Association of the combination of weight gain after 20 years of age and current obesity with chronic kidney disease in Japan: a cross-sectional study

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ABSTRACT

Objectives Weight gain after 20 years of age is associated with chronic kidney disease (CKD). However, the impact of weight gain on CKD might differ by current obesity status. We investigated the association of the combination of weight gain after 20 years of age and current obesity with CKD among adults in Japan.

Design A cross-sectional study.

Setting and participants We analysed data from 94 822 adults aged 40–64 years who had an annual health check-up in Japan from April 2013 to March 2014.

Primary outcome measure CKD was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m² and/or proteinuria.

Results Both weight gain ≥10 kg after 20 years of age plus obesity (OR 2.21, 95% CI 2.07 to 2.36) and weight gain of ≥10 kg plus non-obesity (OR 1.31, 95% CI 1.21 to 1.42) significantly increased the OR for CKD when compared with weight gain <10 kg plus non-obesity in men. In women, weight gain ≥10 kg plus obesity (OR 2.04, 95% CI 1.84 to 2.25) and weight gain ≥10 kg plus non-obesity (OR 1.53, 95% CI 1.36 to 1.72) significantly increased the OR for CKD compared with weight gain <10 kg plus non-obesity. These results persisted even after adjustment for age, lifestyle factors, hypertension, dyslipidaemia and diabetes.

Conclusions Weight gain ≥10 kg after 20 years of age was significantly associated with CKD in both obese and non-obese subjects. Moreover, the influence of weight gain ≥10 kg plus obesity on CKD was greater than that of weight gain ≥10 kg plus non-obesity on CKD. The present study results suggest that it is important to consider weight gain after maturity in both obese and non-obese subjects to prevent CKD among Japanese middle-aged adults.

INTRODUCTION

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease.1 In addition, CKD is a progressive disease associated with a continuous decrease in glomerular filtration rate, leading to end-stage renal disease (ESRD).2 ESRD is a serious health outcome with both high economic and social costs, requiring dialysis or transplantation to sustain life.3 Thus, on a global basis, one can see that CKD is both a public health problem and a socioeconomic issue.4

The proportion of patients with CKD is higher in Japan than in other countries.5 In Japan in 2005, it was estimated that about 13.3 million people (approximately 13% of the adult population) had CKD.6 Moreover, Japan is one of the countries with the highest incidence of ESRD, and the number of Japanese patients with ESRD has increased over the past four decades.7 In addition, cardiovascular disease, anaemia and bone disease were reported to be complications of CKD.8 Therefore, it is very important to prevent CKD for the prevention of ESRD and CKD-related complications in Japan.

For the prevention of CKD, it is effective to focus on factors associated with this disease, and in particular, those factors that can be modified. A previous study showed that increases in body weight are associated with an increased risk for CKD.9 In addition, weight gain after 20 years of age is associated with CKD.10 However, the impact of weight gain on CKD might differ by current obesity status. Thus, it is important...
to examine the association between weight gain and CKD by considering current obesity status. We hypothesised that weight gain after 20 years of age is a risk factor for CKD regardless of current obesity status, and that people who had experienced weight gain after age 20 and are currently obese had higher risk for CKD than those who had experienced weight gain after age 20 but are currently not obese.

Accordingly, we investigated the association of the combination of weight gain after 20 years of age and current obesity with CKD among adults in Japan.

METHODS
Subjects
This was a cross-sectional study that used data from men and women aged 40–64 years old who had an annual health check-up conducted by the All Japan Labor Welfare Foundation, a health service centre in Japan,11 from 1 April 2013 to 31 March 2014. Subjects were mainly Japanese workers but included a small number of their dependents and foreign workers. Of 310 577 subjects, 310 498 participated in the present study. Of 310 498 participants, serum creatinine levels were measured in 129 910. We excluded 35 088 participants from the analysis due to missing data (body mass index (BMI): n=103, smoking status: n=2612, alcohol intake: n=2627, physical activity: n=2874, weight gain after 20 years of age: n=2734, systolic blood pressure: n=21, diastolic blood pressure: n=21, high-density lipoprotein cholesterol (HDL-C): n=114, low-density lipoprotein cholesterol (LDL-C): n=103, triglycerides: n=114, blood glucose level: n=29 697, haemoglobin A1c (HbA1c): n=2131 and proteinuria: n=769). Thus, 94 822 participants were analysed (figure 1).

Written informed consent for use of the data in this study was obtained from all participants.

Data collection
A self-administered questionnaire, which was recommended for specific health examination by the Ministry of Health, Labour and Welfare,11 was used to assess weight gain after 20 years of age, smoking status, alcohol intake and physical activity. The questionnaire was completed at the annual health check-up. Information on weight gain after 20 years of age was obtained by the question ‘Have you gained more than 10 kg after 20 years of age’,10 and study subjects were asked to answer either yes or no.

Height and weight of each subject were measured to the nearest 0.1 cm and 0.1 kg, respectively. The measurement was conducted by trained staff. BMI was calculated as weight (kg) divided by squared height (m). Blood pressure was measured in the sitting position using an automated machine (HEM-907, Omron, Kyoto, Japan).

A venous blood sample was collected, stored in a cooler at 4°C for transportation to an external laboratory (SRL, Tokyo, Japan), and HDL-C, LDL-C, triglycerides, blood glucose, HbA1c and creatinine levels were measured within 24 hours of blood being drawn. HDL-C and LDL-C were determined by a direct method (AU5400, Beckman Coulter, Brea, California, USA), and triglyceride levels were measured by an enzyme method (AU5400, Beckman Coulter). Blood glucose levels were obtained using the hexokinase method (AU5400, Beckman Coulter), and HbA1c was measured by a latex agglutination method (JCA-BM9130, JEOL, Tokyo, Japan). Serum creatinine levels were determined by an enzyme method (AU5400, Beckman Coulter). The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR=194×(serum creatinine−1.094)×(age−0.287)×(0.739 for women). Urinary analysis was performed by dipstick testing. Urinary protein levels were measured as −, ±, 1+, 2+ or 3+.

Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or taking medication for hypertension.11,12 Dyslipidaemia was defined as LDL-C ≥140 mg/dL, HDL-C <40 mg/dL, triglycerides ≥150 mg/dL or taking medication for dyslipidaemia.13 Diabetes was regarded as having a fasting plasma glucose (≥8 hours after the last caloric intake14) ≥126 mg/dL, a random plasma glucose ≥200 mg/dL, an HbA1c (National Glycohemoglobin Standardization Program) ≥6.5% or taking medication for diabetes.13

Definition of obesity and CKD
According to Japan Society for the Study of Obesity, obesity was defined as BMI ≥25 kg/m².15 In accordance with
previous studies, CKD was defined as eGFR <60 mL/min/1.73 m² and/or urinary protein of 1+, 2+ or 3+ (proteinuria).

### Statistical analyses

Data are presented as mean (SD) for continuous variables and n (%) for categorical variables. Because the distribution of data for triglyceride levels was highly skewed, data are shown as medians (25 percentile, 75 percentile). Unpaired t-test, Wilcoxon’s rank sum test or chi-squared test was used to compare characteristics between the group with weight gain ≥10 kg after 20 years of age and the group with weight gain <10 kg after 20 years of age. Logistic regression model was used to calculate the OR and 95% CI for CKD. First, a crude OR was calculated in the first model. A second model controlled for potential confounding factors, including age, smoking status, alcohol intake, physical activity, hypertension, dyslipidaemia and diabetes. A cross-product interaction term included in the logistic regression model was used to assess the interaction.

A p value <0.05 was considered statistically significant. Statistical analyses were performed using SAS software V.9.4 (SAS Institute).
Patient and public involvement statement
No patient was involved in the design and conception of the study.

RESULTS
Tables 1 and 2 show characteristics of study participants by weight gain after 20 years. The proportions of obesity, hypertension, dyslipidaemia, diabetes and proteinuria were significantly higher in participants with weight gain ≥10 kg after 20 years of age than in those without this weight gain. In addition, BMI, systolic blood pressure, diastolic blood pressure, LDL-C, triglycerides, blood glucose, HbA1c and creatinine levels were significantly higher in participants with weight gain ≥10 kg after 20 years of age than in those without this weight gain. In contrast, HDL-C and eGFR levels were significantly lower in participants with weight gain ≥10 kg after 20 years of age than in those without this weight gain. There were statistically significant differences in lifestyle factors (smoking status, alcohol intake and physical activity) between participants with and without weight gain ≥10 kg since 20 years of age. The proportion of CKD in participants with weight gain ≥10 kg after 20 years of age was significantly higher than that in those without the weight gain ≥10 kg.
To our knowledge, this is the first study examining the association with CKD regardless of current obesity status. A previous study showed that increases in body weight were associated with an increased risk for CKD, even when the BMI remained within the normal range.9 The results suggest that it is important to consider weight gain in adults for the prevention of CKD in both obese and non-obese subjects. Therefore, it might be necessary to monitor current obesity status as well as weight gain after 20 years of age to prevent CKD.

The reason weight gain after 20 years of age was associated with CKD might be due to an increased fat mass. A recent study showed that weight gain after maturity largely reflects an increase in fat mass.10 In addition, weight gain from early adulthood can be attributed mainly to the accumulation of adipocytes.22 Moreover, adipose tissue has been shown to be associated with insulin resistance, which is a key metabolic risk promoting CKD.23 Therefore, it is possible that weight gain after 20 years of age shows an increase in fat mass and the fat gain contributes to insulin resistance, resulting in the increased risk for CKD.

Although weight gain ≥10 kg after 20 years of age plus obesity and weight gain ≥10 kg after 20 years of age plus non-obesity were significantly associated with CKD, the influence of the weight gain plus obesity on CKD was greater than that of the weight gain plus non-obesity on CKD. In this study, the interaction of weight gain ≥10 kg after 20 years of age and obesity on CKD was statistically significant, suggesting that the combination of these factors may have a substantial impact on CKD. Weight gain during adulthood was reported to be associated with CKD.

### DISCUSSION

**Summary findings**

The present study investigated the association of the combination of weight gain ≥10 kg after 20 years of age and current obesity with CKD. Results showed that weight gain ≥10 kg after 20 years of age was significantly associated with CKD regardless of current obesity status. To our knowledge, this is the first study examining the association between ‘the combination of weight gain after 20 years of age and obesity’ and CKD.

### Association of the combination of weight gain after 20 years of age and current obesity with CKD

In our study, weight gain after 20 years of age was significantly associated with CKD regardless of current obesity status. A previous study showed that increases in body weight were associated with an increased risk for CKD, even when the BMI remained within the normal range.9 The results suggest that it is important to consider weight gain in adults for the prevention of CKD in both obese and non-obese subjects. Therefore, it might be necessary to monitor current obesity status as well as weight gain after 20 years of age to prevent CKD.

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### Table 3 Association between ‘the combination of weight gain of ≥10 kg after 20 years of age and obesity’ and CKD by sex

|                      | Total   | CKD               | Crude              | Adjusted            |
|----------------------|---------|-------------------|--------------------|---------------------|
|                      | N       | n (%)             | OR (95% CI)        | OR (95% CI)         |
| **Men**              |         |                   |                    |                     |
| Weight gain of ≥10 kg and obesity | 16521   | 1974 (12.0)       | 2.21 (2.07 to 2.36) | 1.92 (1.79 to 2.06) |
| Weight gain of ≥10 kg and non-obesity | 12980   | 967 (7.5)         | 1.31 (1.21 to 1.42) | 1.22 (1.13 to 1.33) |
| Weight gain of <10 kg and obesity | 3975    | 428 (10.8)        | 1.97 (1.76 to 2.20) | 1.79 (1.60 to 2.01) |
| Weight gain of <10 kg and non-obesity | 32324   | 1870 (5.8)        | 1.00               | 1.00                |
| **Women**            |         |                   |                    |                     |
| Weight gain of ≥10 kg and obesity | 4369    | 622 (14.2)        | 2.04 (1.84 to 2.25) | 1.89 (1.70 to 2.10) |
| Weight gain of ≥10 kg and non-obesity | 3504    | 388 (11.1)        | 1.53 (1.36 to 1.72) | 1.43 (1.27 to 1.61) |
| Weight gain of <10 kg and obesity | 1276    | 157 (12.3)        | 1.72 (1.44 to 2.05) | 1.66 (1.39 to 1.98) |
| Weight gain of <10 kg and non-obesity | 19873   | 1499 (7.5)        | 1.00               | 1.00                |

Adjusted for age, smoking status, alcohol intake, physical activity, hypertension, dyslipidaemia and diabetes.

CKD, chronic kidney disease.
CKD. Moreover, Gelber et al reported that compared with those who remained within \( \pm 5\% \) of their baseline BMI, those who reported a BMI increase \( >10\% \) had a significant increase in risk for CKD. In addition, a recent study reported that obesity was associated with CKD. Thus, there might be a synergistic impact of weight gain and obesity on CKD. Further studies are needed to elucidate the biological mechanism of this impact.

Other implications
In this study, 2.7% in men and 4.9% in women had CKD without proteinuria, hypertension and diabetes. In addition, the proportion of participants with CKD without proteinuria, hypertension and diabetes was higher in participants with weight gain \( \geq 10\) kg after 20 years of age than in those without this weight gain. In Japan, the measurement of serum creatinine levels was not mandatory. Thus, our study findings suggest that it is necessary to measure serum creatinine levels among all middle-aged adults, especially those with weight gain \( \geq 10\) kg after 20 years of age, for the early detection of CKD.

Strengths and limitations
The strength of the present study is the large sample size (\( >90\) 000 participants), which contributes to the decrease in random error. Moreover, height and weight of study participants were measured by trained technicians, and these values were used to determine obesity in this study. However, our study has some limitations. First, weight gain in the present study was self-reported. However, it is possible that the influence of self-reported weight gain on the present results was not substantial, as the validity of recall of past body weight has been measured in several studies and tends to be high in young and middle-aged adults. Second, not all potential confounding factors were obtained in our study, which might affect findings. For instance, family history of CKD is reported to be associated with CKD. Therefore, the possibility of residual confounding was not addressed. Third, serum creatinine levels were measured in 129910 of 310498 participants in this study. The reason might be that the measurement of serum creatinine levels was not mandatory in Japan. Comparisons of characteristics between participants with and without serum creatinine levels showed that those with serum creatinine levels tended to be younger and to have a lower proportion of proteinuria than those without serum creatinine levels. These results could limit the generalizability of the present study findings to other populations. Finally, this study design was cross-sectional, which means that no causal relationship can be established. Further cohort studies are needed to establish causality.

CONCLUSIONS
Weight gain \( \geq 10\) kg after 20 years of age was significantly associated with CKD in both obese and non-obese subjects. Furthermore, the influence of the combination of weight gain \( \geq 10\) kg after age 20 plus obesity on CKD was greater than that of the weight gain plus non-obesity. The present study results suggest that it is important to consider weight gain after maturity in both obese and non-obese subjects to prevent CKD among Japanese middle-aged adults.

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