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A community-based cross-sectional and longitudinal study uncovered asymptomatic proteinuria in Japanese adults with low body weight

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Although proteinuria is highly prevalent in obese individuals, the association between proteinuria and low body weight is equivocal. In this study we determine whether low body weight is more strongly associated with proteinuria compared with normal weight. The association between body mass index (BMI) and proteinuria was examined in a cross-sectional study of 62,582 asymptomatic individuals aged 20–70 years without known kidney diseases recruited, based on the results of medical checkups in 1999. We also examined the incidence of recurrent or nonrecurrent proteinuria in an 8-year longitudinal analysis of 12,493 individuals without proteinuria at baseline. The prevalence of proteinuria showed a J-shaped relationship with BMI. Multivariate regression analysis showed that BMI of 27.0 kg/m^2 and above or 18.9 kg/m^2 and less was significantly associated with proteinuria relative to BMI 21.0–22.9 kg/m^2, even after adjusting for relevant cardiometabolic risk factors. In the longitudinal study, similar J-shaped relationships between the incident rates of proteinuria and baseline BMI groups were observed at post-baseline checkups. Baseline BMI 27.0 kg/m^2 and above was associated with significantly greater risk for recurrent and nonrecurrent proteinuria, whereas BMI 18.9 kg/m^2 and less was only associated with nonrecurrent proteinuria. Thus, obesity and low body weight may be associated with different types of proteinuria independent of cardiometabolic risk factors.

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Over the last few decades, proteinuria, a major feature of chronic kidney disease, has become increasingly prevalent worldwide, and is associated with the progression of kidney disease and increased mortality.[1–5] A growing body of clinical evidence has revealed that proteinuria, including albuminuria, is much more common in obese individuals than in normal-weight individuals,[6–9] partly because obese individuals are more likely to develop type 2 diabetes and metabolic syndrome,[10,11] which often accompany diabetic nephropathy and chronic kidney disease.[12,13] Direct effects of obesity on proteinuria have been proposed in addition to the traditional mechanisms mediated by obesity-related complications. The putative effects of obesity on the development of proteinuria include obesity-induced renal hemodynamic changes, glomerular deposition of lipids, insulin resistance, and activation of the renin–angiotensin–aldosterone system.[14–16]

Obesity is less prevalent and low body weight is more prevalent in Asian populations than in Western populations.[17–19] However, it is still equivocal whether proteinuria is also associated with low body weight. About 10 years ago, Ramirez *et al.*[8,20] reported a significant independent association between proteinuria and low body weight in Asian adults and children. However, because of the nature of their cross-sectional study,[8] the causality for proteinuria in adulthood remained unclear. Since then, no other study has addressed the issue of proteinuria in individuals with low body weight. In addition, numerous clinical studies have shown that low body weight is associated with increased mortality, similar to obesity, based on a U- or J-shaped relationship between body mass index (BMI) and mortality.[21–23]

Considering these findings, it seems possible that low body weight is more strongly associated with proteinuria compared with normal weight. To examine this possibility, we investigated the association between low body weight and proteinuria, which was assessed by dipstick urinalysis, in a large cross-sectional study of apparently healthy individuals without known kidney disease. To determine the incidence of proteinuria over time, which was eventually classified as

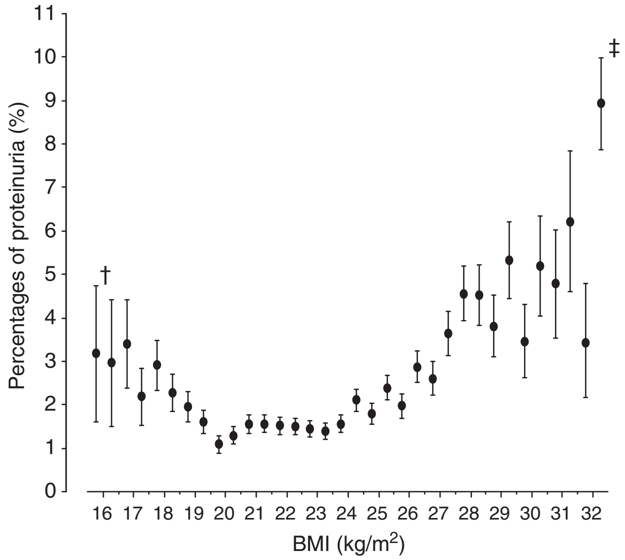

Figure 1 | Proportion of subjects with proteinuria according to body mass index (BMI) categories. The circle in the middle of each bar is the mean percentage of subjects with proteinuria (+1 or greater on dipstick urinalysis) according to BMI intervals (0.5 kg/m^2), and was calculated as the number of subjects with proteinuria/number of subjects in each BMI group×100 for each BMI interval (0.5 kg/m^2 intervals). The vertical bar represents the s.e. when proteinuria is numbered as 1 and nonproteinuria as 0. †BMI from 14.0 to 16.0 kg/m^2; ‡BMI from 32.0 to 55.0 kg/m^2. The number of subjects was 126, 135, 323, 503, 858, 1227, 1687, 2248, 2697, 3082, 3528, 3915, 3958, 4141, 4085, 3926, 3777, 3370, 3126, 2759, 2386, 2090, 1650, 1376, 1118, 886, 708, 639, 462, 366, 293, 225, 184, and 728 for the BMI categories from ⩽16.0 to ⩾32.0 kg/m^2.

recurrent or nonrecurrent proteinuria, we also conducted a longitudinal study on a subgroup of subjects who underwent the same medical checkups four times between 1999 and 2007.

RESULTS

Results of the cross-sectional study in 1999

Overall, the prevalence of proteinuria showed a J-shaped curve with BMI at intervals of 0.5 kg/m^2 (Figure 1). The clinical characteristics of subjects stratified into the six BMI categories are shown in Table 1. All of the parameters and categorical variables increased with increasing BMI category, except for high-density lipoprotein–cholesterol and eGFR, which decreased (all, $P<0.0001$). The proportion of subjects who regularly exercised (⩾30 min exercise per session, ⩾2 times per week) was lower in the high (17.6%) and low (11.3%) BMI categories compared with the other categories.

Multivariate regression analysis showed that compared with the provisional reference category (BMI, 21.0–22.9 kg/m^2), the high BMI and low BMI categories were significantly associated with proteinuria, even after controlling for relevant confounders (Table 2). Positive associations were also observed between proteinuria and BMI as a continuous variable. Further adjustment for eGFR did not alter the overall associations, although the nadir shifted to the next BMI category of 23.0–24.9 kg/m^2 (Model 5).

Figure 2 shows the adjusted odds ratios (ORs) of age and dichotomized cardiometabolic risk factors for proteinuria in

Table 1 | Clinical characteristics of subjects according to BMI category

BMI category (kg/m^2)	Total	⩽18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	⩾27.0
N, (% of total)	62,582	4859 (7.8)	11,555 (18.5)	16,099 (25.7)	14,199 (22.7)	8885 (14.2)	6985 (11.2)
Age (years)	43.2 ± 11.2	38.5 ± 11.9	40.8 ± 11.5	43.1 ± 11.1	44.9 ± 10.7	45.4 ± 10.2	43.9 ± 10.6
Men, *n* (%)	41,456 (66.2)	2114 (43.5)	5981 (51.8)	10,509 (65.3)	10,591 (74.6)	6973 (78.5)	5288 (75.7)
BMI (kg/m^2)	23.1 ± 3.2	18.0 ± 0.8	20.0 ± 0.6	22.0 ± 0.6	23.9 ± 0.6	25.8 ± 0.6	29.2 ± 2.3
Systolic blood pressure (mm Hg)	124 ± 15.9	114 ± 14.5	118 ± 14.6	122 ± 14.8	126 ± 14.9	130 ± 15.0	134 ± 15.5
Diastolic blood pressure (mm Hg)	75 ± 12.1	68 ± 10.2	70 ± 10.5	73 ± 11.1	76 ± 11.6	79 ± 11.8	83 ± 12.3
Total cholesterol (mg/dl)	194 ± 34.6	177 ± 30.5	184 ± 32.3	191 ± 33.1	198 ± 33.8	203 ± 34.9	208 ± 35.4
Triglyceride (mg/dl)	109 (71–170)	69 (51–97)	79 (57–114)	99 (68–148)	126 (85–189)	147 (100–221)	166 (113–249)
HDL-cholesterol (mg/dl)	58.4 ± 14.4	66.9 ± 14.7	64.4 ± 14.6	59.9 ± 13.9	55.9 ± 13.0	52.9 ± 12.4	50.8 ± 11.7
HbA1c (%, NGSP)	5.4 ± 0.7	5.3 ± 0.6	5.3 ± 0.6	5.4 ± 0.6	5.5 ± 0.7	5.5 ± 0.7	5.7 ± 0.9
Proteinuria, *n* (%)	1310 (2.1)	116 (2.4)	159 (1.4)	242 (1.5)	241 (1.7)	216 (2.4)	336 (4.8)
eGFR (available *n*)	6236	468	1104	1561	1434	876	793
(ml/min/1.73 m^2)	(87.9 ± 19.5)	(97.1 ± 24.4)	(91.5 ± 19.8)	(88.6 ± 18.6)	(85.8 ± 18.0)	(84.4 ± 18.0)	(83.3 ± 18.5)
Medication for							
Hypertension, *n* (%)	3439 (5.5)	68 (1.4)	232 (2.0)	634 (3.9)	886 (6.2)	748 (8.4)	871 (12.5)
Dyslipidemia, *n* (%)	1020 (1.6)	14 (0.3)	87 (0.8)	184 (1.1)	294 (2.1)	207 (2.3)	234 (3.4)
Diabetes, *n* (%)	902 (1.4)	41 (0.8)	117 (1.0)	211 (1.3)	217 (1.5)	143 (1.6)	173 (2.5)
Past history of CVD, *n* (%)	685 (1.1)	17 (0.4)	69 (0.6)	153 (1.0)	189 (1.3)	142 (1.6)	115 (1.6)
Daily alcohol consumption, *n* (%)	15,016 (24.0)	823 (16.9)	2402 (20.8)	3962 (24.6)	3890 (27.4)	2455 (27.6)	1484 (21.2)
Current smoker, *n* (%)	23, 562 (37.7)	1540 (31.7)	4075 (35.3)	5994 (37.2)	5531 (39.0)	3651 (41.1)	2771 (39.7)
Having regular exercise, *n* (%)	11,193 (17.9)	551 (11.3)	1813 (15.7)	3014 (18.7)	2853 (20.1)	1733 (19.5)	1229 (17.6)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease (including stroke); eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.

Triglyceride concentrations are expressed as the median (interquartile range). All parameters and categorical values increased significantly with increasing BMI category (analysis of variance/χ^2-test; all $P<0.0001$). Proteinuria was defined as +1 or greater on dipstick urinalysis.

HbA1c was converted to NGSP levels using the following formula: HbA1c (%) (NGSP) = 1.02×HbA1c (Japan Diabetes Society) (%) + 0.25%.[50]

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