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Underweight status and development of end-stage kidney disease: A nationwide population-based study

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Abstract

Background Underweight status increases the risk of cardiovascular disease and mortality in the general population. However, whether underweight status is associated with an increased risk of developing end-stage kidney disease is unknown.

Methods A total of 9 845 420 participants aged ≥20 years who underwent health checkups were identified from the Korean National Health Insurance Service database and analysed. Individuals with underweight (body mass index [BMI] < 18.5 kg/m^2) and obesity (BMI ≥ 25 kg/m^2) were categorized according to the World Health Organization recommendations for Asian populations.

Results During a mean follow-up period of 9.2 ± 1.1 years, 26 406 participants were diagnosed with end-stage kidney disease. After fully adjusting for other potential predictors, the moderate to severe underweight group (<17 kg/m^2) had a significantly higher risk of end-stage kidney disease than that of the reference (normal) weight group (adjusted hazard ratio, 1.563; 95% confidence interval, 1.337–1.828), and competing risk analysis to address the competing risk of death also showed the similar results (adjusted hazard ratio, 1.228; 95% confidence interval, 1.042–1.448). Compared with that of the reference BMI group (24–25 kg/m^2), the adjusted hazard ratios for end-stage kidney disease increased as the BMI decreased by 1 kg/m^2. In the sensitivity analysis, sustained underweight status or progression to underweight status over two repeated health checkups, when compared with normal weight status, had a higher hazard ratio for end-stage kidney disease.

Conclusions Underweight status is associated with an increased risk of end-stage kidney disease, and this association gradually strengthens as BMI decreases.

Keywords body mass index; end-stage kidney disease; risk; underweight

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Introduction

Obesity is a traditional risk factor for hypertension, heart failure, coronary heart disease, obstructive sleep apnoea and chronic kidney disease (CKD), all of which are associated with increased mortality.[1–8] Although the results were conflicting, most previous studies determined an association between cardiovascular disease or CKD and obesity, rather than underweight status, which is defined as a body mass index (BMI) < 18.5 kg/m^2. This is related to the fact that the worldwide prevalence of obesity has nearly doubled over the past two decades.[9] According to a pooled analysis of 2416 population-based studies, the prevalence of moderate and severe underweight status did not change considerably

between 1975 and 2016 compared with that of the increase in the prevalence of obesity.[10] Nevertheless, recent studies have shown that underweight status increases the risk of fractures,[11,12] atrial fibrillation,[13] infection-related in-hospital mortality,[14] lung diseases,[15–17] cardiovascular diseases[18,19] and all-cause mortality, especially in patients with CKD.[20,21] However, large nationwide population-based studies providing evidence that an underweight status increases the risk of kidney failure in the general population are limited by the small sample size and the lower societal concern for underweight status than that for obesity.

To address this knowledge limitation, we evaluated the association between underweight status and the development of end-stage kidney disease (ESKD) using the National Health Insurance Service (NHIS) health checkup data from 2009 to 2018. In this large nationwide population-based study, we aimed to demonstrate the real-world association between the degree of underweight status and the risk of ESKD in Korea using more subdivide BMI categories.

Methods

National Health Insurance Service data source

Anonymized data are publicly available from the NHIS database (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do), which includes all claims data provided by the NHIS and Medical Aid programmes. Data extracted from the NHIS database were considered representative of the entire South Korean population, and the details of this database have been previously described.[22] All insured Koreans aged >40 years undergo a biannual health checkup, whereas insured employees aged >20 years are recommended to undergo an annual health checkup supported by the NHIS.

Main study population and follow-up

We identified 10 586 248 participants aged ≥20 years who had undergone a health checkup in 2009. Individuals with a history of ESKD before the health checkup (n = 17 576) and those with missing data (n = 695 591) were excluded. We also excluded participants who developed ESKD within 1 year of follow-up (n = 27 661). Finally, 9 845 420 participants were included in this study and were followed up from baseline to the date of ESKD diagnosis during the follow-up period, the date of loss of health insurance qualification or the end of the study period (31 December 2018). To determine the effect of sustained underweight status or progression to underweight status on the risk of ESKD, a sensitivity analysis was performed. Among the main population, participants who did not undergo a health checkup in 2011 and who had developed ESKD before the 2011 health checkup were excluded. Finally, 6 694 003 participants were included in the sensitivity analysis. A detailed enrolment flowchart is shown in *Figure 1*.

Measurements and definitions

For each participant, BMI was calculated by dividing body weight (kg) by height squared (m^2). We defined underweight status as a BMI < 18.5 kg/m^2, which was divided into the following two subgroups: moderate to severe underweight (<17 kg/m^2) and mild underweight (<17–18.5 kg/m^2) statuses according to the World Health Organization (WHO) recommendations.[23] We also defined normal weight (18.5–23 kg/m^2), overweight (23–25 kg/m^2), obesity grade 1 (25–30 kg/m^2) and obesity grade 2 (≥30 kg/m^2) according to the WHO recommendations for Asian populations.[24]

Hypertension was defined as a previous diagnosis of hypertension (International Classification of Diseases Tenth Revision, Clinical Modification [ICD-10-CM] codes I10–13 and I15), a history of taking at least one antihypertensive drug or a recorded systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg in the health examination database. Diabetes was defined as a previous clinical diagnosis of diabetes (ICD-10-CM codes E11–14), medical history of diabetes or recorded fasting serum glucose level ≥ 126 mg/dL in the health examination database. Dyslipidaemia was defined as the presence of ICD-10-CM code E78, a history of lipid-lowering drug use or a total serum cholesterol level ≥ 240 mg/dL in the health examination data.[25,26] Previous cancer and myocardial infarction were defined based on the diagnostic codes (ICD-10-CM codes C00–99 and I21–25), and stroke was defined using ICD-10-CM codes I63 and I64. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, which was calculated using the Modification of Diet in Renal Disease formula.[27] The modified diagnostic criteria for metabolic syndrome were used by the International Obesity Task Force of the Asia-Pacific region for Korean adults proposed by the Korean Society for the Study of Obesity.[28] The participants were additionally categorized into three groups according to smoking status (non-smokers, former smokers and current smokers) and into three categories according to alcohol consumption (non-drinkers [0 g alcohol/day], moderate drinkers [<30 g alcohol/day] and heavy drinkers [≥30 g alcohol/day]). Regular exercise was defined as intense physical activity for at least 20 min/day for >3 days or moderate physical activity for at least 30 min/day for >5 days during the previous week.

Proteinuria was measured using a dipstick test. Fasting blood glucose (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), high-density lipoprotein cholesterol (mg/dL), low-density lipoprotein cholesterol (mg/dL), aspartate aminotransferase (IU/L), alanine aminotransferase (IU/L)

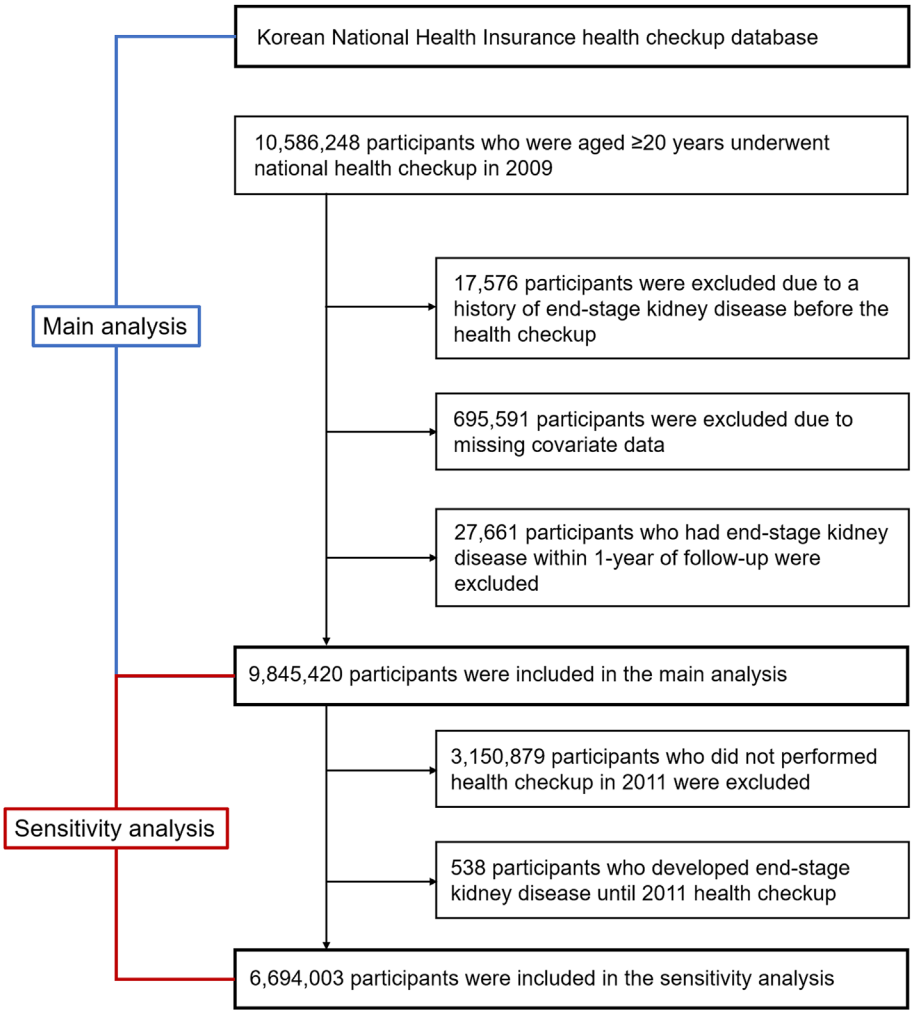

Figure 1 Flowchart of participant enrolment.

and gamma-glutamyl transferase (IU/L) levels were measured in the fasting state. The quality of all laboratory tests was confirmed by the Korean Association for Laboratory Medicine, and the NHIS certified that hospitals participated in the NHIS health checkup programmes.

Study outcomes

The study outcome was incident ESKD, defined as the requirement of haemodialysis, peritoneal dialysis or kidney transplantation. Patients with ESKD were identified using a combination of ICD-10-CM codes (N18–19, Z49, Z94.0 and Z99.2) and a special code (V001, procedure-related outpatient care or inpatient treatment on the day of haemodialysis; V003, peritoneal dialysis; and V005, kidney transplantation).

Statistical analyses

Data are presented as mean ± standard deviation for continuous variables and as numbers with proportions for categorical variables. Non-normally distributed variables are presented as geometric means with 95% confidence intervals (CIs). Intergroup differences were tested using the chi-squared test or analysis of variance, as appropriate. The incidence rates of ESKD are presented per 1000 person-years. To identify the risk of ESKD according to BMI categories, we calculated hazard ratios (HRs) with 95% CIs and analysed these data using multivariable Cox proportional hazard regression models. In Model 1, calculations were adjusted for age and sex. Model 2 was additionally adjusted for smoking, alcohol consumption, regular exercise, history of diabetes, hypertension, dyslipidaemia, eGFR and proteinuria. Model 3 included all covariates in Model 2, along with cardiovascular disease (myocardial infarction or stroke) and

cancer. Moreover, we performed competing risk analysis using the Fine and Gray model, because a mortality event could compete with our outcome of interest.[29,30] Smooth HR curves of the BMI were plotted after adjusting for all covariates (Model 3). Subgroup analyses were conducted according to age, sex, diabetes, hypertension, metabolic syndrome, cardiovascular disease, CKD and proteinuria. For subgroup analyses according to age, the participants were classified into <65- and ≥65-year groups. Interaction terms were added to test for effect modification across the subgroups. Sensitivity analyses were performed to identify the effects of a sustained BMI or a reduction in BMI leading to progression to an underweight status on the risk of ESKD over a 2-year period. BMI status at each evaluation year (pre- and post-BMI) was divided into four categories: underweight, normal, overweight and obesity statuses. All statistical analyses were performed using the Statistical Analysis System (SAS) software (Version 9.4; SAS Institute, Cary, NC, USA), and all two-tailed tests with $P < 0.05$ were considered statistically significant.

Results

Baseline characteristics

The mean baseline age of the participants was 47.2 years, and 54.6% were men. The characteristics of the participants, stratified according to BMI categories, are presented in *Table 1*. In our study population, the percentage of underweight participants was 3.7% (*n* = 364 139), whereas the percentage of those with obesity was 32.6% (*n* = 3 213 808). The participants in the underweight group were less likely to be smokers and alcohol drinkers; had a lower prevalence of diabetes, hypertension, metabolic syndrome and dyslipidaemia; had a better lipid profile; and had a higher eGFR than those in the overweight and obesity groups. However, underweight participants were less likely to exercise regularly and had a higher prevalence of cancer. Underweight and obesity participants have a greater prevalence of proteinuria than that of the normal weight group.

Body mass index categories and risk of end-stage kidney disease

During a mean follow-up period of 9.2 ± 1.1 years, 26 406 participants were diagnosed with ESKD. The associations between the BMI categories and the incidence and risk of ESKD are presented in *Table 2*. The incidence rates of ESKD were 0.273 (per 1000 person-years) in the moderate to severe underweight group, 0.197 in the mild underweight group, 0.239 in the normal weight group, 0.294 in the overweight group, 0.353 in the obesity grade 1 group and 0.464 in the obesity grade 2 group. After fully adjusting for other potential predictors of ESKD (Cox Model 3), the underweight group had a significantly higher risk of ESKD than that of the reference (normal) BMI group. The adjusted HR for ESKD was the highest in the moderate to severe underweight group (adjusted HR, 1.563; 95% CI, 1.337–1.828). Moreover, these results were consistent even after competing risk analysis with death as a competing event for ESKD progression (BMI < 17 kg/m^2: adjusted HR, 1.228; 95% CI, 1.042–1.448; BMI < 17–18.5 kg/m^2: adjusted HR, 1.222; 95% CI, 1.115–1.339). However, participants with obesity showed a lower risk of ESKD than those with normal BMI.

To determine the relationship between the BMI categories and the risk of ESKD more specifically, the incidence rate and adjusted HRs for ESKD were analysed according to a 1 kg/m^2 increase in BMI from 16 to 36 kg/m^2 (*Figure 2*). The incidence of ESKD tended to increase with higher BMI values. However, after multivariable adjustments, the association changed to a more pronounced increased risk of ESKD in the lower BMI categories. Compared with that of the reference BMI of 24–25 kg/m^2, the adjusted HRs for ESKD increased as the BMI decreased. Therefore, the highest HRs were observed in the lowest BMI category (<16 kg/m^2) (adjusted HR, 2.590; 95% CI, 1.963–3.416). These associations were confirmed by smooth HR curve analyses performed after the adjustment of all covariates (*Figure S1*). In contrast, the risk of ESKD significantly decreased in the BMI 25–32 kg/m^2 group, whereas the association between BMI and risk of ESKD disappeared in the BMI > 32 kg/m^2 group.

Subgroup analyses

We further investigated the association between underweight status and the risk of ESKD after stratification according to age, sex, diabetes, hypertension, cardiovascular disease, CKD and the presence of metabolic syndrome and proteinuria in the subgroup analyses (*Table 3*). In all subgroup analyses, underweight status (<18.5 kg/m^2) was consistently associated with the risk of ESKD. The correlation between underweight status and the risk of ESKD was significantly higher in participants aged <65 years than in those aged ≥65 years (P for interaction < 0.001). Underweight participants with a history of diabetes, hypertension, cardiovascular disease, metabolic syndrome or proteinuria had a relatively lower risk of developing ESKD than those without these comorbidities and those with normal body weight. However, the adjusted HRs were not significantly different between participants with and without CKD.

Table 1 Baseline characteristics of the study population according to body mass index status

Characteristics	BMI, kg/m^2						
	<17	≥17 to <18.5	≥18.5 to <23	≥23 to <25	≥25 to <30	≥30	*P* value
Number of participants	67 329 (0.68)	296 810 (3.01)	3 842 439 (39.03)	2 425 034 (24.63)	2 864 438 (29.09)	349 370 (3.55)	
Age, years	42.68 ± 18.93	40.05 ± 16.02	45.38 ± 14.34	48.85 ± 13.31	49.27 ± 13.2	46.35 ± 13.83	<0.001
Sex, male	21 367 (31.74)	99 587 (33.55)	1 810 376 (47.12)	1 448 336 (59.72)	1 801 298 (62.88)	194 815 (55.76)	<0.001
Smoking							
Never	47 770 (70.95)	208 245 (70.16)	2 462 878 (64.1)	1 385 139 (57.12)	1 562 088 (54.53)	200 197 (57.3)	
Former	4520 (6.71)	20 491 (6.9)	428 512 (11.15)	400 652 (16.52)	511 347 (17.85)	46 834 (13.41)	<0.001
Current	15 039 (22.34)	68 074 (22.94)	951 049 (24.75)	639 243 (26.36)	791 003 (27.61)	102 339 (29.29)	
Alcohol consumption							
None	41 040 (60.95)	166 225 (56)	2 058 911 (53.58)	1 224 993 (50.51)	1 413 375 (49.34)	182 330 (52.19)	
Moderate	23 459 (34.84)	116 926 (39.39)	1 541 236 (40.11)	999 093 (41.2)	1 164 951 (40.67)	130 280 (37.29)	<0.001
Heavy	2830 (4.2)	13 659 (4.6)	242 292 (6.31)	200 948 (8.29)	286 112 (9.99)	36 760 (10.52)	
Regular exercise	5513 (8.19)	29 220 (9.84)	627 224 (16.32)	482 804 (19.91)	565 293 (19.73)	59 948 (17.16)	<0.001
Hypertension	8160 (12.12)	28 210 (9.5)	662 981 (17.25)	684 280 (28.22)	1 104 362 (38.55)	180 317 (51.61)	<0.001
Diabetes	2843 (4.22)	9466 (3.19)	214 542 (5.58)	218 988 (9.03)	354 731 (12.38)	61 083 (17.48)	<0.001
Dyslipidaemia	3853 (5.72)	15 814 (5.33)	456 084 (11.87)	476 420 (19.65)	730 944 (25.52)	108 415 (31.03)	<0.001
Cancer	1106 (1.64)	3851 (1.3)	51 401 (1.34)	31 442 (1.3)	34 678 (1.21)	3668 (1.05)	<0.001
Myocardial infarction	208 (0.31)	659 (0.22)	11 041 (0.29)	9793 (0.4)	14 349 (0.5)	1895 (0.54)	<0.001
Stroke	1028 (1.53)	2605 (0.88)	45 102 (1.17)	39 984 (1.65)	55 836 (1.95)	6721 (1.92)	<0.001
Proteinuria	2288 (3.4)	6896 (2.32)	77 778 (2.02)	56 679 (2.34)	86 502 (3.02)	16 327 (4.67)	<0.001
eGFR, mL/min/1.73 m^2	93.26 ± 48.36	93.13 ± 48.57	89.29 ± 45.08	86.55 ± 45.16	85.67 ± 45.13	87.06 ± 45.46	<0.001
Metabolic syndrome	2834 (4.21)	10 656 (3.59)	390 499 (10.16)	556 071 (22.93)	1 257 746 (43.91)	244 445 (69.97)	<0.001
WC, cm	64.29 ± 6.05	66.63 ± 5.54	74.27 ± 6.3	81.22 ± 5.62	87.18 ± 6.17	96.78 ± 7.72	<0.001
SBP, mmHg	113.43 ± 14.86	113.74 ± 13.88	118.66 ± 14.42	123.39 ± 14.43	126.82 ± 14.56	131.29 ± 15.25	<0.001
DBP, mmHg	71.22 ± 9.59	71.3 ± 9.28	73.96 ± 9.63	76.79 ± 9.69	79.03 ± 9.87	82.06 ± 10.51	<0.001
Fasting glucose, mg/dL	91.54 ± 23.49	90.72 ± 19.93	94.06 ± 21.36	97.97 ± 23.77	91.54 ± 23.49	90.72 ± 19.93	<0.001
Total cholesterol, mg/dL	176.87 ± 32.9	177.8 ± 31.98	188.66 ± 34.97	197.65 ± 36.54	202.27 ± 37.49	205.85 ± 38.63	<0.001
Triglycerides, mg/dL	74.86 (74.59–75.12)	74.85 (74.72–74.97)	93.16 (93.11–93.21)	118.98 (118.89–119.06)	140.11 (140.02–140.2)	156.63 (156.34–156.91)	<0.001
HDL, mg/dL	64.31 ± 31.72	63.81 ± 30.42	59.23 ± 28.94	54.83 ± 26.98	52.56 ± 26.73	51.24 ± 25.8	<0.001
Low-density lipoprotein, mg/dL	97.49 ± 36.21	98.83 ± 36.18	109.28 ± 37.72	116.28 ± 38.18	118.23 ± 39.09	119.39 ± 40.12	<0.001
AST, IU/L	21.59 (21.53–21.65)	20.88 (20.85–20.9)	21.92 (21.92–21.93)	23.51 (23.5–23.52)	25.34 (25.33–25.36)	28.49 (28.45–28.53)	<0.001
ALT, IU/L	14.82 (14.77–14.87)	14.85 (14.83–14.88)	17.72 (17.72–17.73)	21.88 (21.87–21.9)	26.44 (26.42–26.46)	33.74 (33.67–33.81)	<0.001
GGT, IU/L	19.1 (19.01–19.19)	18.22 (18.18–18.26)	21.28 (21.26–21.29)	27.39 (27.37–27.42)	33.71 (33.68–33.74)	40.17 (40.07–40.26)	<0.001
Follow-up duration, years	8.7 ± 1.95	9.04 ± 1.36	9.15 ± 1.13	9.18 ± 1.07	9.18 ± 1.05	9.17 ± 1.03	<0.001

Note: Values given for continuous variables as mean ± standard deviation or geometric means (95% confidence intervals) and for categorical variables as number (proportion).
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; SBP, systolic blood pressure; WC, waist circumference.

Table 2 Incidence rates and hazard ratios for end-stage kidney disease according to body mass index status

BMI, kg/m^2	Number of participants	Incidence of ESKD	Follow-up duration, person-years	Incidence rate, per 1000 person-years	Adjusted HR (95% CI)			
					Model 1[a]	Model 2[b]	Model 3[c]	Fine and Gray model[d]
<17	67 329	160	585 906	0.273	1.171 (1.002–1.370)	1.577 (1.348–1.844)	1.563 (1.337–1.828)	1.228 (1.042–1.448)
17–18.5	296 810	528	2 683 625	0.197	1.039 (0.952–1.135)	1.385 (1.269–1.513)	1.379 (1.263–1.507)	1.222 (1.115–1.339)
18.5–23	3 842 439	8416	35 173 146	0.239	1 (reference)	1 (reference)	1 (reference)	1 (reference)
23–25	2 425 034	6538	22 266 679	0.294	1.017 (0.984–1.050)	0.759 (0.734–0.784)	0.761 (0.736–0.786)	0.798 (0.772–0.825)
25–30	2 864 438	9278	26 306 102	0.353	1.200 (1.165–1.236)	0.660 (0.640–0.680)	0.662 (0.642–0.682)	0.707 (0.686–0.730)
≥30	349 370	1486	3 205 078	0.365	1.966 (1.861–2.078)	0.653 (0.618–0.691)	0.656 (0.620–0.694)	0.692 (0.654–0.734)

Abbreviations: BMI, body mass index; CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio.
[a]Model 1 was adjusted for age and sex.
[b]Model 2 was adjusted for age, sex, smoking, alcohol consumption, regular exercise, estimated glomerular filtration rate, proteinuria and history of diabetes, hypertension and dyslipidaemia.
[c]Model 3 was adjusted for age, sex, smoking, alcohol consumption, regular exercise, estimated glomerular filtration rate, proteinuria and history of diabetes, hypertension, dyslipidaemia, myocardial infarction, stroke and cancer.
[d]Fine and Gray model was adjusted for age, sex, smoking, alcohol consumption, regular exercise, estimated glomerular filtration rate, proteinuria and history of diabetes, hypertension, dyslipidaemia, myocardial infarction, stroke and cancer.

Sensitivity analyses

During repeated health checkups, the sustained underweight (<18.5 to <18.5 kg/m^2), progression from underweight to normal (<18.5 to 18.5–23 kg/m^2), progression from normal to underweight (18.5–23 to <18.5 kg/m^2) and progression from overweight to underweight (23–25 to <18.5 kg/m^2) groups had a higher HR for ESKD even after fully adjusting for potential predictors than that of the sustained normal weight group (18.5–23 to 18.5–23 kg/m^2) (*Table 4*). In addition, the adjusted HR for ESKD was the highest in the group whose BMI progressed from overweight to underweight status over a 2-year period (adjusted HR, 2.339; 95% CI, 1.258–4.351). However, the risk of ESKD decreased in participants whose BMI progressed from normal to overweight, those with a sustained overweight status and those whose BMI progressed from overweight to obesity, according to sensitivity analyses (Models 2 and 3).

Discussion

Our results showed that underweight individuals (<18.5 kg/m^2) had a higher risk of ESKD than those with normal BMI. Moreover, as underweight status worsened, the adjusted HRs for ESKD tended to increase gradually. Our sensitivity analyses showed that persistent underweight status or progression to underweight status was associated with the development of ESKD. Considering these results, our large population-based study that included 9.8 million individuals suggests that severe and progression to underweight status may be a considerable risk factor for the development of ESKD in the Korean population.

Obesity is a major health issue with an increasing incidence worldwide and is considered an important risk factor for hypertension, diabetes and cardiovascular diseases.[1,2,20] Therefore, most previous studies have focused on determining the association between obesity and CKD progression or the development of ESKD in the general population[3–8,31] while excluding underweight individuals. Although some data exist on the relationship between underweight status and kidney outcomes, the results are conflicting. For example, in a retrospective cohort study using health checkup data from Korea, underweight status rather than obesity was associated with the development of albuminuria in healthy women.[32] In addition, a small retrospective study showed that graft survival was low in kidney transplant recipients with low BMI (<23 kg/m^2).[33] Moreover, similar to our findings on the association between underweight status and the risk of ESKD, a Chinese cohort study identified that underweight individuals (<18 kg/m^2) had a higher risk of ESKD than those with a normal weight.[34] Conversely, in another study, underweight status in adolescents, defined as a BMI below the fifth

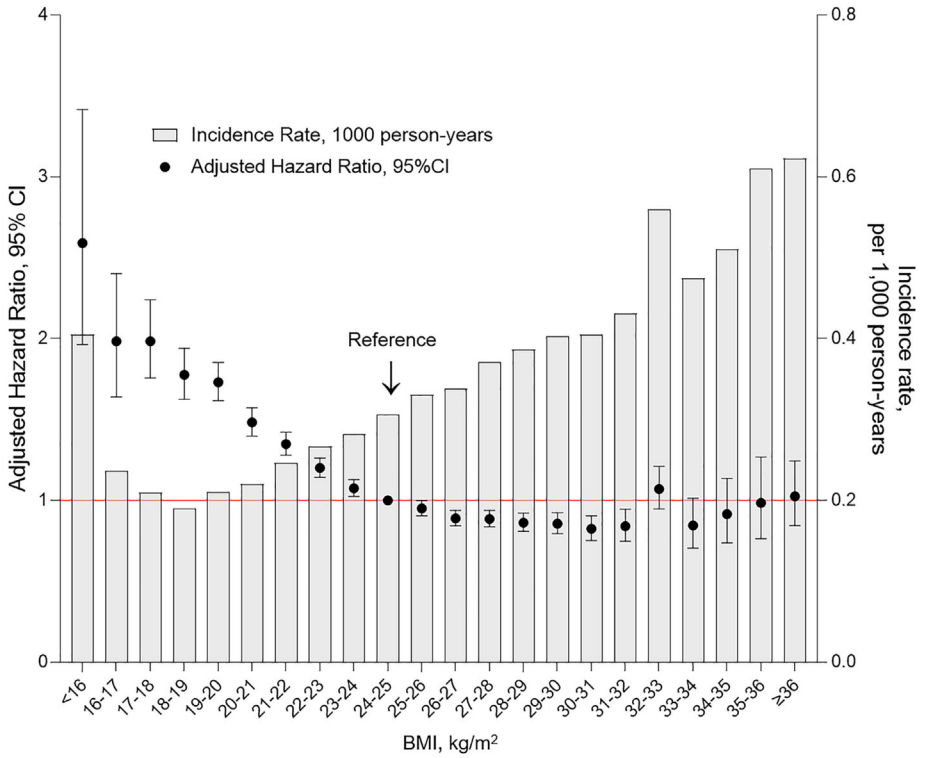

Figure 2 Incidence rates and adjusted hazard ratios for the development of end-stage kidney disease according to a 1 kg/m^2 increase in body mass index (BMI). Vertical lines represent the range for 95% confidence intervals (CIs). Models were adjusted for age, sex, smoking, alcohol consumption, regular exercise, estimated glomerular filtration rate, proteinuria and previous history of diabetes, hypertension, dyslipidaemia, myocardial infarction, stroke and cancer.

percentile, was not significantly associated with the future risk of ESKD.[35] These conflicting results might be explained by the relatively smaller population of underweight individuals than those with obesity, their single-centre nature and the inclusion of various ethnicities among the studies.

The main strength of the current study was the enrolment of a large general population of approximately 10 million Koreans from a nationwide health checkup database. Although underweight participants accounted for a relatively small proportion of our entire study population compared with those with obesity (3.7% vs. 32.6%), a large absolute number of underweight participants (n = 364 139) were analysed in our study. This allowed us to subdivide the underweight population into mild and moderate to severe categories to evaluate the association between the severity of underweight status and the development of ESKD. Our results showed that this association strengthened as the severity of underweight status increased.

In addition, we were able to identify all participants who developed ESKD, because all dialysis and kidney transplant recipients were registered as special Medical Aid programme beneficiaries. Moreover, we excluded participants who developed ESKD within 1 year of follow-up to account for the possibility of reverse causation, and we performed a sensitivity analysis to evaluate the effect of sustained or progression to underweight status on ESKD. Through careful collection of outcomes and additional analyses, we obtained highly reliable evidence that underweight status is associated with the risk of ESKD in the Korean population.

Our subgroup analyses showed that the relative risk of ESKD attributable to underweight status might be increased in participants aged <65 years or those without comorbid conditions such as diabetes, hypertension, cardiovascular disease or proteinuria. These findings suggest that the relative effect of being underweight per se on the risk of ESKD is lower when it is accompanied by traditional risk factors for ESKD. Nevertheless, the adjusted HRs for ESKD were significantly higher in the underweight group than in the normal weight group, regardless of age, sex or comorbid conditions in the general population.

The mechanisms by which underweight status may contribute to CKD progression or the development of ESKD are not clearly understood. One explanation for this association between underweight status and the risk of ESKD is that decreased muscle mass is associated with systemic oxidative stress and inflammation.[36] The activation of pro-inflammatory cytokines (e.g., interleukin-6 or tumour necrosis factor-α) and chemokines leads to cell death, which contributes to CKD progression.[37] In our study, although this positive effect disappeared with increased BMI ≥ 32 kg/m^2, partici-

Table 3 Subgroup analysis of incidence rates and hazard ratios for end-stage kidney disease according to age, sex, diabetes mellitus, hypertension, metabolic syndrome, cardiovascular disease, chronic kidney disease and proteinuria

Group	Subgroup	BMI, kg/m^2	Number of participants	Incidence of ESKD	Follow-up duration, person-years	Incidence rate, per 1000 person-years	Adjusted HR (95% CI)[a]	*P* for interaction
Age, years	<65	<17	54 349	107	498 430	0.251	2.076 (1.714–2.515)	<0.0001
		17–18.5	262 627	360	2 427 727	0.173	1.506 (1.353–1.676)	
		18.5–23	3 393 500	5292	31 439 002	0.143	1 (reference)	
		23–25	2 090 005	3879	19 366 828	0.168	0.720 (0.691–0.751)	
		25–30	2 450 870	5549	22 682 739	0.200	0.608 (0.585–0.632)	
		≥30	306 961	1002	2 833 568	0.257	0.616 (0.575–0.660)	
	≥65	<17	12 980	53	87 476	0.534	1.063 (0.810–1.395)	
		17–18.5	34 183	168	255 898	0.669	1.162 (0.995–1.357)	
		18.5–23	448 939	3124	3 734 144	0.661	1 (reference)	
		23–25	335 029	2659	2 899 851	0.837	0.828 (0.787–0.872)	
		25–30	413 568	3729	3 623 363	0.917	0.757 (0.721–0.794)	
		≥30	42 409	484	371 510	1.055	0.728 (0.662–0.802)	
Sex	Male	<17	21 367	78	172 618	0.452	1.504 (1.202–1.881)	0.0003
		17–18.5	99 587	308	869 873	0.354	1.470 (1.310–1.65)	
		18.5–23	1 810 376	5267	16 402 703	0.321	1 (reference)	
		23–25	1 448 336	4367	13 240 975	0.330	0.751 (0.722–0.782)	
		25–30	1 801 298	5914	16 498 474	0.358	0.636 (0.612–0.660)	
		≥30	194 815	762	1 784 213	0.427	0.606 (0.561–0.655)	
	Female	<17	45 962	82	413 288	0.198	1.647 (1.323–2.051)	
		17–18.5	197 223	220	1 813 752	0.121	1.280 (1.117–1.468)	
		18.5–23	2 032 063	3149	18 770 442	0.168	1 (reference)	
		23–25	976 698	2171	9 025 704	0.241	0.774 (0.733–0.818)	
		25–30	1 063 140	3364	9 807 628	0.343	0.710 (0.676–0.745)	
		≥30	154 555	724	1 420 864	0.510	0.722 (0.665–0.783)	
Diabetes	No	<17	64 486	108	566 736	0.191	1.667 (1.377–2.018)	<0.0001
		17–18.5	287 344	326	2 610 175	0.125	1.307 (1.168–1.463)	
		18.5–23	3 627 897	4598	33 334 300	0.138	1 (reference)	
		23–25	2 206 046	3252	20 332 702	0.160	0.798 (0.763–0.835)	
		25–30	2 509 707	4427	23 135 406	0.191	0.755 (0.724–0.788)	
		≥30	288 287	648	2 655 683	0.244	0.823 (0.757–0.894)	
	Yes	<17	2843	52	19 169	2.713	1.431 (1.088–1.881)	
		17–18.5	9466	202	73 450	2.750	1.575 (1.367–1.815)	
		18.5–23	214 542	3818	1 838 846	2.076	1 (reference)	
		23–25	218 988	3286	1 933 978	1.699	0.715 (0.682–0.749)	
		25–30	354 731	4851	3 170 697	1.530	0.578 (0.554–0.603)	
		≥30	61 083	838	549 395	1.525	0.543 (0.503–0.585)	
Hypertension	No	<17	59 169	75	527 955	0.142	1.914 (1.521–2.408)	<0.0001
		17–18.5	268 600	214	2 458 466	0.087	1.288 (1.120–1.481)	
		18.5–23	3 179 458	2501	29 356 157	0.085	1 (reference)	
		23–25	1 740 754	1338	16 111 127	0.083	0.772 (0.722–0.825)	
		25–30	1 760 076	1432	16 288 900	0.088	0.746 (0.699–0.796)	
		≥30	169 053	158	1 563 065	0.101	0.856 (0.729–1.006)	
	Yes	<17	8160	85	57 951	1.467	1.356 (1.095–1.681)	
		17–18.5	28 210	314	225 159	1.395	1.469 (1.311–1.645)	
		18.5–23	662 981	5915	5 816 989	1.017	1 (reference)	

(*Continues*)

Table 3 (continued)

Group	Subgroup	BMI, kg/m^2	Number of participants	Incidence of ESKD	Follow-up duration, person-years	Incidence rate, per 1000 person-years	Adjusted HR (95% CI)[a]	*P* for interaction
		23–25	684 280	5200	6 155 552	0.845	0.753 (0.725–0.782)	
		25–30	1 104 362	7846	10 017 202	0.783	0.642 (0.621–0.664)	
		≥30	180 317	1328	1 642 012	0.809	0.629 (0.592–0.668)	
Metabolic syndrome	No	<17	64 495	117	565 663	0.207	1.681 (1.399–2.019)	0.0373
		17–18.5	286 154	369	2 599 407	0.142	1.352 (1.215–1.503)	
		18.5–23	3 451 940	4445	31 734 544	0.140	1 (reference)	
		23–25	1 868 963	2253	17 250 640	0.131	0.714 (0.679–0.751)	
		25–30	1 606 692	1816	14 846 756	0.122	0.647 (0.613–0.684)	
		≥30	104 925	107	969 254	0.110	0.661 (0.546–0.801)	
	Yes	<17	2834	43	20 243	2.124	1.419 (1.050–1.916)	
		17–18.5	10 656	159	84 218	1.888	1.573 (1.342–1.843)	
		18.5–23	390 499	3971	3 438 602	1.155	1 (reference)	
		23–25	556 071	4285	5 016 039	0.854	0.758 (0.725–0.791)	
		25–30	1 257 746	7462	11 459 346	0.651	0.621 (0.597–0.645)	
		≥30	244 445	1379	2 235 824	0.617	0.602 (0.566–0.641)	
CVD	No	<17	66 121	155	578 432	0.268	1.617 (1.379–1.896)	0.0001
		17–18.5	293 625	501	2 660 939	0.188	1.382 (1.262–1.513)	
		18.5–23	3 787 503	7796	34 722 534	0.225	1 (reference)	
		23–25	2 376 329	5969	21 847 774	0.273	0.751 (0.726–0.777)	
		25–30	2 795 712	8420	25 705 164	0.328	0.650 (0.630–0.671)	
		≥30	340 944	1330	3 131 077	0.425	0.630 (0.594–0.669)	
	Yes	<17	1208	5	7474	0.669	0.760 (0.315–1.832)	
		17–18.5	3185	27	22 687	1.190	1.285 (0.874–1.89)	
		18.5–23	54 936	620	450 612	1.376	1 (reference)	
		23–25	48 705	569	418 905	1.358	0.874 (0.780–0.979)	
		25–30	68 726	858	600 939	1.428	0.805 (0.726–0.893)	
		≥30	8426	156	74 000	2.108	0.983 (0.825–1.172)	
CKD	No	<17	63 092	81	553 379	0.146	1.527 (1.225–1.902)	0.4024
		17–18.5	281 140	292	2 549 906	0.115	1.384 (1.228–1.558)	
		18.5–23	3 610 734	4159	33 130 858	0.126	1 (reference)	
		23–25	2 251 676	2963	20 723 452	0.143	0.744 (0.709–0.780)	
		25–30	2 640 583	4183	24 312 099	0.172	0.657 (0.629–0.687)	
		≥30	322 049	656	2 963 323	0.221	0.614 (0.565–0.668)	
	Yes	<17	4237	79	32 526	2.429	1.561 (1.250–1.951)	
		17–18.5	15 670	236	133 719	1.765	1.328 (1.164–1.514)	
		18.5–23	231 705	4257	2 042 288	2.084	1 (reference)	
		23–25	173 358	3575	1 543 227	2.317	0.782 (0.748–0.817)	
		25–30	223 855	5095	1 994 003	2.555	0.670 (0.643–0.698)	
		≥30	27 321	830	241 754	3.433	0.680 (0.631–0.733)	
Proteinuria	No	<17	65 041	110	567 597	0.194	1.904 (1.576–2.300)	<0.0001
		17–18.5	289 914	327	2 624 886	0.125	1.381 (1.234–1.544)	
		18.5–23	3 764 661	5125	34 501 079	0.149	1 (reference)	
		23–25	2 368 355	3806	21 772 249	0.175	0.764 (0.733–0.797)	
		25–30	2 777 936	5315	25 543 387	0.208	0.708 (0.681–0.737)	
		≥30	333 043	788	3 060 090	0.258	0.753 (0.698–0.812)	

(*Continues*)

Table 3 (continued)

Group	Subgroup	BMI, kg/m^2	Number of participants	Incidence of ESKD	Follow-up duration, person-years	Incidence rate, per 1000 person-years	Adjusted HR (95% CI)[a]	*P* for interaction
	Yes	<17	2288	50	18 309	2.731	1.110 (0.839–1.468)	
		17–18.5	6896	201	58 739	3.422	1.376 (1.194–1.587)	
		18.5–23	77 778	3291	672 067	4.897	1 (reference)	
		23–25	56 679	2732	494 431	5.526	0.753 (0.715–0.792)	
		25–30	86 502	3963	762 715	5.196	0.602 (0.574–0.631)	
		≥30	16 327	698	144 987	4.814	0.561 (0.516–0.609)	

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease (myocardial infarction and stroke); ESKD, end-stage kidney disease; HR, hazard ratio.
[a]Model was adjusted for age, sex, smoking, alcohol consumption, regular exercise, estimated glomerular filtration rate, proteinuria and history of diabetes, hypertension, dyslipidaemia, myocardial infarction, stroke and cancer.

Table 4 Sensitivity analysis of incidence rates and hazard ratios for end-stage kidney disease for sustained or altered body mass index status

Pre-BMI, kg/m^2	Post-BMI, kg/m^2	Number of participants	Incidence of ESKD	Follow-up duration, person-years	Incidence rate, per 1000 person-years	Adjusted HR (95% CI)		
						Model 1[a]	Model 2[b]	Model 3[c]
<18.5	<18.5	140 722	202	1 149 191	0.176	1.051 (0.912–1.211)	1.434 (1.244–1.653)	1.424 (1.235–1.642)
	18.5–23	79 355	110	651 716	0.169	1.024 (0.847–1.238)	1.298 (1.073–1.570)	1.295 (1.071–1.566)
	23–25	1002	5	7948	0.629	2.167 (0.901–5.210)	2.255 (0.938–5.421)	2.265 (0.942–5.445)
	≥25	595	1	4778	0.209	0.643 (0.091–4.567)	0.433 (0.061–3.072)	0.435 (0.061–3.092)
18.5–23	<18.5	69 105	176	556 764	0.316	1.442 (1.240–1.678)	1.720 (1.478–2.002)	1.720 (1.478–2.001)
	18.5–23	2 094 803	3606	17 332 644	0.208	1 (reference)	1 (reference)	1 (reference)
	23–25	383 297	719	3 175 959	0.226	1.057 (0.976–1.145)	0.900 (0.831–0.976)	0.902 (0.832–0.977)
	≥25	34 360	96	282 552	0.340	1.687 (1.377–2.066)	1.060 (0.865–1.298)	1.061 (0.866–1.300)
23–25	<18.5	1036	10	7739	1.292	3.340 (1.798–6.203)	2.377 (1.279–4.418)	2.339 (1.258–4.351)
	18.5–23	312 741	896	2 572 203	0.348	1.310 (1.218–1.410)	0.948 (0.881–1.020)	0.949 (0.882–1.022)
	23–25	1 025 739	2068	8 510 448	0.243	0.954 (0.904–1.008)	0.698 (0.661–0.737)	0.699 (0.662–0.738)
	≥25	353 480	741	2 930 279	0.253	1.108 (1.024–1.199)	0.758 (0.700–0.821)	0.759 (0.701–0.822)

Abbreviations: BMI, body mass index; CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio.
[a]Model 1 was adjusted for age and sex.
[b]Model 2 was adjusted for age, sex, smoking, alcohol consumption, regular exercise, estimated glomerular filtration rate, proteinuria and history of diabetes, hypertension and dyslipidaemia.
[c]Model 3 was adjusted for age, sex, smoking, alcohol consumption, regular exercise, estimated glomerular filtration rate, proteinuria and history of diabetes, hypertension, dyslipidaemia, myocardial infarction, stroke and cancer.

pants with obesity had a lower risk of ESKD than those with a normal weight. Similar to our findings, the obesity paradox has been observed in older adults and in patients with cardiovascular disease.[1,38] The favourable effects of obesity are explained by haemodynamic stability and attenuation of the renin–angiotensin response in addition to altered cytokine profiles.[39] Consequently, chronic systemic inflammation or malnutrition and the diminished effect of the obesity paradox may also play a role in the development of ESKD in underweight individuals.

Our study has several limitations. First, the study was limited to the Korean population. As Asians have a lower prevalence of obesity than that of Caucasians, the BMI cut-off values for overweight status and obesity are different in Asian populations.[40] Although relevant studies are lacking, ethnic disparities may be observed in underweight individuals. Therefore, our findings cannot be generalized to other ethnicities. Second, BMI alone does not accurately predict body fat distribution or adiposity. A previous study showed that increased visceral-to-subcutaneous fat area was associated with all-cause mortality.[41] Nevertheless, BMI can be easily measured in a clinical setting, and a low BMI can be predicted to lead to the development of ESKD in the general population. Third, because of the retrospective nature of this study, the causal relationship between underweight status and the development of ESKD could not be confirmed. However, to clarify causality, we excluded participants with a history of ESKD and those with newly developed ESKD during the first year of follow-up.

In conclusion, this Korean nationwide population-based cohort study found that being underweight was associated with an increased risk of developing ESKD. Furthermore, this association became progressively stronger as BMI decreased, which was particularly evident in the group with sustained low BMI. Further studies are needed to determine the mechanism linking the development of ESKD and underweight status, as well as to determine whether intentional weight gain in individuals with a low BMI can decrease the risk of ESKD.

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Conflict of interest statement

The authors declare no conflict of interest.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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