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Changes in Body Weight and Concurrent Changes in Cardiovascular Risk Profiles in Community Residents in Japan: the Hisayama Study

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Aim: We investigated the influence of weight change on concurrent changes in predicted cardiovascular disease (CVD) risk and individual CVD risk factors over time.

Methods: A total of 2,140 community-dwellers aged 40–74 years participated in both 2002 and 2007 health examinations. Obesity was defined as body mass index ≥ 25 kg/m^2. Weight trajectories were classified as: "stable obese" (obese at both examinations), "obese to nonobese" (obese in 2002 but nonobese in 2007), "nonobese to obese" (nonobese in 2002 but obese in 2007), or "stable nonobese" (nonobese at both examinations). We compared changes in the model-predicted risk for CVD and individual CVD risk factors across weight-change categories.

Results: The predicted risk for CVD increased during 5 years in all groups; the increment in the predicted risk for CVD was smallest in the obese to nonobese participants and steepest in the nonobese to obese subjects. Compared with the stable obese participants, the obese to nonobese participants had greater favorable changes in waist circumferences, blood pressure, fasting plasma glucose, serum high-density lipoprotein cholesterol, serum triglycerides, and liver enzymes. For all these parameters, opposite trends were observed when comparing the nonobese to obese participants with the stable nonobese group.

Conclusions: We demonstrated the favorable association of losing weight in obese people and avoiding excessive weight gain in nonobese people with global risk of future CVD and individual CVD risk factors in a real-world setting. The findings could improve behavioral lifestyle interventions that provide information on the health consequences of weight change at health checkups.

Key words: Longitudinal study, Cardiometabolic risk factors, Weight change

Introduction

Cardiovascular disease (CVD) is one of the leading causes of death worldwide. To date, there has been clear evidence that weight management is a key factor in the primary prevention of non-communicable diseases including CVD[1-4]. Behavioral lifestyle interventions have been widely used in clinical practice for modifying unhealthy lifestyles and managing body weight to halt the progression to CVD[5]. As a part of the behavioral modification strategy, providing individuals with information about

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their estimated global risk for future CVD or asymptomatic atherosclerotic status could promote understanding of the importance of lowering cardiovascular risk and could enhance their motivation to pursue lifestyle modification or therapy[6, 7]. In addition, the provision of information about the health consequences of CVD could guide shared decision-making between individuals and their care providers to slow the development of CVD[8]. Therefore, in order to enhance weight management programs with lifestyle modification for the prevention of CVD in practice, it is crucial that practitioners have specific information about how weight change would increase or decrease future CVD risk in their patients.

Randomized controlled trials have shown that lifestyle interventions for weight reduction have efficacy for preventing cardiovascular outcomes, especially in at-risk subjects[4, 9-10]. However, findings from randomized controlled trials of lifestyle-based weight loss intervention in clinical settings often do not reflect exposure-outcome relationships in real-world settings[11]. The translation of these trials to lifestyle modification programs for real-world populations, especially in community settings, might result in more modest effects compared with those seen in the original randomized controlled trials[12, 13]. Therefore, the investigation of weight change in population-based studies is needed in order to directly evaluate the influence of body weight trajectory on cardiovascular risks in community settings. However, there have been few population-based studies examining changes in the CVD risk factors or global CVD-risk of individuals in relation to changes in their body weight.

Aim

In the present study, we aimed to examine the influence of body weight change on the concurrent changes in the model-predicted global risk of CVD and in individual cardiovascular risk factors using observational longitudinal data on health checkup examinations in a Japanese community. The findings of our study will help practitioners to make a more realistic appraisal of the influence of weight change and simultaneous changes in global risks of cardiovascular disease and to enhance effective communication with their patients to realize the appropriate behavioral modifications.

Method

Participants

This longitudinal study was conducted using the data of the Hisayama Study. The Hisayama Study is a population-based cohort study of CVD and its risk factors that has been ongoing in the town of Hisayama, a suburb of Fukuoka City in southwestern Japan. Details of the Hisayama Study have been described elsewhere[14]. We conducted the present analysis using data from the examination in 2002 as a baseline. A total of 2,735 community residents aged between 40 and 74 participated in health checkups and consented to participate in the study in 2002 (participation rate, 77.1%).

We excluded 27 subjects who did not consent to participate in the study, 125 subjects who had a history of cancer, 32 subjects who were not fasting, and 47 subjects who had no valid low density lipoprotein (LDL) cholesterol value by the Friedewald formula[15] (i.e., serum triglycerides of >400 mg/dL or a negative value of calculated LDL cholesterol) at the baseline examination in 2002. Among those 2,504 subjects, 2,213 were re-examined in 2007. We further excluded 73 subjects with invalid data on blood profiles (nonfasting or invalid LDL cholesterol value) at the 2007 examination. As a result, 2,140 participants were included in the present study (follow-up rate 85.5% of the initial sample). The participants had not undergone any experimental treatment or intervention from the study team beyond the health checkups provided by the town during the study period of 2002 to 2007.

The study protocol was approved by the Kyushu University Institutional Review Boards for Clinical Research. All participants provided written informed consent.

Exposure

Body height and weight were measured in light clothing without shoes at both the 2002 and 2007 health examinations. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m^2). Obesity was defined as BMI ≥ 25 kg/m^2. We classified weight change status during the 5-year follow-up period into four categories as follows: "stable obese" (obese at both examinations), "obese to nonobese" (obese in 2002 and nonobese in 2007), "nonobese to obese" (nonobese in 2002 and obese in 2007), and "stable nonobese" (nonobese at both examinations). For a sensitivity analysis, we also calculated the percent weight change from 2002 to 2007 using the following formula: ([weight in 2007] – [weight in 2002]) / [weight in 2002] × 100. The

percent weight change was divided into six categories at a 3% interval (≤ -6%, -6< to ≤ -3%, -3< to ≤ 0%, 0< to ≤ +3%, +3< to ≤ +6%, and >+6%), in accordance with the recommendation of ≥ 3% body weight loss for patients with obesity by the Guidelines for the Management of Obesity Disease 2016 issued by the Japan Society for the Study of Obesity[16].

Outcome

To estimate the global risk of CVD in each individual, we calculated the predicted cumulative risk for CVD using a risk prediction model that we developed previously in the Hisayama Study[17]. The original prediction formula was developed based on the Cox proportional hazards model for the development of CVD in the Hisayama study cohort established in 1988. The predictors of the prediction model include age, sex, systolic blood pressure, the presence of diabetes, serum high density lipoprotein (HDL) cholesterol, serum LDL cholesterol, smoking status, and regular exercise habits. The formula used for the present study was as follows:

predicted cumulative risk for CVD (%) = $1 - 0.936^{\exp(\Sigma\beta x - 5.867)}$,

where $\Sigma\beta x$ was calculated as:

(0.067 × age in years) + (0.559 if male sex) + (0.013 × systolic blood pressure in mmHg) + (0.412 if diabetes) + (-0.009 × serum HDL cholesterol in mg/dL) + (0.003 × serum LDL cholesterol in mg/dL) + (0.338 if current smoker) + (-0.420 if having regular exercise). We set a baseline survival function as 0.936 for 10-year CVD cumulative incidence and an average sum of products of the coefficients and the value of each risk factor as 5.867 from our previous observation of the Hisayama population examined in 1988. To confirm the validity of this risk prediction model, we applied the model to the 10-year follow-up of the study participants who were free from cardiovascular disease at baseline examination in 2002. The risk prediction model performed well (Harrell's concordance statistics C = 0.776, 95% confidence interval 0.745–0.808) in the study participants.

We also studied individual cardiovascular risk factors including waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, hemoglobin A1c, serum lipids (HDL cholesterol, LDL cholesterol, and serum triglycerides), estimated glomerular filtration rate (eGFR), serum liver enzymes (aspartate aminotransferase [AST], serum alanine aminotransferase [ALT], and serum gamma-glutamyl transferase [GGT]) in both 2002 and 2007 health examinations. All these indices are measured at the Specific Health Checkups[18], Japan's mandatory health check-ups for all insured persons and their dependents aged between 40 and 74, which have been performed since fiscal year 2008.

Waist circumference was measured at the umbilical level in a standing position by a trained staff member. Blood pressure was measured three times using an automated sphygmomanometer with subjects in the sitting position after at least 5 minutes of rest. The average of the three measurements was used for the present analysis. Blood samples were collected from an antecubital vein after an overnight fast. Plasma glucose levels were measured by using the hexokinase method. Hemoglobin A1c was measured by a latex aggregation immunoassay using a Determiner HbA1c kit (Kyowa Medex, Tokyo). The value for hemoglobin A1c was converted into the National Glycohemoglobin Standardization Program equivalent value using the following formula: hemoglobin A1c (%) = 1.02 × hemoglobin A1c (Japan Diabetes Society) (%) + 0.25%. Serum total cholesterol, HDL cholesterol, and triglycerides were measured using the enzymatic method, and LDL cholesterol was calculated based on the Friedewald formula[15]. Serum ALT, AST, and GGT levels were enzymatically measured in accordance with the consensus method of the Japan Society of Clinical Chemistry. Serum creatinine concentrations were measured using the enzymatic method. The eGFR values were calculated using the Chronic Kidney Disease Epidemiology Collaboration equation multiplied by the coefficient 0.813 for the Japanese population[19].

Covariates

Each subject completed a self-administered questionnaire covering medical history, current use of antihypertensive agents, glucose-lowering agents, and lipid-modifying agents, smoking habits, alcohol intake, and regular exercise habits. Smoking and drinking habits were categorized as either current use or not. Regular exercise was defined as being engaged in leisure-time exercise at least 3 times a week.

Statistical Analysis

The predicted risk for CVD was log-transformed prior to the analyses and back-transformed for data presentation because the variable was right-skewed **(Supplementary Fig. 1)**. In addition, the serum levels of triglycerides, ALT, AST, and GGT were log-transformed due to their skewed distributions. Participants' characteristics at baseline were summarized according to the weight change status, and Dunnett's test was used for pairwise comparison. A repeated measures analysis of covariance was used to examine the adjusted mean values (95% confidence interval [CI]) of the predicted risk for CVD at the

2002 and 2007 examinations according to weight change categories. The differences in the 5-year change rate (2002-2007) in the predicted risk for CVD across the weight change status were tested based on the interaction term of the time and the weight change status. The model was adjusted for age and sex in order to illustrate their naïve change over time.

To assess the influence of weight loss over 5 years on each cardiovascular risk factor in subjects who were initially obese, the changes in cardiovascular risk factors were compared between the obese to nonobese group and the stable obese group using analyses of covariance. For this analysis, the average changes in each cardiovascular risk factor, calculated by subtracting each value in 2007 from the value in 2002, were used as dependent variables. The models were adjusted for the baseline value of each outcome variable of interest and other baseline covariates, including age, sex, BMI, smoking habits, drinking status, exercise habits, and medication use for hypertension, diabetes, or dyslipidemia. The results are presented as the adjusted mean differences (95% CI) for variables that were normally distributed, and the adjusted geometric mean ratios (95% CI) for log-transformed variables. The standardized mean differences, as effect size measures, were presented in order to directly compare the magnitudes of influence of weight loss on each cardiovascular risk factor. The same analyses were performed for the comparison between the nonobese to obese group and the stable nonobese group—that is, those who were initially nonobese—to assess the influence of weight gain over time. We found no evidence of sex- or age-interaction in the aforementioned analyses. The sensitivity analysis after excluding 880 subjects who took any medications for hypertension, diabetes, and/or dyslipidemia at either examination was performed in a similar manner. Another analysis using the six categories of percent weight change was performed to examine the dose-response relationships between changes in body weight and cardiovascular risk factors in the whole study sample. The standardized mean differences between the groups with weight change of ≤ -6% and >6% were calculated to compare the influence of weight change on outcomes.

Finally, we assessed which component of the cardiovascular risk factors could best explain the association between the weight change status and the predicted risk of cardiovascular disease. We compared the model fitness by adding sets of cardiovascular risk factor changes to a linear regression model regressing the changes in the predicted cardiovascular disease (log-transformed value in 2007 minus that in 2002) on the weight change status. We assessed the following sets of cardiovascular risk factors: blood pressure (systolic and blood pressure and use of antihypertensive medication), glucose (fasting plasma glucose, hemoglobin A1c, and use of glucose-lowering medication), lipids (serum triglycerides, HDL and LDL cholesterol, and use of lipid-modifying medication), liver enzymes (serum ALT, AST, and GGT), and renal function (eGFR). We added the changes (Δ) in these cardiovascular risk factors from baseline (2002) to follow-up (2007) to the model including age and sex, and computed the R squared (R^2) value for each model. A larger R^2 indicates better fitness: that is, the model with larger R^2 explained more variance in the change in predicted risk of cardiovascular disease. A two-sided value of $p<0.05$ was considered statistically significant in all analyses. Statistical analyses were performed using SAS software ver. 9.4 (SAS Institute, Cary, NC).

Results

On average, participants ($n=2,140$) lost 1.6% of their body weight (standard deviation ±5.4) over the 5-year study period (mean body weight change -0.9 ± 3.2 kg). In the study participants, 496 subjects (23.2%) were classified as stable obese and 103 subjects (4.8%) were classified as obese to nonobese. Also, 1462 subjects (68.3%) and 78 subjects (3.6%) were classified as stable nonobese and nonobese to obese. The obese to nonobese group had about a 5 kg-greater decrease in body weight compared with the stable obese group (adjusted value of Δbody weight: -0.7 kg [95% CI, -0.9 to -0.4] in the stable obese group, -5.7kg [95% CI, -6.4 to -5.1] in the obese to nonobese group). The mean weight changes in the nonobese to obese group and the stable nonobese group were +3.9 kg (95% CI +3.2 to +4.5) and -0.1 kg (95% CI -1.1 to -0.8), respectively. **Table 1** shows the cardiovascular risk profiles and covariates of participants at baseline according to the weight change status. We found no group differences in age and sex when comparing to the stable nonobese group or to the stable obese group. The anthropometry measures varied significantly across the weight status categories. All indices of blood pressure, blood glucose and lipids, liver enzymes, and kidney function significantly differed between the stable nonobese and the stable obese groups. The proportions of current smokers were lower in the nonobese to obese and the stable obese group compared with the stable nonobese group. No significant group differences in drinking or exercise habits were observed.

Fig. 1 illustrates the changes in the predicted risks for CVD according to the weight change status.

Table 1. Age- and sex-adjusted characteristics of subjects according to weight change categories (2002-2007)

Variables at baseline (2002)	Weight change status over 5 years			
	Stable nonobese (n = 1462)	Nonobese to obese (n = 78)	Obese to nonobese (n = 103)	Stable obese (n = 497)
Age, year	57.6 (0.2)	58.1 (1.0)	59.7 (0.9)	58.6 (0.4)
Sex, female, %	60.5 (1.3)	53.9 (5.6)	54.6 (4.9)	57.0 (2.2)
Weight, kg	54.1 (0.2)$^{\$}$	60.7 (0.7)$^{*\$}$	64.0 (0.6)$^{*\$}$	68.9 (0.3)*
Waist circumference, cm	78.3 (0.2)$^{\$}$	84.4 (0.8)$^{*\$}$	87.7 (0.7)$^{*\$}$	92.0 (0.3)*
BMI, kg/m^2	21.7 (0.1)$^{\$}$	24.1 (0.2)$^{*\$}$	25.8 (0.2)$^{*\$}$	27.8 (0.1)*
Systolic blood pressure, mmHg	126.9 (0.5)$^{\$}$	131.8 (2.1)$^{\$}$	135.3 (1.8)*	137.7 (0.8)*
Diastolic blood pressure, mmHg	76.6 (0.3)$^{\$}$	79.3 (1.2)$^{\$}$	81.7 (1.1)*	83.0 (0.5)*
Use of antihypertensive agents, %	14.6 (1.0)$^{\$}$	20.8 (4.6)	17.2 (3.6)	27.2 (2.1)*
Fasting plasma glucose, mg/dL	106.7 (0.6)$^{\$}$	110.4 (2.4)	110.5 (2.1)	115.5 (1.0)*
Hemoglobin A1c, %	5.3 (0.0)$^{\$}$	5.4 (0.1)$^{\$}$	5.5 (0.1)	5.6 (0.0)*
Use of glucose-lowering agents, %	2.9 (0.5)$^{\$}$	7.8 (2.8)*	2.5 (1.3)	5.0 (0.9)*
Serum HDL cholesterol, mg/dL	65.5 (0.4)$^{\$}$	62.8 (1.7)$^{\$}$	58.6 (1.5)*	58.2 (0.7)*
Serum LDL cholesterol, mg/dL	116.9 (0.8)$^{\$}$	126.1 (3.5)*	128.4 (3.1)*	125.6 (1.4)*
Serum triglycerides, mg/dL[1)]	91.9 (89.7 - 94.2)$^{\$}$	97.8 (87.9 - 108.9)$^{\$}$	114.2 (104.0 - 125.3)*	114.5 (109.8 - 119.5)*
Use of lipid-modifying agents, %	6.0 (0.6)$^{\$}$	9.0 (3.0)	6.3 (2.1)	11.7 (1.5)*
Serum AST, U/L[1)]	24.5 (24.1 - 24.8)$^{\$}$	24.7 (23.2 - 26.3)*	27.1 (25.7 - 28.6)*	25.8 (25.2 - 26.4)*
Serum ALT, U/L[1)]	18.1 (17.7 - 18.6)$^{\$}$	21.1 (19.0 - 23.4)*	25.1 (22.8 - 27.5)*	23.9 (22.9 - 24.9)*
Serum GGT, U/L[1)]	26.1 (25.2 - 27.0)$^{\$}$	27.3 (23.7 - 31.5)$^{\$}$	33.4 (29.5 - 37.8)*	35.3 (33.4 - 37.4)*
eGFR, mL/min/1.73 m^2	81.0 (0.2)$^{\$}$	80.1 (1.0)	79.5 (0.8)	79.9 (0.4)*
Current smoking, %	16.1 (1.1)$^{\$}$	18.3 (4.5)	6.2 (2.0)*	11.8 (1.5)*
Current drinking, %	47.5 (1.5)	42.9 (6.4)	37.8 (5.3)	46.5 (2.5)
Regular exercise, %	10.7 (0.8)	7.3 (2.9)	8.0 (2.6)	10.0 (1.3)

Abbreviations: BMI, body mass index; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate
Values are expressed as adjusted means or frequencies with standard errors except where noted.
1) Data are shown as geometric means (95% confidence intervals).
$^{*}p<0.05$ vs. stable nonobese, $^{\$}p<0.05$ vs. stable obese.

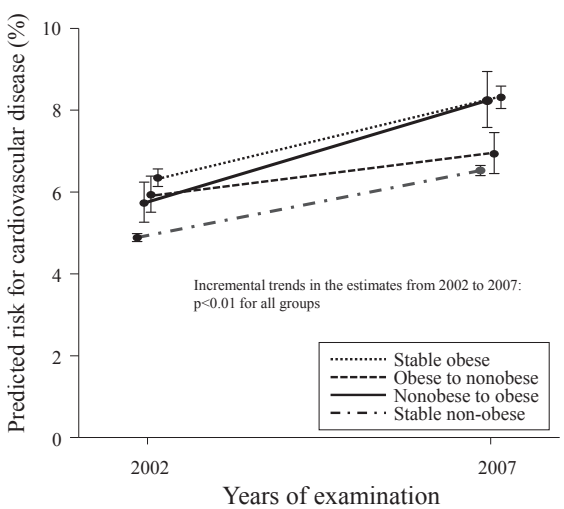

Fig. 1. Change in the age- and sex-adjusted predicted risk for cardiovascular disease according to weight change status

Solid circles and vertical bars indicated the age- and sex-adjusted, back-transformed means and 95% confidence intervals of the predicted 10-year cumulative risk for cardiovascular disease. The predicted risks were presented according to weight status groups: stable nonobese (n=1,462), nonobese to obese (n=78), obese to nonobese (n=103), and stable obese (n=497). Data were log-transformed for analysis and back-transformed for presentation. The asterisk indicates a significant difference ($p<0.05$) in the estimates at each time point. The detailed data are shown in supplementary Table 1.

Table 2. Multivariable-adjusted mean changes in cardiovascular risk factors by weight change status in the stable obese and the obese to nonobese subjects (2002-2007)

Variables	Stable obese[1] (n=497)	Obese to nonobese[1] (n=103)	Differences in Δ parameter	p for group difference	Magnitude of difference in change[2]
ΔWaist circumference, cm	3.9 (3.4 to 4.3)	-1.7 (-2.7 to -0.8)	-5.6 (-6.7 to -4.5)	<0.001	0.98
ΔSystolic blood pressure, mmHg	0.4 (-1.0 to 1.7)	-3.3 (-6.3 to -0.2)	-3.6 (-7.0 to -0.2)	0.04	0.21
ΔDiastolic blood pressure, mmHg	0.3 (-0.4 to 1.0)	-1.8 (-3.4 to -0.2)	-2.1 (-3.9 to -0.3)	0.02	0.22
ΔFasting plasma glucose, mg/dL	-1.6 (-3.4 to 0.3)	-6.5 (-10.7 to -2.2)	-4.9 (-9.6 to -0.2)	0.04	0.21
ΔHemoglobin A1c, %	0.16 (0.10 to 0.22)	0.08 (-0.06 to 0.22)	-0.08 (-0.23 to 0.08)	0.33	0.10
ΔSerum HDL cholesterol, mg/dL	3.7 (2.8 to 4.5)	6.5 (4.7 to 8.3)	2.8 (0.8 to 4.9)	0.006	0.31
ΔSerum LDL cholesterol, mg/dL	-2.0 (-4.5 to 0.5)	-6.8 (-12.5 to -1.2)	-4.8 (-11.1 to 1.44)	0.13	0.15
ΔLog serum triglycerides, mg/dL	0.01 (-0.02 to 0.04)	-0.11 (-0.18 to -0.04)	-0.1 (-0.2 to -0.05)	0.003	0.29
ΔLog serum AST, U/L	-0.12 (-0.14 to -0.10)	-0.20 (-0.25 to -0.15)	-0.1 (-0.2 to -0.03)	0.004	0.31
ΔLog serum ALT, U/L	-0.07 (-0.10 to -0.03)	-0.27 (-0.32 to -0.20)	-0.2 (-0.3 to -0.1)	<0.001	0.50
ΔLog serum GGT, U/L	-0.03 (-0.06 to 0.01)	-0.22 (-0.28 to -0.15)	-0.2 (-0.3 to -0.1)	<0.001	0.48
ΔeGFR, mL/min/1.73 m^2	-6.1 (-6.7 to -5.5)	-4.9 (-6.2 to -3.6)	1.3 (-0.2 to 2.7)	0.09	0.17

Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate
Delta (Δ) indicates absolute changes in each parameter between 2002 and 2007.
Values are expressed as adjusted mean (95% confidence intervals [CI]). The model was adjusted for age, sex, body mass index, use of hypertension, diabetes, and/or dyslipidemia medications, current smoking, current drinking, regular exercise in 2002.
1) ΔWeight values in the stable obese group and the obese to nonobese group were -0.7 (95% CI -0.9 to -0.4) kg and -5.7 (-6.4 to -5.1) kg, respectively.
2) Values are shown as the absolute value of the standardized mean difference in Δparameter between the obese to nonobese and the stable obese groups.

The predicted risks for CVD increased with aging in all weight change groups over the study period (p< 0.05 for all compared with baseline). The obese to nonobese group had a milder slope than the other three groups (predicted risk for CVD of 5.9% in 2002 to 6.9% in 2007, p<0.01 for all comparisons), whereas the steepest increment in the predicted risk for CVD was observed in the nonobese to obese group (predicted risk for CVD of 5.7% in 2002 to 8.2% in 2007, p<0.08 for all comparisons). No significant difference in incremental rate was observed between the stable nonobese and the stable obese groups (p=0.12) **(Supplementary Table 1)**.

Next, we investigated the changes in each cardiovascular risk factor during the 5-year follow-up in obese subjects at baseline—that is, in the stable obese and the obese to nonobese groups **(Table 2)**. The obese to nonobese group showed generally more favorable changes in each risk factor than the stable obese group. In particular, we observed a relatively greater influence of the shift from obese to nonobese on changes in waist circumference, serum HDL cholesterol, and serum levels of liver enzymes, followed by blood pressure and serum triglycerides, across the cardiovascular risk factors. No significant group differences were observed for Δhemoglobin A1c, Δserum LDL cholesterol, and ΔeGFR. In addition, we examined the differences in the change in each cardiovascular risk factor over 5 years between the stable nonobese and the nonobese to obese groups—that is, in subjects without obesity at baseline **(Table 3)**. There were significant group differences in waist circumference, blood pressure, blood lipids except for serum LDL cholesterol, and serum liver enzymes. In addition to Δhemoglobin A1c, Δserum LDL cholesterol, and ΔeGFR, we found no difference in the Δfasting plasma glucose between the stable nonobese and the nonobese to obese groups. The observed associations of weight change status with cardiovascular risk factors were mostly similar to those found in **Table 2**, while the magnitudes of the associations in blood pressure and in serum HDL cholesterol were relatively greater among the outcomes of interest. The sensitivity analysis after excluding subjects who took antihypertensive agents, glucose-lowering agents, or lipid-modifying agents did not make any material difference in the above-mentioned findings **(Supplementary Tables 2, 3, 4)**. In the additional analysis of the associations of the percent weight change with the changes in cardiovascular risk factors, increasing weight was significantly associated with the increasing trends in Δwaist circumference, Δsystolic and diastolic blood pressure, Δfasting plasma glucose, Δhemoglobin A1c, Δserum LDL cholesterol, Δserum triglycerides, Δserum AST, Δserum ALT, and Δserum GGT, and the decreasing

Table 3. Multivariable-adjusted mean change in cardiovascular risk factors by weight change status in the stable nonobese and the nonobese to obese subjects (2002-2007)

Variables	Stable nonobese[1] (n = 1462)	Nonobese to obese[1] (n = 78)	Differences in Δ parameter	p for group difference	Magnitude of difference in change[2]
ΔWaist circumference, cm	3.2 (3.0 to 3.5)	8.4 (7.2 to 9.5)	5.1 (4.0 to 6.3)	<0.001	0.91
ΔSystolic blood pressure, mmHg	1.7 (1.0 to 2.4)	6.3 (3.1 to 9.6)	4.6 (1.3 to 8.0)	0.01	0.29
ΔDiastolic blood pressure, mmHg	1.4 (1.0 to 1.8)	4.8 (2.9 to 6.7)	3.4 (1.4 to 5.4)	0.001	0.36
ΔFasting plasma glucose, mg/dL	-4.8 (-5.5 to -4.1)	-3.3 (-6.5 to -0.1)	1.5 (-1.8 to 4.8)	0.37	0.09
ΔHemoglobin A1c, %	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.1 (0.0 to 0.2)	0.17	0.15
ΔSerum HDL cholesterol, mg/dL	4.8 (4.2 to 5.3)	0.3 (-2.2 to 2.7)	-4.5 (-7.1 to -2.0)	0.001	0.41
ΔSerum LDL cholesterol, mg/dL	2.4 (1.1 to 3.7)	7.5 (1.7 to 13.4)	5.1 (-0.9 to 11.1)	0.10	0.18
ΔSerum triglycerides, mg/dL	0.06 (0.04 to 0.08)	0.17 (0.08 to 0.28)	0.1 (0.0 to 0.2)	0.03	0.23
ΔSerum AST, U/L	-0.12 (-0.13 to -0.11)	-0.06 (-0.11 to 0.00)	0.1 (0.0 to 0.1)	0.02	0.26
ΔSerum ALT, U/L	-0.03 (-0.05 to -0.01)	0.13 (0.04 to 0.22)	0.2 (0.1 to 0.2)	<0.001	0.36
ΔSerum GGT, U/L	0.01 (-0.01 to 0.04)	0.24 (0.13 to 0.36)	0.2 (0.1 to 0.3)	<0.001	0.47
ΔeGFR, mL/min/1.73 m^2	-6.2 (-6.5 to -5.9)	-6.3 (-7.8 to -4.8)	-0.1 (-1.6 to 1.5)	0.94	0.01

Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate
Delta (Δ) indicates absolute changes in each parameter between 2002 and 2007.
Values are expressed as adjusted mean (95% confidence intervals [CI]). The model was adjusted for age, sex, body mass index, use of hypertension, diabetes, and/or dyslipidemia medications, current smoking, current drinking, regular exercise, and each value in 2002.
1) ΔWeight values in the stable nonobese group and the nonobese to obese group were -0.1 (95% CI -1.1 to -0.8) kg and +3.9 (+3.2 to +4.5) kg, respectively.
2) Values are shown as the absolute value of the standardized mean difference in Δparameter between the nonobese to obese and the stable nonobese groups.fig

trends in Δserum HDL cholesterol over the study period **(Supplementary Table 5)**. The patterns of the magnitudes of the associations with the cardiovascular risk factors were similar to those found in **Tables 2 and 3**.

We examined the contribution of change in cardiovascular risk factors during the study period to the association between the weight change status and the predicted risk of cardiovascular disease **(Supplementary Table 6)**. The model in which the measures of blood pressure were added showed the best goodness-of-fit (i.e., the largest R^2), followed by the model that included the measures of blood lipids.

Discussion

In this study, we examined the weight change status and the concurrent changes in the predicted risk for CVD and cardiovascular risk factors over a 5-year follow-up period in Japanese community residents. Among subjects with obesity at baseline, the upward trend in predicted CVD risk was suppressed and the cardiovascular risk factors generally moved towards more favorable profiles during the follow-up period in those who lost weight (the obese to nonobese group) as compared with those who were still obese (the stable obese group). In particular, anthropometry, blood pressure, serum HDL cholesterol, and serum levels of liver enzymes were more likely to be affected by changing weight. Changes in the predicted risk for CVD as well as in cardiovascular risk factors were also observed in nonobese subjects who gained weight (the nonobese to obese group) as compared with those who remained nonobese (the stable nonobese group), but in the opposite direction. Moreover, the differential associations of the weight change status with the predicted risk of cardiovascular disease were likely to be driven by the changes in blood pressure and lipids. The findings of our study will help practitioners to make a more realistic appraisal of the influence of weight change and simultaneous changes in global risks of CVD and will assist research aimed at developing a more effective behavioral intervention strategy through the visualization of risk reduction.

The present study provided real-world evidence based on health check-ups that the rising trend in predicted CVD risk was significantly slowed in those who switched from obese to nonobese over a 5-year period (i.e., from 6.4% to 8.3% in the stable obese group vs. from 6.0% to 6.9% in the obese to nonobese group). In Japan, all health insurers are obliged to provide a health checkup program, the so-called Specific Health Checkups and Specific Health Guidance program, for all enrollees and their dependents, and implement lifestyle modification counseling for people who have or are at risk of

metabolic syndrome[18]. Our findings provide further proof of the benefit of weight management on cardiovascular risk reduction, and this could improve behavioral lifestyle interventions that provide information on the health consequences of weight change.

In the current study, the magnitude of the association between weight change and cardiovascular risk differed among the risk factors studied. It is not surprising that waist circumference, as an anthropometry measure, was the most affected factor. In addition, blood pressure, serum HDL cholesterol, and serum levels of liver enzymes were more sensitive to concurrent weight change than to the other cardiovascular risk factors. Some observational studies previously revealed that body weight change was associated with changes in cardiovascular risk factors including blood pressure, glucose, and lipid measures[20, 21], although inconsistent findings were also reported in other observational studies[22, 23]. Previous clinical studies also reported inconsistent results regarding the influence of behavioral weight loss interventions on cardiovascular risk factors. A clinical study of a behavioral modification program found a significant favorable effect of weight loss on blood lipids but not on fasting plasma glucose levels in obese subjects[24]. Another two-year lifestyle intervention also showed a significant dose-response association of the amount of weight loss with changes in serum triglycerides and HDL cholesterol but not in blood pressure, blood glucose, or serum LDL cholesterol levels[25]. On the other hand, a one-year follow-up of lifestyle intervention through national health checkups in Japan showed favorable changes in all ranges of cardiovascular risks[26]. The exact reasons for the discrepancy of the findings across the studies is not fully elucidated, but the population characteristics within the study (e.g., sex distributions) and/or their initial fat distributions may at least partly explain the inconsistent results across studies, considering the different influences of the changes in visceral and subcutaneous adipose tissue volumes on each cardiovascular risk factor[27]. Nevertheless, based on the present findings there can be no doubt that weight management to prevent obesity has an overall beneficial effect on cardiovascular risk profiles.

In the present study, blood pressure was decreased by weight loss in subjects who were obese at baseline and was increased by weight gain in subjects who were nonobese at baseline. Previous randomized trials of non-surgical weight-reducing interventions showed a significant absolute decline in blood pressure in a linear fashion, but the impact of weight change varied in the range from 0.2 mmHg to 1 mmHg decline in SBP and DBP per 1-kg weight reduction expected[28, 29]. The magnitude of association observed in the current study was comparable to that found in a German population-based study with a 5-year follow-up[30]. These findings and our current observations suggested that weight reduction through a lifestyle change could alter concurrent blood pressure levels, but the magnitude was not very large in the population-based studies.

With regard to the lipid parameters, a significantly greater elevation in serum HDL cholesterol and a significantly greater reduction in serum triglycerides were found by losing weight among subjects who were obese subjects at baseline. The opposite changes were observed in nonobese subjects who gained weight compared with those who were stable nonobese. Conversely, there was no significant change of serum LDL cholesterol by the weight change. In support of these findings, a previous study showed that significant improvements in HDL cholesterol and triglycerides but not in LDL cholesterol were observed in subjects who achieved weight reduction through 2-year lifestyle interventions[25]. On the other hand, meta-analyses of observational and intervention studies found that the effects of non-surgical weight loss on HDL cholesterol levels varied among studies[31, 32]. In addition, a population-based study in the US[22] and the above-mentioned meta-analyses[31, 32] consistently showed that weight loss had a greater effect on LDL cholesterol levels than on HDL cholesterol or triglyceride levels. The discrepancy between our findings and those reported in the literature may be attributable to the differences in study periods, populations, and phases of weight change (i.e., active vs. stabilized).

We observed significant associations between changes in weight status and concurrent changes in the serum levels of liver enzymes. The present study revealed that both weight loss and weight gain were associated with relatively large changes in the serum levels of liver enzymes, suggesting that the serum indicators of liver damage were sensitive to the changes in body weight. In support of these observations, a prior 6-month dietary intervention study on women with obesity and non-alcoholic fatty liver disease found that weight reduction of 5%–6% was accompanied by a 20% to 40% reduction in AST and ALT[33]. The improvement in liver biomarkers in the weight loss group was possibly due to decreased liver fat and consequent improvement in nonalcoholic fatty liver disease[34, 35]. It is noteworthy that serum levels of liver enzyme were not included in the risk prediction model for CVD we used. Considering previous reports showing that GGT could increase

risk of development of atherosclerotic CVD by promoting LDL oxidation[36, 37], further studies will be needed to evaluate the role of liver enzymes in the association between body weight change and changes in CVD risk.

A large body of evidence supports the notion that obesity has a hazardous effect on glycemic control via its deterioration of insulin resistance in the liver and skeletal muscle, while weight reduction exerts a beneficial effect on glucose measures in individuals with prediabetes or diabetes[38, 39]. On the other hand, the present study did not find consistent associations between changes in the weight status and glycemic measures. Thus, we observed a significant difference in the change in fasting plasma glucose only between the stable obese group and the obese to nonobese group, and not between the stable nonobese group and the nonobese to obese group. The magnitude of the influence of weight loss on fasting plasma glucose levels was relatively small among cardiovascular risk factors, which is in accordance with the findings of a previous behavioral weight loss intervention for overweight and obese adults[24]. The reason for the modest influence of weight change on glycemic measures is unclear, but the follow-up period may have been insufficient to definitively elucidate the influence of weight change on plasma glucose levels. The difference in the baseline glucose levels across the studies may also explain the inconsistency, because most of the study participants had glucose measures within the normal range.

Our present results showed that the lipid parameters exhibited the greatest magnitude of changes in association with weight alteration, followed by the liver enzymes. We also found that both blood pressure and lipid parameters strongly explained the associations between weight change and the predicted risk of cardiovascular disease even though the influence of the weight change on blood pressure was relatively small. This may be primarily because of the greater contribution of blood pressure to the prediction of cardiovascular disease, since the contribution of the risk factors is determined not only by the associations between weight change and the risk factors, but also by the association between the change of risk factors due to weight change and the predicted risk for CVD. Taken together, our findings highlight the importance of weight reduction in those with lipid abnormalities and with elevated blood pressure accompanied with obesity. On the other hand, our finding that liver enzymes were less likely to explain the association between the weight change status and the predicted risk of CVD should be interpreted with caution. The finding that the liver enzymes made only a limited contribution was probably due to a weak association between serum liver enzymes and the estimated CVD risk, because the prediction model did not include liver enzymes as a predictor. However, abnormal liver function is likely to reflect fatty liver due to obesity, and fatty liver induces insulin resistance and consequently hypertension, diabetes and dyslipidemia[40]. Therefore, the importance of weight management for maintaining liver function should not be understated, given the general consequences of abnormal liver enzymes. Both controlled intervention and real-world data are needed to further evaluate the role of these risk factors in the prevention of CVD through weight management programs.

The strengths of our study included its high participation rate and follow-up rate in spite of the community setting, and the use of the previously validated risk prediction model for CVD risk. Some limitations should also be noted. First, although we adjusted for lifestyle behaviors at baseline in the model, we did not have information on the means by which the participants achieved weight change. For example, quitting smoking is often accompanied by weight gain, and there has been discussion about whether the weight gain after smoking cessation could weaken the global CVD benefits of smoking cessation[41, 42]. In the present study, however, there were only 5 subjects who quit smoking during the study period in the nonobese to obese group, and only 2 subjects in the obese to nonobese group. Therefore, weight change after smoking cessation was not likely to have influenced the present findings. Second, we could not differentiate between intentional and unintentional weight change (e.g. changing lifestyle or getting sick). It would be of value to examine whether the association between weight change and cardiovascular risk factors differs according to the causes of weight change. Especially in initially lean persons, weight loss is often caused by disorders that affect metabolism, such as malignant tumor and thyroid diseases, so the question of whether the weight loss was intentional should be carefully considered. Given the adverse consequences of weight loss, such as muscle atrophy and impaired function, the influence of weight change should be interpreted with caution. Third, we did not include a detailed analysis of the impact of medications that affect body weight, although the findings were not altered substantially in the sensitivity analyses after excluding subjects who took antihypertensive agents, glucose-lowering agents and/or lipid-modifying agents. Fourth, we could not address the influence of body weight change on the development of cardiovascular events, because there

were only 47 cardiovascular events among our participants over the study period, and this number would not be sufficient to perform a reliable analysis. Further studies investigating this association using large-scale longitudinal data are warranted.

Conclusion

The present study demonstrated changes in the predicted CVD risk as well as in the individual cardiovascular risk factors along with concurrent changes in weight status. Our findings reinforce existing evidence on the favorable association between weight loss in obese people and avoidance of excessive weight gain in nonobese people—especially in those with abnormal lipid parameters and an elevated blood pressure—and the global risk of future CVD. These findings could improve the behavioral counselling strategies provided by health practitioners at health checkups in order to inform patients about the health consequences of weight change.

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Conflict of Interest

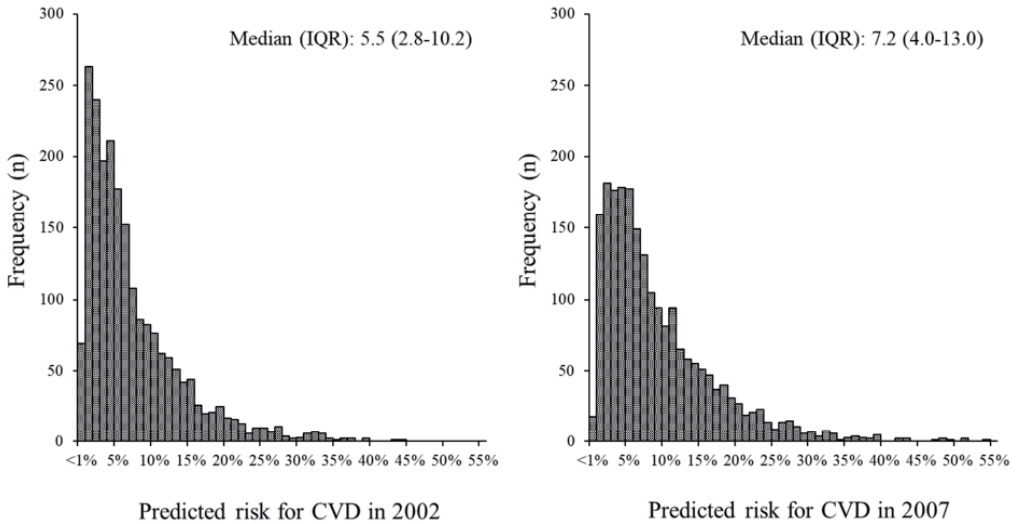
MO and KN are employed by Janssen Pharmaceutical K.K. TN obtained research funds from Janssen Pharmaceutical K.K. The other authors have no conflict of interest.

References

1) Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, and Eckel RH: American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism: Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation, 2006; 113: 898-918
2) Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, and Binno S: ESC Scientific Document Group 2016 European guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J, 2016; 37: 2315-2381
3) Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, Kushner RF, Daniels SR, Wadden TA, Tsai AG, Hu FB, Jakicic JM, Ryan DH, Wolfe BM, and Inge TH: The science of obesity management: an EndocrineSociety scientific statement. Endocr Rev, 2018; 39: 79-132
4) Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, and MacLennan G: Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. BMJ, 2017; 359: j4849
5) Patnode CD, Evans CV, Senger CA, Redmond N, and Lin JS: Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention inadults without known cardiovascular disease risk factors: updated evidence report and systematic review for the US preventive services task force. JAMA, 2017; 318: 175-193
6) Navar AM, Wang TY, Mi X, Robinson JG, Virani SS, Roger VL, Wilson PWF, Goldberg AC, and Peterson ED: Influence of cardiovascular risk communication tools and presentation formats on patient perceptions and preferences. JAMA Cardiol, 2018; 3: 1192-1199
7) Näslund U, Ng N, Lundgren A, Fhärm E, Grönlund C, Johansson H, Lindahl B, Lindahl B6, Lindvall K, Nilsson SK, Nordin M, Nordin S, Nyman E, Rocklöv J, Vanoli D,

Weinehall L, Wennberg P, Wester P, and Norberg M: VIPVIZA trial group: Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial. Lancet, 2019; 393: 133-142
8) Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC Jr, Virani SS, Williams KA Sr, Yeboah J, and Ziaeian B: 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 2019; 140: e596-e646
9) Norris SL, Zhang X, Avenell A, Gregg E, Schmid CH, and Lau J: Long-term non-pharmacological weight loss interventions for adults with prediabetes. Cochrane Database Syst Rev, 2005: CD005270
10) Franz MJ, Boucher JL, Rutten-Ramos S, and VanWormer JJ: Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet, 2015; 115: 1447-1463
11) Heneghan C, Goldacre B, and Mahtani KR: Why clinical trial outcomes fail to translate into benefits for patients. Trials, 2017; 18: 1-7
12) Dunbar JA, Hernan Al, Janus ED, Vartiainen E, Laatikainen T, Versace VL, Reynolds J, Best JD, Skinner TC, O'Reilly SL, Mc Namara KP, Stewart E, Coates M, Bennet CM, and Carter R: Challenges of diabetes prevention in the real world: results and lessons from the Melbourne Diabetes Prevention Study. BMJ Open Diabetes Res Care, 2015; 3: e000131
13) Pomeroy J and Palacios C: Translating findings from lifestyle intervention trials of cariovascualr disease and diabetes to the primary care setting. Curr Nutr Rep, 2012; 1: 215-221
14) Ninomiya T: Japanese legacy cohort studies: the Hisayama Study. J Epidemiol, 2018; 28: 444-451
15) Friedewald W, Levy R, and Fredrickson D: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem, 1972; 18: 499-502
16) Japan Society for the Study of Obesity. Guidelines for the management of obesity disease. 2016. Life Science Publishing Co. 2016
17) Honda T, Yoshida D, Hata J, Hirakawa Y, Ishida Y, Shibata M, Sakata S, Kitazono T, and Ninomiya T: Development and validation of modified risk prediction models for cardiovascular disease and its subtypes: the Hisayama Study. Atherosclerosis, 2018; 279: 38-44
18) Tsushita K, Hosler AS, Miura K, Ito Y, Fukuda T, Kitamura A, and Tatara K: Rationale and descriptive analysis of specific health guidance: the nationwide lifestyle intervention program targeting metabolic syndrome in Japan. J Atheroscler Thromb, 2018; 25: 308-322
19) Horio M, Imai E, Yasuda Y, Watanabe T, and Matsuo S: Modification of the CKD Epidemiology Collaboration (CKD-EPI) Equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis, 2010; 56: 32-38
20) Hillier TA, Fagot-Campagna A, Eschwège E, Vol S, Cailleau M, and Balkau B: D.E.S.I.R. Study group: Weight change and changes in the metabolic syndrome as the French population moves towards overweight: the D.E.S.I.R. cohort. Int J Epidemiol, 2006; 35: 190-19618
21) Lee JS, Kawakubo K, Kobayashi Y, Mori K, Kasihara H, and Tamura M: Effects of ten year body weight variability on cardiovascular risk factors in Japanese middle-aged men and women. Int J Obes, 2001; 25(7): 1063-1067. doi: 10.1038/sj.ijo.0801633
22) Truesdale KP, Stevens J, and Cai J: The effect of weight history on glucose and lipids: the Atherosclerosis Risk in Communities Study. Am J Epidemiol, 2005; 161: 1133-1143
23) Truesdale KP, Stevens J, and Cai J: Differences in cardiovascular disease risk factors by weight history: the Aerobics Center Longitudinal Study. Obesity, 2009; 19: 2063-2068
24) Brown JD, Buscemi J, Milsom V, Malcolm R, and O'Neil PM: Effects on cardiovascular risk factors of weight losses limited to 5–10%. Transl Behav Med, 2016; 6(3): 339-346
25) Vetter ML, Wadden TA, Chittams J, Diewald LK, Panigrahi E, Volger S, Sarwer DB, and Moore RH: POWER-UP Research Group: Effect of lifestyle intervention on cardiometabolic risk factors: results of the POWER-UP trial. Int J Obes, 2013; 37: S19-S24
26) Muramoto A, Matsushita M, Kato A, Yamamoto N, Koike G, Nakamura M, Numata T, Tamakoshi A, and Tsushita K: Three percent weight reduction is the minimum requirement to improve health hazards in obese and overweight people in Japan. Obes Res Clin Pract, 2014; 8: e466-e475
27) Borel AL, Nazare JA, Baillot A, Alméras N, Tremblay A, Bergeron J, Poirier P, and Després JP: Cardiometabolic risk improvement in response to a 3-yr lifestyle modification program in men: contribution of improved cardiorespiratory fitness vs. weight loss. Am J Physiol - Endocrinol Metab, 2017; 312: E273-E281
28) Aucott L, Poobalan A, Smith WCS, Avenell A, Jung R, and Broom J: Effects of weight loss in overweight/obese individuals and long-term hypertension outcomes: a systematic review. Hypertension, 2005; 45: 1035-1041
29) Aucott L, Rothnie H, McIntyre L, Thapa M, Waweru C, and Gray D: Long-term weight loss from lifestyle intervention benefits blood pressure?: a systematic review. Hypertension, 2009; 54: 756-762
30) Markus MRP, Ittermann T, Baumeister SE, Troitzsch P, Schipf S, Lorbeer R, Aumannn N, Wallaschofski H, Dörr M, Rettig R, and Völzke H: Long-term changes in body weight are associated with changes in blood pressure levels. Nutr Metab Cardiovasc Dis, 2015; 25: 305-311
31) Poobalan A, Aucott L, Smith WCS, Avenell A, Jung R, Broom J, and Grant AM: Effects of weight loss in overweight/obese individuals and long-term lipid outcomes: a systematic review. Obes Rev, 2004; 5: 43-50
32) Dattilo AM and Kris-Etherton PM: Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr, 1992; 56: 320-328
33) Rodríguez-hernández H, Cervantes-huerta M, Rodríguez-moran M, and Guerrero-romero F: Decrease of

aminotransferase levels in obese women is related to body weight reduction, irrespective of type of diet. Ann Hepatol, 2019; 10: 486-492
34) Koutoukidis DA, Astbury NM, Tudor KE, Morris E, Henry JA, Noreik M, Jebb SA, and Aveyard P: Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. JAMA Intern Med, 2019; 179: 1262-1271
35) Marchesini G, Petta S, and Dalle Grave R: Diet, weight loss, and liver health in nonalcoholic fatty liver disease: pathophysiology, evidence, and practice. Hepatology, 2016; 63: 2032-2043
36) Ghouri N, Preiss D, and Sattar N: Liver enzymes, nonalcoholic fatty liver disease, and incident cardiovascular disease: a narrative review and clinical rerspective of prospective data. Hepatology, 2010; 52: 1156-1161
37) Targher G and Byrne CD: Circulating markers of liver function and cardiovascular disease risk. Arter Thromb Vasc Biol, 2015; 35: 2290-2296
38) Kim JH, Shin JH, Lee HJ, Kim SY, and Bae HY: Discordance between HbA1c and fasting plasma glucose criteria for diabetes screening is associated with obesity and old age in Korean individuals. Diabetes Res Clin Pract, 2011; 94: 10-12
39) Amedican Diabetes Association. 8. Obesity management for the treatment of type 2 diabetes: standards of medical care in diabetes-2020. Diabetes Care, 2020; 43: S89-S97
40) Diehl AM: Fatty liver, hypertension, and the metabolic syndrome. Gut, 2004; 53: 923-924
41) Tamura U, Tanaka T, Okamura T, Kadowaki T, Yamato H, Tanaka H, Nakamura M, Okayama A, Ueshima H, and Yamagata Z, for the HIPOP-OHP Research Group: Changes in weight, cardiovascualr risk factors, and estimated risk of coronary heart disease following smoking cessation in Japanese male workers: HIPOP-OHP Study. J Atheroscler Thromb, 2010; 17: 12-20
42) Takayama S, Takase H, Tanaka T, Sugiura T, Ohte N, Dohi Y: Smoking cessation without educational instruction could promote the development of metabolic syndrome. J Atheroscler Thromb, 2018; 25: 90-97



Supplementary Fig. 1. Distribution of the predicted risk for cardiovascular disease in 2002 and 2007

IQR, interquartile range. CVD, cardiovascular disease. The predicted risk for CVD was calculated based on a previously published risk prediction model for 10-year cumulative risk for the development of CVD.

Supplementary Table 1. Change in the age- and sex-adjusted predicted risk for cardiovascular disease according to weight change status over 5-years (2002-2007)

Variables	Weight change status over 5 years							
	Stable nonobese ($n=1462$)		Nonobese to obese ($n=78$)		Obese to nonobese ($n=103$)		Stable obese ($n=497$)	
	2002 examination	2007 examination	2002 examination	2007 examination	2002 examination	2007 examination	2002 examination	2007 examination
Predicted risk for CVD [1)]	4.9 (4.8-5.0)	6.5 (6.4-6.7)	5.7(5.3-6.3)	8.2 (7.6-8.9)	6.0 (5.5-6.4)	6.9 (6.4-7.4)	6.4 (6.2-6.6)	8.3 (8.0-8.6)
5-year change rate for the predicted risk for CVD (2002 to 2007) [1, 2)]	1.34 (1.32-1.36), $p<0.001$		1.43 (1.33-1.54), $p<0.001$		1.16 (1.09-1.23), $p<0.001$		1.30 (1.27-1.34), $p<0.001$	
Ratio for the change in predicted risk for CVD compared with that in the stable obese [1, 3)]	1.03 (0.99-1.06), $p=0.12$		1.10 (1.02-1.19), $p=0.02$		0.89 (0.83-0.95), $p<0.001$		reference	

Abbreviations: BMI, body mass index; CVD, cardiovascular disease

1) The values indicated the age- and sex-adjusted, back-transformed means and 95% confidence intervals of the predicted 10-year cumulative risk for cardiovascular disease. Data were log-transformed for analysis and back-transformed for presentation.

2) The values were presented as ratios (95% confidence intervals) comparing the risk estimates at 2007 to that at 2002 examination.

3) The values were presented as ratios (95% confidence intervals) comparing the change rates of the risk estimates (regression slope) from 2002 to 2007 in each group to that in the stable obese group.

Supplementary Table 2. Age- and sex-adjusted characteristics of participants at baseline (2002) according to weight change over 5 years (2002-2007) after excluding subjects who were taking medication for hypertension, diabetes, and/or dyslipidemia

Variables at baseline (2002)	Weight change status over 5 years			
	Stable nonobese (n=958)	Weight gain (n=41)	Weight loss (n=49)	Stable obese (n=212)
Age, year	55.0 (0.3)	54.2 (1.4)	56.3 (1.3)	55.3 (0.6)
Sex, female, %	61.1 (1.6)	53.5 (7.8)	51.4 (7.2)	56.7 (3.4)
Weight, kg	54.3 (0.2)$^{\$}$	60.7 (1.0)$^{*\$}$	64.8 (0.9)$^{*\$}$	68.9 (0.4)*
Waist circumference, cm	77.3 (0.2)$^{\$}$	82.2 (1.1)$^{*\$}$	87.4 (1.0)$^{*\$}$	90.8 (0.5)*
BMI, kg/m^2	21.5 (0.1)$^{\$}$	24.0 (0.3)$^{*\$}$	25.8 (0.3)$^{*\$}$	27.5 (0.1)*
Systolic blood pressure, mmHg	120.5 (0.5)$^{\$}$	122.5 (2.4)$^{\$}$	125.1 (2.2)	129.3 (1.0)*
Diastolic blood pressure, mmHg	73.6 (0.3)$^{\$}$	75.1 (1.5)	76.9 (1.4)*	78.8 (0.7)*
Fasting plasma glucose, mg/dL	102.6 (0.4)$^{\$}$	103.4 (1.7)	108.0 (1.6)*	106.5 (0.8)*
Hemoglobin A1c, %	5.2 (0.0)$^{\$}$	5.1 (0.1)$^{\$}$	5.4 (0.1)*	5.3 (0.0)*
Serum HDL cholesterol, mg/dL	66.2 (0.5)$^{\$}$	62.6 (2.5)	58.4 (2.2)*	59.7 (1.1)*
Serum LDL cholesterol, mg/dL	116.4 (1.0)$^{\$}$	129.3 (4.7)*	129.2 (4.3)*	127.1 (2.1)*
Serum triglycerides, mg/dL[1)]	86.8 (84.3 - 89.5)$^{\$}$	97.1 (84.0 - 112.2)	108.8 (95.3 - 124.2)*	108.7 (102.0 - 115.9)*
Serum AST, U/L[1)]	23.6 (23.2 - 24.0)	24.7 (22.7 - 26.8)	27.2 (25.2 - 29.3)$^{*\$}$	24.3 (23.5 - 25.2)
Serum ALT, U/L[1)]	17.4 (16.9 - 18.0)$^{\$}$	21.7 (18.8 - 25.0)*	26.3 (23.1 - 29.9)*	22.4 (21.1 - 23.8)*
Serum GGT, U/L[1)]	23.9 (23.0 - 24.8)$^{\$}$	26.1 (21.6 - 31.6)$^{\$}$	34.3 (28.9 - 40.8)*	34.1 (31.4 - 37.1)*
eGFR, mL/min/1.73 m^2	83.1 (0.2)$^{\$}$	82.1 (1.2)$^{\$}$	81.1 (1.1)	81.5 (0.5)*
Current smoking, %	17.4 (1.5)	32.2 (8.8)	7.9 (3.1)	12.8 (2.3)
Current drinking, %	47.6 (1.8)	39.1 (8.5)	36.0 (7.5)	51.5 (3.8)
Regular exercise, %	9.9 (1.0)	9.5 (4.6)	5.6 (3.2)	9.5 (2.0)

Abbreviations: BMI, body mass index; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, Alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate Values are expressed as adjusted means or frequencies with standard errors except where noted.
1) Data are shown as geometric means (95% confidence interval).
$^{*}p<0.05$ vs. stable non-obese, $^{\$}p<0.05$ vs. stable obese.

Supplementary Table 3. Multivariable-adjusted changes in cardiovascular risk factors over 5 years by weight change status in the stable obese and the obese to nonobese subjects (2002-2007) after excluding subjects who took antihypertensive agents, glucose-lowering agents and/or lipid-modifying agents (n=261)

Variables	Stable obese[1] (n=212)	Obese to nonobese[1] (n=49)	Differences in Δ parameter	p for group difference	Magnitude of difference in change[2]
ΔWaist circumference, cm	4.4 (3.8 to 5.1)	-1.1 (-2.6 to 0.3)	-5.6 (-7.2 to -4.0)	<0.001	0.96
ΔSystolic blood pressure, mmHg	6.7 (4.8 to 8.6)	2.8 (-1.3 to 6.8)	-4.0 (-8.5 to 0.6 to 8.5)	0.09	0.28
ΔDiastolic blood pressure, mmHg	4.1 (3.1 to 5.1)	1.4 (-0.7 to 3.5)	-2.7 (-5.0 to -0.4)	0.02	0.36
ΔFasting plasma glucose, mg/dL	-1.5 (-3.3 to 0.2)	-6.0 (-9.7 to -2.3)	-4.5 (-8.6 to -0.3)	0.03	0.33
ΔHemoglobin A1c, %	0.20 (0.14 to 0.26)	0.15 (0.02 to 0.28)	-0.1 (-0.2 to 0.1)	0.49	0.11
ΔSerum HDL cholesterol, mg/dL	3.4 (2.1 to 4.6)	8.5 (5.8 to 11.2)	5.2 (2.1 to 8.2)	0.001	-0.54
ΔSerum LDL cholesterol, mg/dL	6.5 (3.5 to 9.5)	-2.8 (-9.3 to 3.7)	-9.3 (-16.5 to -2.0)	0.01	0.38
ΔLog serum triglycerides, mg/dL	0.05 (0.00 to 0.11)	-0.11 (-0.21 to -0.01)	-0.19 (-0.35 to -0.05)	0.01	0.39
ΔLog serum AST, U/L	-0.11 (-0.14 to -0.07)	-0.18 (-0.24 to -0.11)	-0.08 (-0.19 to 0.01)	0.10	0.26
ΔLog serum ALT, U/L	-0.05 (-0.10 to 0.00)	-0.21 (-0.29 to -0.11)	-0.19 (-0.36 to -0.05)	0.008	0.38
ΔLog serum GGT, U/L	0.00 (-0.06 to 0.05)	-0.14 (-0.23 to -0.03)	-0.16 (-0.32 to -0.01)	0.03	0.33
ΔeGFR, mL/min/1.73 m^2	-5.2 (-5.9 to -4.5)	-4.3 (-5.8 to -2.8)	1.0 (-0.7 to 2.7)	0.27	-0.15

Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate
Delta (Δ) indicates absolute changes in each parameter between 2002 and 2007.
Values are expressed as adjusted mean (95% confidence intervals [CI]). The model was adjusted for age, sex, body mass index, current smoking, current drinking, regular exercise, and each value in 2002.
1) ΔWeight values in the stable obese group and the obese-to-nonobese group were -0.3 kg (95% CI -0.7 to +0.1) and -5.5 kg (-6.4 to -4.6), respectively.
2) Values are shown as the absolute values of the standardized mean differences in Δparameters between the stable obese and the obese-to-nonobese groups.

Supplementary Table 4. Multivariable-adjusted change in cardiovascular risk factors over 5 years by weight change in the stable nonobese and the nonobese to obese subjects (2002-2007) after excluding subjects who were taking antihypertensive agents, glucose-lowering agents and/or lipid- modifying agents (n=999)

Variables	Stable nonobese[1] (n=958)	Nonobese to obese (n=41)	Differences in Δ parameter	p for group difference	Magnitude of difference in change[2]
ΔWaist circumference, cm	3.6 (3.2 to 3.9)	8.9 (7.4 to 10.5)	5.4 (3.8 to 7.0)	<0.001	0.95
ΔSystolic blood pressure, mmHg	4.7 (3.9 to 5.5)	10.9 (7.0 to 14.7)	6.2 (2.3 to 10.1)	0.002	0.49
ΔDiastolic blood pressure, mmHg	3.2 (2.8 to 3.7)	6.9 (4.5 to 9.2)	3.6 (1.2 to 6.0)	0.003	0.46
ΔFasting plasma glucose, mg/dL	-4.1 (-4.7 to -3.5)	-2.6 (-5.6 to 0.4)	1.5 (-1.6 to 4.5)	0.34	0.16
ΔHemoglobin A1c, %	0.2 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.0 (-0.1 to 0.1)	0.62	0.08
ΔSerum HDL cholesterol, mg/dL	4.8 (4.1 to 5.4)	-1.3 (-4.6 to 2.0)	-6.1 (-9.5 to -2.7)	<0.001	-0.57
ΔSerum LDL cholesterol, mg/dL	7.1 (5.8 to 8.4)	15.0 (8.5 to 21.5)	7.9 (1.2 to 14.5)	0.02	0.36
ΔLog serum triglycerides, mg/dL	0.07 (0.05 to 0.10)	0.15 (0.03 to 0.29)	0.08 (-0.04 to 0.21)	0.22	0.17
ΔLog serum AST, U/L	-0.12 (-0.13 to -0.11)	-0.07 (-0.14 to -0.01)	0.05 (-0.02 to 0.13)	0.18	0.20
ΔLog serum ALT, U/L	-0.03 (-0.05 to -0.01)	0.13 (0.02 to 0.25)	0.16 (0.05 to 0.29)	0.01	0.40
ΔLog serum GGT, U/L	0.03 (0.00 to 0.05)	0.26 (0.13 to 0.41)	0.23 (0.10 to 0.37)	<0.001	0.56
ΔeGFR, mL/min/1.73 m^2	-5.7 (-6.0 to -5.4)	-5.3 (-6.9 to -3.8)	0.3 (-1.3 to 1.9)	0.69	0.06

Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate
Delta (Δ) indicates absolute changes in each parameter between 2002 and 2007.
Values are expressed as adjusted mean (95% confidence intervals [CI]). The model was adjusted for age, sex, body mass index, current smoking, current drinking, regular exercise, and each value of interest in 2002.
1) ΔWeight values in the stable nonobese group and the nonobese-to-obese group were -0.7 kg (95% CI -0.9 to -0.6) and +4.2kg (+3.4 to +5.0), respectively.
2) Values are shown as the absolute values of the standardized mean differences in Δparameters between the stable non-obese and the nonobese-to-obese groups.

Supplementary Table 5. Multivariable-adjusted change in cardiovascular risk factors over 5 years (2002-2007) according to the six categories of percent change in weight

	Percent change of weight							
	≤ -6% (*n* = 384)	-6< to ≤ -3% (*n* = 404)	-3< to ≤ 0% (*n* = 580)	0< to ≤ +3% (*n* = 408)	+3< to ≤ +6% (*n* = 208)	>6% (*n* = 156)	*P* for trend	Magnitude of difference in change[1]
ΔWaist circumference, cm	-1.6 (-2.0 to -1.2)	1.9 (1.5 to 2.3)	3.3 (3.0 to 3.7)	5.3 (4.9 to 5.7)	7.1 (6.5 to 7.6)	9.1 (8.5 to 9.8)	<0.001	1.88
ΔSystolic blood pressure, mmHg	-3.6 (-5.0 to -2.2)	-0.7 (-2.0 to 0.7)	2.0 (0.8 to 3.1)	2.5 (1.1 to 3.8)	5.2 (3.3 to 7.1)	7.8 (5.6 to 10.1)	<0.001	0.67
ΔDiastolic blood pressure, mmHg	-1.4 (-2.2 to -0.6)	0.1 (-0.6 to 0.9)	1.5 (0.8 to 2.1)	1.7 (0.9 to 2.4)	3.4 (2.3 to 4.4)	4.5 (3.3 to 5.8)	<0.001	0.61
ΔFasting plasma glucose, mg/dL	-6.3 (-7.9 to -4.7)	-4.0 (-5.6 to -2.4)	-3.7 (-5.0 to -2.4)	-4.5 (-6.1 to -3.0)	-2.8 (-5.0 to -0.6)	-0.8 (-3.4 to 1.7)	0.002	0.30
ΔHemoglobin A1c, %	0.0 (0.0 to 0.1)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.2)	0.1 (0.1 to 0.2)	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.3)	0.001	0.34
ΔSerum HDL cholesterol, mg/dL	7.7 (6.7 to 8.7)	5.6 (4.6 to 6.6)	5.1 (4.2 to 5.9)	2.8 (1.8 to 3.8)	2.0 (0.6 to 3.4)	-1.3 (-2.9 to 0.3)	<0.001	0.86
ΔSerum LDL cholesterol, mg/dL	-4.9 (-7.6 to -2.3)	1.0 (-1.5 to 3.5)	3.7 (1.6 to 5.8)	0.6 (-1.9 to 3.2)	4.2 (0.6 to 7.7)	4.3 (0.1 to 8.4)	<0.001	0.30
ΔLog serum triglycerides, mg/dL	-0.09 (-0.12 to -0.06)	-0.02 (-0.05 to 0.02)	0.06 (0.03 to 0.09)	0.12 (0.08 to 0.16)	0.14 (0.08 to 0.20)	0.21 (0.14 to 0.29)	<0.001	0.65
ΔLog serum AST, U/L	-0.16 (-0.18 to -0.13)	-0.14 (-0.16 to -0.12)	-0.11 (-0.13 to -0.09)	-0.12 (-0.15 to - 0.10)	-0.09 (-0.12 to - 0.06)	-0.06 (-0.10 to - 0.02)	<0.001	0.38
ΔLog serum ALT, U/L	-0.15 (-0.18 to -0.11)	-0.10 (-0.14 to -0.07)	-0.04 (-0.06 to -0.01)	-0.01 (-0.05 to 0.02)	0.03 (-0.02 to 0.09)	0.14 (0.08 to 0.21)	<0.001	0.67
ΔLog GGT, U/L	-0.11 (-0.14 to -0.07)	-0.07 (-0.10 to -0.03)	0.00 (-0.04 to 0.03)	0.04 (0.00 to 0.09)	0.13 (0.07 to 0.19)	0.21 (0.13 to 0.29)	<0.001	0.69
ΔeGFR, mL/min/1.73 m^2	-5.8 (-6.4 to -5.1)	-6.3 (-6.9 to -5.6)	-6.2 (-6.7 to -5.6)	-6.5 (-7.1 to -5.8)	-5.9 (-6.8 to -5.0)	-5.9 (-6.9 to -4.9)	0.73	0.02

Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate. Delta (Δ) indicates absolute changes in each parameter between 2002 and 2007.
Values are expressed as adjusted mean (95% confidence intervals [CI]). The model was adjusted for age, sex, body mass index, use of hypertension, diabetes, and/or dyslipidemia medications, current smoking, current drinking, regular exercise, and each value in 2002.
1) Values were calculated as the absolute values of the standardized mean differences in Δparameters between the >6% group and the ≤ -6% groups.

Supplementary Table 6. Comparison of goodness-of-fit statistics by adding cardiovascular risk factors to the model examining the association between the weight change status and the predicted risk of cardiovascular disease

Model	R-squared	Change in R-squared by adding each set of cardiovascular risk factors to the model including age and sex
Age and sex only	0.030	Reference
+ Blood pressure (systolic and diastolic)	0.450	+ 0.420
+ Glucose (fasting glucose and hemoglobin A1c)	0.051	+ 0.021
+ Lipids (HDL and LDL cholesterol and triglycerides)	0.218	+ 0.188
+ Liver enzymes (ALT, AST, GGT)	0.049	+ 0.019
+ Renal function (eGFR)	0.035	+ 0.005

Each set of cardiovascular risk factors was added separately to the model including age and sex.
Abbreviations: HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; eGFR, estimated glomerular filtration rate.