension, which are well-established mediators between obesity and kidney disease.²²

The exact mechanisms by which weight gain over a relatively short period of time is associated with the development of CKD have yet to be elucidated, even though neither overweight nor obese individuals had an increased risk for developing CKD during the same period. Although BMI measures not only adiposity but also muscle mass, it is highly correlated with adiposity,²⁴ and relatively small changes in weight could have a significant effect on body fat²⁵ and influence cardiovascular or metabolic risk.^{26,27} There is increasing evidence that weight gain in adulthood increases the risk for chronic disease, such as hypertension, type 2 diabetes, and coronary heart diseases.^{18,28–30} In addition, excessive adiposity may be associated with renal injury.²¹ As with obesity-induced hypertension and

diabetes, the pathophysiology of obesity-related kidney disease may function through more subtle mechanisms, such as a variety of hormonal and cytokine influences.^{31,32} Further study is needed on the mechanisms by which weight gain increases CKD independent of obesity, hypertension, and diabetes.

Our finding of an increased risk for CKD associated with the weight loss category should be interpreted with caution. Few studies have examined the association between low body weight or weight loss and future risk for kidney disease. In a large cross-sectional population study, Ramirez *et al.*³³ found a J-shaped relationship between BMI and the prevalence of proteinuria. A recent prospective study showed a J-shaped relationship between BMI and the risk for ESRD in China.³⁴ In addition, all-cause mortality studies have reported U-shaped or J-shaped relationships between BMI and mortality.^{35–39} In this study, the underweight individuals (BMI <18.5 kg/m²) had NS increases in CKD risk compared with normal-weight men (18.5 ≤ BMI <23.0 kg/m²). In addition, there was an increase in risk for CKD associated with the weight loss category of <−0.75 kg/yr in both the normal-weight and overweight groups. A previous study showed that weight loss among obese individuals without overt renal diseases was associated with an improvement in glomerular hemodynamic abnormalities.⁴⁰ We suggest three possible explanations for these contradictory results. First, the individuals with weight loss during the study period may have been more likely to have unfavorable health status at baseline. In contrast to individuals with weight gain or without weight change, those with weight loss were more obese

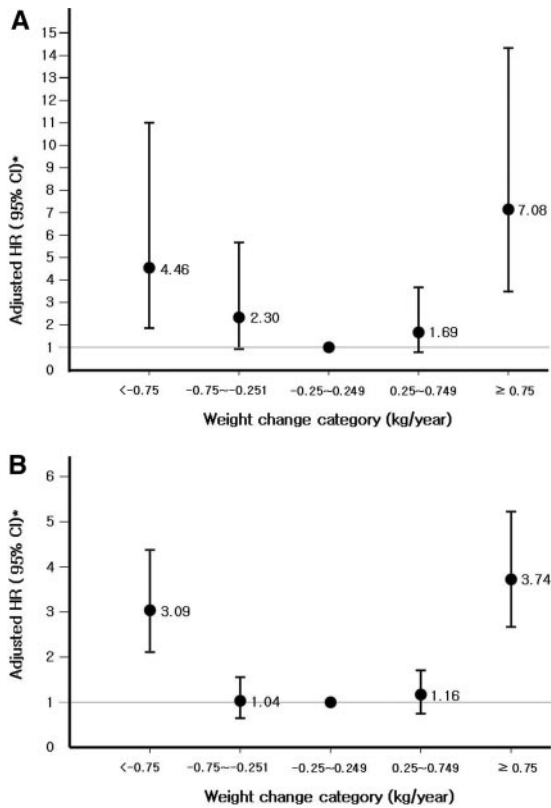


Figure 1. (A and B) Association between the development of CKD and weight change per year among 3139 men with baseline BMI ≥ 18.5 and < 23.0 kg/m² (A) and 5491 men with baseline BMI ≥ 23 kg/m² (B). *Adjustment for age, baseline GFR, BMI, HDL cholesterol, FBG, uric acid, and regular exercise.

and more likely to have dyslipidemia and MetS in this study. In addition, GGT, hsCRP, and HOMA-IR were higher and GFR was lower for those with weight loss. Thus, individuals who had a less favorable metabolic profile at baseline and were more overweight/obese were likely to be encouraged by the examining physician to implement dietary changes, exercise interventions, or smoking cessation. After adjustment for potential confounders at baseline, however, weight loss still increased the risk for CKD. Second, the weight loss during the study period may have been caused by an unintended weight loss. Because no information on weight loss intention was recorded, we could not differentiate between the effects of intentional and unintentional weight loss. Finally, weight and BMI do not indicate the proportion of fat-free mass and body fat gain with weight gain or loss. Further study on the role of weight loss on the development of CKD is needed.

Our study had several limitations. First, we used an estimated GFR instead of a directly measured GFR to define CKD. A recent review article reported that current GFR estimates had a greater inaccuracy in populations without known CKD than in those with the disease.⁴¹ Nonetheless, current GFR estimates facilitate the detection, evaluation, and management of CKD, and many organizations recommend the use of equations that

estimate GFR in epidemiologic studies and in clinical practice for the evaluation of renal function.⁴¹ Second, an abbreviated Modification of Diet in Renal Disease (MDRD) equation was not generated using longitudinal data within individuals; therefore, if weight gain increases creatinine production, then a slight increase in serum creatinine (*i.e.*, decrease in GFR) would be expected at the same true creatinine clearance. However, weight gain during adulthood is predominantly fat gain.⁴² In this study, weight changes were significantly associated with persistent CKD on follow-up. Third, we could not obtain information of family history of CKD, although family history is associated with the development of CKD.⁴³ Fourth, bias from loss to follow-up may have influenced our results. The baseline characteristics of the participants who were not included in the analysis were not significantly different from those in the analytic cohort, with the exception of age, cigarette smoking, and alcohol consumption. It is likely, however, that loss to follow-up will be encountered, especially in those who are in poor health. This loss to follow-up of high-risk people would likely lead to a conservative bias and subsequent underestimation of risk. Fifth, these results may not be extrapolated to women. Finally, ethnic factors that are characteristic of the Asian population are not well established with respect to using equations that estimate GFR; therefore, these equations need to be validated in large Asian cohorts with additional studies.

In conclusion, weight gain in this study was significantly associated with an increased risk for development of CKD. The strength of this study was the large sample size, which allowed us to identify the effect among stratified subgroup analyses. Even in normal-weight participants, an increase in body weight of approximately ≥ 0.75 kg/yr predicted incident CKD. Our findings support that, even in a normal-weight population, a low initial BMI does not ameliorate the increase in risk for CKD with weight gain; therefore, avoidance of weight gain, even among lean individuals, is important to reduce the risk for this disease.

CONCISE METHODS

Study Population

The study population was composed of Korean male workers and is described in detail previously.⁴⁴ The study population included workers who were ≥ 40 yr of age and underwent an annual comprehensive health examination and workers who were 30 to 39 yr of age and underwent a biennial comprehensive health examination. In 2002, 15,347 workers aged 30 to 59 yr participated in the comprehensive health examinations at a university hospital in Seoul, Korea. A total of 3628 men were excluded on the basis of the following exclusion criteria that might influence kidney function: 27 had a history of malignancy, 16 had a history of cardiovascular disease, 125 were taking medication for dyslipidemia, seven were taking medication for current kidney disease, 337 lacked data on their medical history or had not undergone urinalysis, 279 were taking medication for diabetes or had fasting glucose concentrations ≥ 126 mg/dl, 2688 were taking medication for hypertension or had BP $\geq 140/90$ mmHg at their ini-

tial examinations, 260 had a dipstick-positive proteinuria, and 566 had GFR of <64 ml/min per 1.73 m² at initial examination. Because some individuals had more than one exclusion criterion, the total number of eligible study participants was 11,719. This cohort that was free of CKD as well as risk factors for CKD, including hypertension and diabetes, was reexamined at the same hospital annually or biennially until September 2007. After exclusion of the 1298 men who did not complete their follow-up examinations, 1453 men with just one follow-up examination, and 176 men with fewer than two weight values before the assumed time of CKD development, 8792 male workers were included in the final analysis, and their mean (SD) follow-up periods were 4.13 (0.72) yr. This study was approved by the institutional review board at Kangbuk Samsung Hospital.

Measurements

The initial health examinations in 2002 included a medical history, physical examination, questionnaire on health-related behavior, and anthropometric and biochemical measurements. The medical history and history of prescription drug use were assessed by the examining physicians. All participants were asked to respond to a questionnaire on health-related behavior such as alcohol consumption, smoking status, and physical activity.⁴⁴

The blood specimens were sampled from an antecubital vein after >12 h of fasting. The serum levels of FBG, total cholesterol, TG, LDL cholesterol, HDL cholesterol, and GGT were measured using the Bayer Reagent Packs on an automated chemistry analyzer (ADVIA 1650 Autoanalyzer; Bayer HealthCare Ltd., Tarrytown, NY). The principles of the measurement were hexokinase method for glucose; enzymatic colorimetric assay for LDL cholesterol, HDL cholesterol, total cholesterol, and TG; and immunoradiometric assay (Biosource, Nivelles, Belgium) for insulin. Insulin resistance was assessed with HOMA-IR: Fasting blood insulin (μ U/ml) \times FBG (mg/dl)/405. hsCRP was analyzed by particle-enhanced immunonephelometry with the BN II System (Dade Behring, Marburg, Germany). The serum creatinine level was measured by means of the alkaline picrate (Jaffe) method. The within-run and total coefficients of variation for creatinine determinations were no greater than 3% from 2002 to 2006. The clinical laboratory has participated in the inspection and survey by the Korean Association of Quality Assurance for Clinical Laboratories annually and been verified for its ability of quality control and performance of various measurements.

All of the individuals in this study had a urinalysis at the time of the baseline examination. Urine protein was determined at each examination by single urine dipstick semiquantitative analysis (URiSCAN Urine strip; YD Diagnostics, Yong-In, Korea). Dipstick urinalysis was performed on fresh, midstream urine samples collected in the morning. The amount of urine protein was reported as the following six grades, which corresponded to the protein levels that were undetectable, or with 10, 30, 100, 300, and 1000 mg/dl protein, respectively: Absent, trace, 1+, 2+, 3+, and 4+. Proteinuria was defined as grades of $\geq 1+$.

GFR was estimated by using the simplified MDRD equation,⁴⁵ as recommended by the National Kidney Foundation⁴⁶: $\text{GFR (ml/min per } 1.73 \text{ m}^2 \text{ body surface area)} = 186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$. CKD was defined as GFR <64 ml/min per 1.73 m², which was the gender-specific, fifth percentile in our study population.

Trained nurses measured sitting BP levels with a standard mercury sphygmomanometer. Body weight was measured in light clothing (prepared uniform) without shoes to the nearest 0.1 kg using a digital weight scale. Height was measured to the nearest 0.1 cm. The BMI was calculated as weight (kg) divided by height squared (m²). According to ATP III,⁴⁷ the following five abnormalities define MetS: (1) abdominal obesity, (2) FBG ≥ 110 mg/dl, (3) TG ≥ 150 mg/dl, (4) HDL cholesterol <40 mg/dl, and (5) BP $\geq 130/85$ mmHg. Because measurement of waist circumference was not available for all individuals, we substituted abdominal obesity with overall adiposity as a BMI of ≥ 25 kg/m², which was proposed as a cutoff for diagnosis of obesity in Asians.¹⁶ Individuals with three or more of the five abnormalities were considered to have MetS.

Statistical Analysis

The χ^2 test and one-way ANOVA were used to analyze the statistical differences among the characteristics of the study participants in relation to the weight changes. The weight change per year for each individual was calculated as the slope (β) of the regression model. For incident CKD, regression modeling was carried out using a weight value before an assumed time of CKD development. Weight change per year was grouped into the following categories: <-0.75 , -0.75 to <-0.25 , -0.25 to <0.25 , 0.25 to <0.75 , and ≥ 0.75 in the CKD-free cohort. The distributions of continuous variables were evaluated, and transformations were used in the analysis as required. The incidence density of CKD was estimated as the number of new cases divided by the number of person-years at risk. For incident CKD cases, the time of CKD onset was assumed to be midpoint between the assessment at which CKD was diagnosed and the previous assessment. The person-years were calculated as the sum of follow-up times from the baseline until an assumed time of CKD development or until the final examination of each individual.

Standard Cox proportional hazards model was used to calculate the adjusted hazard ratios in the model for CKD. The data were adjusted first for age alone, then for the multiple covariates. In the multivariate models, we included the following variables that might confound the relation between weight change and CKD: Age, baseline GFR, BMI, FBG, SBP, DBP, TG, HDL cholesterol, HOMA-IR, hsCRP, smoking, alcohol consumption, incident diabetes, and incident hypertension. For the linear trends of risk, we treated the categories of weight change as a continuous variable in the Cox proportional hazards regression models. For tests of quadratic trend, we squared the linear trend variable after centering it on median weight change. The association between weight change and the risk for CKD was also assessed using Cox proportional hazards modeling that incorporated weight change as a time-dependent variable.

In sensitivity analysis, we also examined the association of weight change with incident CKD when the definition of incident CKD was limited to persistent CKD on follow-up or when we reclassified CKD as a GFR <60 ml/min per 1.73 m². In addition, linear mixed-effect models were used to analyze the effect of weight change over time on longitudinal changes in GFR across the weight change groups. The statistical data analysis was performed with SAS 9.1 software (SAS Institute, Cary, NC). All of the reported *P* values were two-tailed, and statistical significance was set at $P < 0.05$.

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DISCLOSURES

None.

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