Nephrol Dial Transplant (2014) 29: 2106–2113
doi: 10.1093/ndt/gfu221
Advance Access publication 18 June 2014

The association between underweight and the development of albuminuria is different between sexes in relatively healthy Korean subjects

Cheol Min Jang, Young Youl Hyun, Kyu Beck Lee and Hyang Kim

Department of Internal Medicine, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Republic of Korea

Correspondence and offprint requests to: Young Youl Hyun; E-mail: femur0@naver.com

ORIGINAL ARTICLE

ABSTRACT

Background. There are limited data on the association between underweight and albuminuria. The aim of this study is to verify the effect of underweight on the development of albuminuria.

Methods. Participants who underwent two health check-ups with a 2-year interval at a tertiary hospital in Korea between 2002 and 2009 were studied. After exclusion of participants with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or dipstick albuminuria ≥1+ at the first check-up, 53 876 participants were enrolled. We measured the incidence of albuminuria at the second check-up and calculated the odds ratio (OR) for the development of albuminuria according to body mass index (BMI).

Results. After 2 years, 746 cases of incident albuminuria were observed among 53 876 participants. The effect of BMI on the development of albuminuria was modified by sex in a multivariate logistic model with adjustment for age, diabetes, hypertension, dyslipidaemia, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, uric acid, eGFR, current smoking status and alcohol intake (P-value for interaction <0.001). Compared with participants in the normal weight range (BMI, 18.5–22.9), the ORs for incident albuminuria were 1.93 [95% confidence interval (CI), 1.35–2.76; P ≤ 0.001], 1.19 (0.84–1.67; P = 0.329) and 0.71 (0.43–1.17; P = 0.177) in underweight (BMI, <18.5), overweight (BMI, 23.0–24.9) and obese (BMI, ≥25) women. However, the ORs were 0.9 (95% CI, 0.39–2.05; P = 0.794), 1.08 (0.84–1.38; P = 0.567) and 1.38 (1.09–1.75; P = 0.007) for each corresponding group of men.

Conclusions. Underweight was significantly associated with the development of albuminuria after 2 years in relatively healthy Korean females, but this relationship was not significant in males. This study suggests the need for more studies on the role of underweight in renal injury in men and women.

Keywords: albuminuria, body mass index, underweight

INTRODUCTION

Albuminuria is not only a risk factor for renal function decline or end-stage renal disease, but also a strong predictor of cardiovascular disease (CVD) and cardiovascular-related and all-cause death [1]. Efforts to detect albuminuria are recommended for populations with risk factors for chronic kidney disease (CKD) [2, 3], and identifying individuals at risk of albuminuria is also important.

Obesity is defined by a high body mass index (BMI) and is a major health issue in the modern world because it is associated with health problems such as hypertension, diabetes, CVD and higher mortality. Previous studies have shown that the development of albuminuria is also associated with higher BMI [4, 5].

Being underweight is also associated with cardiovascular and all-cause mortality; therefore, the relationship between BMI and mortality is U-shaped [6, 7]. The worse outcome of underweight individuals is also apparent in patients with CKD. For example, haemodialysis patients with low BMI show higher mortality than those with higher BMI [8] and kidney transplant recipients with low BMI show low graft survival [9].

However, there are few data about the relationship between underweight and the development of albuminuria. Two cross-sectional studies have shown an association between underweight and the presence of albuminuria [10, 11], and there are two longitudinal studies on the association between underweight and the development of albuminuria with conflicting results [4, 12]. The aim of this study was to verify the effect of underweight on the development of albuminuria by analysing data from health check-ups of relatively healthy Korean subjects.

MATERIALS AND METHODS

Study design and population

We constructed a retrospective cohort using participants of regular health check-up programmes at the Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. In South Korea, employees are required to participate in annual or biennial health examinations by the Industrial Safety and Health Law. Our participants include employees, their family members and individuals who had check-ups voluntarily. A total of 74 289 participants who visited this centre two times with a 2-year interval between 2002 and 2009 were considered for inclusion in this retrospective cohort. We included only adult subjects aged ≥19 years. We first excluded records with missing data for the variables of interest and then excluded participants with a history of disease that can severely affect BMI, such as tuberculosis, liver disease, cancer and CVD. CVD was defined as a history of heart disease, coronary disease or previous stroke. We also excluded participants with positive results for hepatitis B surface antigen and anti-HCV antibodies. From this potential cohort, we further excluded participants with CKD at baseline. CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or dipstick albuminuria ≥1+. The final analysis included 53 876 participants. Figure 1 summarizes the process of constructing this retrospective cohort. This study was approved by the institutional review board at Kangbuk Samsung Hospital.

Clinical and laboratory measurements

The health check-up consisted of medical history, physical examination, a health-related behaviour questionnaire, biochemistry studies and anthropometric measures. The examining physicians assessed the medical history and prior use of medications.

Height and weight were measured with an automated scale while the participants were wearing a light hospital gown without shoes. BMI was calculated as weight (kg) divided by height squared (m^2). Trained nurses measured systolic blood pressure (SBP) and diastolic blood pressure (DBP) with a standard mercury sphygmomanometer on the right arm of the subject who was in a seated position after at least 5 min of rest. Waist circumference was measured at the level of the umbilicus by a single examiner with the subject in the standing position.

Blood specimens were sampled from an antecubital vein after >12 h of fasting. Plasma glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and uric acid levels were measured using an autoanalyser (Advia 1650 Autoanalyser, Bayer Diagnostics, Leverkusen, Germany). In this study, dyslipidaemia was defined as total cholesterol >240 mg/dL or a previous history

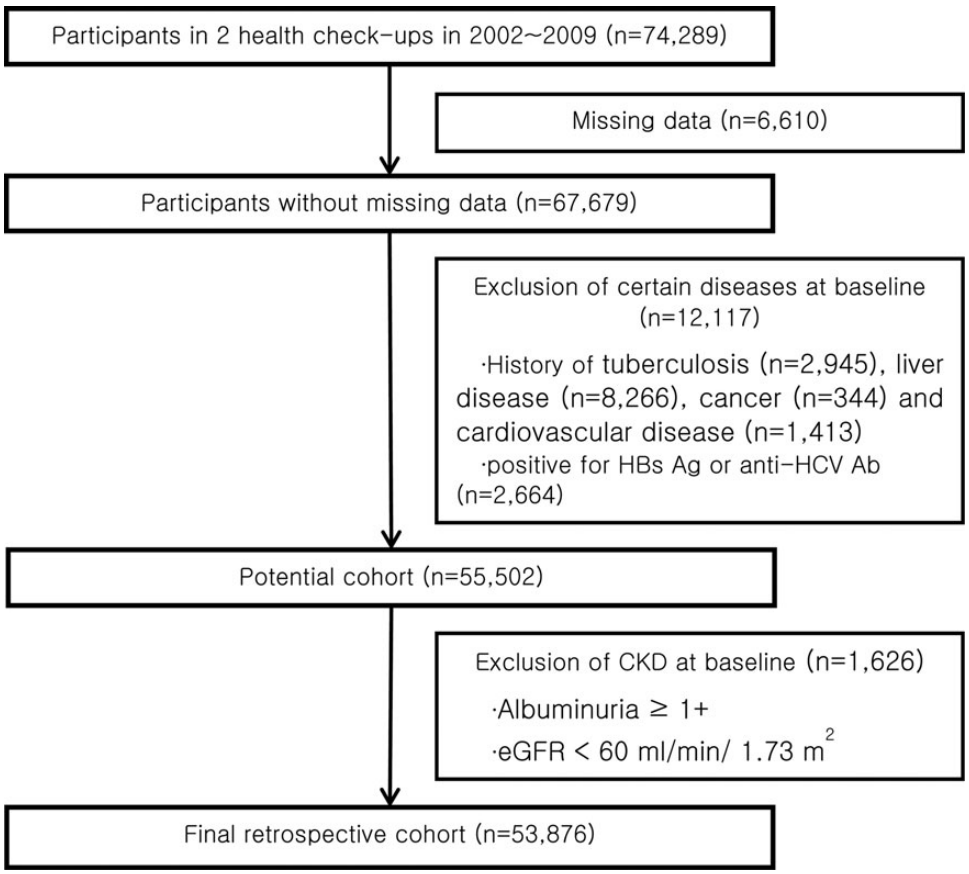

FIGURE 1: Flow diagram for the selection of the retrospective study cohort. A total of 53 876 participants without CKD at baseline were included. eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Table 1. Baseline characteristics according to BMI category

	Total	BMI				P-value	P-value for trend
		Underweight (< 18.5)	Normal weight (18.5–22.9)	Overweight (23.0–24.9)	Obese (≥25)		
N	53 876	2314	24 217	13 097	14 238		
BMI (kg/m^2)	23.2 ± 3	17.7 ± 0.7	21.1 ± 1.2	24.0 ± 0.6	27.0 ± 1.8		
Age (years)	34.9 ± 6.0	33.1 ± 4.5	34.5 ± 5.6	35.4 ± 6.4	35.5 ± 6.3	<0.001	<0.001
Sex (male)	33 940 (63.0%)	608 (26.4%)	11 564 (47.8%)	9856 (75.3%)	11 912 (83.6%)	<0.001	<0.001
SBP (mmHg)	110 (104–120)	106 (100–110)	110 (100–120)	110 (110–120)	120 (110–130)	0.001	<0.001
DBP (mmHg)	70 (70–80)	70 (60–70)	70 (60–80)	70 (70–80)	80 (70–80)	0.001	<0.001
WC (cm)	78.9 ± 9.2	64.2 ± 4.5	73.0 ± 6.0	81.3 ± 5.1	88.6 ± 6.0	<0.001	<0.001
Glucose (mg/dL)	93 ± 12	89 ± 8	91 ± 10	94 ± 12	96 ± 14	<0.001	<0.001
TC (mg/dL)	191.6 ± 33.9	174.1 ± 28.3	183.6 ± 31.2	195.6 ± 33.3	204.3 ± 34.7	<0.001	<0.001
LDL cholesterol (mg/dL)	112 ± 29	93 ± 23	104 ± 26	116 ± 28	123 ± 29	<0.001	<0.001
HDL cholesterol (mg/dL)	55 ± 12	63 ± 13	58 ± 12	53 ± 11	50 ± 10	<0.001	<0.001
Uric acid (mg/dL)	5.4 ± 1.4	4.4 ± 1.1	4.9 ± 1.3	5.7 ± 1.3	6.2 ± 1.4	<0.001	<0.001
HOMA-IR	1.9 ± 0.8	1.6 ± 0.6	1.7 ± 0.6	1.9 ± 0.7	2.3 ± 1.0	<0.001	<0.001
BUN (mg/dL)	13.3 ± 3.2	12.2 ± 3.1	12.9 ± 3.1	13.6 ± 3.2	14.0 ± 3.2	<0.001	<0.001
Creatinine (mg/dL)	1.0 ± 0.2	0.9 ± 0.1	1.0 ± 0.2	1.1 ± 0.1	1.1 ± 0.1	<0.001	<0.001
eGFR (mL/min/1.73 m^2)	79.9 ± 9.1	82.2 ± 9.5	80.7 ± 9.2	79.4 ± 8.9	78.4 ± 8.9	<0.001	<0.001
Diabetes	806 (1.5%)	8 (0.4%)	203 (0.8%)	209 (1.6%)	386 (2.7%)	<0.001	<0.001
Hypertension	6 101 (11.3%)	49 (2.1%)	1398 (5.8%)	1581 (12.1%)	3073 (21.6%)	<0.001	<0.001
Dyslipidaemia	4788 (8.9%)	59 (2.6%)	1248 (5.2%)	1300 (9.9%)	2181 (15.3%)	<0.001	<0.001
Current smoking	15 564 (28.9%)	349 (15.1%)	5244 (21.7%)	4338 (33.1%)	5633 (39.5%)	<0.001	<0.001
Alcohol intake (g/day)	3 (0–12)	0 (0–3)	3 (0–8)	6 (0–15)	6 (0–15)	<0.001	<0.001

Values are reported as a number (percentage) for categorical variables and as mean ± standard deviation or median (interquartile range) for continuous variables. P-values were obtained using the analysis of variance or Kruskal–Wallis test for continuous variables and the χ^2 test for categorical variables.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment of insulin resistance; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

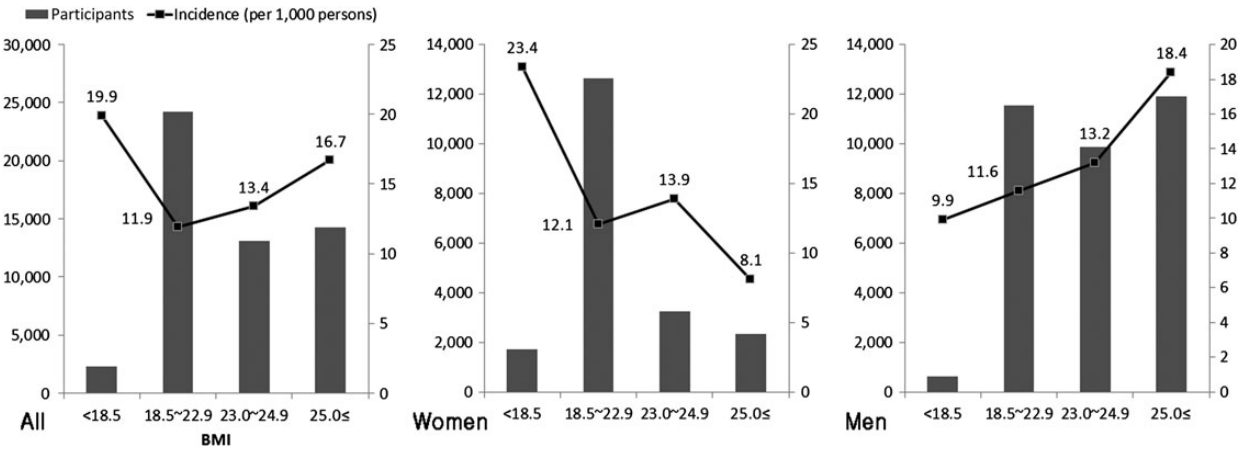

FIGURE 2: Incidence of albuminuria after 2 years according to BMI categories. During the study period 746 cases of albuminuria developed in 53 876 participants. BMI, body mass index.

of dyslipidaemia. Insulin was measured by immunoradiometric assay (Biosource, Nivelles, Belgium). Insulin resistance was assessed with homoeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR was calculated according to the following equation: fasting blood insulin (μU/mL) × fasting blood glucose (mg/dL)/405. Serum creatinine level was measured by the alkaline picrate (Jaffe) method. Trained medical technicians performed regular calibration and quality control for creatinine measurements during the study period using a validated calibrator and quality control materials. Our clinical laboratory has participated in annual inspection and survey by the Korean Association of Quality Assurance for Clinical Laboratories and is certified for quality control and the performance of various measurements. eGFR was calculated using the four-variable Modification of Diet in Renal Disease Study equation [13] as follows: eGFR (mL/min/1.73 m^2 body surface area) = 186.3 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$.

Urine albumin was determined at each examination with a single urine dipstick semi-quantitative analysis (URiSCAN Urine Strip; YD Diagnostics, Yongin, Korea). Dipstick urinalysis was performed on fresh, midstream urine samples collected in the morning. The amount of urine albumin was reported

as absent, trace, 1+, 2+, 3+ or 4+, which correspond to undetectable, 10, 30, 100, 300 or 1000 mg/dL albumin, respectively. Albuminuria was defined as a grade of ≥1+.

In this study, diabetes was defined as a fasting glucose of ≥126 mg/dL, a history of previously diagnosed diabetes or the use of anti-diabetic medications. Hypertension was defined as an SBP ≥140 mmHg or DBP ≥90 mmHg, a history of hypertension or the use of antihypertensive medications.

Table 2. Baseline characteristics in individuals with and without albuminuria at follow-up

Characteristics	Without albuminuria	With albuminuria	P-value
N	53 130	746	
Age	34.9 ± 6.0	35.4 ± 6.4	0.051
Male sex	33 451 (63.0%)	489 (65.6%)	0.146
BMI	23.2 ± 3.0	23.5 ± 3.3	0.020
SBP (mmHg)	110 (104–120)	110 (104–120)	0.027
DBP (mmHg)	70 (70–80)	75 (70–80)	<0.001
WC (cm)	78.8 ± 9.2	79.6 ± 10.0	0.128
Glucose (mg/dL)	93 ± 12	95 ± 18	<0.001
TC (mg/dL)	191.6 ± 33.9	191.8 ± 34.3	0.857
LDL cholesterol (mg/dL)	112 ± 29	111 ± 28	0.731
HDL cholesterol (mg/dL)	55 ± 12	54 ± 12	0.232
Uric acid (mg/dL)	5.4 ± 1.4	5.5 ± 1.4	0.428
HOMA-IR	1.9 ± 0.8	2.1 ± 1.1	<0.001
BUN (mg/dL)	13.3 ± 3.2	13.5 ± 3.2	0.181
Creatinine (mg/dL)	1.03 ± 0.16	1.04 ± 0.0.16	0.143
eGFR (mL/min/1.73 m^2)	79.9 ± 9.1	79.6 ± 9.2	0.414
Diabetes	780 (1.5%)	26 (3.5%)	<0.001
Hypertension	5969 (11.2%)	132 (17.7%)	<0.001
Dyslipidaemia	4718 (8.9%)	70 (9.4%)	0.631
Current smoking	15319 (28.8%)	245 (32.8%)	0.016
Alcohol intake (g/day)	3 (0–12)	6 (0–15)	0.007

Values are reported as a number (percentage) for categorical variables and as mean ± standard deviation or median (interquartile range) for continuous variables. P-values were obtained using the *t*-test or Mann–Whitney *U*-test for continuous variables and the χ^2 test for categorical variables.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model assessment of insulin resistance; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

Statistical analyses

Continuous variables were expressed as mean ± SD or median (interquartile range). Continuous variables were compared between the two groups using Student's *t*-test or the Mann–Whitney *U*-test. For comparisons among the four groups, the analysis of variance or Kruskal–Wallis test was used. Categorical variables are expressed as percentages and compared using the χ^2 test. We used multivariate logistic regression analysis to determine odds ratios (ORs) for developing albuminuria according to the categories of BMI. Participants were divided into four categories according to their BMI as follows: underweight, <18.5; normal weight, 18.5–22.9; overweight, 23.0–24.9 and obese, ≥25.0. This categorization was based on the proposed classifications of BMI in Asian adults by the International Obesity Task Force and the World Health Organization Regional Office for the Western Pacific Region. [14] Covariates in the multivariate analysis included sex, age, diabetes, hypertension, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid, eGFR, current smoking status and alcohol intake. Interactions were tested using the likelihood-ratio tests (lrtest in STATA) comparing models with and without multiplicative interaction terms. For statistical calculations, we used STATA version 11 (StataCorp LP, College Station, TX). P-values of <0.05 were considered statistically significant. OR with the 95% confidence intervals in parentheses are indicated.

RESULTS

The baseline characteristics of study participants according to the BMI categories are summarized in Table 1. The percentage of men increased with an increase in BMI from 26.4% in the underweight category to 83.6% in the obese category. As expected, subjects who were in the higher categories of BMI had worse metabolic characteristics. For example, SBP (mmHg) was 106 (100–110), 110 (100–120), 110 (110–120) and 120 (110–130) (P < 0.001) for the lowest to highest BMI categories, respectively. The percentage of participants with diabetes

Table 3. Logistic regression analysis for the development of albuminuria

BMI	Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Women						
Underweight (<18.5)	1.94 (1.36–2.77)	<0.001	1.91 (1.34–2.73)	<0.001	1.93 (1.35–2.76)	<0.001
Normal weight (18.5–22.9)	Reference		Reference		Reference	
Overweight (23.0–24.9)	1.17 (0.83–1.64)	0.370	1.19 (0.84–1.68)	0.318	1.19 (0.84–1.67)	0.329
Obese (≥25)	0.69 (0.42–1.12)	0.134	0.71 (0.43–1.18)	0.187	0.71 (0.43–1.17)	0.177
Men						
Underweight (<18.5)	0.89 (0.39–2.03)	0.782	0.89 (0.39–2.03)	0.783	0.9 (0.39–2.05)	0.794
Normal weight (18.5–22.9)	Reference		Reference		Reference	
Overweight (23.0–24.9)	1.09 (0.85–1.39)	0.492	1.09 (0.85–1.39)	0.510	1.08 (0.84–1.38)	0.567
Obese (≥25)	1.43 (1.15–1.78)	<0.001	1.43 (1.13–1.81)	0.003	1.38 (1.09–1.75)	0.007
P-value for interaction by sex	<0.001		<0.001		<0.001	

Model 1: adjustment for age, diabetes and hypertension.
Model 2: adjustment for age, diabetes, hypertension, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid and eGFR.
Model 3: adjustment for age, diabetes, hypertension, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid, eGFR, current smoking status and alcohol intake.
CI, confidence interval; BMI, body mass index.

Table 4. OR of other covariates used in multivariate logistic Model 3 for the development of albuminuria

Variable	Women		Men	
	OR (95% CI)	P-value	OR (95% CI)	P-value
BMI				
Normal weight (18.5–22.9)	Reference		Reference	
Age	1.00 (0.98–1.02)	0.930	1.01 (1.00–1.03)	0.155
Diabetes	1.22 (0.38–3.90)	0.736	2.07 (1.33–3.24)	0.001
Hypertension	0.84 (0.42–1.70)	0.626	1.66 (1.34–2.06)	<0.001
Dyslipidaemia	0.72 (0.35–1.46)	0.361	1.15 (0.83–1.58)	0.406
HDL cholesterol	1.00 (0.99–1.01)	0.434	0.99 (0.98–1.00)	0.116
LDL cholesterol	1.00 (0.99–1.00)	0.719	1.00 (0.99–1.00)	0.342
Uric acid	1.06 (0.91–1.24)	0.444	0.95 (0.88–1.03)	0.219
eGFR (mL/min/1.73 m^2)	1.00 (0.99–1.02)	0.494	1.00 (0.98–1.01)	0.428
Current smoking	0.42 (0.10–1.76)	0.236	1.18 (0.98–1.42)	0.073
Alcohol intake	1.01 (0.99–1.04)	0.276	1.01 (1.00–1.01)	0.050

CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate.

Table 5. Logistic analysis for the development of albuminuria in different subgroups

BMI	Women			Men		
	N	OR (95% CI)	P-value	*N*	OR (95% CI)	P-value
Without diabetes[a]	19 702			33 368		
Underweight (<18.5)		1.95 (1.36–2.79)	<0.001		0.9 (0.39–2.05)	0.795
Normal weight (18.5–22.9)		Reference			Reference	
Overweight (23.0–24.9)		1.19 (0.84–1.68)	0.328		1.06 (0.83–1.37)	0.627
obese (≥25)		0.74 (0.45–1.23)	0.246		1.38 (1.08–1.75)	0.010
Without diabetes or hypertension[b]	18 803			28 443		
Underweight (<18.5)		1.93 (1.35–2.77)	<0.001		0.99 (0.43–2.28)	0.990
Normal weight (18.5–22.9)		Reference			Reference	
Overweight (23.0–24.9)		1.14 (0.8–1.64)	0.463		1.02 (0.78–1.35)	0.871
Obese (≥25)		0.75 (0.45–1.27)	0.288		1.26 (0.96–1.66)	0.096
With CRP reported[c]	15 345			22 119		
Underweight (<18.5)		1.95 (1.34–2.84)	0.001		0.92 (0.37–2.28)	0.857
Normal weight (18.5–22.9)		Reference			Reference	
Overweight (23.0–24.9)		1.21 (0.85–1.73)	0.296		1.15 (0.87–1.5)	0.324
Obese (≥25)		0.64 (0.37–1.1)	0.108		1.39 (1.07–1.81)	0.014
With vigorous activity[d] ≥1 week[e]	6198			163 48		
Underweight (<18.5)		2.39 (1.19–4.79)	0.014		Empty	
Normal weight (18.5–22.9)		Reference			Reference	
Overweight (23.0–24.9)		1.34 (0.79–2.29)	0.282		1.02 (0.71–1.46)	0.916
Obese (≥25)		0.6 (0.25–1.45)	0.260		1.38 (0.98–1.93)	0.065

CI, confidence interval; BMI, body mass index; CRP, C-reactive protein.
[a]Adjustment for age, hypertension, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid, eGFR, current smoking status and alcohol intake.
[b]Adjustment for age, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid, eGFR, current smoking status and alcohol intake.
[c]Adjustment for age, diabetes, hypertension, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid, eGFR, current smoking status, alcohol intake and CRP.
[d]Vigorous activity means frequency of vigorous leisure time physical activity per week.
[e]Adjustment for age, diabetes, hypertension, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid, eGFR, current smoking status and alcohol intake.

in the corresponding groups was 0.4, 0.8, 1.6 and 2.7% ($P < 0.001$), respectively.

At the second check-up 2 years later, 746 cases of incident albuminuria were recorded among the cohort of 53 876 participants. The degree of albuminuria was 1+ in 575 participants, 2+ in 166 participants, 3+ in 3 participants and 4+ in 2 participants. The numbers of patients with incident albuminuria for the lowest to highest BMI categories were 46, 287, 175 and 238, respectively. The corresponding incidence per 1000 persons for each category was 19.9, 11.9, 13.4 and 16.7, respectively (Figure 2). However, the trends were different between sexes: the incidence of albuminuria was highest in the underweight category among women but was highest in the obese category among men.

The characteristics of the participants with incident albuminuria were compared with those of patients without albuminuria as shown in Table 2. Participants with incident albuminuria had a slightly more unhealthy profile than those without albuminuria, with higher BMI (23.5 ± 3.3 versus 23.2 ± 3.0, $P = 0.020$), DBP [75 (70–80) versus 70 (70–80), $P < 0.001$], serum glucose (95 ± 18 versus 93 ± 12, $P < 0.001$), HOMA-IR (2.1 ± 1.1 versus 1.9 ± 0.8, $P < 0.001$) and daily alcohol intake [3 (0–12) versus 6 (0–15), $P = 0.007$]. Participants with incident albuminuria were also more likely to have diabetes (3.5 versus 1.5%, $P < 0.001$) or hypertension (17.7 versus 11.2%, $P < 0.001$) and to be a current smoker (32.8 versus 28.8%, $P = 0.016$).

Table 3 summarizes the results of the multivariate logistic regression analysis and shows the association between BMI categories and the development of albuminuria. All ORs were calculated compared with normal weight category. The effect of BMI on the development of albuminuria was modified by sex in all three multivariate logistic models (P-values for interaction < 0.001). For women, underweight was associated with the development of albuminuria in all three models. For example, OR for underweight was 1.93 (1.35–2.76) in Model 3 adjusted for age, diabetes, hypertension, dyslipidaemia, HDL cholesterol, LDL cholesterol, uric acid, eGFR, current smoking status and alcohol intake. However, overweight and obese categories were not associated with the development of albuminuria in the same model [OR = 1.19 (0.84–1.67) and 0.71 (0.43–1.17), respectively]. However, the data showed an opposite trend in men. Applying Model 3 for men, the obese category was associated with the development of albuminuria with an OR of 1.38 (1.09–1.75) but underweight and overweight categories were not associated with the development of albuminuria [OR = 0.9 (0.39–2.05) and 1.08 (0.84–1.38), respectively]. Table 4 shows ORs of other covariates used in Model 3. Interestingly, no other variable in women and only diabetes and hypertension in men were associated with the development of albuminuria.

Table 5 shows the association between BMI categories and the development of albuminuria in different subgroups. When we restricted participants to women without diabetes and women without both diabetes and hypertension, the association between underweight and the development of albuminuria was significant with ORs of 1.95 (1.36–2.79) and 1.93 (1.35–2.77), respectively. Some participants had data on C-reactive protein (CRP) levels and when we further adjusted for CRP in this subgroup, the association was still significant with an OR of 1.95 (1.34 ± 2.84). Finally, when we analysed female participants who took part in vigorous recreational physical activity at least once a week, the association between underweight and the development of albuminuria was also significant in this group with an OR of 2.39 (1.19–4.79). For male participants, overweight rather than underweight was associated with the development of albuminuria in subgroups without diabetes and in subgroups with reported CRP [OR = 1.38 (1.08–1.75) and 1.39 (1.07 ± 1.81), respectively]. No other association was significant.

DISCUSSION

The major finding of this study is that underweight is associated with the development of albuminuria in relatively healthy Korean women who participated in routine health check-ups. Additionally, the effect of underweight on the development of albuminuria was different between the sexes, and in men obesity rather than underweight was associated with the development of albuminuria.

Most previous studies on the development of albuminuria focused on high BMI because obesity is a major health problem that places a tremendous socioeconomic burden on society. Both high and low BMI are known to be important issues related to the outcome of patients with renal disease [8, 9], but there are few data on the association between low BMI and albuminuria. There are two published studies of Asians, both of which were a cross-sectional design and used dipstick proteinuria ≥1+ as the definition of proteinuria. The first study analysed 189 117 Asian adults who participated in a screening programme for renal disease.[10] In this study, both BMI ≤18 and BMI ≥25 were associated with the presence of proteinuria but there were no results in the difference between sexes. The second study used a nationwide health check-up database of 212 251 Japanese aged >20 years [11]. This study showed not only a U-shaped relationship between BMI and proteinuria, but also an effect modification by sex such that BMI < 18.5 and ≥22.5 were associated with proteinuria in women, but BMI < 20.5 and ≥25.5 were associated with proteinuria in men. We could find only two longitudinal studies that analysed the influence of BMI ranges on the development of proteinuria. Both of them also used dipstick proteinuria ≥1+ as the definition of proteinuria. The first study used Japanese health examination data collected in 1997 and 1999. In this study, BMI < 18.5 in women showed a trend for increased development of albuminuria visually but the data were not significant [4]. The second study also used Japanese data collected in 1999 and 2007. In this study, BMI ≤18.9 was associated with non-recurrent proteinuria. However, the interaction by sex was not analysed [12].

The mechanism underlying the association between underweight and albuminuria is not clear, but we can suggest some hypotheses. The first explanation is the presence of undetected chronic illness or renal disease at the first check-up. Comorbid conditions that can cause weight loss could act as confounding factors. Controlling for such factors is one of the major problems associated with interpreting the association between low BMI and worse health outcome such as high mortality [15]. We excluded participants with a history of CVD, cancer, liver disease and tuberculosis. We also excluded participants with potential CKD based on eGFR and albuminuria, and participants with serologic evidence of hepatitis B or C infection. Hepatitis B is not only quite prevalent in Korea [16], but also an important cause of secondary glomerulonephritis. However, despite all these efforts, we cannot be sure that we completely removed confounders.

Secondly, low muscle mass might be a mediator between underweight and albuminuria. BMI is known to correlate well with lean body mass [17], thus individuals with low BMI are likely to have low muscle mass as confirmed in a previous study with older men and women [18]. Although most results are from elderly patients, decreased muscle mass is also associated with systemic oxidative stress and inflammation [19]. These factors have been described as common components of mechanisms underlying kidney injury in different conditions [20, 21] and might be the link between underweight and a well-known marker of kidney injury and albuminuria.

Finally, previous cross-sectional studies suggested smoking, alcohol intake, chronic lung disease, malignancy and hyperfiltration by a small number of nephrons as factors associated with an increased risk of albuminuria in subjects with low BMI [11]. We also analysed the association of smoking status and alcohol intake with albuminuria. Although both the prevalence of current smokers and the daily alcohol intake

were higher in participants who developed albuminuria, (Table 2) smoking status and alcohol intake were not significant predictors of albuminuria in multivariate logistic model of both women and men (Table 4). To account for malignancy, we excluded all participants with a history of cancer. It is likely that many of the women with lower BMI had lower birthweight because birthweight is a predictor of adult BMI [22]. They are more likely to have lower nephron numbers and to be at higher risk of hyperfiltration, resulting in albuminuria. In this manner, our finding is compatible to the studies from Australian aborigines where the effect of lower birthweight on the development of albuminuria was prominent in women [23]. Therefore, lower birthweight could be a possible explanation for the association between low BMI and albuminuria although the data are not available in our study.

One other important question raised by this study is why the influence of BMI on the development of albuminuria is so different between sexes. In women, the underweight category was significantly associated with the development of albuminuria in a final logistic model. However, it is not clear why underweight increases albuminuria only in women. If we accept the hypothesis that decreased muscle mass in underweight is important in the development of albuminuria, the fact that women have a smaller muscle mass than men with the same BMI [17] could be one explanation.

A different effect on the development of albuminuria between sexes was also observed in the obesity category. Neither obesity nor well-known risk factors for albuminuria such as diabetes or hypertension showed significant association in women. On the contrary, obesity, diabetes and hypertension were associated with the development of albuminuria in men (Table 4). Current smoking and higher daily alcohol intake showed a trend towards an association in men although neither was statistically significant.

Although the fact that obese women are not at risk of albuminuria seems to contradict current knowledge, previous studies have shown that metabolically unhealthy risk factors are more important in men than in women. One study showed that urine albumin excretion increases more steeply in men than in women as BMI increases, and that the association between cardiovascular risk factors and urine albumin excretion was more prominent in men [24]. In a Swedish analysis of 926 patients with moderate-to-severe CKD and 998 control subjects, the high BMI associated with CKD was >30 in men but >35 in women [25]. Another recent study in which 241 high-risk patients were followed up over 20 years showed that BMI was associated with eGFR decline and albuminuria development only in men [26]. In general, male gender is a risk factor for renal disease progression and one proposed cause of this relationship is the action of sex hormones [27]. The effect of obesity on renal injury might similarly be under the influence of sex hormones.

This study has several limitations. First, urinalysis was performed only once at each check-up. Transient albuminuria can be observed in conditions such as febrile illness, strenuous exercise or emotional stress [28], and the result of albuminuria on the second check-up might not be persistent or related to renal diseases. Second, we did not measure urine protein-to-creatinine ratio or albumin-to-creatinine ratio. For better quantitation of albuminuria, adjustment by urine creatinine concentration is needed because albuminuria in dipstick urinalysis is influenced by urine concentration. Third, we do not have information on medications that might influence the level of albuminuria such as angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers, although the result was the same when we excluded participants with hypertension. Finally, follow-up time in this study (2 years) is probably short for detecting the incidence of albuminuria among healthy subjects, although we believe that the large size of the study population may have compensated for this. Despite these limitations, this study has some strengths that differentiate it from previous studies, including the relatively large sample size, adjustment for various data associated with albuminuria and its longitudinal design. As far as we know, this is the first study that has shown the association between underweight and the development of albuminuria which is different between sexes. This study suggests that we should pay more attention to individuals with low BMI to prevent CKD as well as obese patients. Especially, we should be careful not to overlook their co-morbid conditions such as malnutrition, chronic inflammatory diseases and sarcopenia. However, we need more studies before we can be more conclusive on this suggestion and longer studies with different cut-offs of BMI would be helpful.

In conclusion, underweight rather than obesity was associated with the development of albuminuria over 2 years in relatively healthy Korean females who participated in health check-up programmes. This relationship was modified by sex, such that obesity rather than underweight was associated with the development of albuminuria in male participants. Further studies are warranted to elucidate the exact mechanism underlying renal injury caused by underweight and the clinical implications of underweight for renal diseases.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Levey AS, de Jong PE, Coresh J *et al.* The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011; 80: 17–28
2. Levey AS, Atkins R, Coresh J *et al.* Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. Kidney Int 2007; 72: 247–259
3. Li PK, Chow KM, Matsuo S *et al.* Asian chronic kidney disease best practice recommendations: positional statements for early detection of chronic kidney disease from Asian Forum for Chronic Kidney Disease Initiatives (AFCKDI). Nephrology (Carlton) 2011; 16: 633–641
4. Tozawa M, Iseki K, Iseki C *et al.* Influence of smoking and obesity on the development of proteinuria. Kidney Int 2002; 62: 956–962
5. Afghahi H, Cederholm J, Eliasson B *et al.* Risk factors for the development of albuminuria and renal impairment in type 2 diabetes—the Swedish National Diabetes Register (NDR). Nephrol Dial Transplant 2011; 26: 1236–1243
6. Calle EE, Thun MJ, Petrelli JM *et al.* Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999; 341: 1097–1105
7. Zheng W, McLerran DF, Rolland B *et al.* Association between body-mass index and risk of death in more than 1 million Asians. N Engl J Med 2011; 364: 719–729

8. Jialin W, Yi Z, Weijie Y. Relationship between body mass index and mortality in hemodialysis patients: a meta-analysis. Nephron Clin Pract 2012; 121: c102–c111
9. Rettkowski O, Wienke A, Hamza A *et al.* Low body mass index in kidney transplant recipients: risk or advantage for long-term graft function? Transplant Proc 2007; 39: 1416–1420
10. Ramirez SP, McClellan W, Port FK *et al.* Risk factors for proteinuria in a large, multiracial, southeast Asian population. J Am Soc Nephrol 2002; 13: 1907–1917
11. Sato Y, Fujimoto S, Konta T *et al.* U-shaped association between body mass index and proteinuria in a large Japanese general population sample. Clin Exp Nephrol 2014; 18: 75–86
12. Muneyuki T, Sugawara H, Suwa K *et al.* A community-based cross-sectional and longitudinal study uncovered asymptomatic proteinuria in Japanese adults with low body weight. Kidney Int 2013; 84: 1254–1261
13. Levey AS, Bosch JP, Lewis JB *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130: 461–470
14. World Health Organization Regional Office for the Western Pacific Region IAftSoO, International Obesity Task Force. The Asian-Pacific Perspective: Redefining Obesity and Its Treatment. Sydney: Health Communications Australia, 2000.
15. Allison DB, Faith MS, Heo M *et al.* Hypothesis concerning the U-shaped relation between body mass index and mortality. Am J Epidemiol 1997; 146: 339–349
16. Chae HB, Kim JH, Kim JK *et al.* Current status of liver diseases in Korea: hepatitis B. Korean J Hepatol 2009; 15(Suppl 6): S13–S24
17. Romero-Corral A, Somers VK, Sierra-Johnson J *et al.* Accuracy of body mass index in diagnosing obesity in the adult general population. Int J Obes (Lond) 2008; 32: 959–966
18. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci 2002; 57: M772–M777
19. Meng SJ, Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. Int J Mol Sci 2010; 11: 1509–1526
20. Navarro-Gonzalez JF, Mora-Fernandez C, Muros de Fuentes M *et al.* Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nat Rev Nephrol 2011; 7: 327–340
21. Mennuni S, Rubattu S, Pierelli G *et al.* Hypertension and kidneys: unraveling complex molecular mechanisms underlying hypertensive renal damage. J Hum Hypertens 2014; 28: 74–79
22. Rogers I. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. Int J Obes Relat Metab Disord 2003; 27: 755–777
23. Hoy W, McDonald SP. Albuminuria: marker or target in indigenous populations. Kidney Int Suppl 2004; 66: S25–S31
24. Verhave JC, Hillege HL, Burgerhof JG *et al.* Cardiovascular risk factors are differently associated with urinary albumin excretion in men and women. J Am Soc Nephrol 2003; 14: 1330–1335
25. Ejerblad E, Fored CM, Lindblad P *et al.* Obesity and risk for chronic renal failure. J Am Soc Nephrol 2006; 17: 1695–1702
26. Nagel G, Zitt E, Peter R *et al.* Body mass index and metabolic factors predict glomerular filtration rate and albuminuria over 20 years in a high-risk population. BMC Nephrol 2013; 14: 177
27. Neugarten J, Golestaneh L. Gender and the prevalence and progression of renal disease. Adv Chronic Kidney Dis 2013; 20: 390–395
28. Waller KV, Ward KM, Mahan JD *et al.* Current concepts in proteinuria. Clin Chem 1989; 35: 755–765

Received for publication: 12.2.2014; Accepted in revised form: 21.5.2014

Nephrol Dial Transplant (2014) 29: 2113–2120
doi: 10.1093/ndt/gfu224
Advance Access publication 18 June 2014

ORIGINAL ARTICLE

The impact of warfarin on the rate of progression of aortic stiffness in hemodialysis patients: a longitudinal study

Fabrice Mac-Way[1,2], Aurélie Poulin[1,2], Mihai Silviu Utescu[1,2], Sacha A. De Serres[1,2], Karine Marquis[1], Pierre Douville[3,4], Simon Desmeules[1,2], Richard Larivière[1,2], Marcel Lebel[2] and Mohsen Agharazii[1,2]

[1]CHU de Québec Research Center, L'Hôtel-Dieu de Québec Hospital, Québec, QC, Canada, [2]Division of Nephrology, Faculty of Medicine, Université Laval, Québec, QC, Canada, [3]Département de biologie moléculaire, de biochimie médicale et de pathologie, Faculty of Medicine, Université Laval, Québec, QC, Canada and [4]Département de biologie médicale, L'Hôtel-Dieu de Québec Hospital, CHU de Québec, Québec, QC, Canada

Correspondence and offprint requests to: Mohsen Agharazii; E-mail: mohsen.agharazii@crhdq.ulaval.ca

ABSTRACT

Background. Accelerated progression of aortic stiffness in patients with advanced chronic kidney disease is not well explained by the traditional cardiovascular risk factors. We hypothesized that vitamin K deficiency may result in an accelerated progression of aortic stiffness in the pro-calcifying uremic milieu.