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Individualized Effects of Weight Gain in Adulthood on the Development of MASLD in Japanese Non-Obese Individuals

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ABSTRACT

Background: This study aimed to estimate the individualized effect of weight change since age 20 on the development of metabolic dysfunction–associated steatotic liver disease (MASLD) in Japanese non-obese individuals. We also assessed the clinical characteristics of high-risk individuals with weight gain.

Method: This retrospective cohort study included non-obese individuals who underwent health examinations at St. Luke's International Hospital between 2008 and 2018. We developed a counterfactual prediction model using logistic regression to predict the risk of MASLD onset within 3 years and predicted counterfactual risks for 5 weight change scenarios: (i) weight loss < -3 kg, (ii) weight maintenance: ± 3 kg, (iii) 3.1–6 kg gain, (iv) 6.1–9.9 kg gain, and (v) major weight gain ≥ 10 kg. Individualized effects of weight change were estimated using a risk difference scale, with variability assessed through their distributions and forest plots.

Results: A total of 20 886 individuals (64.4% women) were included, and 2016 (9.6%) developed MASLD within 3 years. The counterfactual prediction model showed the average risk difference for major weight gain ≥ 10 kg was 6.6% (median: 5.1%), with individual risk differences varied from 2% to 19% across individuals. Forest plot showed an increased average risk of 5% for men, abdominal obesity, dyslipidemia, hyperuricemia, and high ALT levels.

Conclusion: Weight change since age 20 is a significant risk factor for MASLD development in non-obese populations, but its impact varies widely among individuals. Men and individuals with abdominal obesity, dyslipidemia, hyperuricemia, and high ALT levels are particularly susceptible to the effects of weight gain.

1 | Introduction

Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is the most prevalent liver disease worldwide, affecting 25% of the global population [1]. An estimated 14% of MASLD patients develop metabolic dysfunction–associated steatohepatitis (MASH) [2], previously known as nonalcoholic steatohepatitis (NASH), which carries severe prognoses, including cirrhosis and hepatocarcinoma. In addition, MASLD is an independent risk factor for cardiovascular diseases, diabetes mellitus, and nonhepatic malignancies [3–6]. As the improvement of

Abbreviations: AUC, area under curve; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BWC20, body weight change since age 20; CI, confidence interval; FBG, fasting blood glucose; GGTP, gamma-glutamyl transpeptidase; HDL-cho, high-density lipoprotein cholesterol; LDL-cho, low-density lipoprotein cholesterol; MASLD, metabolic dysfunction–associated steatotic liver disease; MASH, metabolic dysfunction–associated steatohepatitis; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; RD, risk difference.

MASLD not only reduces chronic liver diseases but also the risk of extrahepatic complications, its prevention and early detection are of great clinical concern.

Although MASLD has a strong association with obesity, a notable problem is that a relatively high prevalence (7%–20%) of MASLD was observed even in non-obese individuals in Asian populations [7–11]. Among several risk factors, including metabolic syndrome findings [10] and genetic factors [12, 13], weight change since the age of 20 years has been reported to be strongly associated with MASLD, particularly in non-obese individuals [14, 15]. Several longitudinal studies have also demonstrated that weight change is a risk factor for the development of MASLD in non-obese individuals [16, 17], underscoring the importance of monitoring weight change in adulthood for MASLD prevention.

In primary care and health screening settings, it is crucial to identify an individual's absolute risks and high-risk individuals who are particularly susceptible to weight gain. Despite its importance, previous research has mainly focused on the population-level effects of weight change, leaving individual-level effects underexplored. Therefore, there is a pressing need for more tailored and individualized risk estimates to enhance preventive strategies and effectively mitigate the risk of MASLD.

The counterfactual prediction model, a prediction model under a causal inference framework, can be used to provide individualized effects of weight change [18–20]. Unlike the factual prediction model, this approach can predict the disease risk under both hypothetical exposure (hypothetical weight change) and actual exposure (actual weight change). Individualized effects can be assessed by calculating the risk differences for each individual.

In this study, we developed a counterfactual prediction model for MASLD development using annual health examination data (2008–2018) in Japan. This study aimed to estimate the individualized effects of weight change in adulthood on the development of MASLD in a non-obese population. We also aimed to determine the clinical characteristics of individuals at a higher risk with weight gain.

2 | Method

2.1 | Study Design and Participants

In accordance with the updated international consensus, the term MASLD has replaced NAFLD. However, because this study began before the consensus was reached, we used the previous NAFLD definition for our analysis.

This retrospective cohort study included participants who underwent health examinations at the Center for Preventive Medicine, St. Luke's International Hospital in Tokyo, Japan. In Japan, mandatory annual health screenings are required for all employed persons; 70% of this sample was referred from employer-sponsored programs, and 30% consisted of community self-referrals.

This study included individuals aged 30–69 years who underwent health examinations between January 2008 and December 2018. Baseline was defined as the initial examination after 30 years of age. At baseline, we excluded individuals who met any of following criteria: (i) body mass index (BMI): $\geq 25\,kg/m^2$; (ii) extreme body weight at age 20: $\leq 30\,kg$ or $\geq 150\,kg$; (iii) excessive alcohol intake: $> 30\,g/day$ for men and $> 20\,g/day$ for women; (iv) fatty liver; (v) hepatitis B or C, liver cirrhosis, or medically treated liver diseases; (vi) no abdominal ultrasonography; (vii) pregnant; (viii) history or medically treated cancer; (ix) history or current hormone therapy; and (x) medically treated for diabetes. In addition, we excluded participants with no ultrasonography follow-up data after baseline (loss to follow-up).

This study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, University of Tokyo (approval no. 2022177NI) and St. Luke's International Hospital Institutional Review Board (approval no. 22-R107). This study was conducted in accordance with both the Declarations of Helsinki. Participants were able to withdraw their consent for the use of their records in research.

2.2 | Collected Data

Demographic and clinical data were collected from all participants during health examinations. Physical measurements, including weight and height, were obtained using a digital scale, and BMI was calculated by dividing weight (kg) by height squared (m^2). Waist circumference was measured at the midpoint between the lowest ribs and iliac crest. Blood samples were collected during each visit to measure albumin, uric acid, fasting blood glucose (FBG), HbA1c, low-density lipoprotein cholesterol (LDL-cho), high-density lipoprotein cholesterol (HDL-cho), triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGTP) after a 12-h fasting period. Systolic blood pressure and diastolic blood pressures were measured.

Participants completed questionnaires about their medical history, current illness, medication use, smoking status (non-smoker/ex-smoker/current smoker), alcohol consumption (grams per week), exercise frequency (no exercise/1–2 times per week/3–5 times per week/6–7 times per week), and weight change since age 20. Trained nurses verified the responses in face-to-face interviews during the health checkups.

2.3 | Outcome

The outcome of this study was the development of MASLD within 3 years of the baseline visit. Fatty liver was diagnosed using ultrasonography based on four established criteria [14]: hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring. MASLD was defined as signs of fatty liver in the absence of excessive alcohol consumption (defined as $> 30\,g/d$ for men and $> 20\,g/d$ for women), after the exclusion of secondary etiologies, including hepatitis B and C.

2.4 | Variables

Weight change since age 20 was calculated as the difference between the weight at baseline and the weight at age 20, and was divided into five categories: (i) < −3 kg (weight loss group), (ii) ± 3 kg (weight maintenance group), (iii) 3.1–6.0 kg weight gain group, (iv) 6.1–9.9 kg weight gain group, and (v) ≥ 10 kg (major weight gain group).

Obesity was defined according to the BMI classification for Asian populations proposed by the World Health Organization (BMI ≥ 25 kg/m^2) [21]. Non-obese individuals were further classified into three categories: underweight (< 18.5 kg/m^2), standard weight (18.5–22.9 kg/m^2), and overweight (23–24.9 kg/m^2).

We used the standard cutoffs for defining metabolic abnormalities in Japan [22]: abdominal obesity (waist circumference ≥ 85 cm for men and ≥ 90 cm for women), dyslipidemia (triglycerides ≥ 150 mg/dL or high-density lipoprotein cholesterol < 40 mg/dL), hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg), and hyperglycemia (fasting blood glucose ≥ 110 mg/dL). In addition, the cutoffs for kidney and liver function were defined as follows [23]: hyperuricemia (uric acid level > 7 mg/dL), high ALT (alanine aminotransferase level > 30 units/dL), and high AST (aspartate aminotransferase level > 30 units/dL).

2.5 | Statistical Analysis

The baseline characteristics of the study participants were summarized according to sex. Continuous variables are presented as means and standard deviations, and categorical variables are summarized as counts and proportions.

The study population was randomly divided into two datasets: one for model learning (70% of the population) and the other for model validation (30% of the population).

We constructed a counterfactual prediction model for MASLD development using a model learning dataset. Univariate and multivariate logistic regression analyses were performed to estimate the odds ratio (OR) for weight change in adulthood. The multivariate model was adjusted for 12 potential confounders: age, sex, BMI, exercise frequency, smoking status, abdominal obesity, dyslipidemia, hypertension, hyperglycemia, hyperuricemia, high ALT levels, and high AST levels. No variable selection was performed during the model building.

The performance of the constructed model was evaluated using discrimination and calibration analyses on a validation dataset. Discrimination was assessed using the area under curve (AUC) of the receiver operating characteristic curve. Calibration was graphically assessed for agreement between the observed outcome proportions and predicted probabilities.

Based on the constructed prediction model, counterfactual risks of developing MASLD were predicted for all participants according to five weight change scenarios: (i) < −3 kg (weight loss), (ii) ± 3 kg (weight maintenance), (iii) 3.1–6.0 kg weight gain, (iv) 6.1–9.9 kg weight gain, and (v) ≥ 10 kg (major weight gain). Using the counterfactual risks from each scenario, we calculated the risk difference, with the weight maintenance scenario (±3 kg) as a reference. In the main text, we describe the risk difference for major weight gain (≥ 10 kg); other scenarios are summarized in the Supporting Information S1. To assess the distribution of risk differences, we constructed forest plots stratified according to clinical findings. In addition, multivariate regression analysis was performed with risk differences as outcomes. Details of the counterfactual prediction model used in this study are described in the Supporting Information S1.

All statistical analyses were performed using SAS Version 9.4 and R Version 4.2.1.

3 | Results

3.1 | Baseline Characteristics of Participants

Among the 98 234 participants who underwent health checkups between 2008 and 2018, 20 886 were included in this study (Figure 1). Table 1 shows the baseline characteristics of the eligible participants: 13469 (64.4%) were women, and the mean age for both men and women was 45 years. The mean weight change from age 20 was 4.3 kg (standard deviation: 5.6 kg) for men and 1.4 kg (standard deviation: 5.0 kg) for women. Notably, 14.4% of men and 4.6% of women have gained more than 10 kg from age 20. Among the eligible population, 2016 (9.6%) developed MASLD within 3 years.

3.2 | Model Building and Internal Validation

A counterfactual prediction model was developed using 14 620 individuals from a learning dataset. Table 2 shows the association between weight change from age 20 and MASLD development. Logistic regression analysis showed that weight change since age 20 was associated with development of MASLD, with higher risks observed with greater weight gain: (i) < −3 kg weight loss group (OR: 0.77 [0.60–1.00]), (iii) 3.1–6 kg weight gain group (OR: 1.37 [1.16–1.62]), (iv) 6.1–9.9 kg weight gain group (OR: 1.87 [1.58–2.21]), and (v) ≥ 10 kg weight gain group (OR: 2.32 [1.90–2.83]). Other risk factors, including male sex, overweight, current smoking, dyslipidemia, hypertension, hyperuricemia, and high ALT levels were also associated with an increased risk of MASLD (Supporting Information S2).

Discrimination and calibration analyses were performed to assess the model performance using 6266 individuals in the validation dataset. The AUC was 0.76 (0.74–0.78), indicating a moderate ability to distinguish between individuals who developed MASLD and those who did not. Calibration analyses showed that the model overestimated risk of MASLD in individuals with predicted risk greater than 25%. However, in most of the study populations, the predicted risk was less than 25%, and the model demonstrated accurate predictions within this range (Supporting Information S3).

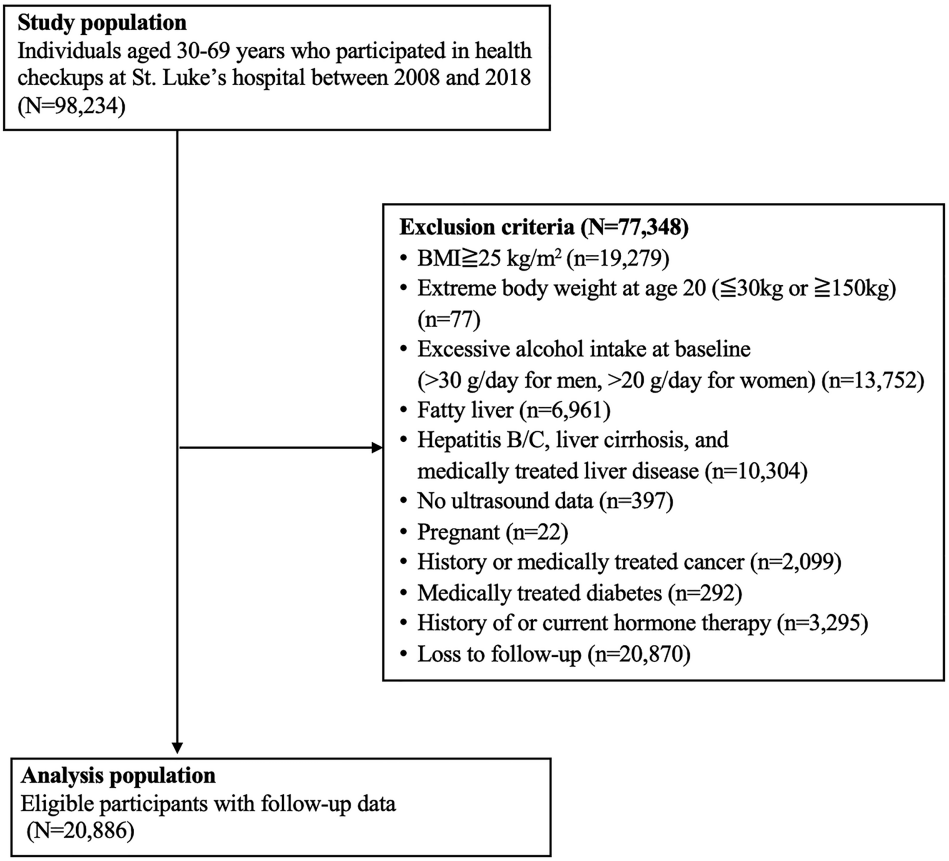

FIGURE 1 | Flowchart of participant selection.

3.3 | Individualized Effect of Weight Change in Adulthood

Among the eligible population, the average risks predicted for each weight change scenario were as follows: (i) 5.6% for weight loss, (ii) 7.4% for weight maintenance, (iii) 9.9% for 3.1–6 kg gain, and (iv) 12.8% for 6.1–9.9 kg gain, (v) 13.4% for major weight gain (Supporting Information S4).

For major weight gain (≥ 10 kg), the risk difference demonstrated a right-skewed distribution with a mean and median risk increases of 6.6% and 5.1%, respectively (Figure 2). Individual risk differences ranged from 2% to 19%, indicating that the magnitude of the increased risk due to weight gain varied widely among individuals. Other weight change scenarios are summarized in the Supporting Information S5.

Figure 3 depicts a forest plot stratified by the demographic and clinical findings. Men had larger risk differences compared to women (mean risk difference: 10.5% for men, 4.5% for women). Individuals with abdominal obesity, dyslipidemia, hyperuricemia, and high ALT level also showed a risk increase greater than 5% compared with those within normal ranges. Among all participants, 256 (1.2%) were men who had all the above clinical findings. The average risk difference in the high-risk population was 18.1% (minimum: 15.9%, maximum: 18.9%), considerably larger risk increase than overall population (6.6%).

In multiple regression analysis for risk difference, hyperlipidemia, male sex, and high ALT level had a greater contribution (> 3%) to the risk difference in this order, suggesting that individuals with these clinical backgrounds are particularly susceptible to the effects of weight gain (Supporting Information S6).

4 | Discussion

In the present study, we developed a counterfactual prediction model that adjusted for potential confounders and predicted the risk of developing MASLD associated with weight change in adulthood. The regression model showed that weight change in adulthood was a significant risk factor for the development of MASLD in non-obese individuals. This result is consistent with previous studies showing that the risk of MASLD increases with the amount of weight gained [14–16]. This finding highlights the importance of monitoring the history of weight change in adulthood to assess the risk of MASLD even among apparently healthy non-obese individuals. Individuals with major weight gain require careful follow-up during annual health checkups and may require preventive measures to mitigate the risk of MASLD.

A notable aspect of this study is the use of a counterfactual prediction model that provides the absolute risk of developing MASLD under different weight change scenarios. Given that

TABLE 1 | Baseline characteristics of eligible participants.

Characteristics	Men ($n = 7417$)	Women ($n = 13\,469$)
Age (years)[a]	45.0 (10.5)	45.4 (9.7)
BMI (kg/m^2)[b] (%)		
< 18.5	316 (4.3)	2694 (20.0)
18.5–22.9	4838 (65.2)	9450 (70.2)
23–24.9	2263 (30.5)	1325 (9.8)
Waist circumference (cm)[a]	78.6 (5.8)	73.2 (6.3)
Weight change since age 20 (kg)[a]	4.3 (5.6)	1.4 (5.0)
Weight change since age 20 (kg)[b] (%)		
< −3 kg	568 (7.6)	2422 (18.0)
−3–3 kg	2322 (31.3)	6215 (46.1)
3.1–6 kg	1721 (23.2)	2531 (18.8)
6.1–9.9 kg	1741 (23.5)	1680 (12.5)
≥ 10 kg	1065 (14.4)	621 (4.6)
Smoking status[b] (%)		
Non-smoker	3696 (49.8)	11 358 (84.3)
Ex-smoker	2331 (31.4)	1399 (10.4)
Current smoker	1390 (18.7)	712 (5.3)
Exercise frequency[b] (%)		
No exercise	2359 (31.8)	5255 (39.0)
1–2 times per week	3067 (41.4)	4783 (35.5)
3–5 times per week	1186 (16.0)	2289 (17.0)
6–7 times per week	805 (10.9)	1142 (8.5)
Systolic blood pressure (mmHg)[a]	117.4 (14.0)	110.2 (15.1)
Diastolic blood pressure (mmHg)[a]	72.2 (10.0)	67.2 (10.2)
Triglycerides (mg/dL)[a]	92.7 (53.3)	65.7 (32.5)
LDL-cho (mg/dL)[a]	117.6 (28.0)	111.1 (28.9)
HDL-cho (mg/dL)[a]	58.1 (12.9)	70.7 (13.9)
FBG (mg/dL)[a]	98.7 (8.6)	93.5 (7.5)
HBA1c (%)[a]	5.5 (0.4)	5.5 (0.4)
Uric acid (mg/dL)[a]	5.9 (1.1)	4.3 (0.85)
Albumin (g/dL)[a]	4.5 (0.2)	4.3 (0.2)
AST (U/L)[a]	20.9 (5.9)	19.4 (8.5)
ALT (U/L)[a]	21.5 (9.7)	16.1 (9.4)
GGTP (U/L)[a]	32.7 (32.8)	18.3 (15.5)
Metabolic syndrome findings[b] (%)		
Abdominal obesity (%)	1022 (13.8)	72(0.5)
Dyslipidemia (%)	990 (13.3)	345 (2.6)
Hypertension (%)	1503 (20.0)	1612 (12.0)
Hyperglycemia (%)	590 (8.0)	332 (2.5)
Hyperuricemia (%)	1314 (17.7)	40 (0.3)
High AST (%)	366 (4.9)	373 (2.8)
High ALT (%)	948 (12.8)	427 (0.2)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FGB, fasting blood glucose; GGTP, gamma-glutamyl transpeptidase; HDL-cho, high-density lipoprotein cholesterol; LDL-cho, low-density lipoprotein cholesterol.
[a]Mean (standard deviation) is reported for continuous characteristics.
[b]Number (%) is reported for categorical characteristics.

approximately 10% of individuals in the non-obese population develop MASLD, maintaining body weight (average risk: 7.4%) reduces the population's risk by several percent, which could be a fundamental basis for public health prevention measures.

In addition, the model used in this study provides more detailed insight into the impact of weight change. Generally, conventional approaches using logistic regression report only the ORs common to the population. The model used in this study, on the other hand, allows for the evaluation of individualized effect of weight change by calculating absolute risk differences for each individual. The mean and median risk difference for major weight gain (≥ 10 kg) was 6.6% and 5.1%, respectively, which was non-negligible impact considering the overall incidence of MASLD. More notably, the distribution of the risk difference varied from 2% to 19%, indicating that some individuals are not significantly affected by weight gain in adulthood and others are substantially affected. In particular, men and those with abdominal obesity, dyslipidemia, hyperuricemia, and elevated ALT levels were strongly affected by weight gain. The risk was further increased by the combination of two or more of these findings. Although there were only approximately 1% of non-obese individuals who had all these findings, it is clinically important to identify high-risk individuals for weight gain to implement intensive prevention and early detection.

The mechanisms underlying this heterogeneity have yet to be elucidated. However, it has been shown that weight gain increases insulin resistance even within normal weight range [24]. The increase in insulin resistance leads to pathophysiological abnormalities such as hyperinsulinemia and an increased delivery of free fatty acids (FFAs) [25]. Hyperinsulinemia promotes lipogenesis, which can be contributing factors for MASLD development, and the increase in FFAs is involved in the elevated hepatic triglyceride influx. Previous studies have shown that weight gain in adulthood is a risk factor for metabolic syndrome components, including dyslipidemia, in the non-obese population [26, 27]. It is likely that the progression of insulin resistance caused by weight gain, in combination with metabolic syndrome, contributes to the development of MASLD. Specifically, Asians are known to have a higher complication rate of visceral fat and insulin resistance than Westerners, even if they are not obese; minor heterozygosity and homozygosity of the gene polymorphism PNPLA3 have been reported to be a cause of this complication [28, 29]. Individuals with metabolic abnormalities, despite their standard weight, may be more susceptible to weight changes, which further increases the risk of developing MASLD.

TABLE 2 | Association of each risk factor with development of MASLD.

Weight change since age 20	Unadjusted	Adjusted[a]
	OR (95% CI)	OR (95% CI)
<−3 kg (weight loss)	0.63 (0.49–0.82)	0.77 (0.60–1.00)
±3 kg (weight maintenance)	[Reference]	[Reference]
3.1–6 kg weight gain	1.87 (1.60–2.19)	1.37 (1.16–1.62)
6.1–9.9 kg weight gain	3.20 (2.75–3.72)	1.87 (1.58–2.21)
≥ 10 kg (major weight gain)	5.16 (4.35–6.13)	2.32 (1.90–2.83)

Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.
[a]Adjusted covariates: sex, age, BMI, smoking status, exercise frequency, abdominal obesity, hyperlipidemia, hypertension, hyperglycemia, hyperuricemia, high ALT, high AST.

The present study has several limitations. First, weight change since age 20 was collected from a self-reported questionnaire, which may be subject to recall bias [30]. Additionally, intermediate weight changes were not accounted for in this study, and substantial weight fluctuations (e.g., rapid weight gain followed by rapid weight loss) may have influenced the study outcome. Second, the diagnosis of MASLD in this study relied solely on ultrasound findings. Consequently, early-stage MASLD may have been overlooked [31], and the absence of biopsy confirmation leaves the possibility of other chronic liver diseases, such as autoimmune hepatitis, unexcluded. Third, the model used in this study was adjusted only for clinical covariates; other important risk factors, such as genetic factors and dietary habits, were not included. These unmeasured risk factors may play a substantial role in the variation of weight change effects on MASLD development. Additionally, although we predicted the individualized effects of weight change using the developed model, the individual effects could not be verified using the observed data. However, internal validation of the model showed a relatively good fit for discrimination and calibration, suggesting that the individualized effect should also be reasonably predicted.

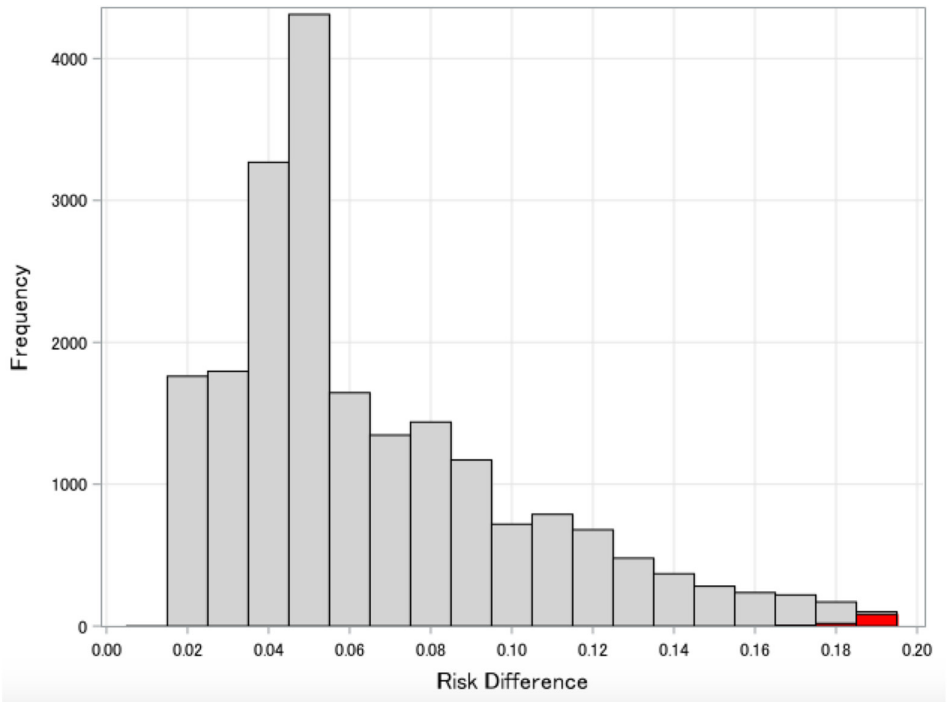

FIGURE 2 | Distribution of risk difference for weight gain of 10 kg or more. The gray histogram depicts the distribution of individualized effect of major weight gain (≥ 10 kg) for all individuals. The weight maintenance scenario (±3 kg) was set as the reference group. The red histogram depicts the risk difference for men participants who had abdominal obesity, dyslipidemia, hyperuricemia, and high ALT level.

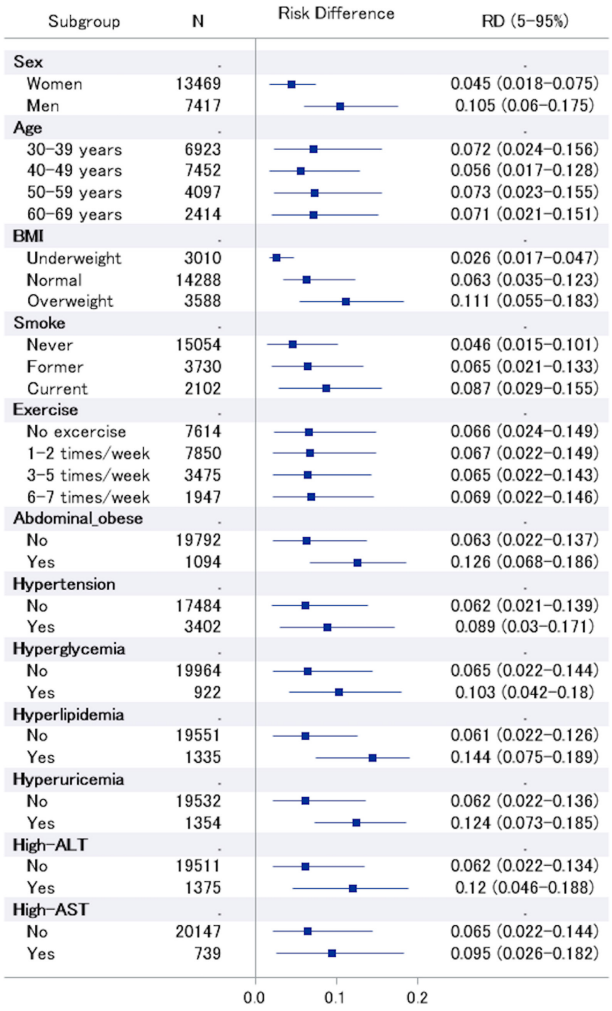

FIGURE 3 | Forest plot of the major weight gain effect. Risk difference for major weight gain is stratified according to demographic or clinical factors. The blue square in the graph provides the mean value of the risk difference, and the error bars indicate the 5% and 95% points of the risk difference. The mean, 5% point, and 95% point of the risk difference are shown on the right side of the graph. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; N, number of subjects; RD, risk difference [Correction added on 18 March 2025, after first online publication: Figure 3 has been corrected in this version.].

Finally, although a recent consensus revised the nomenclature and criteria for MASLD, this study applied the previous NAFLD definition. As 98% of NAFLD patients meet MASLD criteria [32], the impact is likely minimal; however, further research is needed on MASLD's distinct diagnostic criteria.

Despite these limitations, counterfactual prediction models have several clinical implications. In clinical settings, individual responses to exposure or treatment often exhibit heterogeneity. However, conventional regression analyses typically estimate the relative effects that are common to the population and often neglect the absolute magnitude of risk and the heterogeneity of effects among individuals. The counterfactual prediction model used in this study offers a new approach for predicting individualized absolute risks by considering the differences in individuals' backgrounds. It also provides insight into the heterogeneity of effects, which may lead to new clinical knowledge on treatment and disease by investigating the clinical and genetic factors underlying this heterogeneity in future research.

In conclusion, this study demonstrated that weight change since age 20 is a significant risk factor for MASLD development in a non-obese population, although the impact of weight change varied widely among individuals. In particular, men, individuals with abdominal obesity, and those with dyslipidemia, hyperuricemia, and elevated ALT levels exhibited stronger associations with weight gain and MASLD risk. These findings underscore the importance of considering weight history from the non-obese stage in health screening programs in combination with high-risk clinical findings.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.