

Effect of Weight Change on the Progression to Diabetes among Non-obese Individuals

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Abstract

Background: Weight gain in adulthood has been shown to be a risk factor for diabetes mellitus in middle-to-late adulthood. However, this relationship in Asian populations has less well been studied, for which the prevalence of diabetes is considered high among adults with similar body mass index (BMI) levels compared to Caucasians and non-obese diabetes is becoming a major issue for public health. **Objective:** To examine the association of weight change in middle-to-late adulthood with progression to diabetes in non-obese Japanese adults with BMI ≤ 25 kg/m². **Methods:** From data derived in Yuport study, which was a longitudinal cohort based on annual health checkup of middle-aged and older Japanese adults, data of 8,225 non-obese subjects were chosen based on the criteria of BMI ≤ 25 kg/m² and without known diabetes nor high fasting plasma glucose (FPG) (>126 mg/dL) at baseline. We set the average 5.4-years follow-up period. Development of diabetes was defined as the initial observation of FPG higher than 126 mg/dL. Multivariate Cox proportional hazard models were used to examine the relationship of weight change from baseline to the final follow-up and development of FPG-based diabetes in follow-up. **Results:** For the 8,225 non-obese subjects with baseline BMI ≤ 25 kg/m², mean weight gain was 0.09 and 0.48 kg respectively for subjects who developed FPG-based diabetes during follow-up and those who did not. The hazard ratio of weight loss (-1 kg) for FPG-based diabetes incidence during follow-up, adjusted for baseline covariates of sex, age, BMI and FPG was 0.88 (95% CI: 0.83-0.93). For both stratified groups with BMI ≤ 21.94 kg/m² as well as with 21.94 kg/m² $<$ BMI ≤ 23.35 kg/m², weight gain was associated with the development of diabetes. **Conclusion:** Multivariate Cox proportional hazard models suggest that weight gain and loss is a factor that independently associates with higher and lower incidence, respectively, of diabetes in non-obese Japanese adults with BMI ≤ 25 kg/m².

Introduction

Obesity is a well-known factor that increases the risk of development of various cardiovascular complications and Type 2 diabetes mellitus (T2DM). T2DM is now a major epidemic disease at world level, whose prevalence is continuously increasing both in high and low income countries. Primary prevention of diabetes is therefore an urgent issue in public health. Previous studies have reported that long-term weight change during early adulthood increases incidence of T2DM [1,2]. Physical exercise and balanced diet is considered essential for the prevention of diabetes [3]. It has further been shown that abdominal obesity is associated with systemic low grade inflammation induce to insulin resistance and metabolic disorders. Based on these and other findings, promotion of weight loss has been considered the primary treatment for obese patients with T2DM. In addition, promotion of weight loss and/or prevention of weight gain has been shown to be effective for the prevention of diabetes [4-7].

Recently, non-obese diabetes is gaining increasing interest among researchers. In Asia, in particular, it has been shown that T2DM phenotype is more commonly observed among non-obese populations whose BMI levels are not high compared to Western populations. Accordingly, non-obese diabetes is of particular concern in Asian countries where the

prevalence of T2DM is increasing despite a major proportion of people consisting of the non-obese. The proportion of non-obese cases in among total adult cases of diabetes has been estimated to range 60-70% in men and 50-60% in women [8], which has been confirmed by our recent study based on a large Japanese cohort data [9]. This regional difference presents a problem as a majority of previous studies have examined obese populations with mean BMI >25 kg/m². For example, prospective studies from the Diabetes Prevention Program have reported weight loss with lifestyle intervention to be effective for reduction of diabetes risk [6,10,11], but the participants of these studies had mean weight of 93.7 kg [6], 95.4 kg [10], and mean BMI of 33.9 kg/m² [11], respectively. The prevalence of normal weight patients (BMI: 18.5-25) at incident diabetes was 12% in overall of the five cohort studies in the US [12], and 20% of patients with diabetes are non-obese in northern European countries [13]. Such small proportions might have led to a limited number of studies focusing on non-obese populations.

Apart from regional and/or racial differences, non-obese diabetes may have etiological implications. The development of T2DM in non-obese individuals has been reported to be characterized by impaired pancreatic insulin secretion and less severe insulin resistance, as compared with obese individuals [13,14]. Of practical importance, it remains largely unknown whether promotion of weight loss and/or

prevention of weight gain may be recommended for non-obese individuals as primary or secondary prevention of T2DM. This consideration prompted us to conduct an observational cohort study to follow-up incident diabetes in a Japanese non-obese ($BMI \leq 25.0 \text{ kg/m}^2$) population, focusing on weight change and other risk factors.

Subjects and Methods

Laboratory test was conducted using the same methods in baseline and follow-up period as described in our previous report [9]. Statistical analysis was performed using SPSS 20 J (Tokyo, Japan). A $p\text{-value} < 0.05$ was taken as a statistical significance. This study was approved by the ethics committee of Teikyo University (No: 15-205).

Participants and setting

In this study, we used a dataset derived from the annual health screening program performed by the Yuport Medical Checkup Center that collected longitudinal health check-up data for a population of middle-aged and older adults living in Tokyo and the surrounding areas. In this study, we set the four-year baseline period of April 1998–March 2002 followed by the follow-up period of 5.4 years on average. During the baseline period, 21,885 persons underwent checkups at least once during this period in total 49,390 checkups. For subjects who underwent multiple checkups during the baseline period, only the first checkup was taken as the baseline data. Subjects basically attended the checkup during the follow-up once a year and all the data obtained during follow-up period were used to identify incident diabetes. Follow-up data were merged with baseline data, yielding 10,999 who had been examined during both time periods (Figure 1). To focus on non-obese population, at first, 2,512 persons with baseline $BMI > 25 \text{ kg/m}^2$ were excluded. Next, 75 persons with known diabetes at baseline were excluded. Then, 187 persons with $FPG \geq 7.00 \text{ mmol/L}$ (126 mg/dL) were excluded, so we ultimately analyzed 8,225 persons (3,928 men and 4,297 women) with no known diabetes, with $FPG < 126 \text{ mg/dL}$ and $BMI \leq 25.0 \text{ kg/m}^2$ at baseline.

In this study, weight change was defined as the body weight at the final attendance (checkup) during follow-up period relative to the body weight at baseline. We also compared the weight changes of subjects categorized according to the baseline BMI.

Main exposure: Weight change during follow-up period.

Main outcome: Incident diabetes diagnosed based on $FPG \geq 7.00 \text{ mmol/L}$ (126 mg/dL)

Statistical analysis: Multivariate Cox proportional hazard models were used to examine the relationship of weight change and development of FPG-based diabetes in follow-up.

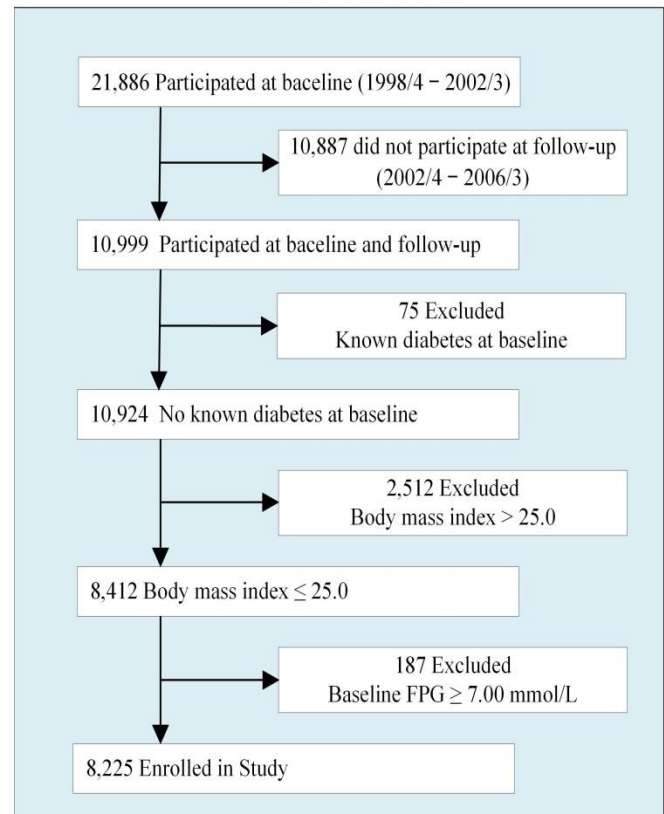


Figure 1: Flowchart of subjects enrollment.

Results

During the mean follow-up of 5.4 years, 171 subjects (2.1%) developed diabetes. Subjects who developed diabetes had been older, more male, more obese and worse profiles of cardiovascular risks including plasma glucose and HbA1c than those who did not at baseline (Table 1). BMI at baseline was 21.7 and 22.7 kg/m^2 and mean weight change during follow-up was 0.09 and 0.48 kg in 8,054 subjects who did not develop diabetes and 171 who developed diabetes, respectively. Incident diabetes in each BMI quartile subgroup is shown in Table 2. With adjustment regarding age and sex, the Cox proportional hazard model analysis showed that the hazard ratio (HR) for a 1 kg weight loss for FPG-based diabetes development during follow-up was 0.94 (Table 3). Of note, the HR for 1 kg weight loss for FPG-based diabetes after adjustment for multiple baseline covariates (sex, age, BMI and FPG) was 0.88 (95% CI: 0.83-0.93). Baseline BMI and FPG also remained as an independent risk for incident diabetes, with HR of 1.11 and 2.43, respectively (Table 3). To examine the association of the baseline BMI with the weight change in the subjects who developed FPG-based diabetes and those who did not, the subjects were categorized into quartile groups; Group 1, $BMI \leq 20.33 \text{ kg/m}^2$; Group 2, $20.33 \text{ kg/m}^2 < BMI \leq 21.94 \text{ kg/m}^2$; Group 3, $21.94 \text{ kg/m}^2 < BMI \leq 23.35 \text{ kg/m}^2$; and Group 4, $BMI > 23.35 \text{ kg/m}^2$.

Mean body weight (with standard error) at baseline and follow-up in subjects who did not develop FPG-based diabetes and those who developed diabetes are shown in Figure 2. For those who developed FPG-based diabetes, the difference of BMIs between at baseline and follow-up were marginal, yet Group 1 and 2 shows statistical significance

(Figure 2A). BMI increase for the subjects who developed FPG-based diabetes was more prominent for Group 1-3 (Figure 2B) relative to the subjects who did not develop diabetes, although statistically not significant except Group 1 likely due to a small number of diabetes incidence of this study.

| | All subjects | Diabetes during follow-up | | |
|---|--------------|---------------------------|--------------------|---------|
| | | Not developed n=8,054 | Developed n=171 | p-value |
| Age (year) | 52.9 (11.8) | 52.8 (11.89) | 57.9 (8.5) | <0.001 |
| Male sex, n (%) | 3928 (47.8) | 3807 (47.3) | 121 (70.8) | <0.001 |
| Height (m) | 161.5 (8.6) | 161.5 (88.6) | 163.1 (8.1) | 0.009 |
| Weight (kg) | 56.9 (8.4) | 56.8 (8.4) | 60.7 (7.2) | <0.001 |
| Body mass index (kg/m ²) | 21.7 (2.0) | 21.7 (2.0) | 22.8 (1.5) | <0.001 |
| Fasting plasma glucose (mg/dL) | 93.9 (8.9) | 93.5 (8.5) | 112.2 (8.7) | <0.001 |
| Hemoglobin A _{1c} (%) | 5.0 (0.4) | 4.9 (0.4) | 5.7 (0.7) | <0.001 |
| Systolic blood pressure (mmHg) | 121.4 (17.3) | 121.2 (17.2) | 127.4 (18.2) | <0.001 |
| Diastolic blood pressure (mmHg) | 73.4 (10.7) | 73.3 (10.7) | 76.3 (10.7) | <0.001 |
| Triglycerides (mg/dL) | 89 (62, 125) | 88 (65, 124) | 120 (81, 162) | <0.001 |
| Total cholesterol (mg/dL) | 201.7(34.8) | 201.6 (34.8) | 205.6 (36.8) | 0.097 |
| HDL cholesterol (mg/dL) | 60.9 (15.2) | 61.0 (15.2) | 53.5 (14.1) | <0.001 |
| Aspartate aminotransferase (U/L) | 20 (17, 24) | 20 (17, 24) | 22 (19, 26) | <0.001 |
| Alanine aminotransferase (U/L) | 17 (13, 23) | 17 (13, 23) | 22 (17, 29) | <0.001 |
| γ-Glutamyl transpeptidase (U/L) | 15 (10, 25) | 15 (10, 25) | 22 (15, 40) | <0.001 |
| White blood cell count (10 ⁹ /L) | 54 (46, 64) | 54 (46, 64) | 59 (50, 68) | 0.011 |
| Follow-up (years) | 5.4 (1.7) | 5.4 (1.7) | 5.7 (1.69) | 0.005 |
| Weight change (kg) | 0.10 (3.01) | 0.09 (3.00) | 0.48 (3.27) | 0.005 |
| Body mass index change (kg/m ²) | 0.2 (1.1) | 0.1 (1.1) | 0.3 (1.2) | 0.011 |

Data are expressed as mean ± SD, median (25-75% range) or number (%). p-values are for comparison of categories of means (unpaired t-test) or percentages (chi-square test). For comparison of means, triglycerides, Aspartate aminotransferase, Alanine aminotransferase, γ-Glutamyl transpeptidase and White blood cell count was log-transformed for their skewed distributions.

Table 1: Baseline characteristics of 8,225 subjects categorized based on the development/absence of FPG-based diabetes during follow-up.

| Baseline BMI subgroups | | Number of each group subjects | Number of subjects who developed FPG-based diabetes (%) |
|------------------------|--------------------------|-------------------------------|---|
| No | BMI (kg/m ²) | | |
| 1 | ≤ 20.3 | 2,057 | 18 (0.9) |
| 2 | 20.3-21.9 | 2,056 | 34 (1.7) |
| 3 | 21.9-23.3 | 2,055 | 65 (2.6) |
| 4 | 23.3-25.0 | 2,057 | 65 (3.2) |
| Total | | 8,255 | 171 (2.1) |

Table 2: Incident diabetes according to BMI quartile subgroups.

| Predictor | Hazard Ratio (95% CI) | |
|-------------------------------------|-----------------------|--------------------|
| | Age / Sex Adjusted* | Multiple** |
| Baseline BMI (1 kg/m ²) | 1.24 (1.13 - 1.35) | 1.11 (1.01 - 1.23) |
| Fasting plasma glucose (5 mg/dL) | 2.37 (2.19-2.56) | 2.43 (2.23 - 2.63) |
| Weight change (-1 kg) | 0.94 (0.90 - 0.99) | 0.88 (0.83 - 0.93) |

*Cox-hazard regression analysis was used.
**Adjustments were made for age, sex, BMI, Fasting plasma glucose. p-value of hazard ratio was <0.05 in all analyses

Table 3: Hazard ratios of predictors for the progression of diabetes among the 8,225 subjects.

Figure 3 shows mean BMI (with standard error) between baseline and follow-up in subjects who did not develop diabetes (green) and developed diabetes (pink). BMIs tended to increase, with Group 1 and 2 showing statistical significance. In particular, for the slimmest group (BMI ≤ 20.33 kg/m²), those subjects who developed FPG-based diabetes had remarkably higher weight gain than those who did not.

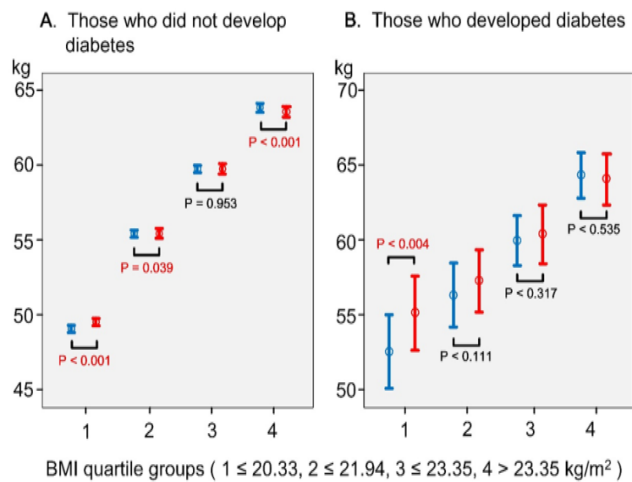


Figure 2: Body weight at baseline (blue) and the final follow-up (red) for stratified subjects according to baseline BMI quartiles. Paired-t test was used. (A) The subjects who did not develop FPG-based diabetes. (B) The subjects who developed FPG-based diabetes.

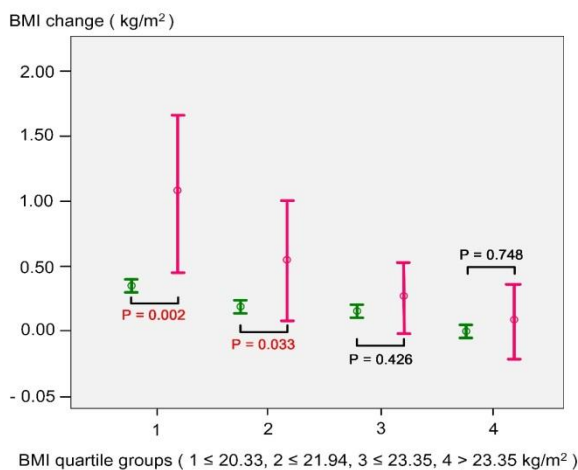


Figure 3: Mean of BMI change from baseline to the final follow-up for subjects who developed FPG-based diabetes (pink) and did not (green). For statistical test, analysis of variance adjusted by age and sex was used.

Discussion

This study confirmed that even in non-obese individuals, weight gain can be a risk factor for development of diabetes. This finding corroborates a recent study by Zhang et al. that reported that, regardless of the presence of overweight, the

long-term weight-change was significantly associated with the increased risk of T2DM [15]. Cox proportional hazard regression models of Zhang et al. and our study support a view that weight loss/hold may protect non-obese people from developing diabetes.

A number of population-based studies have suggested that weight loss to be effective to prevent incident diabetes among obese people. However, less is known regarding whether this interpretation may be applicable for non-obese individuals. Of more interest, in the subjects who developed diabetes, slender subjects had higher weight gain than more plump ones (Figures 2 and 3). This finding may be one feature of this study.

Recent studies on weight change in relation to diabetic risk that were not exclusive to but covered non-obese Asian populations include Sun et al. [16] and Chiu et al. [17]. Using self-reported weight data and conducting cross-stratification based on BMI at 20 y.o. and BMI change between 20 and 40 y.o. as well as a logistic regression analysis, Sun et al. showed that even in non-obese population, as the weight gain increases, the odds ratio for diabetes also increases. Chiu et al. showed that the subjects who developed diabetes tended to have undergone weight gain in early adulthood while they did not show weight gain immediately prior to diabetes incidence. Of note, Chiu et al. did not stratify the subjects with BMI ≤ 24 kg/m² and we surmise that the trend in population with BMI < 22 kg/m² might have been overdominated by that in population with 22 kg/m² $<$ BMI ≤ 24 kg/m². Compared with these two reports, our analysis was acknowledgeably based on short-term weight change records. On the other hand, merits of our approach is the setting that enabled the use of Cox proportional hazard model, and this might have provided an advantage in statistical power. Further, our approach focusing on stratification of BMI ≤ 25 kg/m² was informative, as features of slim populations can be reflected only via careful stratification.

Of etiological interest, it has been reported that individuals with normal BMI may develop diabetes mainly through impaired insulin secretion, whereas individuals with high BMI may develop diabetes primarily through insulin resistance [14]. According to this argument, in non-obese people, impaired insulin secretion may be the primary pathogenesis for diabetes rather than insulin resistance. Nagaya et al. reported even within the non-obese level (BMI ≤ 25 kg/m²), baseline BMI is a dose-dependent risk factor for diabetes mellitus in middle-aged Japanese. Increase in BMI of 1 kg/m² (corresponding to body-weight gain of 2.4-2.9 kg) raises the risk of incident diabetes by about 25% [18]. From their and our studies, reducing or keeping body weight may be beneficial for prevention of diabetes in non-obese individuals.

We note that there are several limitations in this study. First, the obtained finding may not provide sufficient evidence for intervention due to the study design of observational nature. Therefore, we may not identify factors associated with weight loss such as exercise, dietary change or other lifestyle modifications. To resolve this issue, well-controlled trial is necessary. Further, our argument on effect of weight loss using Cox proportional hazard regression model is based on the assumption that one model can universally describe both

effects of weight gain and those of weight loss, while a greater proportion of subjects undergo weight gain in studies of this type compared to the proportion who undergo weight loss [17].

Non-obese persons who have future risk of diabetes may have potential impairment of insulin secretion that are consumed to the limit, even if they are slim and demand for insulin secretion is small. If this is the case, however, more evidence will be needed to advise non-obese or slim persons not to gain weight. Future studies may well attempt to integrate the assessment of ability to secrete insulin, insulin resistance, and weight change under, if possible, interventional study design.

Conclusions

This study suggests that, even in non-obese individuals, weight hold or loss reduces the risk of incident diabetes. In particular, effect of weight gain to increase the risk of diabetes was more evident in a strictly non-obese population with BMI ≤ 20.33 kg/m² compared to a modestly non-obese population with 21.94 kg/m² < BMI ≤ 25 kg/m².

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