子である．糖尿病性腎症の血糖管理目標はHbA1c(JDS値)<6.1％［HbA1c(国際標準値)<6.5％］未満である．重篤な腎障害では経口糖尿病薬の使用は避け，インスリン治療を原則とする．

### 腎性貧血の治療(「造血薬」505頁参照)

CKDに伴う腎性貧血は腎障害の進展を促進し，CVDの危険因子にもなる．腎性貧血はESA(erythropoiesis stimulating agent：赤血球造血刺激因子製剤)で治療する．Hbの目標値は11～12 g/dLである．保存期ではエポエチンアルファ(エスポー)またはエポエチンベータ(エポジン)を2週に1回6000～12000 IU皮下注，維持血液透析患者では週2～3回500～3000 IU静注する．保存期の腎不全患者には，ダルベポエチン(ネスプ)を月1～2回，40～120 μgを皮下注，維持透析患者には週1回15～60 μg静注，貧血改善が維持されれば2週に1回30～120 μg静注する．腹膜透析患者では4週に1回60～180 μg皮下注または静注する．

### CKD-MBD

CKDにおける骨・ミネラル代謝異常は，骨病変だけでなく血管の石灰化なども促進し生命予後を悪化させる全身疾患として捉えられる．これをCKD-MBD(骨・ミネラル代謝異常)と総称する．食事療法や高リン血症治療薬で血清リンをコントロールしてから活性型ビタミンDを用いる．血清Pを低下させるためには，沈降炭酸カルシウム(カルタン)，セベラマー(レナジェル，フォスブロック)，炭酸ランタン(ホスレノール)のようなP吸着薬を用いるとともに，食事療法も重要となる．血清Ca，リンおよびPTHの管理目標値は日本透析医学会の「慢性腎臓病におけるCKD-MBD診療ガイドライン」参照．

維持透析患者の二次性副甲状腺機能亢進症に対してCa受容体作動薬であるシナカルセト(レグパラ)が使用できる．本剤は，PTHの分泌を持続的に抑制し，さらに細胞増殖も抑制する．

### 高K血症，代謝性アシドーシスの治療

腎機能が低下するとアシドーシスとなり血清Kは上昇する．ACE阻害薬，ARB，K保持性利尿薬は高K血症の原因や悪化因子となる．β遮断薬やNSAIDsも高K血症の原因となりうる．高K血症の治療には重曹によるアシドーシスの是正と共に，ポリスチレンスルホン酸カルシウム(カリメート)のような陽イオン交換樹脂を使う．緊急を要する場合は，グルコン酸カルシウム水和物(カルチコール)の静注(適応外)による致死的不整脈の抑制とインスリン-グルコースの静注により速やかな血清Kの低下を図る．

### その他

個別の腎疾患に対する治療に関しては診療指針参照．図1に微小変化型ネフローゼ症候群の治療アルゴリズムを示す．

血液透析患者の瘙痒症に対して選択的オピオイドκ受容体作動薬であるナルフラフィン(レミッチ)を使用する．クレメジン，キューカルは球形吸着炭で，尿毒症物質を吸着するため，尿毒症症状を軽減する．またCKDの進行速度を遅くすることも示されている．透析液の一覧を表4に示す．

## 2 腎疾患に注意しなければならない薬剤

腎排泄型の薬剤はすべて減量投与または中止が必要になる．β遮断薬，ACE阻害薬，抗菌薬，$H_2$ブロッカーなどである．

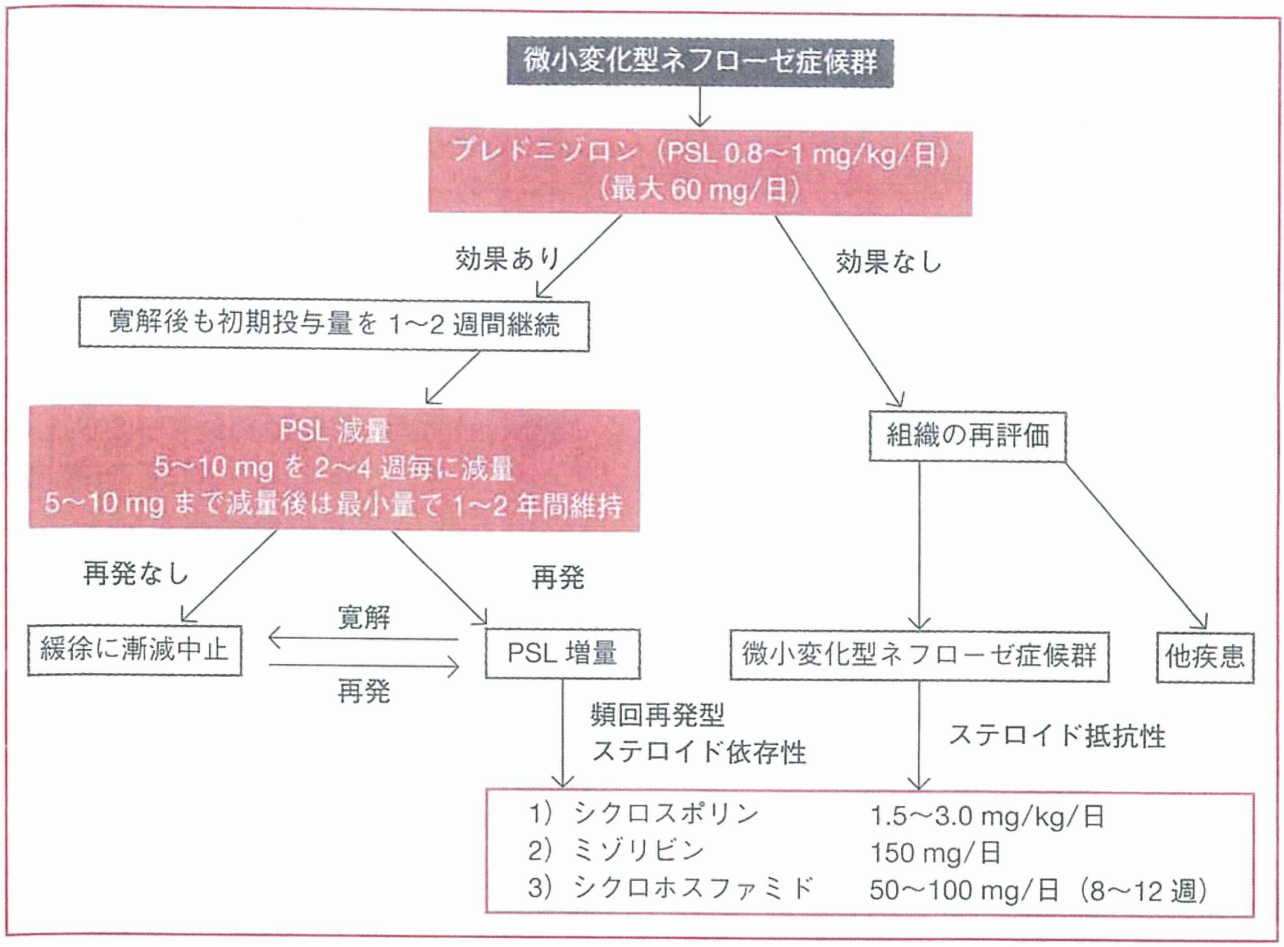


図 1　微小変化型ネフローゼ症候群の治療アルゴリズム
（厚生労働省研究班：ネフローゼ症候群診療指針．日腎会誌 53：78-122，2011）

また，腎障害性の薬剤はその副作用が腎機能が低下するほど発現しやすい．抗菌薬，NSAIDs，造影剤などである．また，腎障害ではマグネシウムが体内に蓄積しやすいため酸化マグネシウムなどのマグネシウム製剤は投与を控える．

## 服薬指導のポイント

- ACE 阻害薬，ARB は脱水（夏期の発汗，下痢，嘔吐など）や過度の食塩制限で極端に血圧が下がることがある．
- 血圧の過度な低下から腎機能が急激に低下し AKI を引き起こすことがある．特に，高齢者で頻度が高い．下痢や嘔吐，食欲不振時は服用を中止するように患者，家族に指導する．

## ケア・看護のポイント

［在宅での薬物療法〜家庭血圧測定の重要性］

- 臓器障害の発症進展は外来血圧よりも家庭血圧に相関する．家庭血圧を朝食前と就寝前に測定して記録を主治医に見せる．
- CKD では血圧の急激な低下により腎機能が低下することがある．普段からどの程度，血圧が低下したらどの薬物を中止するかなどきめ細かい治療計画を立てる．
- sick day（下痢，嘔吐，食欲不振など）には利尿薬やレニン-アンジオテンシン系阻害薬は患者自ら中止するように指導する．

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ORIGINAL ARTICLE

# Weight gain after 20 years of age is associated with prevalence of chronic kidney disease

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**Abstract**
*Background* Weight gain after maturity is a risk factor for diabetes, coronary heart disease, and stroke, even in individuals with a normal body mass index; however, there is little information about the influence of weight gain after maturity on chronic kidney disease (CKD). Therefore, we examined the association between weight gain after 20 years of age and the prevalence of CKD.
*Methods* A cross-sectional study was performed on 28,151 women and 21,110 men aged between 40 and 59 years who participated in the specific health check and guidance system of Japan in 2008. We compared prevalence of CKD between participants with and without weight gain of at least 10 kg after 20 years of age. Multivariate logistic regression models and stratified analyses were used to adjust for possible confounding factors.
*Results* The prevalence of CKD among participants with weight gain was significantly higher than among those without weight gain both in women (11.8 vs 8.3%, $p < 0.0001$) and in men (12.2 vs 9.2%, $p < 0.0001$). After adjustment for age, smoking, regular exercise, alcohol intake, history of kidney disease, hypertension, diabetes, and hypercholesterolemia, the odds ratio (95% confidence interval) for CKD was 1.24 (1.14–1.36) in women and 1.15 (1.05–1.26) in men with weight gain of at least 10 kg after the age of 20 years. Even in participants without metabolic syndrome, weight gain was independently associated with CKD in both genders.
*Conclusions* Weight gain after 20 years of age is associated with CKD among Japanese, even those without metabolic syndrome.

**Keywords** Weight gain · Chronic kidney disease · Obesity · General population · Cross-sectional study

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## Introduction

The prevalence of obesity in Japan has increased over the past several decades [1], and is a worldwide public health problem of growing importance. Obesity is an established risk factor for several chronic diseases, including hypertension and diabetes mellitus. Even in individuals with a normal body mass index (BMI), weight gain after maturity is an important risk factor for diabetes [2, 3], coronary heart disease [4, 5], and stroke [6].

Obesity has also been recognized as a risk factor for chronic kidney disease (CKD). Weight gain has been reported to be associated with the incidence of CKD among Korean men, even when BMI remained within the normal range [7]. However, information is lacking about the influence of weight gain after maturity on CKD among

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women, because previous studies of the association between obesity and CKD defined obesity by the BMI or waist circumference [8, 9]. An increase of weight after maturity largely reflects increased fat mass, so such an increase may be more closely associated with the risk of CKD, especially among participants with a normal BMI or waist circumference. The average BMI of Asian populations is lower than that of non-Asian populations, although the tendency for abdominal obesity might be greater than in non-Asian populations [10]. Weight gain after maturity might be a basis for recommendations on lifestyle modification, and it may be especially attractive to use this measure for Asian populations. Measures such as weight and weight gain are also attractive from a public education perspective, because they are much easier for the general population to understand than BMI and can be measured more accurately than waist circumference.

In this study, we examined the effect of weight gain after maturity on the prevalence of CKD among Japanese. We hypothesized that the prevalence of CKD might be associated with weight gain after maturity, even for individuals within the normal range of BMI or waist circumference.

## Methods

### Study population

We used data from 68 areas of 7 prefectures obtained by the Japanese specific health check and guidance system (SHC) in 2008; the SHC has been described elsewhere [11]. In brief, participants answered a self-administered questionnaire that covered their medical history, smoking habits, alcohol intake, and exercise pattern. Trained staff then measured the height, weight, blood pressure, and waist circumference of each participant, after which serum and spot urine samples were collected. We only included participants aged between 40 and 59 years in this study, because previous reports have indicated that metabolic syndrome was a risk factor for CKD only for younger participants ($\leq$60 years) among men [12, 13] and because body weight might decrease due to comorbidities >60 years. Participants with missing information were also excluded. All of the participants remained anonymous and the study was conducted according to Japanese privacy protection laws and the ethical guidelines for epidemiological studies published by the Ministry of Education, Science and Culture and the Ministry of Health, Labor and Welfare in 2005.

### Proteinuria and CKD

Proteinuria was defined by a dipstick urinalysis score of $\geq$1+ proteinuria (equivalent to $\geq$30 mg/dl) because of poor discrimination between negative and trace positive dipstick readings [14]. The primary endpoint was the prevalence of CKD, which was defined as $\geq$1+ proteinuria on urinalysis, a glomerular filtration rate (GFR) <60 ml/min/1.73 $m^2$ as calculated by using the estimated GFR (eGFR) formula shown below for Japanese [15], or both [16].

$$\text{eGFR} = 194 \times (\text{serum creatinine}^{-1.094}) \times (\text{age}^{-0.287}) \times (0.739 \text{ for females}).$$

### Weight gain, obesity, and metabolic syndrome

Information about weight gain was collected from the self-administered questionnaire, which included the following item: "Have you gained more than 10 kg since 20 years of age?" Participants answered yes or no. Using BMI values (calculated as weight in kilograms/(height in meters)$^2$), the subjects were categorized as non-obese (<25 kg/$m^2$) or obese ($\geq$25 kg/$m^2$). Using waist circumference measured at the umbilicus, they were categorized as having abdominal obesity ($\geq$90 cm for women and $\geq$85 cm for men) or not (<90 cm for women and $\leq$85 cm for men) according to the definition of the metabolic syndrome in the SHC [11]. The SHC definition of the metabolic syndrome is not the same as that used by the World Health Organization or the Japanese Society of Internal Medicine [17, 18]. Instead, metabolic syndrome is defined as abdominal obesity (waist circumference $\geq$90 cm in women and $\geq$85 cm in men) and/or obese (BMI $\geq$25 kg/$m^2$) plus any two of the following three categories: (1) fasting blood glucose $\geq$100 mg/dl, hemoglobin $A_{1c}$ $\geq$5.2%, use of insulin, and/or oral antidiabetic medication; (2) triglycerides $\geq$150 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, and/or the use of cholesterol-lowering medication; or (3) blood pressure $\geq$130/85 mmHg and/or use of antihypertensive medication.

### Covariates

Information about current smoking, alcohol, and exercise habits, a history of stroke, heart disease, CKD, or dialysis, and use of medication for diabetes mellitus, hypertension, or hypercholesterolemia was collected from the questionnaire. Diabetes mellitus was defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose $\geq$126 mg/dl, or both. Hypertension was defined as the use of antihypertensive medication, a systolic blood pressure $\geq$140 mmHg and/or a diastolic blood pressure $\geq$90 mmHg, or both. Hypercholesterolemia was defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level $\geq$140 mg/dl, or both.

### Statistical analysis

We analyzed the data separately by gender, because previous reports have indicated that the influence of BMI or

metabolic syndrome on CKD differs between men and women [12, 13, 19]. We used the Chi-squared test, Student's *t* test, and the Mann–Whitney *U* test to assess differences among the characteristics of the study participants in relation to weight gain. We conducted multivariate analyses using logistic regression models. The data were initially adjusted for age alone, and then for multiple covariates. In the multivariate models, we included the following covariates that might confound the relationship between weight and CKD: age, current smoking, regular exercise, alcohol intake, a history of kidney disease, and current hypertension, diabetes, and hypercholesterolemia. Because hypertension, diabetes, and hypercholesterolemia are likely to be intermediate factors on the pathway between weight gain and CKD, we did not adjust for these variables in the primary analyses, but we added them sequentially to multivariate models in the secondary analyses. We also performed analyses stratified by presence or absence of metabolic syndrome, abdominal obesity, and obesity or non-obesity. We compared the sensitivity and specificity of weight gain, BMI, and waist circumference for identifying CKD. We calculated 95% confidence intervals (CI) using Wilson's method [20]. A $p$ value of $<0.05$ was considered to indicate statistical significance and all tests were two-tailed. All statistical analyses were performed with the SPSS for Windows statistical package (Version 18.0; SPSS, Chicago, IL, USA).

## Results

A total of 189,709 residents and workers of the target districts aged between 40 and 59 years participated in the SHC. Among them, complete data were available for 28,151 women (27.1%) and 21,111 men (24.6% of participants in this age range). There were no differences between the included and excluded subjects with regard to characteristics such as age, BMI, and waist circumference. Among the 28,151 women and 21,111 men, 8,494 women (30.2%) and 10,485 men (49.7%) answered that their weight had increased by at least 10 kg since 20 years of age.

**Table 1** Clinical characteristics of 28,151 women stratified by weight gain after 20 years of age

| Variable | Weight gain | | *p* value |
|---|---|---|---|
| | <10 kg ($n$ = 19,657) | ≥10 kg ($n$ = 8,494) | |
| Age [years; mean (SD)] | 51.9 (5.9) | 52.4 (5.7) | <0.0001 |
| BMI [kg/m$^2$; mean (SD)] | 20.9 (2.5) | 25.9 (3.6) | <0.0001 |
| Waist circumference [cm; mean (SD)] | 76.5 (7.8) | 88.7 (9.1) | <0.0001 |
| Current smoker (%) | 13.2 | 13.3 | 0.73 |
| Regular exercise, yes (%) | 26.8 | 25.0 | 0.002 |
| Alcohol intake (%) | | | |
| Every day | 14.1 | 10.8 | <0.0001 |
| Sometimes | 26.7 | 24.2 | |
| Never | 59.3 | 65.0 | |
| History of stroke (%) | 1.0 | 1.6 | <0.0001 |
| History of cardiac disease (%) | 1.8 | 2.9 | <0.0001 |
| History of kidney disease (%) | 0.4 | 0.5 | 0.24 |
| Systolic blood pressure [mmHg; mean (SD)] | 118.1 (16.8) | 125.7 (17.5) | <0.0001 |
| Diastolic blood pressure [mmHg; mean (SD)] | 71.9 (11.0) | 76.6 (11.2) | <0.0001 |
| Antihypertensive medication, yes (%) | 9.2 | 20.9 | <0.0001 |
| Fasting blood glucose [mg/dl; mean (SD)] | 90.3 (15.3) | 97.2 (21.3) | <0.0001 |
| Hemoglobin $A_{1c}$ [%; mean (SD)] | 5.1 (0.5) | 5.3 (0.7) | <0.0001 |
| Antidiabetic medication, yes (%) | 1.3 | 3.5 | <0.0001 |
| Low-density lipoprotein cholesterol [mg/dl; mean (SD)] | 122.8 (31.7) | 134.5 (32.4) | <0.0001 |
| Medication for hypercholesterolemia, yes (%) | 6.8 | 12.3 | <0.0001 |
| Triglycerides [mg/dl; median (IQR)] | 77 (57, 107) | 108 (77, 155) | <0.0001 |
| High-density lipoprotein cholesterol [mg/dl; mean (SD)] | 71.4 (16.5) | 61.5 (14.4) | <0.0001 |
| Creatinine [mg/dl; mean (SD)] | 0.61 (0.15) | 0.61 (0.13) | 0.66 |
| eGFR [ml/min/1.73 m$^2$; mean (SD)] | 82.4 (16.2) | 82.5 (16.8) | 0.71 |
| Proteinuria[a] (%) | 2.9 | 5.6 | <0.0001 |
| Chronic kidney disease[b] (%) | 8.3 | 11.8 | <0.0001 |

*SD* standard deviation, *IQR* interquartile range

[a] Defined as the presence of ≥1+ proteinuria on urinalysis

[b] Defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m$^2$ or as proteinuria on urinalysis

**Table 2** Clinical characteristics of 21,110 men stratified by weight gain after 20 years of age

| Variable | Weight gain | | *p* value |
|---|---|---|---|
| | <10 kg ($n$ = 10,625) | ≥10 kg ($n$ = 10,485) | |
| Age [years; mean (SD)] | 50.9 (6.0) | 51.3 (5.8) | 0.31 |
| BMI [kg/m$^2$; mean (SD)] | 22.3 (2.6) | 26.0 (3.1) | <0.0001 |
| Waist circumference [cm; mean (SD)] | 80.7 (7.1) | 90.5 (7.9) | <0.0001 |
| Current smoker (%) | 40.1 | 37.5 | <0.0001 |
| Regular exercise, yes (%) | 31.6 | 27.6 | <0.0001 |
| Alcohol intake (%) | | | |
| Every day | 44.2 | 39.9 | <0.0001 |
| Sometimes | 27.6 | 30.7 | |
| Never | 28.2 | 29.4 | |
| History of stroke (%) | 1.9 | 2.1 | 0.24 |
| History of cardiac disease (%) | 2.7 | 3.5 | <0.0001 |
| History of kidney disease (%) | 0.3 | 0.5 | 0.06 |
| Systolic blood pressure [mmHg; mean (SD)] | 123.1 (16.6) | 127.9 (16.1) | <0.0001 |
| Diastolic blood pressure [mmHg; mean (SD)] | 72.6 (11.5) | 80.5 (11.3) | <0.0001 |
| Antihypertensive medication, yes (%) | 11.7 | 19.9 | <0.0001 |
| Fasting blood glucose [mg/dl; mean (SD)] | 98.1 (26.2) | 102.7 (26.5) | <0.0001 |
| Hemoglobin $A_{1c}$ [%; mean (SD)] | 5.2 (0.8) | 5.4 (0.8) | <0.0001 |
| Antidiabetic medication, yes (%) | 3.5 | 4.4 | 0.0001 |
| Low-density lipoprotein cholesterol [mg/dl; mean (SD)] | 119.6 (31.4) | 129.8 (31.9) | <0.0001 |
| Medication for hypercholesterolemia, yes (%) | 4.8 | 9.0 | <0.0001 |
| Triglycerides [mg/dl; median (IQR)] | 103 (73, 156) | 142 (99, 211) | <0.0001 |
| High-density lipoprotein cholesterol [mg/dl; mean (SD)] | 61.0 (16.4) | 53.0 (13.1) | <0.0001 |
| Creatinine [mg/dl; mean (SD)] | 0.80 (0.26) | 0.83 (0.37) | <0.0001 |
| eGFR [ml/min/1.73 m$^2$; mean (SD)] | 83.4 (17.0) | 80.6 (16.2) | <0.0001 |
| Proteinuria[a] (%) | 5.9 | 8.2 | <0.0001 |
| Chronic kidney disease[b] (%) | 9.2 | 12.2 | <0.0001 |

*SD* standard deviation, *IQR* interquartile range

[a] Defined as the presence of ≥1+ proteinuria on urinalysis

[b] Defined as an estimated glomerular filtration rate <60 ml/min per 1.73 m$^2$ or as proteinuria on urinalysis

Clinical characteristics of the participants stratified by weight gain status are listed in Tables 1 and 2. As expected, both women and men with at least 10 kg of weight gain had a higher BMI, larger waist circumference, higher blood pressure, higher blood glucose, and higher low-density lipoprotein cholesterol and triglyceride levels. They were also more likely to have a history of cardiac disease, lower alcohol consumption, and less physical activity in both genders. The prevalence of CKD among the participants with weight gain was significantly higher than among those without weight gain both in women (11.8 vs 8.3%, $p \leq 0.0001$) and in men (12.2 vs 9.2%, $p \leq 0.0001$). The prevalence of proteinuria among the participants with weight gain was also significantly higher than among those without weight gain both in women (5.6 vs 2.9%, $p \leq 0.0001$) and in men (8.2 vs 5.9%, $p \leq 0.0001$).

In the age-adjusted analysis, the odds ratios for CKD increased along with increasing age in both genders (Tables 3, 4). Multivariate analysis revealed that weight gain was significantly associated with the prevalence of CKD, even after adjusting for hypertension, diabetes, and hypercholesterolemia. Thus, weight gain was independently associated with CKD in both genders. When the participants with a history of kidney disease were excluded, the results of the models also remained similar (Appendix). When proteinuria was replaced by the prevalence of CKD, multivariate analysis revealed that weight gain was significantly associated with proteinuria, even after adjusting for hypertension, diabetes, and hypercholesterolemia [the odds ratio (95% CI) 1.43 (1.25–1.63) in women and 1.16 (1.04–1.30) in men].

Stratified analysis showed that weight gain was independently associated with the prevalence of CKD among the subgroup without metabolic syndrome in both genders (Table 5). Among women, weight gain was also independently associated with the prevalence of CKD in the subgroup without abdominal obesity (waist circumference ≤90 cm).

The sensitivity and specificity of weight gain, BMI, and waist circumference for identifying CKD are shown in Table 6. Weight gain among women showed highest sensitivity (38%), but lowest specificity (71%), among the

**Table 3** Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among women

| Variable | Age-adjusted (95% CI) | Model 1[a] Odds ratio (95% CI) | Model 2[b] Odds ratio (95% CI) |
|---|---|---|---|
| Weight gain after 20 years | | | |
| <10 kg (ref) | 1.00 | 1.00 | 1.00 |
| ≥10 kg | 1.43 (1.32–1.56) | 1.43 (1.31–1.55) | 1.24 (1.14–1.36) |
| Age | | | |
| 40–44 (ref) | 1.00 | 1.00 | 1.00 |
| 45–49 | 1.22 (1.02–1.46) | 1.21 (1.01–1.45) | 1.14 (0.95–1.37) |
| 50–54 | 2.06 (1.76–2.42) | 2.04 (1.74–2.39) | 1.82 (1.54–2.13) |
| 55–59 | 2.40 (2.07–2.78) | 2.35 (2.03–2.73) | 1.99 (1.71–2.32) |
| Current smoker | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 1.05 (0.93–1.19) | 1.05 (0.93–1.19) |
| Regular exercise | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 0.88 (0.81–0.96) | 0.88 (0.81–0.97) |
| Alcohol intake | | | |
| Every day (ref) | | 1.00 | 1.00 |
| Sometimes | | 1.07 (0.92–1.23) | 1.07 (0.92–1.24) |
| Little or never | | 1.14 (1.00–1.30) | 1.15 (1.00–1.31) |
| History of kidney disease | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 3.34 (2.18–5.13) | 3.07 (1.99–4.72) |
| Hypertension[c] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.57 (1.43–1.72) |
| Diabetes mellitus[d] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.47 (1.26–1.71) |
| Hypercholesterolemia[e] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.16 (1.06–1.26) |

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, history of kidney disease, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

three variables, while weight gain showed middle-level sensitivity (57%) and specificity (51%) among men.

## Discussion

The present study demonstrated that weight gain of at least 10 kg after 20 years of age was independently associated with the prevalence of CKD. This association was recognized even in the subgroup of participants without metabolic syndrome in both genders. The present study also showed that weight gain was independently associated with the prevalence of CKD in the subgroup of women without abdominal obesity (waist circumference ≤90 cm). These results suggest that using the assessment of weight gain for prevention of obesity may protect individuals who are within the current guidelines from potentially avoidable risks related with obesity to CKD, particularly for women.

Obesity is not only indirectly associated with CKD through various risk factors, such as hypertension and diabetes, but has also been recognized to directly influence the development of kidney dysfunction [9, 21–24]. Although the exact mechanism by which obesity is associated with CKD has not yet been elucidated, intra-abdominal fat mass plays a key role in metabolic syndrome. Weight gain after maturity largely reflects an increased fat mass, and thus may be a more direct (i.e., better) predictor of CKD than BMI or waist circumference. In addition, because the median BMI of Asians is lower than that of non-Asians [10], weight gain may be a more effective predictor of CKD in Asian populations. In fact, weight gain has been reported to be associated with the incidence of CKD among Korean men, even when BMI remained within the normal range [7].

**Table 4** Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among men

| Variable | Age-adjusted (95% CI) | Model 1[a] Odds ratio (95% CI) | Model 2[b] Odds ratio (95% CI) |
|---|---|---|---|
| Weight gain after 20 years | | | |
| <10 kg (ref) | 1.00 | 1.00 | 1.00 |
| ≥10 kg | 1.37 (1.26–1.49) | 1.34 (1.23–1.47) | 1.15 (1.05–1.26) |
| Age | | | |
| 40–44 (ref) | 1.00 | 1.00 | 1.00 |
| 45–49 | 1.30 (1.11–1.52) | 1.31 (1.12–1.53) | 1.20 (1.02–1.40) |
| 50–54 | 1.44 (1.24–1.67) | 1.47 (1.27–1.71) | 1.22 (1.05–1.42) |
| 55–59 | 1.83 (1.60–2.09) | 1.87 (1.63–2.15) | 1.43 (1.27–1.64) |
| Current smoker | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 1.05 (0.96–1.15) | 1.05 (0.96–1.15) |
| Regular exercise | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 1.05 (0.96–1.16) | 1.04 (0.94–1.14) |
| Alcohol intake | | | |
| Every day (ref) | | 1.00 | 1.00 |
| Sometimes | | 1.21 (1.08–1.35) | 1.24 (1.11–1.39) |
| Little or never | | 1.40 (1.26–1.56) | 1.48 (1.33–1.65) |
| History of kidney disease | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 9.43 (6.05–14.69) | 8.11 (5.15–12.77) |
| Hypertension[c] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 2.07 (1.88–2.27) |
| Diabetes mellitus[d] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 2.00 (1.78–2.25) |
| Hypercholesterolemia[e] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.24 (1.13–1.37) |

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, history of kidney disease, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

The present study also found weight gain was independently associated with the prevalence of CKD among both genders, even individuals without metabolic syndrome. To our knowledge, this is the first study to demonstrate a relationship between weight gain after maturity and CKD among women.

The present study also showed that weight gain among women had the highest sensitivity, but the lowest specificity, for CKD among the three measurements used to evaluate obesity. It is theoretically desirable for a screening test to be both highly sensitive and highly specific, but it is difficult to achieve this because of a trade-off between sensitivity and specificity. For public health activities aimed at preventing obesity, a test with high sensitivity may be more useful than one with high specificity. Thus, using the assessment of weight gain for prevention of obesity and CKD is attractive from a public health perspective, particularly for women.

Several studies revealed that the clinical implication of CKD and obesity or metabolic syndrome may be different according to gender. [12, 13, 19] Menopausal status has been suggested to be one of the candidates in determining the gender differences, because metabolic syndrome was a risk factor for CKD in postmenopausal women, but not in premenopausal women [13]. Because the mean age at menopause was reported to be 48.3 years and 80% of females had their menopause between 45 and 54 years of age in Japan [25], our study must include both premenopausal and postmenopausal women. Some differences between men and women in this study might be associated with menopausal status, whereas the information regarding menopausal status of participants was lacking in this study.

**Table 5** Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease in subgroups

| Gender and subgroup | Number of participants | Odds ratio (95% CI) | *p* value |
|---|---|---|---|
| Women | | | |
| Body mass index (kg/m$^2$) | | | |
| <25 | 22,363 | 1.13 (0.99–1.27) | 0.06 |
| 25+ | 5,788 | 1.08 (0.88–1.33) | 0.44 |
| Waist circumference (cm) | | | |
| <90 | 23,656 | 1.15 (1.03–1.29) | 0.01 |
| 90+ | 4,495 | 1.23 (0.97–1.55) | 0.08 |
| Metabolic syndrome[a] | | | |
| No | 26,218 | 1.15 (1.03–1.28) | <0.0001 |
| Yes | 1,933 | 1.55 (1.04–2.31) | 0.03 |
| Men | | | |
| Body mass index (kg/m$^2$) | | | |
| <25 | 13,500 | 1.00 (0.87–1.14) | 0.98 |
| 25+ | 7,610 | 0.90 (0.76–1.07) | 0.24 |
| Waist circumference (cm) | | | |
| <85 | 10,247 | 0.94 (0.79–1.12) | 0.50 |
| 85+ | 10,863 | 1.05 (0.91–1.20) | 0.50 |
| Metabolic syndrome[a] | | | |
| No | 10,979 | 1.24 (1.07–1.43) | 0.01 |
| Yes | 10,131 | 1.04 (0.92–1.18) | 0.50 |

Models adjusted for age, smoking, regular exercise, alcohol intake, history of kidney disease, place of residence, hypertension, diabetes, and hypercholesterolemia

[a] Defined as abdominal obesity (waist circumference ≥90 cm for women and ≥85 cm for men) plus any two of the following three categories: (1) fasting blood glucose ≥100 mg/dl, and/or hemoglobin $A_{1c}$ ≥ 5.2%, and/or the use of insulin, and/or oral antidiabetic medication; (2) triglycerides ≥150 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl, and/or cholesterol-lowering medication; and (3) blood pressure ≥130/85 mmHg, and/or use of antihypertensive medication

**Table 6** Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of three weight indicators for detecting chronic kidney disease

| | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|---|---|---|---|---|
| Women | | | | |
| Weight gain after 20 years | 0.38 (0.36–0.40) | 0.71 (0.70–0.71) | 0.12 (0.11–0.13) | 0.92 (0.91–0.92) |
| Body mass index | 0.29 (0.27–0.31) | 0.80 (0.80–0.81) | 0.13 (0.12–0.14) | 0.92 (0.91–0.92) |
| Waist circumference | 0.23 (0.22–0.25) | 0.85 (0.84–0.85) | 0.14 (0.13–0.15) | 0.91 (0.91–0.92) |
| Men | | | | |
| Weight gain after 20 years | 0.57 (0.55–0.59) | 0.51 (0.51–0.52) | 0.12 (0.12–0.13) | 0.91 (0.90–0.91) |
| Body mass index | 0.49 (0.47–0.52) | 0.66 (0.65–0.66) | 0.15 (0.14–0.16) | 0.92 (0.91–0.92) |
| Waist circumference | 0.63 (0.61–0.65) | 0.50 (0.49–0.51) | 0.13 (0.13–0.14) | 0.92 (0.91–0.92) |

*CI* confidence interval

Our study had several limitations. First, the actual body weight gain could not be confirmed, but bias resulting from this factor is not likely because body weight gain is easy to measure. Second, CKD was defined from a single creatinine value and measurements of creatinine can vary among different laboratories. In addition, a single measurement of urinary protein was used because of the nature of an annual health check program. Therefore, it is not possible in this study to confirm whether participants fulfilled CKD criteria for at least a 3-month period. Finally, this was a cross-

sectional study, which makes it difficult to establish causal relationships. Further longitudinal investigations will be needed to clarify whether weight gain after maturity is an independent factor in the development of CKD.

Despite these limitations, there were several strengths to our study. As far as we know, this is the first report about weight gain after maturity and CKD among women from the general population. Our study also had a large sample size, which allowed us to perform stratified subgroup analyses.

## Conclusions

Weight gain ≥10 kg after maturity was independently associated with the prevalence of CKD among the Japanese population, even those without metabolic syndrome. Because weight gain is more easily understood by the general population than BMI and can be more accurately measured than waist circumference, advice to limit weight gain to <10 kg after 20 years of age is recommended to avoid an obesity-related increase in the risk of CKD, particularly for women.

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**Conflict of interest** The authors have declared that no conflict of interest exists.

## Appendix

When the participants with a history of kidney disease were excluded, weight gain was independently associated with CKD in both genders (Tables 7 and 8).

**Table 7** Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among women without history of kidney disease ($n$ = 28,026)

| Variable | Age-adjusted (95% CI) | Model 1[a] Odds ratio (95% CI) | Model 2[b] Odds ratio (95% CI) |
|---|---|---|---|
| Weight gain after 20 years | | | |
| <10 kg (ref) | 1.00 | 1.00 | 1.00 |
| ≥10 kg | 1.43 (1.31–1.55) | 1.42 (1.30–1.54) | 1.25 (1.14–1.36) |
| Age | | | |
| 40–44 (ref) | 1.00 | 1.00 | 1.00 |
| 45–49 | 1.21 (1.01–1.45) | 1.20 (1.00–1.43) | 1.14 (0.95–1.36) |
| 50–54 | 2.04 (1.74–2.40) | 2.04 (1.74–2.39) | 1.81 (1.53–2.12) |
| 55–59 | 2.39 (2.06–2.76) | 2.38 (2.05–2.76) | 1.99 (1.70–2.32) |
| Current smoker | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 1.05 (0.92–1.19) | 1.06 (0.93–1.20) |
| Regular exercise | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 1.14 (1.04–1.25) | 1.13 (1.04–1.24) |
| Alcohol intake | | | |
| Every day (ref) | | 1.00 | 1.00 |
| Sometimes | | 1.05 (0.91–1.22) | 1.06 (0.91–1.22) |
| Little or never | | 1.15 (1.01–1.31) | 1.14 (1.00–1.30) |
| Hypertension[c] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.54 (1.29–1.75) |
| Diabetes mellitus[d] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.50 (1.40–1.69) |
| Hypercholesterolemia[e] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.16 (1.06–1.26) |

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure of ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

**Table 8** Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among men without history of kidney disease ($n = 21,027$)

| Variable | Age-adjusted (95% CI) | Model 1[a] Odds ratio (95% CI) | Model 2[b] Odds ratio (95% CI) |
|---|---|---|---|
| Weight gain after 20 years | | | |
| <10 kg (ref) | 1.00 | 1.00 | 1.00 |
| ≥10 kg | 1.37 (1.25–1.50) | 1.34 (1.23–1.47) | 1.15 (1.05–1.26) |
| Age | | | |
| 40–44 (ref) | 1.00 | 1.00 | 1.00 |
| 45–49 | 1.29 (1.11–1.51) | 1.31 (1.12–1.53) | 1.20 (1.03–1.41) |
| 50–54 | 1.41 (1.22–1.64) | 1.47 (1.26–1.71) | 1.22 (1.05–1.42) |
| 55–59 | 1.80 (1.57–2.06) | 1.86 (1.62–2.14) | 1.43 (1.24–1.64) |
| Current smoker | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 1.06 (0.96–1.16) | 1.05 (0.96–1.16) |
| Regular exercise | | | |
| No (ref) | | 1.00 | 1.00 |
| Yes | | 1.05 (0.95–1.15) | 1.03 (0.93–1.14) |
| Alcohol intake | | | |
| Every day (ref) | | 1.00 | 1.00 |
| Sometimes | | 1.20 (1.08–1.35) | 1.24 (1.10–1.39) |
| Little or never | | 1.40 (1.26–1.56) | 1.48 (1.32–1.65) |
| Hypertension[c] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 2.04 (1.85–2.24) |
| Diabetes mellitus[d] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 2.00 (1.78–2.25) |
| Hypercholesterolemia[e] | | | |
| No (ref) | | | 1.00 |
| Yes | | | 1.24 (1.13–1.36) |

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

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# Association of High Pulse Pressure With Proteinuria in Subjects With Diabetes, Prediabetes, or Normal Glucose Tolerance in a Large Japanese General Population Sample

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**OBJECTIVE**—To examine whether there is a difference in the association between high pulse pressure and proteinuria, independent of other blood pressure (BP) indices, such as systolic or diastolic BP, among subjects with diabetes, prediabetes, or normal glucose tolerance.

**RESEARCH DESIGN AND METHODS**—Using a nationwide health checkup database of 228,778 Japanese aged ≥20 years (mean 63.2 years; 39.3% men; none had pre-existing cardiovascular disease), we examined the association between high pulse pressure, defined as the highest quintile of pulse pressure (≥63 mmHg, $n$ = 40,511), and proteinuria (≥1+ on dipstick, $n$ = 12,090) separately in subjects with diabetes ($n$ = 27,913), prediabetes ($n$ = 100,214), and normal glucose tolerance ($n$ = 100,651).

**RESULTS**—The prevalence of proteinuria was different among subjects with diabetes, prediabetes, and normal glucose tolerance (11.3 vs. 5.0 vs. 3.9%, respectively; $P < 0.001$). In subjects with diabetes, but not those with prediabetes or normal glucose tolerance, high pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (odds ratio 1.15 [95% CI 1.04–1.28]) or diastolic or mean BP (all $P < 0.01$). In patients with diabetes, a +1 SD increase of pulse pressure (+13 mmHg) was associated with proteinuria, even after adjustment for systolic BP (1.07 [1.00–1.13]) or diastolic or mean BP (all $P < 0.05$).

**CONCLUSIONS**—Among the Japanese general population, there was a significant difference in the association between high pulse pressure and proteinuria among subjects with diabetes, prediabetes, and normal glucose tolerance. Only in diabetes was high pulse pressure associated with proteinuria independent of systolic, diastolic, or mean BP levels.

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In the systemic circulation, the kidney has unique features: vascular resistance in the glomerular afferent arterioles is low, and the myogenic response of the glomerular arterioles is insensitive to changes in the other BP indices of systolic blood pressure (BP), including pulse pressure (1–3). These characteristics suggest that pressure pulsatility may contribute to barotrauma-induced renal microvascular injury, and in turn causes glomerular ultrastructural changes (e.g., podocyte loss and glomerular basement membrane thickness) (1–6).

In fact, several cross-sectional studies performed in general or hypertensive populations have demonstrated a significant association between pulse pressure and albuminuria (7,8), and some longitudinal studies have underscored the importance of pulse pressure as a risk factor for increased albuminuria in general or hypertensive populations (9,10); however, few studies have directly examined the impact of high pulse pressure on albuminuria with adjustment for other BP components, such as systolic BP, diastolic BP, and/or mean BP levels. Since renal autoregulation is particularly impaired in patients with diabetes (1–3,11–13), we hypothesized that the association between high pulse pressure and albuminuria would be more prominent in patients with diabetes than in subjects without diabetes (14–16); as of yet, however, there have been no studies examining this hypothesis directly in a large database. Furthermore, the association of pulse pressure with albuminuria has never been explored in prediabetics, who are classified as being at an intermediate stage between normal glucose tolerance and diabetes (17), but prediabetics have been shown to have a significantly increased risk of developing not only diabetes but also cardiovascular disease (18).

In the current study, therefore, we examined the association of high pulse pressure with proteinuria separately in each of subjects with diabetes, prediabetes, and normal glucose tolerance, using a large nationwide


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database of subjects recruited from the national health checkup system in Japan.

## RESEARCH DESIGN AND METHODS

### Study population

This study was performed as a part of the prospective ongoing "Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan" project. A new annual health check program, "The Specific Health Check and Guidance in Japan", was started by the Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. The target population comprises Japanese citizens between the ages of 40 and 74 years. In Japan, there are 47 administrative divisions (prefectures), and 13 of these prefectures (Yamagata, Miyagi, Fukushima, and Niigata from the Tohoku region in northeastern Japan; Tokyo, Kanagawa, and Ibaraki from the Kanto region in central Japan; Osaka, Okayama, and Kochi from the Kansai, Tyugoku, or Shikoku region in western Japan; and Fukuoka, Miyazaki, and Okinawa from the Kyushu region in southern Japan), which were randomly distributed across Japan, agreed with the aims of this study and performed data collection prospectively from 2008 to 2009. Data were sent to an independent data center, the nonprofit organization Japan Clinical Research Support Unit after anonymization in a linkable fashion, and verified by trained staff (K.I. and Y.O.). After that, the database was locked with a security password, which contained the participant's information managed by a research ID number but did not contain the participant's name, and was sent to each investigator on a recordable compact disc.

There were a total of 346,942 subjects (mean age, 63.4 years; 41% [$n$ = 141,938] men) for whom information on age, sex, BP, BMI, habitual smoking or drinking, use of antihypertensive drugs, and previous history of cardiovascular diseases (i.e., stroke and cardiac diseases such as angina and myocardial infarction) were available, as well as data on the serum creatinine level and dipstick urine test for proteinuria (19). Some of the regions participating in our project (i.e., Okinawa and Osaka) concomitantly performed regular health checkups for employees as legally mandated in Japan; as a result, the database used in the present analysis also included subjects aged 20–39 years ($n$ = 2,025). Among the 346,942 subjects, 29,820 subjects with a previous history of cardiovascular disease, 243 subjects with chronic kidney disease stage 5 (estimated glomerular filtration rate [eGFR] $<$15 mL/min/1.73m$^2$), and 47 subjects with both were excluded from the present analysis. Moreover, 88,101 subjects with insufficient blood sampling data of glucose and lipid parameters were excluded. Supplementary Table 1 shows the differences in clinical characteristics between subjects who were included in the present analysis ($n$ = 228,778) and those who had missing data ($n$ = 88,101).

The study was conducted according to the guidelines of the Declaration of Helsinki and Ethical Guidelines for Epidemiological Research (1 November 2007, Ministry of Education, Culture, Sports, Science, and Technology and Ministry of Health, Labor, and Welfare of Japan). Ethical approval from the respective institutional review boards was also granted.

### Baseline measurement

All subjects completed a self-administered questionnaire to document their medical history, current medications, smoking habits (current smoker or not), and alcohol intake (daily drinker or not). The study physicians performed a physical examination of each subject and rechecked their medical history to improve the precision of the information. Body height and weight were measured in light clothing without shoes, and the BMI was calculated (kg/m$^2$). BP measurement and blood and urine sampling were performed at each local medical institution to cooperate with the nationwide medical checkup. According to the recommendations of the Japanese Ministry of Health, Labor, and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured by medical staff using a standard sphygmomanometer or an automated device on the right arm after the subject had rested for 5 min in a seated position with the legs not crossed. Conversation as well as alcohol/caffeine consumption was also avoided before measurement. Pulse pressure was calculated as systolic BP − diastolic BP, and mean BP was calculated as diastolic BP + (pulse pressure/3).

Blood samples were collected after an overnight fast and were assayed within 24 h with an automatic clinical chemical analyzer. All measurements were conducted locally rather than at a central laboratory without calibration among different laboratories, despite the fact that beginning several years ago, standardized methods to measure laboratory data were recommended and widely adopted by the activity of the Japan Society of Clinical Chemistry.

The value for hemoglobin $A_{1c}$ ($HbA_{1c}$) was estimated as a National Glycohemoglobin Standardization Program equivalent value calculated with the following equation (20): $HbA_{1c}$ (%) = $HbA_{1c}$ (Japan Diabetes Society) (%) + 0.4%.

Diabetes was defined in accordance with American Diabetes Association guidelines (17) as a fasting glucose concentration of 126 mg/dL or higher, $HbA_{1c}$ 6.5% or higher, or self-reported use of antihyperglycemic drugs. Diagnosis of prediabetes was based on the new American Diabetes Association criterion of impaired fasting glucose (fasting plasma glucose 100–125 mg/dL) or $HbA_{1c}$ 5·7–6·4%, or both (17).

Urinalysis by the dipstick method was performed on a single spot urine specimen collected in the early morning after overnight fasting. Urine dipstick results are interpreted by the medical staff in each local medical institution and recorded as −, ±, 1+, 2+, and 3+. In Japan, it is recommended and widely adopted by the activity of the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) that all urine dipstick tests be manufactured so that a urine dipstick result of 1+ will correspond to a urinary protein level of 30 mg/dL. In the current study, proteinuria was defined as 1+ or more. eGFR was derived using the following equation (21): eGFR (mL/min/1.73 m$^2$) = 194 × age (years)$^{-0.287}$ × serum creatinine (mg/dL)$^{-1.094}$ (if women ×0.739).

### Statistical analysis

All statistical analyses were performed with SPSS version 18.0 J software (SPSS, Chicago, IL). Data were expressed as the means ± SD (age, BMI, eGFR, and BP values) or median and interquartile range (glucose and lipid parameters). Clinical parameters and BP or metabolic values according to the presence of diabetes or prediabetes were compared using ANOVA, and categorical parameters were compared with the $\chi^2$ test. We subdivided the study population according to the quintiles of pulse pressure, and the prevalence of proteinuria (≥1+) was compared by $\chi^2$ test among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The highest quintile of pulse pressure (≥63 mmHg, $n$ = 40,511) was defined as the high pulse pressure group in the present analysis.

Next, we used a multivariable logistic regression analysis to examine the independent

association of high pulse pressure with proteinuria (≥1+) separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. In the initial model (Model 1), these associations were assessed with adjustment for age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and eGFR. Extended models were used to assess whether the association of high pulse pressure with proteinuria (≥1+) was attenuated by the potential confounding effects of glucose and lipid parameters (Model 2) and systolic BP (Model 3). In addition, to minimize the influence of systolic BP in the association between pulse pressure and proteinuria, we examined the association only in patients with diabetes whose systolic BP was within the normal BP range (i.e., <130 mmHg) (22). Finally, we examined the association of a +1 SD increase of pulse pressure (+13 mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes by a multivariable logistic regression analysis. Statistical significance was defined as $P < 0.05$.

## RESULTS

### Clinical characteristics of the study population

The mean age ± SD of the 228,778 subjects was 63.2 ± 8.9 years, and 89,877 of the subjects (39.3%) were men. There were 27,913 subjects (12.2% of the total subject population) with diabetes, of whom 10,980 subjects (39.1%) were taking antihyperglycemic medications. There were 100,214 subjects (43.8%) with prediabetes. The clinical characteristics according to the presence of diabetes or prediabetes are shown in Table 1. Compared with subjects with normal glucose tolerance (as a reference), the odds ratio (OR) for the increased risk of proteinuria (≥ 1+) in diabetes itself was 2.14 (95% CI 2.03–2.25), and that in prediabetes was 1.10 (1.05–1.14), even after adjustment for significant covariates, such as age, sex, BMI, current smoking and daily drinking, the presence of antihypertensive medications, and systolic BP level (both $P < 0.001$).

### Pulse pressure and proteinuria

Clinical characteristics and metabolic or BP parameters according to the quintile of pulse pressure are shown in Supplementary Table 2. The increasing prevalence of proteinuria (≥1+) in accordance with the increasing pulse pressure was more prominent in subjects with diabetes than those without diabetes (Fig. 1). Supplementary Table 3 shows the prevalence of proteinuria subdivided by the dipstick positive scale according to the quintile of pulse pressure with or without diabetes.

Next, a multivariable logistic regression analysis was performed to examine the independent association between the highest quintile of pulse pressure and proteinuria, separately in subjects with diabetes, prediabetes, and normal glucose tolerance. In patients with diabetes, the highest quintile of pulse pressure (≥63 mmHg) was positively associated with proteinuria, independently of significant covariates, including systolic BP (Models 1–3 in Table 2). When we examined the association between pulse pressure and proteinuria only in patients with diabetes whose systolic BP was within the normal range (i.e., <130 mmHg, $n$ = 11,074 [39.7%]), the highest quintile of pulse pressure still remained significantly associated with proteinuria (OR 1.46 [95% CI 1.03–2.08]; $P = 0.04$, respectively), even after adjustment for significant covariates, as shown in Model 2 in Table 2. When diastolic BP or mean BP was entered into Model 3 in Table 3 in place of systolic BP, the association between the highest quintile of pulse pressure and proteinuria still remained significant (1.61 [1.49–1.75] and 1.42 [1.31–1.55]; both $P < 0.001$, respectively). In contrast, the highest quintile of pulse pressure in subjects with prediabetes or normal glucose tolerance was not associated with proteinuria independently of systolic BP (Model 3 in Table 2). When

Table 1—*Characteristics of the study population according to the presence of diabetes or prediabetes*

| | Diabetes ($n$ = 27,913) | Prediabetes ($n$ = 100,214) | Normal glucose tolerance ($n$ = 100,651) | $P$ value |
|---|---|---|---|---|
| Age (years) | 65.2 ± 7.3 | 64.2 ± 7.9 | 61.6 ± 9.8 | <0.001 |
| Men, $n$ (%) | 14,626 (52.4) | 40,077 (40.0) | 35,174 (34.9) | <0.001 |
| BMI (kg/m$^2$) | 24.1 ± 3.7 | 23.3 ± 3.3 | 22.5 ± 3.1 | <0.001 |
| Current smoker, $n$ (%) | 4,846 (17.4) | 12,960 (12.9) | 13,971 (13.9) | <0.001 |
| Daily drinker, $n$ (%) | 7,162 (25.7) | 22,825 (22.8) | 21,521 (21.4) | <0.001 |
| eGFR (mL/min/1.73 m$^2$) | 76.2 ± 17.8 | 74.7 ± 15.6 | 76.1 ± 15.9 | <0.001 |
| Proteinuria (≥1+), $n$ (%) | 3,164 (11.3) | 5,013 (5.0) | 3,913 (3.9) | <0.001 |
| Glucose and lipid parameters | | | | |
| Fasting glucose (mg/dL)* | 125.0 (100.0–143.0) | 98.0 (90.0–105.0) | 89.0 (84.0–93.0) | <0.001 |
| $HbA_{1c}$ (%)* | 6.2 (5.6–6.9) | 5.4 (5.3–5.6) | 5.0 (4.8–5.1) | <0.001 |
| Triglycerides (mg/dL)* | 112.0 (79.0–162.0) | 101.0 (74.0–142.0) | 91.0 (67.0–127.0) | <0.001 |
| LDL (mg/dL)* | 123.0 (104.0–145.0) | 127.0 (108.0–148.0) | 124.0 (105.0–144.0) | <0.001 |
| HDL (mg/dL)* | 57.0 (48.0–68.0) | 60.0 (51.0–72.0) | 63.0 (53.0–75.0) | <0.001 |
| Antihypertensive drugs, $n$ (%) | 11,101 (39.8) | 29,157 (29.1) | 21,410 (21.3) | <0.001 |
| Antihyperlipidemic drugs, $n$ (%) | 6,823 (24.4) | 17,440 (17.4) | 12,233 (12.2) | <0.001 |
| Antihyperglycemic drugs, $n$ (%) | 10,980 (39.1) | 0 (0) | 0 (0) | <0.001 |
| BP parameters | | | | |
| Systolic BP (mmHg) | 133.4 ± 17.5 | 129.7 ± 17.0 | 125.7 ± 17.2 | <0.001 |
| Diastolic BP (mmHg) | 77.1 ± 10.8 | 76.8 ± 10.5 | 75.1 ± 10.7 | <0.001 |
| Pulse pressure (mmHg) | 56.2 ± 13.4 | 52.9 ± 12.4 | 50.6 ± 12.2 | <0.001 |

Data are expressed as the means ± SD or percentage. $P$ values were obtained by ANOVA or $\chi^2$ test. *Variables with skewed distribution are expressed as median (interquartile range).

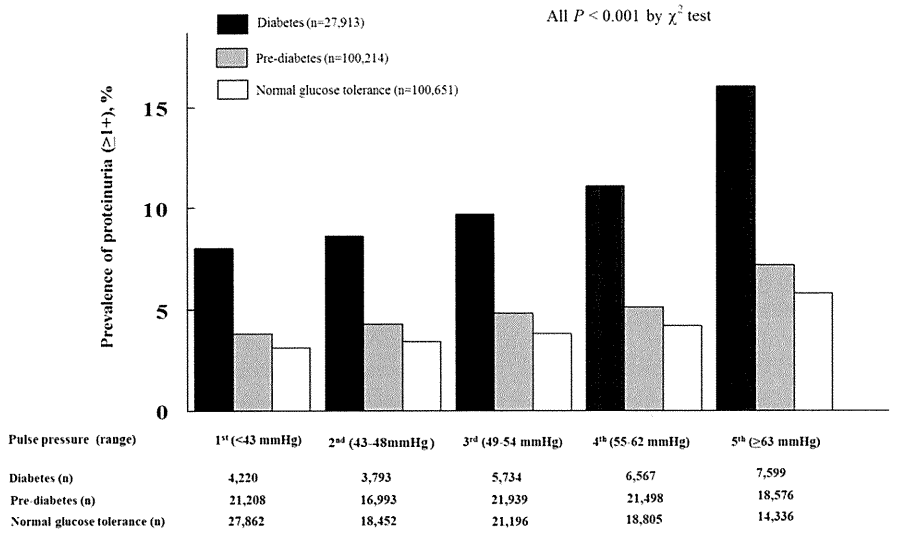


**Figure 1**—*Prevalence of proteinuria according to the quintile of pulse pressure in subjects with diabetes, prediabetes, or normal glucose tolerance. The prevalence of proteinuria (≥1+) was calculated among each group of the quintiles of pulse pressure separately in subjects with diabetes, prediabetes, or normal glucose tolerance, respectively. The* P *value was obtained by a* $\chi^2$ *test among each group of the quintiles of pulse pressure.*

we examined the risk of the highest quintile of pulse pressure on proteinuria among subjects without antihypertensive medications ($n$ = 167,110), the conclusion remained unchanged (Model 4 in Table 2). Use of antihyperglycemic or antihyperlipidemic drugs did not influence any of the above results (data not shown). In contrast, systolic BP, used as an adjusted factor in Model 3 in Table 2, showed significant associations with proteinuria in subjects with diabetes, prediabetes, and normal glucose tolerance (data not shown).

Finally, we analyzed the association of a +1 SD increase of pulse pressure (+13 mmHg), rather than pulse pressure as a dichotomous variable, with proteinuria in patients with diabetes. We found that a +1 SD increase of pulse pressure was associated with proteinuria independently of significant covariates, including systolic BP (Table 3), diastolic BP, or mean BP (data not shown).

**CONCLUSIONS**—In this nationwide study of 228,778 Japanese people (mean age 63.2 years) who had no known cardiovascular disease, we demonstrated for the first time that there was a significant difference in the association between the highest quintile of pulse pressure (≥63 mmHg) and proteinuria (≥1+ on dipstick) among subjects with diabetes, prediabetes, and normal glucose tolerance. The cross-sectional design of the current study did not allow us to elucidate the pathophysiological pathway linking high pulse pressure and proteinuria (≥1+). However, there are some possible explanations for the observed association.

## Pulse pressure, proteinuria, and patients with diabetes

Since the glomerular afferent arterioles provide relatively low resistance, the glomerulus is susceptible to barotrauma if the pulse pressure is elevated (1–6). In fact, prior studies have demonstrated an association of high pulse pressure with microalbuminuria even in subjects without diabetes (7,8). In the current study, we examined the possible association of high pulse pressure and proteinuria (≥1+), i.e., macroalbuminuria, and found that this association was not significant independently of systolic BP in subjects without diabetes. In contrast, systolic BP was significantly associated with proteinuria in these subjects. Although the usefulness of the urine dipstick test for risk stratification of renal and cardiovascular disease has been recognized, this method is a less sensitive measure of albuminuria compared with the measurement of urinary albumin excretion (23–26). Accordingly, we cannot deny the possibility of an association between high pulse pressure and microalbuminuria in subjects without diabetes.

**Table 2**—*OR for the highest quintile of pulse pressure in the association of proteinuria (≥1+) according to the presence of diabetes or prediabetes*

| Model | Adjusted covariates | OR (95% CI) | | |
|---|---|---|---|---|
| Overall ($n$ = 228,778) | | Diabetes ($n$ = 27,913) | Prediabetes ($n$ = 100,214) | Normal glucose tolerance ($n$ = 100,651) |
| Model 1 | Age + sex + BMI + current-smoking + daily drinking + antihypertensive medications + eGFR | 1.72 (1.59–1.87)‡ | 1.45 (1.35–1.55)‡ | 1.48 (1.37–1.61)‡ |
| Model 2 | Model 1 + fasting glucose + triglycerides + HDL + LDL | 1.63 (1.50–1.77)‡ | 1.41 (1.31–1.50)‡ | 1.48 (1.36–1.60)‡ |
| Model 3 | Model 2 + systolic BP | 1.16 (1.05–1.29)† | 0.97 (0.89–1.05) | 1.08 (0.98–1.20) |
| Subjects without antihypertensive medications ($n$ = 167,110) | | Diabetes ($n$ = 16,812) | Prediabetes ($n$ = 71,057) | Normal glucose tolerance ($n$ = 79,241) |
| Model 4 | Age + sex +BMI + current smoking + daily drinking + eGFR + fasting glucose + triglycerides + HDL + LDL + systolic BP | 1.21 (1.03–1.43)* | 1.09 (0.97–1.23) | 1.13 (0.98–1.29) |

OR (95% CI) of proteinuria (≥1+) was calculated for highest quintile of pulse pressure (≥63 mmHg, $n$ = 40,511) vs. lower quintiles of pulse pressure (<63 mmHg) in each model. Statistical significance was defined as $P < 0.05$. *$P < 0.05$. †$P < 0.01$. ‡$P < 0.001$.

Table 3—*OR (95% CI) for proteinuria in diabetes (n = 27,913)*

| Model | OR (95% CI) | *P* value |
|---|---|---|
| Age (+9 years)* | 0.94 (0.89–1.00) | 0.04 |
| Sex (0, men; 1, women) | 0.55 (0.50–0.60) | <0.001 |
| BMI (+3 kg/m$^2$)* | 1.18 (1.14–1.22) | <0.001 |
| Current smoking (0, no; 1, yes) | 1.49 (1.35–1.65) | <0.001 |
| Daily drinking (0, no; 1, yes) | 0.90 (0.82–0.99) | 0.04 |
| Antihypertensive medications (0, no; 1, yes) | 0.59 (0.54–0.64) | <0.001 |
| eGFR (+16 mL/min/1.73 m$^2$)* | 0.76 (0.73–0.79) | <0.001 |
| Fasting glucose (+21 mg/dL)* | 1.20 (1.18–1.22) | <0.001 |
| Triglycerides (+78 mg/dL)* | 1.06 (1.03–1.09) | <0.001 |
| LDL (+30 mg/dL)* | 1.07 (1.03–1.11) | <0.001 |
| HDL (+16 mg/dL)* | 1.02 (0.98–1.07) | 0.39 |
| Systolic BP (+17 mmHg)* | 1.27 (1.20–1.36) | <0.001 |
| Pulse pressure (+13 mmHg)* | 1.08 (1.01–1.14) | 0.02 |

Statistical significance was defined as $P < 0.05$. *The OR (95% CI) of proteinuria (≥1+) was calculated for a +1 SD increase of each indicated variable as well as dichromatic variables.

In spite of the strict collinearity between systolic BP and pulse pressure, the OR of high pulse pressure to proteinuria was reduced but remained significant even after adjustment for systolic BP in patients with diabetes (Table 2). Table 3 also shows that a +1 SD increase of systolic BP and a +1 SD increase of pulse pressure were associated with proteinuria independently of each other, with the OR of the systolic BP increase on proteinuria being higher than that of the pulse pressure increase. These findings indicate that high systolic BP showed a confirmed association with proteinuria and is an important confounder explaining the association between high pulse pressure and proteinuria; however, even after adjustment for systolic BP, the pulsatile component of BP itself was still significantly associated with proteinuria in patients with diabetes. Intriguingly, even in the patients with diabetes who were within the normal range of systolic BP values, high pulse pressure was associated with proteinuria. Some possible explanations for these findings exist. First, since renal autoregulation is impaired in diabetes (1–3,11–13), it may be possible that when pulse pressure is elevated, more barotrauma-induced glomerular ultrastructural changes leading to albuminuria occur in subjects with diabetes than in those without diabetes (1–5). Second, much as in the previous reports (27,28), higher pulse pressure was observed in diabetes than nondiabetes (Table 1), suggesting the possibility that diabetes accelerates aortic and large arterial stiffness (29). Aortic stiffness itself has a potential etiologic role in the causation and progression of renal dysfunction (30–32), because loss of the damping of ventricular ejection in the stiffened aortae could lead to an increase in the transmission of these pressure changes to the renal microcirculation. In the current study, however, we did not use any measure of vascular stiffness more direct than pulse pressure, such as pulse wave velocity, and thus the potential efficacy of such measures will need to be investigated in the future. Third, overt proteinuria in patients with diabetes, which is observed in long-standing diabetes, together with hypertension and increased arterial stiffness, is a surrogate marker not only for renal structural damages but also generalized vascular damages (3,6,24,25). Therefore, we speculate that patients with diabetes with proteinuria are likely to have systemic vasculopathy, and as a consequence, they have high pulse pressure. Lastly, since the current study is a cross-sectional analysis, we have to pay attention to another possibility that diabetic renal disease indicated by greater proteinuria raises systolic BP as well as pulse pressure rather than the reverse in patients with diabetes.

## Pulse pressure, proteinuria, and prediabetes

The current study provided the first examination of the association of pulse pressure with proteinuria in prediabetes using a large sample size. Understanding such risk estimates is important, given the increases in the prevalence of prediabetes that have occurred in many populations in conjunction with the increasing prevalence of obesity, particularly in Asian populations (33,34). In the current study, the prevalence of prediabetes was substantially high (44%). Another Japanese study performed in healthy Japanese people ($n$ = 6,636, mean age 50 years) demonstrated that the prevalence of prediabetes was 32% (35). This survey was performed between 1997 and 2003, and since the prevalence of diabetes in Asian populations has increased rapidly in recent years (33,34), the high prevalence of prediabetes in the current study was not entirely unexpected.

Several limitations of our study should be mentioned. First, single-measurement readings of BP, fasting glucose or $HbA_{1c}$, and proteinuria cannot be considered fully accurate. In particular, some of the dipstick-positive proteinuria could have been transient, and thus could not be taken as definitive evidence of the presence of persisting proteinuria. These factors may introduce a source of variability that could have led to a tendency to underestimate the true association between pulse pressure and proteinuria. Second, we could not separate diabetes into type 1 or type 2 diabetes. However, the incidence of type 1 diabetes is extremely low (approximately two cases/year/100,000 individuals), and Japan has one of the lowest incidence rates of type 1 diabetes in the world (36). Third, we could not assess the diabetes- and atherosclerosis-related information, such as the duration of diabetes and the presence of diabetes complications (e.g., neuropathy), which would be informative and extend the knowledge achieved in the current study. Lastly, we could not assess what kinds of antihypertensive drugs had been prescribed in treated hypertensive subjects. Some antihypertensive drugs (e.g., angiotensin receptor blockers or angiotensin enzyme–converting inhibitors) have more favorable effects on vascular and renal protection (37). Therefore, their use was potentially confounding, although our conclusions remained unchanged when we analyzed our data while excluding the subjects with antihypertensive medications.

In conclusion, among the Japanese general population, high pulse pressure, particularly in individuals with diabetes, was associated with proteinuria, and this information has the potential to supplement other BP indices. To confirm our findings, a prospective study as well as interventions that examine whether or not reduction of pulse pressure can enhance nephron-protective benefits in diabetes will be required.

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Y.Y. and Y.S. analyzed the data. S.F. designed the study, collected data, and wrote the paper. T.K. and K.I. designed the study and collected data. T.M., K.Y., K.T., H.Y., K.A., I.K., Y.O., and T.W. designed the study, collected data, supervised the study, and revised the manuscript. S.F. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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●慢性腎臓病 ●足の痛み ●漢方で対処―慢性の痛み ●食道がん ●震災後のケア

# NHKテレビテキスト きょうの健康

3
2012

わかりやすく、確かな情報で

2月27日～3月29日
教育テレビ(Eテレ) 月～木
午後8時30分～8時45分

再放送(翌週)
教育テレビ(Eテレ) 月～木
午後0時30分～0時45分



## 気になる足の痛み
外反母趾 足底腱膜炎 大人のへん平足

## 食道がん
●早期発見の決め手 ●治療最前線

## 震災後のこころのケア

【特集】
## 慢性腎臓病
●腎臓健康度チェック ●進行を防ぐ
●透析治療 ●食事の対策

## 漢方で対処！慢性の痛み
腰痛・関節痛 頭痛 長引く痛み

食で健康 簡単！カロリー把握術
運動で健康 しつこい頭痛 痛み軽減体操
アンコール 見逃さないで！高血圧
テキスト企画 股関節の痛みを和らげる運動

# 腎臓病


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2月27日放送
腎臓健康度チェック
→6ページ

2月28日放送
血糖・血圧下げて進行を防ぐ
→12ページ

イラスト・奥田志津男