Scientific Reports
https://doi.org/10.1038/s41598-026-39383-w
Article in Press

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Received: 15 June 2025
Accepted: 4 February 2026
Published online: 08 February 2026
Cite this article as: Fujii H., Kodani E., Kaneko T. *et al.* One-year body weight loss and gain as independent predictors of frailty-related outcomes and mortality in an aging Japanese population. *Sci Rep* (2026). https://doi.org/10.1038/s41598-026-39383-w

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Title

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Abstract

This study investigates short-term fluctuations in body weight (BW) as potential early indicators of frailty and their association with subsequent adverse outcomes in an aging Japanese population. Using longitudinal data from Tama City's national health insurance cohort, we examined adults aged 40 years and older who had BW measurements at baseline (2016) and a follow-up in 2017, with subsequent health, nursing-care, and mortality data through 2023. Participants were categorized into three BW-change groups between 2016 and 2017: weight loss of 5% or more (n=1,080), weight change within ±5% (13,661), and weight gain of 5% or more (959). Kaplan–Meier analyses demonstrated that BW change within one year was associated with higher incidences of dementia onset, hospitalization for congestive heart failure, need for long-term care, and all-cause mortality, with the pattern BW loss > BW gain > stable in event rates ($p<0.05$). Multivariate Cox proportional hazards models identified BW loss as an independent predictor for multiple adverse outcomes, including bone fracture, dementia, need for long-term care, stroke, CHF, and all-cause mortality. BW gain also had a significantly higher incidence of need for care (Hazard Ratio 1.159) and mortality (1.491). Medications such as hypnotics, proton pump inhibitors, anticoagulants, and antihypertensives, and sodium-glucose cotransporter 2 inhibitors were significantly predicted specific conditions related to frailty and/or atherosclerotic conditions.

The findings in our study suggest that both short-term BW reductions and increases can signal imminent frailty development in older adults, potentially mediated by malnutrition, sarcopenia, edema, or fluid overload. BW dynamics, together with routine biomarkers (creatinine, Hb, ALT, lipid profiles), appear valuable for risk stratification and timely intervention in community-dwelling older adults.

Clinically, these results advocate for dynamic nutritional surveillance and integrated management strategies aimed at maintaining weight stability and addressing reversible contributors to BW fluctuations. Limitations include the observational design and the specific regional, publicly insured cohort, which may limit generalizability. The causal relationships between specific medications and conditions related to frailty remain unclear. Further studies across diverse populations are warranted to confirm causal links between BW dynamics, frailty trajectories, and related health outcomes.

Keywords: Frailty, dementia, bone fracture, need for care, mortality, polypharmacy

Introduction

With rapid population aging in Japan, overcoming frailty and extending healthy lifespan is critical both for improving public health and reducing the associated economic burden. In Tama City, a western suburb of Tokyo, 28.9% of the population was more than 65 years old in 2021. The local government of Tama City is taking steps to support older individuals to maintain their health and ability to perform activities of daily living,

The TAMA CITY Medical Association and Nippon Medical School, Tama Nagayama Hospital have been cooperating to investigate the risk factors for the development of health conditions such as frailty [1,2,3], atrial fibrillation (AF) [4,5], and chronic kidney disease (CKD) [6,7,8], and to educate health care providers and citizens. We have made cooperating relationship with Tama city itself, so we have had the opportunities to discuss with local government officers and public health nurses. We also had lectures for the citizens in Tama city. From health professional points of view to intervene people's lifestyle to prevent non-communicable diseases, the target conditions were gradually moved from cardiovascular disease to the diseases draw frail and needs of care. We considered watching over the body weight change is quite a simple way to apply to public health practice. The fact that frailty develops with BW loss and low BMI have been well known, however the influence of BW gain in short term has not been discussed. Therefore, we decided to study both side of fluctuation. We focused on weight change in a short time period (change from baseline within 1 year) to identify the relationship with subsequent comorbidities and disabilities.

Methods

Subjects

We obtained data for baseline and seven consecutive years (2016 to 2023) from the Kokuho national health insurance database. 22,981 individuals who were 40 years and older, underwent annual health checkups in the 2016 fiscal year (from April 2016 to March 2017), 17,305 of them had paired body weight data in annual checkup data in 2017 fiscal year (from April 2017 to March 2018). Finally, we selected15,700 data that had follow-up data in medical and welfare receipt after 2017 fiscal year (Figure S1 in the Supplementary Appendix, and Figure 1). We collected information about diagnosis, such as bone fracture, dementia, cancer, cardiovascular and cerebrovascular diseases, congestive heart failure (CHF), hospitalizations, assessment of the need for long-term nursing care, death, and pharmacotherapies from 2017 to 2023.

Variables

As baseline variables, we selected data in 2016 such as sex, age, body mass index (BMI), systolic blood pressure (sBP: mmHg) and diastolic blood pressure (dBP: mmHg), pre-metabolic syndrome (pre-MetS), and MetS. MetS was defined as waist circumference (WC) ≥ 85 cm in males, ≥ 90 cm in females, plus ≥ 2 of the following three factors: (1) high-density lipoprotein cholesterol (HDL-c)< 40 mg/dL or triglyceride (TG) ≥ 150 mg/dL or medication for hyperlipidemia; (2) fasting plasma glucose ≥ 110 mg/dL or medication for diabetes; and (3) blood pressure ≥ 130 mm Hg in sBP and/or 85 mm Hg in dBP or taking an antihypertensive. pre-MetS was defined by waist ≥ 85 cm in males, ≥ 90 cm in females plus one of the three factors. Additionally, we used WC, albumin (ALB: g/dL), estimated glomerular filtration rate (eGFR: mL/min/1.73m^2), creatinine (Cr: mg/dL), Hemoglobin (Hb: g/dL), and HbA1c (%).

As dependent variables, we used medical and welfare receipt records from 2017 to 2023 to identify hospitalizations, and diagnosis used the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10) for CHF (I500), bone fracture (M80, S00-T14), and cancer (C00-C97). The diagnosis of bone fracture and CHF were confirmed with hospitalization to limit the sample to relatively serious conditions. The presence of diabetes and dementia was defined by diagnosis and start of medications to guarantee the reliability of diagnosis. Need for care was defined by the certification of the long-term care insurance system.

Medication was defined as prescription more than four times per year (for dementia, more than once a year) and classified as follows.

Anticoagulants: Warfarin, dabigatran, rivaroxaban, apixaban, edoxaban.

Antiplatelet drugs: Clopidogrel sulfate, ticlopidine hydrochloride, prasugrel hydrochloride, triflusal, oxagrelate sodium hydrate, oxagrel sodium, aspirin, dipyridamole, epoprostenol sodium, beraprost sodium, triflusal, cilostazol, selexipag, caplacizumab, nicorandil, ramiprost alpha-decanone, sarpogrelate hydrochloride, eicosapent ethyl.

Antihypertensive drugs: Angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, calcium channel blockers, thiazide diuretics.

Diabetes medications: Biguanides, thiazolidinediones, sulfonylureas, glinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, alpha-glucosidase inhibitors, sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors), insulins.

Bisphosphonates: Etidronate disodium, pamidronate disodium hydrate, alendronate sodium hydrate, ibandronate sodium hydrate, risedronate sodium hydrate, zoledronic acid hydrate, minodronate hydrate.

Proton pump inhibitors (PPIs): Omeprazole, omeprazole sodium, lansoprazole, rabeprazole sodium, esomeprazole magnesium hydrate, pantoprazole fumarate.

Histamine 2 blockers (H2B): Cimetidine, famotidine, nizatidine, ranitidine oxychloride, rofecoxib.

Dementia medications: Donepezil hydrochloride, rivastigmine, galantamine hydrobromide, memantine hydrochloride.

Sleep medications: Benzodiazepines, barbiturates, and thiobarbiturates, other hypnotic sedatives and anxiolytics, chlorpromazine, phenothiazines, tricyclic antidepressants, difenylmethane, butyrophenones, tetracyclic antidepressants, indole derivatives, benzamides, lithium, difenylbutylpiperazine, other antipsychotics, serotonin-noradrenaline reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, other antidepressants, organic bromide compounds, hydrated chloral derivatives, bromide salts, and other neuropsychiatric medications.

Statins: Atorvastatin, simvastatin, rosuvastatin, pravastatin, fluvastatin, pitavastatin.

Comparison among body weight-change groups at baseline

We classified subjects into three groups according to the change in their body weight (BW; kg) between 2016 and 2017 and divided them into three groups: A (individuals whose BW decreased by 5% or more), B (individuals whose BW changed less than 5%), C (individuals whose BW increased by 5% or more). We compared baseline data: numbers, sex, BMI, WC, MetS, medications; for diabetes, sleep, hypertension, statins, bisphosphonate, anticoagulant (and antiplatelets), PPIs, H2Bs, Cr, eGFR, TG, HDL-c, low-density lipoprotein cholesterol (LDL-c; mg/dL), aspartate aminotransferase (AST; IU/L), alanine aminotransferase (ALT; IU/L), γ-glutamyl transpeptidase (γ-GTP: IU/L), HbA1c, Hb, uric acid (UA; mg/dL), sBP, dBP. We analyzed the data using chi-squire tests for categorical data, and Kruskal–Wallis tests for continuous data.

Kaplan–Meier method and log-rank test among three BW-change groups

We performed Kaplan–Meier analysis and diagnosis and/or start medications for dementia, hospitalizations for CHF, certification of need for care, and death from all causes. The data were analyzed using the Kaplan–Meier method and log-rank tests. Additionally, post-hoc pairwise comparisons (Holm-Bonferroni method) between groups were used after significant log-rank tests to analyze whether these three BW groups at baseline had different event rates prospectively from one another. We also analyzed the events of hospitalization for bone fracture (Fig.S2), cerebral Infarction (Fig.S3), stroke (Fig.S4), myocardial infarction (Fig.S5).

Univariate and multivariate Cox proportional hazard analysis for BW loss

First, we conducted a univariate analysis of the relationship between weight loss and baseline factors, then performed multivariate analysis using all significant variables in a univariate analysis.

Multivariate Cox proportional hazard analysis for variable outcomes to be predicted

We selected the events (outcomes) that occurred after 2017 and obtained a hazard ratio for each of the baseline characteristics (in 2016) using a multivariate method. We included the characteristics of BW change in 1 year from 2016.

Statistical analysis

We analyzed categorical data using chi-square tests. For continuous variables, we used Kruskal–Wallis tests. We used the Cox proportional hazards test to identify prognostic factors and hazard ratios with 95% confidence intervals, and used Kaplan–Meier curves with log-rank tests to compare three BW-change groups on a timeline. All statistical tests were two-tailed, and $p<0.05$ was considered to indicate statistical significance. We used Python (version 3.9.21) for all of our statistical analyses, mostly the lifelines package for survival analysis and the stats model's package for Cox proportional hazards modeling. We used pandas and numpy to change the data. The figure of Kaplan–Meier curve was made with R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Age and body weight change distribution of the participants (Table1)

We collected 15,700 individuals (Figure 1, and S1) who were 40 years or older (93.5% was 60 years or older, 67.0% was 70 years and older), with paired BW of 2016 and 17, and medical and welfare receipt data. They were divided into three groups (Figure 1): group A (6.9% of all participants) contained individuals whose BW decreased by 5% or more in 1 year; group B (87.1%) contained individuals whose body weight changed less than 5% in 1 year; group C (6.1%) contained individuals whose BW increased by 5% or more in 1 year (Table 1).

Group A contained more women (61.9%), and more MetS (19.7%) than other groups, and individuals in this group were older, and took various medications other than SGLT2 inhibitors, insulins, and H2 blockers ($p < 0.05$; chi-square test). As well as having a lower eGFR, higher TG, lower HDL-c, higher AST and γ-GTP, higher sBP, and a higher number of medications compared with the other two groups ($p < 0.05$; Kruskal–Wallis test).

Kaplan–Meier curve and log-rank tests for three BW-change groups (Figure 2)

We performed Kaplan–Meier tests on the three BW-change groups at baseline: group A (lost weight, 5% of BW or more), B (weight change of less than 5% of BW), and C (gained weight, 5% of BW or more). Analysis of onset of dementia (diagnosis and start of medication, Fig. 2a), hospitalization for CHF (Fig. 2b), need for care (Fig. 2c), and all-cause mortality (Fig. 2d) indicated that the survival rates of the three BW groups were significantly different to each another, and the event rate increased in the order of A > C > B.

Also, in the analysis of the rates of hospitalization for bone fracture (Fig.S2), cerebral infarction (CI; Fig.S3), stroke (including cerebral infarction and hemorrhage; Fig.S4), angina pectoris, and myocardial infarction

(MI; Fig.S5), statistical significance was found in the results of Kaplan-Meier Analysis (Log-rank test $p<0.001$).

Multivariate Cox proportional hazard analysis of BW changes at baseline (Table 2)

In multivariate analysis using the Cox proportional hazard analysis for BW change of 5% or more, age, medications for sleep, antiplatelets, PPIs, Hb, sBP, HDL-c, and number of medications were the independent risk factors for BW decrease (left part of Table 2). Lower Hb and lower HDL-c were predictive factors for BW loss. For BW increase (right part of Table 2), medications for sleep, lower BMI at baseline, and lower Hb were found to be predictive factors.

Multivariate Cox proportional hazard analysis of predictors for events in future (Table 3)

Multivariable analysis using the Cox proportional hazard model was performed to predict future events such as hospitalization for bone fracture, onset of dementia, need for care, death, stroke, atrial fibrillation (AF), hospitalization for CHF, myocardial infarction (MI), and hospitalization for cancer.

Age was an independent risk factor in all events. Cancer, stroke, AF, and all-cause mortality. were more likely to occur in men, but bone fracture was more likely to occur in women. Sex was not a significant factor in dementia, CHF, MI, or the need for care.

Weight loss was an independent risk factor for most of the events, but not for AF, MI, nor cancer. Weight gain as well as weight loss was an independent risk factor for the need for care, and death.

Lower BMI at the baseline was a predictive factor for bone fracture, dementia, need for care, and death.

Metabolic syndrome (MetS), TG and UA were not significant factors for any conditions in multivariate analysis. SGLT2 inhibitors were weakly predictive only for stroke. Sleep medications were risk factors for bone fracture, dementia, stroke, and need for care. Taking bisphosphates was a risk for bone fracture, stroke, and need for care.

Both anticoagulant and antiplatelet therapy were predictive factors for stroke, AF, CHF, and death. However, dementia, MI, and need for care were only related to antiplatelet therapy.

Anti-hypertension medication was a predictive factor for AF, CHF, and MI. PPIs but not H2 blockers (H2B) were significant risk factors for bone fracture, need for care, stroke, AF, CHF, and MI.

Lower eGFR was predictive factor to all events except for cancer. Higher HbA1c was a risk factor to stroke and death. Lower Hb was a risk factor to bone fracture, dementia, need for care, death, and CHF. Higher sBP was a predictor for dementia, need for care, death, and also for stroke, AF, ands CHF but not for MI. Contrary, lower dBP was an independent risk factor for need for care, death, and CHF. Lower HDL-c was predictive for death and MI. Lower LDL-c was predictive for dementia, need for care, death and CHF but not for MI nor stroke in our study. Lower ALT was an independent risk factor for dementia, need for care, and death. Higher γ-GTP was predictive only for cancer. Number of medications was a risk factor for dementia, need for care, death, AF, CHF, CHF, and MI, but not for bone fracture, stroke, nor cancer.

Discussion

This study evaluated a population enrolled under the national health insurance system. The cohort had a mean age of 72.6 years (standard deviation 9.0), with 93.5% aged 60 years or older and 67.0% aged 70 years or older (Figure 1). The elderly subgroup was followed prospectively to characterize the development of comorbidity, frailty-related conditions, and mortality.

An event of BW loss of 5% or more occurred at an approximately 7% annual rate, with a slightly higher incidence among participants aged ≥80 years, in both sexes. The rate of BW gain was of a similar magnitude (Figure 1).

In multivariable models adjusting for potential confounders (Table 2), BW loss was more likely in older individuals and in anemic or hypertensive (sBP), or low HDL-c. It was associated with polypharmacy, including antiplatelet agents, PPIs, and hypnotics.

BW gain was associated to higher BMI at baseline, anemia, and hypnotics.

Consistent with frailty assessment criteria [9], BW loss is readily detectable and potentially modifiable through dietary and physical activity interventions feasible in public health settings. Conversely, BW gain, the moment of change has not been focused as a risk [10] comparing to overweight itself [11] to our best knowledge.

BW loss was an independent risk of long-term care dependence and mortality, as well as weight gain in older adults—potentially related to anemia and/or edema—may portend adverse outcomes. A cross-sectional, lower BMI was also an independent predictor of fracture, dementia, need for care, and mortality, suggesting that sustained underweight status in older age remains a clinically meaningful marker of future frailty-related conditions. Although prior studies [11][12][13] have implicated “sarcopenic obesity” as a driver of inflammatory pathways and frailty-related outcomes, our longitudinal findings did not show an adverse effect of higher BMI on the studied outcomes. This observation is consistent with the so-called “obesity paradox” reported in some elderly populations, including Japanese cohorts [14], and also even in the United States [15], where obesity or overweight status did not correlate with higher mortality risk in late life; however, these patterns may reflect competing risks and heterogeneity in health status among older adults.

Regardless of baseline BMI, BW loss emerged as an independent risk factor for incident bone fracture, dementia, need for long-term care, stroke, CHF, and death.

In contrast, no significant associations were observed between BW loss and AF, MI, or cancer (Table 3). The observed lack of association with these cancer and non-frailty–specific outcomes may reflect heterogeneity within the cancer category or divergent etiologies and risk profiles across diseases. CHF hospitalization appeared related to BP (higher sBP and lower dBP), anemia, and lower LDL-c, which may reflect cachexia or fluid overload states; these findings should be interpreted in the context of the broader frailty spectrum, an end stage of heart disease.

Medication exposure yielded several notable associations. SGLT2 inhibitors showed a modest but statistically significant association with stroke (including intracerebral hemorrhage and ischemic stroke); however, reduction in CHF was not observed in this cohort. In clinical practice, clinicians often withhold SGLT2 inhibitors from older, multimorbid patients or from those with dehydration or polycythemia [16], yet these agents are increasingly indicated for CHF and chronic kidney disease due to added benefits [17]. This juxtaposition underscores a potential double-edged effect of SGLT2 inhibitor use in real clinical setting. Bisphosphonates were associated with fractures and the subsequent need for care, which is plausible given their target populations and indications. Sleep medications correlated with higher risks of fracture, dementia, long-term care dependence, and stroke, but not mortality. Anticoagulants and antiplatelet agents are prescribed for secondary prevention; while anticoagulants are more closely linked to AF, CHF, cerebral infarction, and mortality, antiplatelet agents—more widely used in older adults—were independently associated with frailty-related outcomes (dementia, stroke, and long-term care need) in addition to atherosclerotic events. PPIs, often co-prescribed with anticoagulants and antiplatelets, predicted both atherosclerotic and frailty-related outcomes, potentially via impaired nutrient absorption [18][19]; may be cause of bone fracture. We examined H2 blockers to determine whether similar association existed, however, no significant relationship was observed. Antihypertensive medications were associated with AF, CHF, and MI—conditions largely driven by atherosclerosis—consistent with their roles in primary and secondary prevention. Polypharmacy has previously been linked to fracture risk [20], dementia [21], long-term care needs [22], and mortality [23], with hypnotics and antihypertensives potentially elevating fall risk or altering consciousness; on the other hand, the underlying clinical conditions necessitating polypharmacy are likely to be more severe. The causal inferences remain limited given the observational nature of the data.

Baseline biomarker analyses identified reduced eGFR as a risk factor for all outcomes except cancer, consistent with the relationship between renal impairment, frailty, and systemic inflammation. Higher HbA1c despite therapy was independently associated with stroke and mortality. Low Hb was a risk factor for frailty-related outcomes, including CHF, likely reflecting anemia and/or CKD. Persistently elevated sBP despite treatment predicted atherosclerotic outcomes and frailty-related outcomes (dementia, long-term care need) and mortality; conversely, reduced dBP, a potential marker of advanced atherosclerosis or poor perfusion, predicted need for care, CHF, and mortality. LDL-c was not a significant predictor for stroke, AF, or MI in this cohort, as literature [24] suggests a ‘cholesterol paradox’ that acute coronary syndrome patients with low LDL-c had poor long-term prognosis. They speculated that frailty, systemic inflammation, and worse endothelial function were related to the low LDL-c. In our study, statins were prescribed for 20–30% of participants, with a mean LDL-C around 120 mg/dL (Table1); low LDL-c was associated with dementia, long-term care need, mortality, and CHF but not with stroke, AF, or MI. By contrast, lower HDL-C levels were significantly predictive of MI and mortality in our study. ALT levels showed a protective association against dementia and long-term care need. Because ALT is involved in hepatic and muscular gluconeogenesis [24],[25], this finding related to frailty conditions is biologically plausible.

Overall, our data suggest that both short-term BW decreases and increases may serve as early indicators of frailty onset, underscoring the importance of monitoring nutritional status, fluid balance, and readily available biomarkers (creatinine, Hb, ALT, LDL-C, HDL-C, HbA1c) to facilitate frailty prevention and timely intervention. The patterns observed for BW change and biomarker trajectories imply that dynamic monitoring, rather than static measurements, may enhance risk stratification for frailty-related outcomes in community-dwelling older adults.

This study has several limitations. Tama City represents a suburban, rapidly aging population; in 2024, 29.4% of residents were aged 65 years or older, among the highest proportions in Tokyo. The national health insurance cohort predominantly includes unemployed, self-employed, and older individuals, contributing to an older study population than the general Tama City population or national demographics. Participation in annual health checkups tends to be higher among older adults; thus, the study sample, relying on anthropometric data and biomarkers from routine examinations, may be subject to selection bias with healthier individuals disproportionately represented. Consequently, external validity and generalizability to younger populations or different health systems may be limited.

Translation of the original observational data into policy- and practice-relevant conclusions should be undertaken with caution, and future prospective studies in more diverse populations are warranted to confirm these associations and to explore causal pathways between BW dynamics, biomarker trajectories, and frailty outcomes.

Informed Consent

Due to the retrospective nature of the study, Institutional Review Board of Tama Center Mirai Clinic (no. 2024014) waived the need of obtaining informed consent.

Tama City included information on the application form for the checkup explaining that participants' anonymized data may be analyzed and published for public health research and that they have the right to opt out or refuse their consent. The same information was provided on the TAMA CITY Medical Association website.

Our study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). We obtained Institutional Review Board approval from the Tama Center Mirai Clinic (no. 2024014).

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication: Not required.

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Acknowledgments

We thank all of the participants covered by Tama City national health insurance who provided consent to use their data. We thank the members of the Tama City Medical Association for their cooperation. We thank Mr. Hirohito Watanabe and Ms. Ayaka Hiratsuka (Hankyu Hanshin Holdings, Inc., Group Business Development Div., Business Development Dept.) for performing the statistical analysis. We thank Benjamin Knight, MSc., from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Author contributions

HF performed the data collection and analysis and wrote the paper. HF is responsible for the overall content as a guarantor. HF accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish. HN, HS, and YT performed the data collection and participated in discussions. EK and TK designed the study and provided expert clinical knowledge during critical revision. All authors approved the final version of the submitted manuscript.

Data availability:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because they contain information that could compromise the privacy of research participants. The data that supports the findings of this study are available on request until March, 2026.

Funding

This work was supported by the Tama City Medical Association as one of its research projects.

The authors declare no conflicts of interest.

Figure legends

Figure 1. Histogram of the participants and prevalence of body weight change from 2016 to 2017

Number of men (left) and women (right). Participants who lost 5% or more of their body weight in 1 year (blue), those who gained 5% or more of their body weight in 1 year (orange), and those who exhibited no change in body weight (gray).

Figure 2 a. Kaplan–Meier curve for the onset of dementia, with log-rank test $p < 0.001$.

The outcome was the onset of dementia and start of medication for dementia. The numbers listed below the graph are the numbers of participants who were undergoing follow-up and were still at risk. The three groups were: participants who lost 5% or more of their body weight in 1 year (red), those who gained 5% or more of their body weight in 1 year (green), and those who exhibited no change in body weight (black).

Figure 2b. Kaplan–Meier curve for the hospitalization for congestive heart failure with log-rank test $p < 0.001$

CHF: congestive heart failure

The outcome was hospitalization for bone fracture. The numbers listed below the graph are the numbers of participants who were undergoing follow-up and were still at risk. The three groups were: participants who lost 5% or more of their body weight in 1 year (red), those who gained 5% or more of their body weight in 1 year (green), and those who exhibited no change in body weight (black).

Figure 2c. Kaplan–Meier curve for the need for long-term care with log-rank test $p < 0.001$

The outcome was certification of the need for long-term nursing care. The numbers listed below the graph are the numbers of participants who were undergoing follow-up and were still at risk. The three groups were: participants who lost 5% or more of their body weight in 1 year (red), those who gained 5% or more of their body weight in 1 year (green), and those who exhibited no change in body weight (black).

Figure 2d. Kaplan–Meier curve of all-cause mortality with log-rank test $p < 0.001$

The outcome was all-cause mortality. The numbers listed below the graph are the numbers of participants who were undergoing follow-up and were still at risk. The three groups were: participants who lost 5% or more of their body weight in 1 year (red), those who gained 5% or more of their body weight in 1 year (green), and those who exhibited no change in body weight (black).

Table 1. Baseline characteristics of each group (lost weight, stable, gained weight at baseline, 2016–2017)

Data in 2016 (n/%)	A. Lost weight ≥ 5%/y	(%)	B. No change/y	(%)	C. Gained weight ≥ 5%/y	(%)	p (chi-square test)
all	1,080	(6.9)	13661	(87.1)	959	(6.1)	
Women	**669**	**(61.9)**	**7,901**	**(57.8)**	**590**	**(61.5)**	**0.004**
BMI□ 18.5□ 25.0 kg/m^2	**712**	**(65.9)**	**9,690**	**(70.9)**	**686**	**(71.5)**	**< 0.001**
BMI ≥25.0	**296**	**(27.4)**	**2,871**	**(21.0)**	**135**	**(14.1)**	
BMI ≤ 18.5	**72**	**(6.7)**	**1,100**	**(8.1)**	**138**	**(14.4)**	
Pre-metabolic syndrome	119	(11.0)	1,452	(10.6)	80	(8.3)	0.071
Metabolic syndrome	**213**	**(19.7)**	**2,363**	**(17.3)**	**120**	**(12.5)**	**< 0.001**
Medication for diabetes	**142**	**(13.1)**	**1,335**	**(9.8)**	**86**	**(9.0)**	**< 0.001**
SGLT2 inhibitors	9	(0.8)	79	(0.6)	6	(0.6)	0.575
Insulins	16	(1.5)	166	(1.2)	10	(1.0)	0.650
Medication for sleep	**262**	**(24.3)**	**2,375**	**(17.4)**	**251**	**(26.2)**	**< 0.001**
Statins	**320**	**(29.6)**	**3,578**	**(26.2)**	**222**	**(23.1)**	**0.004**
Bisphosphonates	**96**	**(8.9)**	**943**	**(6.9)**	**71**	**(7.4)**	**0.045**
Anticoagulants	**52**	**(4.8)**	**468**	**(3.4)**	**38**	**(4.0)**	**0.047**
Antiplatelets	**166**	**(15.4)**	**1,745**	**(12.8)**	**149**	**(15.5)**	**0.004**
Medication for hypertension	**528**	**(48.9)**	**5,916**	**(43.3)**	**419**	**(43.7)**	**0.002**
Proton pump inhibitors	**188**	**(17.4)**	**1,644**	**(12.0)**	**150**	**(15.6)**	**< 0.001**
H2 blockers	49	(4.5)	620	(4.5)	51	(5.3)	0.535
Mean (SD)	A. Lost weight ≥ 5%/y	(SD)	B. No change/y	(SD)	C. Gained weight ≥ 5%/y	(SD)	p (Kruskal–Wallis test)
Age (years)	**74.5**	**(9.7)**	**72.4**	**(8.7)**	**72.5**	**(10.2)**	**< 0.001**
BMI (mean/SD)	**23.1**	**(3.3)**	**22.6**	**(3.1)**	**21.7**	**(3.2)**	**< 0.001**
Waist circumference (cm)	**83.6**	**(9.4)**	**82.6**	**(9.0)**	**80.9**	**(9.2)**	**< 0.001**
eGFR (mL/min.)	**66.4**	**(15.6)**	**68.1**	**(14.2)**	**68.7**	**(16.0)**	**0.002**
Creatinine (mg/dL)	0.8	(0.2)	0.8	(0.2)	0.8	(0.2)	0.092
Triglyceride (mg/dL)	**116.6**	**(66.5)**	**111.6**	**(64.2)**	**105.4**	**(58.7)**	**< 0.001**
HDL-c (mg/dL)	**60.8**	**(15.9)**	**63.0**	**(16.0)**	**63.8**	**(16.2)**	**< 0.001**
LDL-c (mg/dL)	120.0	(29.7)	121.6	(29.0)	121.1	(30.8)	0.103
AST (U/L)	**24.5**	**(9.3)**	**24.4**	**(8.4)**	**23.8**	**(9.1)**	**0.002**
ALT (U/L)	**19.8**	**(11.8)**	**20.1**	**(10.9)**	**18.5**	**(10.3)**	**< 0.001**
γ-GTP (U/L)	**32.4**	**(33.8)**	**31.5**	**(30.8)**	**30.0**	**(33.8)**	**< 0.001**
HbA1c (%)	**5.8**	**(0.7)**	**5.7**	**(0.6)**	**5.7**	**(0.6)**	**< 0.001**
Hemoglobin (g/dL)	**13.3**	**(1.3)**	**13.6**	**(1.3)**	**13.3**	**(1.4)**	**< 0.001**
Uric acid (mg/dL)	**5.2**	**(1.3)**	**5.3**	**(1.3)**	**5.1**	**(1.3)**	**0.005**
Systolic blood pressure (mmHg)	**131.0**	**(16.1)**	**129.2**	**(16.1)**	**128.3**	**(16.9)**	**< 0.001**
Diastolic blood pressure (mmHg)	72.9	(10.6)	73.2	(10.2)	72.5	(10.4)	0.143
Number of medications	**1.7**	**(2.2)**	**1.3**	**(1.8)**	**1.4**	**(1.9)**	**< 0.001**

BMI: Body mass index is the weight in kilograms divided by the square of the height in meters.

Metabolic syndrome was defined as waist ≥ 85 cm in males, ≥ 90 cm in females, plus ≥ 2 of the following three factors: (1) HDL-c < 40 mg/dL or TG ≥ 150 mg/dL or medication for hyperlipidemia; (2) fasting plasma glucose ≥ 110 mg/dL or medication for diabetes; and (3) blood pressure ≥ 130 mm Hg in sBP and/or 85 mm Hg in dBP or taking an antihypertensive. re-MetS was defined by waist ≥ 85 cm in males, ≥ 90 cm in females plus one of the three factors.

eGFR (estimated filtration rate) was based on the serum creatinine level and was calculated using the Chronic Kidney Epidemiology Collaboration equation.

AST (aspartate aminotransferase), ALT (alanine aminotransferase), γ-GPT (gamma-glutamyl transferase)

Analyzed using chi-square tests and Kruskal–Wallis tests.

Bold characters show statistical difference among groups.

Table 2. Cox proportional hazard analysis of body weight loss 5% or more, and weight gain 5% or more; multivariate analysis

variable in 2016	Multivariate -5% BW HR	95% CI Lower	95% CI Upper	p-value	Multivariate +5% BW HR	95% CI Lower	95% CI Upper	p-value
Men	0.979	0.951	1.007	0.147	0.984	0.956	1.014	0.296
Age	**1.005**	**1.004**	**1.007**	**<0.001**	0.999	0.998	1.001	0.308
Pre-metabolic syndrome					0.968	0.924	1.015	0.179
Metabolic syndrome	1.016	0.978	1.054	0.414	0.978	0.941	1.016	0.256
Medication for diabetes	1.036	0.988	1.086	0.141				
SGLT2 inhibitors								
Insulin								
Medication for sleep	**1.067**	**1.029**	**1.106**	**<0.001**	**1.073**	**1.034**	**1.114**	**<0.001**
Statins	1.011	0.980	1.044	0.494				
Bisphosphonates	1.049	0.994	1.108	0.083	1.017	0.961	1.076	0.559
Anticoagulants	1.030	0.955	1.111	0.446				
Antiplatelets	**1.051**	**1.009**	**1.096**	**0.018**	1.019	0.976	1.063	0.399
Medication for hypertension	1.027	0.998	1.056	0.070				
Proton pump inhibitors	**1.066**	**1.022**	**1.111**	**0.003**	1.018	0.975	1.063	0.416
H2blockers								
BMI	1.002	0.998	1.007	0.337	**0.994**	**0.990**	**0.999**	**0.016**
eGFR	0.999	0.998	1.000	0.124	1.001	1.000	1.002	0.312
HbA1c	1.024	1.000	1.049	0.050	0.990	0.966	1.015	0.415
Hemoglobin	**0.975**	**0.965**	**0.986**	**<0.001**	**0.987**	**0.976**	**0.998**	**0.024**
Systolic blood pressure	**1.001**	**1.000**	**1.002**	**0.038**	1.000	0.998	1.001	0.597
Diastolic blood pressure	0.999	0.998	1.001	0.397	1.000	1.000	1.000	0.504
Triglyceride	1.000	1.000	1.000	0.569				
HDL-c	**0.999**	**0.998**	**1.000**	**0.041**				
LDL-c	1.000	0.999	1.000	0.318				
ALT	0.999	0.998	1.000	0.184	0.999	0.998	1.000	0.102
γ-GTP								
UA					0.994	0.983	1.006	0.348
Number of medications	**1.017**	**1.009**	**1.024**	**<0.001**	1.006	0.998	1.014	0.127
	C-index	*AIC*	*Likelihood ratio test*	*p-value*	*C-index*	*AIC*	*Likelihood ratio test*	*p-value*
	0.603	*72444.4*	*182.686*	*<0.001*	*0.58*	*52050.7*	*45.16*	*<0.001*

CI (confidence interval), Analyzed using Cox proportional hazard multivariate tests. Variables that were significantly related in monovariate tests were included.

SGLT2 (sodium-glucose cotransporter 2), BMI (body mass index; the weight in kilograms divided by the square of the height in meters), eGFR (estimated filtration rate) was based on the serum creatinine level and was calculated with the use of the Chronic Kidney Epidemiology Collaboration equation. ALT (alanine aminotransferase),γ-GPT (gamma-glutamyl transferase), UA (uric acid)

Table 3 Cox proportional hazard multivariate analysis of predictors for events

Variable in 2016	Hospitalization for bone fracture	Dementia	Needs for long-term care	Death	Stroke	Atrial Fibrillation	Hospitalization for CHF	Myocardial infarction	Hospitalization for cancer
Events (n/1000 p. y.)	43.7	80.5	104.9	73.2	85.1	37.4	39	29.0	57.2
men	0.839***	□	□	1.367***	1.145***	1.146**	1.077	□	1.321***
age	1.024***	1.050***	1.061***	1.045***	1.027***	1.019***	1.022***	1.011***	1.016***
-5□BW/□	1.346***	1.477***	1.517***	1.491***	1.165*	□	1.315***	□	□
+5%BW/y	□	□	1.159*	1.161*	□	□	□	□	□
BMI	0.984*	0.975***	0.987*	0.972***	□	1.004	□	□	□
SGLT2inhibitors	□	□	□	□	1.504*	□	□	□	□
medication for sleep	1.165*	1.143**	1.177***	0.996	1.146**	□	1.066	1.056	1.045
bisphosphonates	1.200*	1.12	1.201**	1.01	1.237**	1.046	1.123	□	□
anticoagulants	1.094	1.054	1.022	1.275**	1.316**	4.109***	2.097***	1.169	1.02
antiplatelets	1.041	1.129*	1.200***	1.211***	1.331***	1.180**	1.248***	1.499***	1.03
medication for hypertension	1.049	1.009	1.032	1.031	1.071	1.132**	1.168***	1.121*	1.006
proton pump inhibitors	1.185**	1.079	1.122*	1.081	1.137*	1.238***	1.151*	1.232**	1.106
eGFR	0.997*	0.995***	0.995***	0.995***	0.997*	0.997*	0.993***	0.997*	0.998
HbA1c	□	1.017	1.047	1.074*	1.105**	□	1.009	1.040	1.018
Hemoglobin	0.921***	0.931***	0.919***	0.903***	0.980	0.974	0.940***	□	□
systolic blood pressure	1.002	1.003**	1.005***	1.003*	1.003*	1.003*	1.004**	1.002	1.001
dyastolic blood pressure	0.997	0.997	0.996*	0.994**	0.997	0.998	0.996*	□	□
HDL cholesterol	□	0.998	0.999	0.996**	0.999	0.999	0.998	0.997*	0.999
LDL cholesterol	0.999	0.998*	0.998**	0.998***	1.000	0.999	0.998*	0.999	0.999

ALT	0.998	**0.995***	**0.996***	**0.996***	0.997	0.997	0.998		
γ-GTP	1.000					1.001	1.001		**1.001***
Number of medication	1.017	**1.033****	**1.039*****	**1.053*****	1.020	**1.034****	**1.056*****	**1.031***	1.011
C-index	0.723	0.782	0.793	0.797	0.669	0.691	0.774	0.696	0.635

***p < 0.001, **p < 0.01, *p< 0.05

Analyzed using Cox proportional hazard multivariate tests. Variables that were significantly related in monovariate tests were included.

p.y.(person year)

Pre-MetS (Metabolic syndrome), MetS, medications of diabetes, H2B (Histamine 2 blockers), TG (triglyceride), UA (uric acid) were excluded from the table, because they were not significant for any variables.

SGLT2 (sodium-glucose cotransporter 2) inhibitor, BMI (body mass index; the weight in kilograms divided by the square of the height in meters), eGFR (estimated filtration rate) was based on the serum creatinine level and was calculated using the Chronic Kidney Epidemiology Collaboration equation. ALT (alanine aminotransferase),γ-GPT (gamma-glutamyl transferase), UA (uric aci

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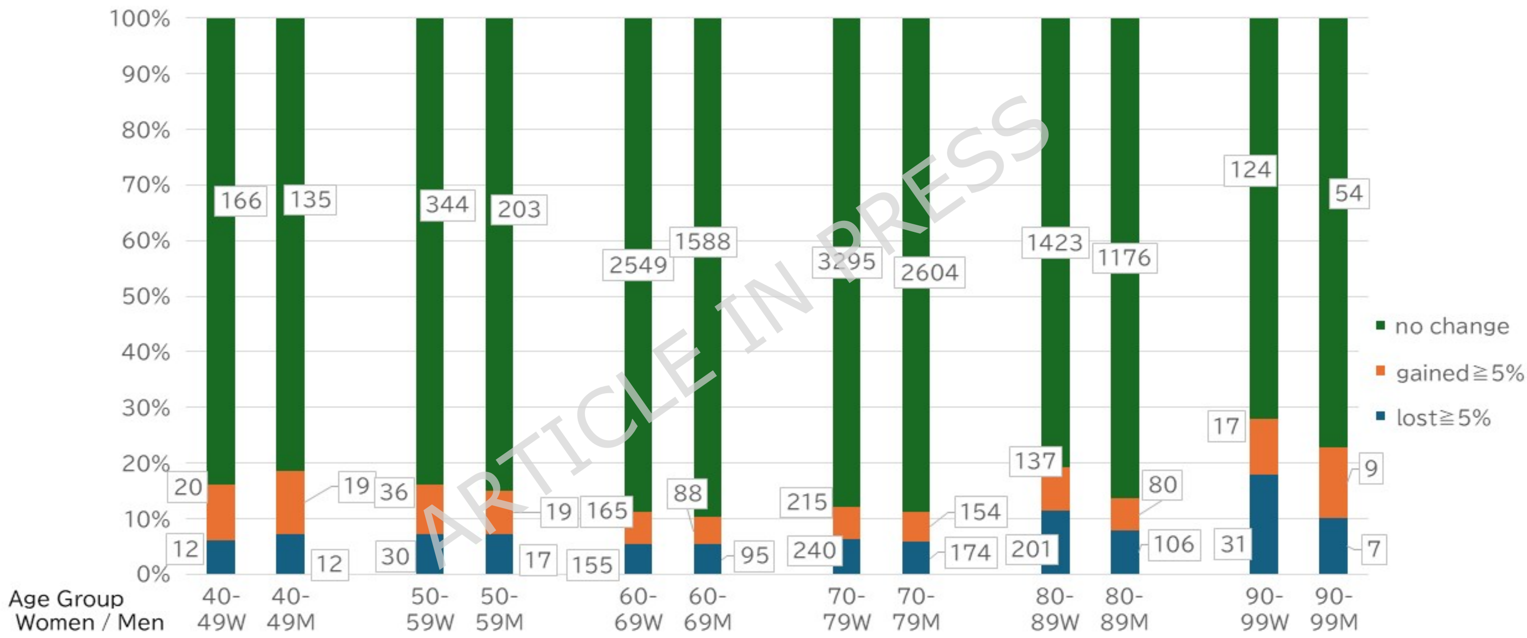
100%
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10%
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Age Group
Women / Men
40-49W
40-49M
50-59W
50-59M
60-69W
60-69M
70-79W
70-79M
80-89W
80-89M
90-99W
90-99M
166
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7
no change
gained≧5%
lost≧5%
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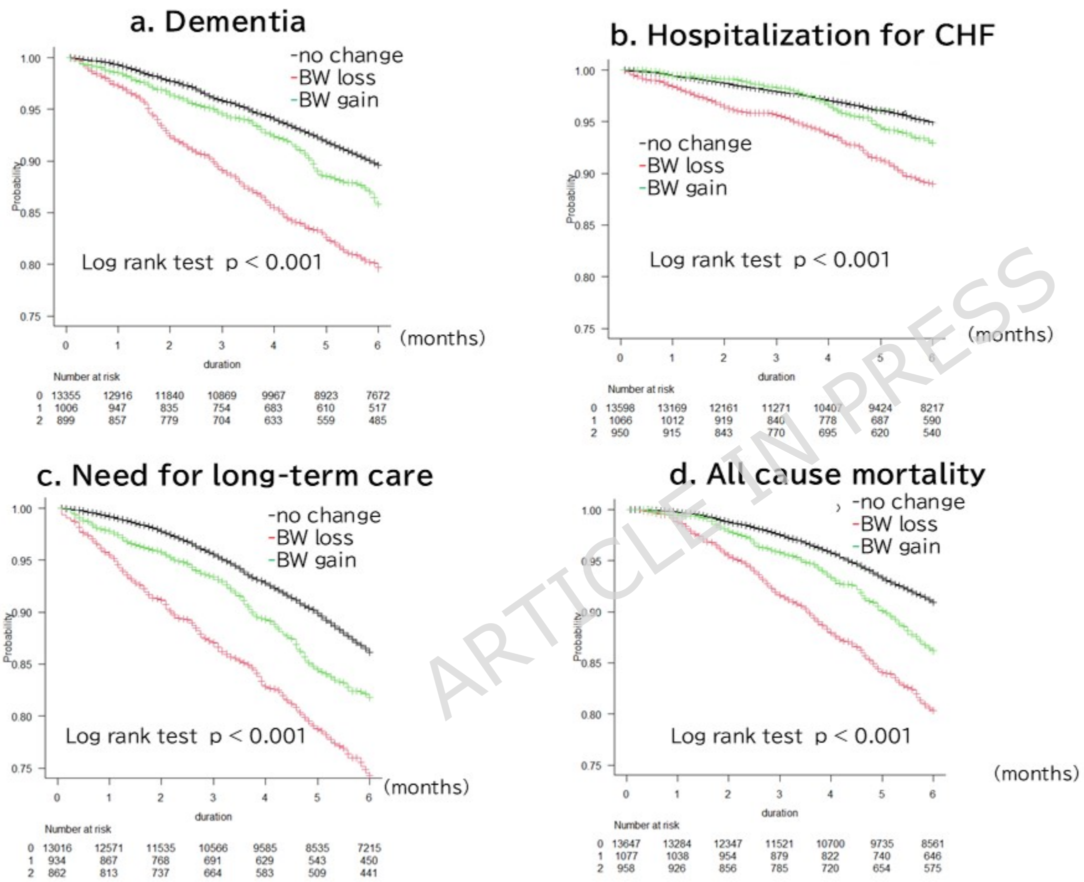
a. Dementia
-no change
-BW loss
-BW gain
Probability
Log rank test p < 0.001
(months)
duration
Number at risk
0 13355 12916 11840 10869 9967 8923 7672
1 1006 947 835 754 683 610 517
2 899 857 779 704 633 559 485
b. Hospitalization for CHF
-no change
-BW loss
-BW gain
Probability
Log rank test p < 0.001
(months)
duration
Number at risk
0 13598 13169 12161 11271 10407 9424 8217
1 1066 1012 919 840 778 687 590
2 950 915 843 770 695 620 540
c. Need for long-term care
-no change
-BW loss
-BW gain
Probability
Log rank test p < 0.001
(months)
duration
Number at risk
0 13016 12571 11535 10566 9585 8535 7215
1 934 867 768 691 629 543 450
2 862 813 737 664 583 509 441
d. All cause mortality
-no change
-BW loss
-BW gain
Probability
Log rank test p < 0.001
(months)
duration
Number at risk
0 13647 13284 12347 11521 10700 9735 8561
1 1077 1038 954 879 822 740 646
2 958 926 856 785 720 654 575