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Body mass index change and estimated glomerular filtration rate decline in a middle-aged population: health check-based cohort in Japan

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ABSTRACT

Background Obesity is a growing public health problem worldwide. We evaluated the mediators and association between changes in obesity metrics and renal outcomes in the general population.

Methods Using the Japanese nationwide health check-based cohort from April 2011 to March 2019, we selected individuals aged 40–74 years, with a baseline estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2, whose body mass index (BMI) change was assessed. The primary outcome was combined 30% decline in eGFR, eGFR <15 mL/min/1.73 m^2 and end-stage renal disease.

Results During 245 147 person-years' follow-up among 50 604 participants (mean eGFR, 83.7 mL/min/1.73 m^2; mean BMI, 24.1 kg/m^2), 645 demonstrated eGFR decline (incidence rate 2.6/1000 person-years, 95% CI: 2.4 to 2.8). We observed continued initial changes in BMI for over 6 years and a U-shaped association between BMI change and eGFR decline. Compared with 0% change in BMI, adjusted HRs for changes of −10%, −4%, 4% and 10% were 1.53 (95% CI: 1.15 to 2.04), 1.14 (95% CI: 1.01 to 1.30), 1.16 (95% CI: 1.02 to 1.32) and 1.87 (95% CI: 1.25 to 2.80), respectively. The percentage of excess risk of BMI increase (>4%) mediated by three risk factors (blood pressure, haemoglobin A1c and total cholesterol), was 13.3%.

Conclusion In the middle-aged Japanese population, both, increase and decrease in BMI were associated with subsequent eGFR decline. Changes in risk factors mediated a small proportion of the association between BMI increase and eGFR decline. Our findings support the clinical significance of monitoring BMI as a renal risk factor.

Strengths and limitations of this study

- Because Japan conducts annual health screenings on a national scale, this study was able to assess changes in obesity and subsequent renal outcomes longitudinally in this large-scale health check-up cohort among middle-aged participants.
- We were able to examine the associations of initial changes in body mass index (BMI) with subsequent renal outcomes over 6 years' follow-up.
- This study assessed how the change in obesity-related renal risk factors mediated the associations between BMI change and renal outcomes.
- We were unable to examine the mechanisms in detail, and unmeasured factors may confound the association between BMI change and renal outcomes.
- Because this study only included Japanese participants with relatively low BMI, careful generalisability of the results is necessary.

INTRODUCTION

Obesity rates are increasing worldwide,[1 2] and obesity itself has become a clinically and socially important issue. Obesity is known as a risk factor for the progression of non-communicable diseases (NCDs) such as cardiovascular disease, hypertension, diabetes, cancer and chronic kidney disease (CKD).[3–5] WHO recommends the use of body mass index (BMI) for the assessment of obesity-related health risks.[6–9] In 2008, the Japanese government introduced an annual health check programme to assess biometric and laboratory data, including BMI, in all adults aged 40 years or older.[10] To reduce premature death and disability caused by NCDs, prevention of CKD progression is one of the most frequently introduced strategies in public health policy globally. This is because patients with severe stage CKD are at high risk of cardiovascular disease and progression to end-stage renal disease, which often requires costly renal replacement therapy.

Clinical guidelines recommend monitoring obesity markers to reduce the obesity-related health risks of CKD in the general population.[11 12] Previous studies have reported that high BMI was a renal risk factor in high-risk populations such as hypertensive, diabetic or patients with CKD.[9 13–17] The value of obesity markers both, at specific timepoints and in respect to their changes across time, is of interest when determining their effect on

health outcomes. However, there is little evidence on the associations between changes in obesity metrics and renal outcomes and their mediators.

The aim of this study was to examine the association between a change in BMI and the subsequent estimated glomerular filtration rate (eGFR) decline in a middle-aged population; it also aimed to assess the mediators of obesity-related risk factors.

METHODS

Setting and participants

We extracted data from a nationwide health check database in Japan. The database contained annual health check data from the fiscal year (FY) 2011 to FY 2018 (April 2011 to March 2019) from nationwide employment-based health insurers in Japan—the Health Insurance Association for Architecture and Civil Engineering Companies. It is mandatory for employees to undergo this annual health check in Japan.

From this 8-year database, we developed the cohort. The first 2 years (FY 2011 and 2012) were used as the baseline period to define exposure variables and covariates, and the last 6 years (FY 2013–2018) were used as the follow-up period to define outcomes.

The analysis included participants aged 40–74 years. eGFR was estimated using the Japanese coefficient-modified CKD Epidemiology Collaboration equation, which has been validated for the Japanese population.[18 19] We excluded participants with progressed kidney disease (baseline eGFR<45 mL/min) and leanness (baseline BMI <18.5 kg/m^2). We finally analysed 50 604 participants. The study participants' selection process is summarised in figure 1.

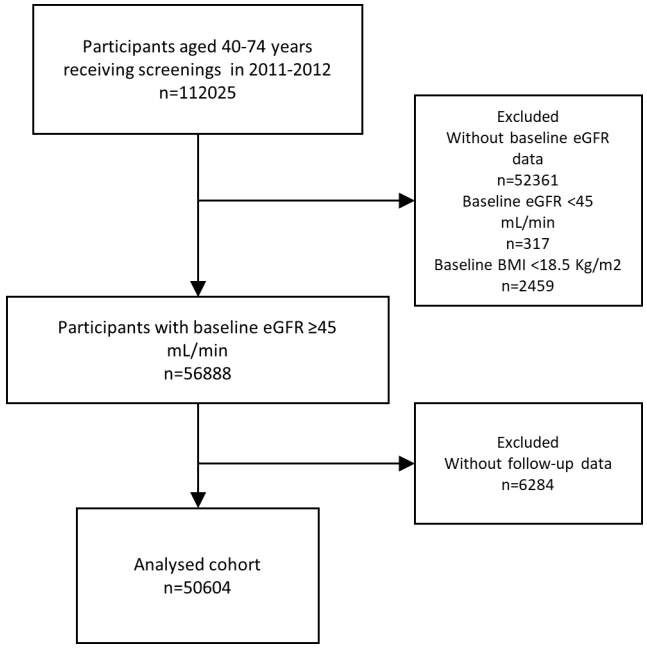

Figure 1 Study participants' selection process.

Exposures of BMI change

We defined changes in BMI using the first 2 years' health check data as our exposure variables. To assess the non-linear associations between exposure variable and outcome, we treated the exposure variable on a continuous scale using the restricted cubic spline function with five knots. BMI was calculated as weight (kg) divided by height (m) squared. According to the results of cubic spline function, we also defined BMI change categories as decreased (<−4%), stable (−4% to 4%) and increased (>4%).

eGFR decline

Our main outcome was eGFR decline during the 6-year follow-up period, which was a composite outcome including 30% eGFR decline, eGFR less than 15 mL/min/1.73 m^2 and end-stage renal disease, whichever occurred first. We followed the participants until incidence of eGFR decline or March 2019. The condition of the composite outcome that came first was defined as the endpoint. We used a 30% decline in eGFR as one of the criteria for eGFR decline because it is validated as an alternative endpoint for CKD progression.[20]

Adjusting factors

Basic characteristics (age and sex), current smoking ('Do you smoke now?'), eGFR, urine proteinuria by dipstick test (−, ±, +, 2+ or greater), haemoglobin A1c (HbA1c) level, systolic blood pressure (SBP), total cholesterol level and drug use (antidiabetic drugs, antihypertensive drugs and antihyperlipidaemic drugs) were measured. We used these measures from the results in FY 2011 as adjusting factors.

Statistical analysis

Baseline characteristics were described using means and SDs for continuous variables and counts and proportions for categorical variables (table 1).

We estimated adjusted HRs for eGFR decline, using a Cox regression model. Only 0.2% (n=122) and 0.6% (n=318) of participants had missing values for urine protein and HbA1c, respectively. Therefore, we included 99.1% (n=50 162) of all participants in the main model (complete case analysis). To examine non-linear associations between BMI change and eGFR decline, we used restricted cubic spline models with BMI change on a continuous scale. After running restricted cubic spline models, we estimated the adjusted HRs and corresponding 95% CIs at each value of change in BMI (each 2% from −10% to 10%) (figure 2). We also defined BMI change categories as decrease (<−4%), stable (−4% to 4%) and increase (>4%). We estimated adjusted HRs of BMI increase and percentage of excess risk medicated (PERM)[21 22] by obesity-related renal risk factors (change in SBP, HbA1c, total cholesterol and their combinations) (table 2). PERM was calculated as follows:

$$\text{PERM} = \frac{\text{HR(confounders adjusted)} - \text{HR(confounders and mediators added)}}{\text{HR(confounders adjusted)} - 1} \times 100$$

Table 1 Participant characteristics by change in BMI

Variables	Total (N=50 604)	Change in BMI: Decreased <−4% (n=4719)	Stable −4% to 4% (n=41 223)	Increased >4% (n=4662)
Age, mean (SD), years	50.1 (7.4)	49.3 (7.2)	50.3 (7.4)	48.5 (7.1)
Male, n (%)	40 639 (80.3)	3855 (81.7)	33 042 (80.2)	3742 (80.3)
eGFR, mean (SD), mL/min/1.73 m^2	83.7 (8.6)	84.3 (8.5)	83.5 (8.5)	84.9 (8.6)
Urinary protein, n (%)				
–	44 709 (88.6)	4133 (87.8)	36 591 (89.0)	3985 (85.7)
±	3551 (7.0)	349 (7.4)	2787 (6.8)	415 (8.9)
+	1593 (3.2)	158 (3.4)	1256 (3.1)	179 (3.8)
++ or greater	629 (1.3)	69 (1.5)	487 (1.2)	73 (1.5)
BMI, mean (SD), kg/m^2	24.1 (3.3)	25.0 (3.6)	24.0 (3.3)	23.6 (3.3)
SBP, mean (SD), mm Hg	126.0 (15.9)	127.7 (16.1)	125.9 (15.9)	124.5 (16.0)
DBP, mean (SD), mm Hg	77.0 (11.8)	78.2 (11.4)	77.0 (11.9)	76.2 (11.3)
Haemoglobin A1c, mean (SD), %	5.6 (0.7)	5.7 (0.9)	5.6 (0.7)	5.6 (0.9)
Total cholesterol, mean (SD), mg/dL	215.8 (43.3)	219.5 (46.3)	215.9 (43.6)	211.5 (36.6)
Current smoking, n (%)	15 639 (30.9)	1487 (31.5)	12 544 (30.4)	1608 (34.5)
Antihypertensive drug, n (%)	7535 (14.9)	650 (13.8)	6281 (15.2)	604 (13.0)
Antidiabetic drug, n (%)	2072 (4.1)	235 (5.0)	1667 (4.0)	170 (3.6)
Antihyperlipidaemic drug, n (%)	4071 (8.0)	351 (7.4)	3389 (8.2)	331 (7.1)

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

To see longitudinal BMI change, we described BMI change over the 6-year follow-up time (FY 2013–2018) according to the initial BMI change categories (figure 3). To compare longitudinal BMI change from 2013 to 2018 between groups of the initial BMI change, we used generalised estimating equations with robust variance.

To assess changes in risk factors by BMI change categories, we compared the change in SBP, diastolic blood pressure (DBP), HbA1c and total cholesterol (online supplemental table 1). P values for differences between categories were estimated from analysis of variance.

All analyses were performed using Stata V.5.1 (StataCorp, College Station, Texas, USA). All tests were two sided; P values<0.05 were considered statistically significant.

Additional analyses

First, to assess the effect of baseline BMI on the associations between BMI change and eGFR decline, we conducted subgroup analyses according to baseline BMI values (<25 and ≥25 kg/m^2). Second, we conducted subgroup analysis (baseline eGFR 45–59 and ≥60 mL/min) to assess the effect of baseline eGFR on associations between BMI change and eGFR decline. Third, to assess the robustness of our results to the presence of drug utilisation at baseline, we conducted a mediation analysis among drug-naive participants. Fourth, to assess the robustness of our mediation analyses to for the cut-off values of BMI, we conducted additional analyses using different cut-off values of BMI change (2% and 6%) (online supplemental table 2). Fifth, to assess the robustness of our results to the presence of drugs utilisation at baseline, we conducted a mediation analysis among drug-naive participants (online supplemental table 3). Finally, to assess the generalisability of our results, we described differences in characteristics between our study population, excluded participants with missing eGFR measurements and the general Japanese population (online supplemental tables 4 and 5). For this purpose, we extracted data from the online portal for the official statistics of Japan (http://www.e-stat.go.jp/).

Patient and public involvement

This research was performed without patient involvement. Patients were not invited to comment on the study design and were not consulted while developing patient-relevant outcomes or interpreting the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Participants' characteristics and renal outcomes

We analysed data from 50 604 participants aged 40–74 years. The mean participant age was 50.1 years, 80.3% of participants were male, and the mean eGFR was 83.7 mL/min/1.73 m^2 at baseline. Regarding BMI change, 4719 (9.3%) of participants had a decreased BMI (<−4%), and 4662 (9.2%) had an increased BMI (>4%). During the follow-up of 245 147 person-years, we found 645 cases of

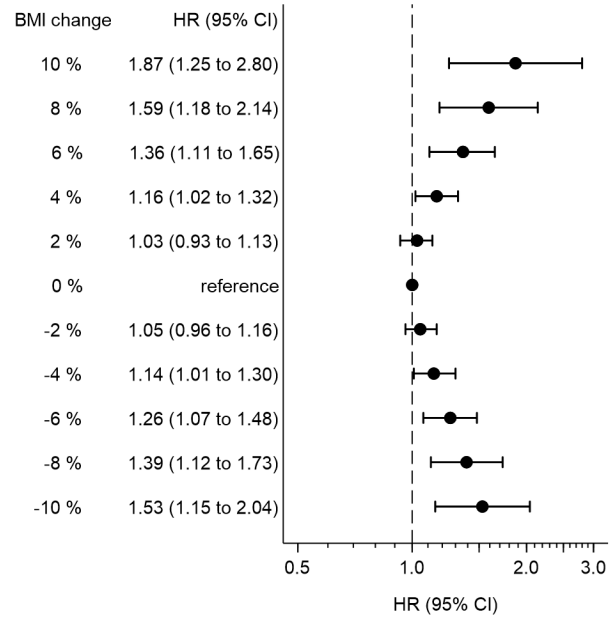

Figure 2 BMI change and eGFR decline. We estimated adjusted HRs for eGFR decline according to changes in BMI. We used a cubic spline Cox regression model with BMI changes on a continuous scale. We adjusted for potential confounders including age, sex, current smoking, estimated GFR, urinary protein, HbA1c levels, total cholesterol levels, systolic blood pressure, antihypertensive drug use, antidiabetic drug use and antihyperlipidaemic drug use. The eGFR decline was a composite outcome including 30% eGFR decline, eGFR less than 15 mL/min/1.73 m^2 and end-stage renal disease, whichever occurred first. BMI, body mass index; eGFR, estimated glomerular filtration rate.

eGFR decline. The incidence rate of eGFR decline was 2.6 per 1000 person-years (95% CI: 2.4 to 2.8).

Age was higher, and eGFR was lower in the 'Stable' BMI group, compared with the other groups. Baseline BMI, blood pressure and total cholesterol were higher in the 'Decreased' BMI group compared with the other groups. Participants in the 'Increased' BMI group were more likely to be smokers.

The study population was slightly healthier (younger age, lower use of medications and lower blood pressure) compared with the age-standardised general Japanese population (online supplemental table 5).

BMI change and eGFR decline

We found a U-shaped association between BMI change and eGFR decline (figure 2). Compared with 0% change in BMI, adjusted HRs for changes of −10%, −4%, 4% and 10% were 1.53 (95% CI: 1.15 to 2.04), 1.14 (95% CI: 1.01 to 1.30), 1.16 (95% CI: 1.02 to 1.32) and 1.87 (95% CI: 1.25 to 2.80), respectively.

Mediators for the associations between BMI increase and eGFR decline

The associations between BMI increase and eGFR decline attenuated after adjusting for mediators. Blood pressure, HbA1c and total cholesterol mediated 9.7%, 1.9% and 0.2% of excess risk, respectively. The percentage of excess risk mediated by three obesity-related renal risk factors (blood pressure, HbA1c and cholesterol) was 13.3% (table 2).

Table 2 HRs of BMI increase and PERM by obesity-related renal risk factors

Models: added variables of change in risk factors	HR (95% CI)	PERM
Original model	1.41 (1.10 to 1.82)	–
Model 1: blood pressure	1.37 (1.07 to 1.77)	9.7%
Model 2: Haemoglobin A1c	1.41 (1.09 to 1.81)	1.9%
Model 3: total cholesterol	1.41 (1.10 to 1.81)	0.2%
Model 4: blood pressure and HbA1c	1.36 (1.06 to 1.76)	11.9%
Model 5: blood pressure and total cholesterol	1.37 (1.07 to 1.76)	10.0%
Model 6: HbA1c and total cholesterol	1.40 (1.09 to 1.80)	3.2%
Model 7: blood pressure, HbA1c and total cholesterol	1.36 (1.06 to 1.75)	13.3%

We estimated HRs of BMI increase (>4%) for eGFR decline, compared with stable BMI (−4% to 4%), in models (Model 1 to Model 7) with different adjustment variables of change in obesity-related risk factors. All HRs were adjusted for age, sex, current smoking, estimated GFR, urine protein, Haemoglobin A1c levels, total cholesterol levels, systolic blood pressure, antihypertensive drug use, antidiabetic drug use, and antihyperlipidaemic drug use. PERM were estimated as follows:

$$\text{PERM} = \frac{\text{HR(confounders adjusted)} - \text{HR(confounders and mediators added)}}{\text{HR(confounders adjusted)} - 1} \times 100$$

BMI, body mass index; PERM, percentage of excess risk medicated.

Longitudinal BMI change according to initial change in BMI

We described longitudinal percent change in BMI according to initial changes in BMI (figure 3). We found continued BMI decrease in the 'Decreased' group (−3.9% (95% CI: −4.1 to −3.8)), and continued BMI increase in the 'Increased' group (5.0% (95% CI: 4.8 to 5.1)), compared with the 'Stable' group.

Change in risk factors by BMI change

We found an increase in SBP, DBP and total cholesterol in the 'Increased' BMI group, and decrease in SBP, DBP, HbA1c and total cholesterol in the 'Decreased' BMI group, compared with the 'Stable' BMI group (online supplemental table 1).

Additional analyses

Similar U-shaped associations between BMI change and outcome were found in both non-overweight and overweight participants (online supplemental figure 1). Among participants with eGFR ≥60 mL/min (n=49 865), we found similar associations to those of our original analysis. However, we did not find significant associations

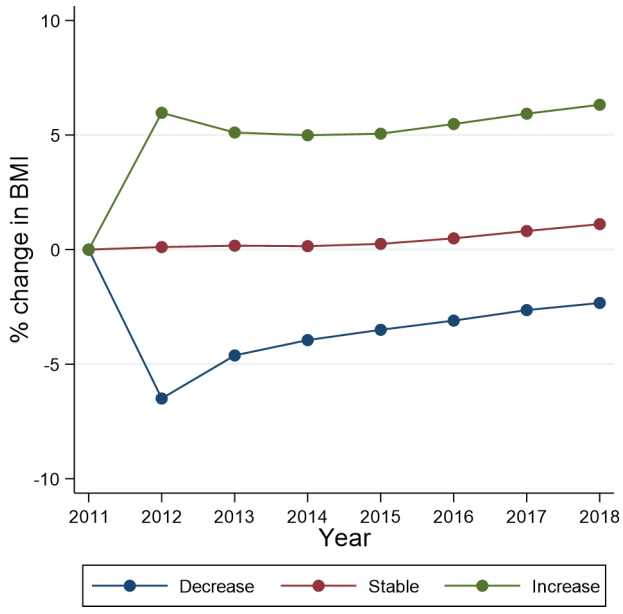

Figure 3 Longitudinal BMI change according to initial change in BMI. We described longitudinal BMI change according to initial changes in BMI. The initial change in BMI was defined as 'Decreased (<−4% change between 2011 and 2012)', 'Stable (−4% to 4% change between 2011 and 2012)' and 'Increased (>4% change between 2011 and 2012)'. We estimated differences in BMI from 2013 to 2018 between the initial change groups using generalised estimating equations with robust variance. We found continued lower BMI in the 'Decreased' group (−3.9% (95% CI: −4.1 to −3.8)) and continued higher BMI in the 'Increased' group (5.0% (95% CI: 4.8 to 5.1)) compared with that in the 'Stable' group. BMI, body mass index; eGFR, estimated glomerular filtration rate.

with wide confidence intervals among participants with eGFR 45–59 mL/min. Owing to the small sample size (n=739) of participants with eGFR 45–59 mL/min, we were not able to discuss the differences between those subgroups (online supplemental figure 2). A small percentage of excess risk mediated by obesity-related risk factors was consistent in drug-naive participants (online supplemental table 3). The results of mediation analyses were not qualitatively unaffected by different cut-off values of BMI (online supplemental table 2). Participants characteristics were similar between participants with and without eGFR measurements (online supplemental table 4). The study participants tended to be predominantly male, use fewer drug users and have lower blood pressure compared with the general Japanese population.

DISCUSSION

In this large health check-based cohort study of a general middle-aged population, we found that both increase and decrease in BMI were associated with a higher incidence of GFR decline after adjusting for basic characteristics, metabolic risk factors, baseline kidney function and medication use. The initial change in BMI continued across 6 years of follow-up. Only a small portion of the association between BMI increase and GFR decline was mediated by obesity-related risk factors. These results indicate the importance of monitoring and maintaining BMI for renal protection in the general population. Therefore, as a public health programme, it may be possible to curtail the deterioration of kidney function by identifying the population at high risk of poor renal outcomes based on changes in BMI.

Previous studies have focused on obesity status at specific timepoints (absolute values),[13 14 23] but not on changes in obesity status.[24] In addition to confirming renal risks with higher baseline BMI values, we identified renal risks with BMI gain and BMI loss. We found an association between stable BMI and lower incidence of GFR decline. We added evidence on the clinical significance of monitoring changes in BMI for the prevention of kidney function deterioration in the general population. Since Japan conducts annual health screenings on a national scale, this study was able to assess changes in obesity and subsequent renal outcomes longitudinally. Relatively short-period changes in obesity status may reflect recent lifestyle shifts, and those changes in obesity status would persist for a longer period. Monitoring these changes would be helpful for lifestyle guidance in renal protection.

The association between BMI increase and GFR decline may be partially explained by deterioration in other obesity-related renal risk factors of blood pressure, blood glucose and blood lipid. In the 'Increased' BMI group, we found an increase of 2.6 mm Hg, 1.7 mm Hg, 0.05 % and 8.6 mg/dL in the SBP, DBP, HbA1c and total cholesterol, respectively. However, only a small portion of the associations between BMI increase and GFR decline was mediated by changes in those obesity-related renal risk factors. Some studies have reported that adiposity may increase the burden on the kidney, such as an excessive glomerular filtration, activation of the renin–angiotensin–aldosterone system, oxidative stress and microinflammation.[16 25 26] Nevertheless, our health check-based data did not include precise data on these factors; we were, therefore, unable to examine these mechanisms in detail. Concurrently, the association between BMI decrease and GFR decline has not been well examined. BMI decrease can lead to worsening renal function through the induction of inflammatory conditions, dehydration and decreased cardiac function, among other conditions.[23 27–29] While maintaining BMI is indicative of a good lifestyle, a change in BMI (both, increase and decrease) may indicate a bad lifestyle. An increasing BMI may be caused by a high-calorie diet[30 31] and less exercise,[32] which places a burden on the kidneys. A decreasing BMI may be caused by strict protein restriction[33] or signs of deteriorating health conditions (eg, undiagnosed comorbidities).[34] In addition, the U-shaped associations between BMI change and eGFR decline were qualitatively similar between the non-overweight and overweight groups (online supplemental figure 1). These results suggest that the clinical significance of the change

in BMI is independent of the baseline BMI level. We were not aiming to verify the causal effect of BMI decrease in this study. It is considered that unmeasured confounding factors in this study may affect the association between BMI change and GFR decline. Future studies need to consider the mechanisms that may underlie these outcomes.

Although this was a large-scale study based on annual health check-up data for obesity and renal outcomes of the general population of middle-aged adults, some limitations should be considered. First, our observational study analysed annual health-check data, which did not include some renal risk factors, such as nephrotoxic drug use, haemodynamic change and other laboratory markers. Second, eGFR is an estimate, but not a direct measure of GFR. For instance, eGFR may be overestimated in lean participants, while the reverse is true in muscular participants.[35–37] In view of these limitations, the use of eGFR is realistic in this large-scale study and is in line with previous studies. Third, proteinuria was measured by dipstick testing only once at baseline. Quantitative and multiple measurements of proteinuria could not be examined in this study. Fourth, there were no validated cut-off values for BMI change. Therefore, we used restricted cubic spine models to consider non-linear associations without specific cut-off values of BMI change. The cut-off value of 4% of BMI change in mediation analysis was defined by the distribution of BMI change (the values of 10% and 90% fractional point). These cut-offs were found to be reasonable choices in terms of their significant associations with a decline in eGFR (figure 2). In addition, the results of mediation analyses were robust for different cut-off values of BMI (online supplemental table 3). Fifth, given that our study focused on screened participants covered by Japanese employment-based health insurance, many of them were working-age men. Therefore, our findings may not be generalisable to the general population. Sixth, we excluded participants who did not undergo measurement of eGFR data. In the health screening programme, eGFR measurement is an option added to the health check-up programme on a per-company basis. Therefore, whether the measure was taken or not did not depend on the choice of the individual participants. As expected, the participants' characteristics were similar between those who did and did not undergo measurement (online supplemental table 4). Therefore, the effect of selection bias caused by the presence or absence of eGFR measurement was assumed to be small. we excluded participants without measurement of eGFR data. In the health screening programme, eGFR measurement is an option that is added to the health check-up programme on a per-company basis. Therefore, the choice by individual participants did not affect whether or not the measure is taken. As expected, the participants characteristics were similar between measurers and non-measurers (online supplemental table 4). Therefore, the effect of selection bias caused by the presence or absence of eGFR measurement is assumed to be small. We also found that the study participants were slightly healthier compared with the age-standardised general Japanese population. Furthermore, the mean BMI in this Japanese population is 24.1 kg/m^2, which is relatively low compared with other countries such as the USA.[38] Future research is needed to analyse populations with more obese participants. Finally, this study included only Japanese participants. A previous study reported racial differences in associations between obesity and renal risk factors.[17] As health risks due to obesity are increasing globally, future studies need to confirm the associations found in the present study in populations of other countries. Considering these research design limitations, careful interpretation of the current results and their generalisability is necessary.

In conclusion, this study found that both an increase and a decrease in BMI were associated with a higher incidence of GFR decline in a middle-aged Japanese population. The initial change of BMI continued over 6 years. Only a small portion of the associations between BMI increase and GFR decline may be explained by changes in blood pressure, blood glucose and blood lipids. These results suggest that changes in BMI can be considered renal risk factors, and that monitoring these indicators may help physicians and public health nurses identify individuals at risk of poor renal outcomes among middle-aged adults in the general population.

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Contributors SF conceived the study and acquired data permissions. SF and TI designed the study. TI managed the data and established the cohort. All authors reviewed the literature. SF performed the data analyses. All authors participated in the discussion and interpretation of the results. SF organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. SF, the corresponding author, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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