Relationship Between Weight Change in Young Adulthood and the Risk of NIDDM

The Sotetsu Study

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OBJECTIVE — To investigate the independent effect of weight change in young adulthood on the risk of prevalent NIDDM among middle-aged Japanese men.

RESEARCH DESIGN AND METHODS — A case-control study was carried out in 895 male employees aged ≥ 30 years of a railway company located in the vicinity of Tokyo. Adjusted odds ratios (ORs) were calculated for prevalent diabetes in each category of weight change (obtained from subjects' medical records) in young adulthood and adulthood. Adjustment for current age, initial BMI, and weight change in each age stratum was performed by the Mantel-Haenszel method or multiple logistic regression analysis.

RESULTS — Weight change between 20 years of age and the age at maximum weight was not associated with the risk of NIDDM. Weight gain between 20 and 25 years of age was significantly and positively associated with the risk of NIDDM (OR 3.87 for gains ≥ 10.0 kg, 2.53 for gains of 5.0–9.9%, and 3.73 for gains $\geq 10.0\%$). On the other hand, moderate weight gain after 30 years of age was significantly inversely associated with NIDDM (OR 0.44 for gains of 5.0–9.9 kg, 0.15 for gains of 10.0–19.9%, and 0.38 for gains of 20.0–29.9%).

CONCLUSIONS — Extreme weight gain between 20 and 25 years of age is a significant predictor of NIDDM, independent of current age, BMI at 20 years of age, and weight change within other age strata.

NIDDM is a common disease in affluent countries and is related to several serious disease conditions, such as cardiovascular disease, cerebrovascular disease, retinopathy, and nephropathy (1,2). Although the effect of genetic factors on the incidence of NIDDM has been emphasized recently, it does not adequately explain the variation of incident NIDDM (1). Obesity is one of the most important environmental and controllable factors of NIDDM. Many studies have demonstrated the association of the risk of NIDDM with current (1,3,4), lifetime maximum (5), and childhood (6) weight. On the other hand, a few studies have examined the association between weight change and the risk of NIDDM. The literature is still inconsistent: positive (3–5,7,8), inverse (9), and no (10,11) association. These studies had various follow-up intervals and start- and/or endpoints of age for investigation. Waaler (12) has demonstrated that BMI, a common indicator of obesity, was dependent on age in both sexes. To evaluate the effect of weight change on the risk of NIDDM, the investigating period and start- and endpoints should be fixed.

We examined the association between the risk of NIDDM and weight change in young adulthood among Japanese men. In addition, a further examination was carried out to investigate the effect of weight change for a fixed period (from 20 to 25 and 25 to 30 years of age) on the risk of NIDDM.

RESEARCH DESIGN AND METHODS — The Sotetsu Study was started in 1993 to investigate the association of the incidence/prevalence of chronic diseases, such as coronary heart disease, diabetes, and hyperlipidemia, with lifestyle risk factors. The cohort was set among the employees of a railway company located in the vicinity of Tokyo.

The subjects were 2,322 male employees, who underwent a health examination from February to May 1995. Employees of this company are required to undergo a health examination at least once a year. This examination includes anthropometric measurement (height and weight), blood pressure measurement, urinalysis, and blood biochemistry. Blood biochemical examinations are performed only on employees aged ≥ 30 years. All subjects were interviewed by physicians, and data on newly diagnosed diseases and treatment were obtained and recorded. Smoking status and family history of diabetes were obtained at the same time.

Data on the weight at entry to this company and in the period from 20 years of age to the current age at 5-year intervals were obtained from the subjects' medical records. Height was also obtained from the records; however, we used current height as the individual height in adulthood, because the mean difference between the height at 20 years of age and the current height was <0.6 cm. Maximum weight was determined as the heaviest weight among the data in nondiabetic subjects and as the heaviest weight before the date of diagnosing diabetes. We also obtained data on current weight, but did not use the values in the following analyses because of the prob-

Table 1—*Numbers of eligible subjects and NIDDM cases and BMI at 20 years of age, weight change between 20 years of age and the age at lifetime maximum weight, between 20 and 25 years of age, between 25 and 30 years of age, and between 30 years of age and the age at lifetime maximum weight for male employees of a railway company in Japan, 1995 (n = 895)*

Variables	30-39 years of age	40-49 years of age	$\geq$50 years of age	P values
Number of subjects	325	318	252	
Number of NIDDM cases	5	15	24	<0.001†
BMI at 20 years of age (kg/m²)	21.3 ± 3.1	20.7 ± 2.0	20.6 ± 1.6	0.0004‡
Weight change between 20 years of age and the age at lifetime maximum weight (kg)*	8.0 ± 5.0	10.0 ± 5.7	9.9 ± 5.9	0.0001‡
Weight change from 20 to 25 years of age (kg)	2.8 ± 3.9	2.5 ± 4.2	1.9 ± 4.1	0.04‡
Weight change from 25 to 30 years of age (kg)	2.6 ± 3.9	2.4 ± 3.7	1.9 ± 3.3	0.053‡
Weight change between 30 years of age and the age at lifetime maximum weight (kg)*	2.7 ± 2.9	5.1 ± 3.8	6.1 ± 4.1	0.0001‡

Data are n or means ± SD.*Lifetime maximum weight for diabetic subjects was the maximum previous to diagnosis. †P value calculated by Mantel-Haenszel extended test; ‡P value calculated by analysis of variance.

ability of postdiagnosed weight reduction (13). BMI was calculated as body weight (in kilograms) divided by the square of height (in meters). Individuals with fasting plasma glucose $\geq$110 mg/dl (6.1 mmol/l) and/or who were positive for glucose by the urine stick test using an enzymatic method (Bayer Diagnostics, Tokyo) were tested further with a 75-g oral glucose tolerance test (OGTT). Plasma glucose levels before and 30, 60, and 120 min after a 75-g OGTT were measured by the glucose oxidase method at an external laboratory (Health Science Research Institute, Yokohama, Japan).

Those with diabetes included *1*) men under treatment by diet, oral hypoglycemic agents, or insulin injection for physician-diagnosed NIDDM and 2) men who were classified as diabetic according to the World Health Organization (WHO) criteria after a 75-g glucose load (those with a fasting plasma glucose level $\geq$140 mg/dl [7.8 mmol/l] and/or a 2-h postload plasma glucose level $\geq$200 mg/dl [11.1 mmol/l] were classified as diabetic and the others as nondiabetic).

Seventeen men, who had experienced a serious disease state before the diagnosis of diabetes, such as a medical history of gastrectomy, neoplasm, coronary heart disease, apoplexy, liver cirrhosis, or hyperthyroidism, and who were under treatment for hyperlipidemia, were excluded. Of 2,305 men, 431 who were younger than 30 years of age were excluded, since NIDDM is an adult-onset disease and none of the cases with known diabetes had an onset before 30 years of age. A total of 923 men did not have their height and weight measured at 20 years of age, because they entered the company at $\geq$21 years of age. Additionally, 56 men for whom there were no data avail-

able on either weight at 20, 25, or 30 years of age were excluded from the comparative analyses of the effects of weight change in young adulthood on risk of diabetes. After the above-described exclusions, 895 men were eligible for enrollment in this study. The current prevalence of diabetes was not significantly different between the excluded cases and the study subjects (4.8 vs. 4.9%, $\chi^2 = 0.027, P = 0.87$).

To evaluate the effect of weight change on diabetes, two separate models were set up: an absolute model and a relative model. The absolute model used differences among the values of weight at 20, 25, and 30 years of age and lifetime maximum weight as an indicator of weight change. The relative model consisted of a weight-gain percentage that was obtained by dividing the weight gain in the interval by the initial weight (weight at 20, 25, or 30 years of age). Weight change in the period from 20 or 30 years of age until the age at lifetime maximum weight was classified as 0.0–4.9, 5.0–9.9, 10.0–19.9, or $\geq$20.0 kg. Since only one person gained over 20.0 kg between 30 years of age and the age at maximum weight, the top and second categories were combined in this age stratum. Weight change from 20 to 25 and 25 to 30 years of age was categorized by 5-kg gains from -5.0 to 10.0 kg. The weight-gain percentage between 20 or 30 years of age and the age at lifetime maximum weight was classified as 0.0–9.9, 10.0–19.9, 20.0–29.9, or $\geq$30.0%, and the percentage values between 20 and 25 years of age or 25 and 30 years of age were categorized as less than -5.0%, -5.0 to 4.9%, 5.0 to 9.9%, or $\geq$10.0%.

Current age, which was categorized as 30–39, 40–49, or 50–65 years, was used as a potential confounder. Initial BMI of the

investigating period was classified into tertiles and was used as a confounding factor for analysis in each absolute model. The waist-to-hip ratio (WHR), which was obtained in 1994 or 1995, was used as an additional confounding factor, as well as smoking status and family history of diabetes. Adjusted odds ratios (ORs) and 95% CIs of diabetes were calculated by means of the Mantel-Haenszel method and multiple logistic regression analysis. The probability of trend (P for trend) was induced by the Mantel-Haenszel extended test. All computations were performed using the Statistical Analysis System (14). Repeated P values were two-sided, and P values of <0.05 were regarded as statistically significant.

RESULTS — Characteristics of the study subjects are shown in Table 1. The proportion of subjects with NIDDM increased with increasing current age. Mean values of weight change from 20 to 25 and 25 to 30 years of age were greater in younger than in older men. On the other hand, the weight change between 30 years of age and the age at lifetime maximum weight was greater in older than in younger men.

Crude and adjusted ORs of NIDDM for each weight change category calculated by absolute models are shown in Table 2. There was no significant association of weight change between 20 years of age and the age at lifetime maximum weight with the risk of NIDDM, irrespective of whether or not adjustments were made for age and initial BMI. Those with weight gains $\geq$10.0 kg between 20 and 25 years of age had significantly greater ORs, compared with those with a weight loss or a gain <5.0 kg (reference) after adjustment for age and initial BMI, and the trend was significantly positive

Table 2—*Crude, age-adjusted, and both age- and initial-BMI–adjusted ORs and 95% CIs of NIDDM by weight change between 20 years of age and the age at lifetime maximum weight, between 20 and 25 years of age, between 25 and 30 years of age, and between 30 years of age and the age at lifetime maximum weight for male employees of a railway company in Japan, 1995 (n = 895)*

Weight change	n	Crude OR	Age-adjusted OR	Age- and initial-BMI–adjusted OR*
Between 20 years of age and age at lifetime maximum weight†				
0 to 4.9 kg	200	Reference	Reference	Reference
5.0 to 9.9 kg	330	0.91 (0.36–2.26)	0.84 (0.33–2.12)	0.82 (0.31–2.16)
10.0 to 19.9 kg	327	1.56 (0.68–3.60)	1.32 (0.56–3.14)	1.46 (0.60–3.53)
≥20.0 kg	38	2.82 (0.84–9.47)	2.26 (0.66–7.75)	1.98 (0.54–7.17)
P for trend		0.07	0.20	0.21
Between ages of 20 and 25 years				
Less than −5.0 kg	10	0.0	0.0	0.0
−5.0 to 4.9 kg	674	Reference	Reference	Reference
5.0 to 9.9 kg	171	1.65 (0.81–3.37)	1.97 (0.95–4.06)	1.89 (0.90–3.96)
≥10.0 kg	40	4.23 (1.76–10.18)	3.99 (1.62–9.85)	3.87 (1.50–9.97)
P for trend		0.002	0.001	0.003
Between ages of 25 and 30 years				
Less than −5.0 kg	14	3.50 (0.82–14.86)	4.91 (1.25–19.38)	3.15 (0.69–14.37)
−5.0 to 4.9 kg	681	Reference	Reference	Reference
5.0 to 9.9 kg	171	1.30 (0.63–2.71)	1.62 (0.76–3.44)	1.67 (0.77–3.63)
≥10.0 kg	29	0.75 (0.10–5.65)	0.85 (0.12–6.18)	0.83 (0.12–5.91)
P for trend		0.82	0.54	0.53
Between age of 30 years and age at lifetime maximum weight†				
0 to 4.9 kg	542	Reference	Reference	Reference
5.0 to 9.9 kg	267	0.55 (0.25–1.20)	0.37 (0.17–0.81)	0.44 (0.19–0.97)
≥10.0 kg	86	1.57 (0.67–3.68)	0.90 (0.37–2.19)	1.18 (0.45–3.09)
P for trend		0.92	0.24	0.56

Data are n or OR (95% CI). *Initial BMI was calculated by using the body weight at the starting point of each investigation term. †Lifetime maximum weight for diabetic subjects was the maximum previous to diagnosis. P value was calculated by Mantel-Haenszel extended test.

(Mantel-Haenszel extended χ^2 = 8.859, P = 0.003). On the other hand, those with a weight gain of 5.0–9.9 kg between 30 years of age and the age at lifetime maximum weight had a significantly lower risk of NIDDM, compared with the reference (weight gain <5.0 kg) after adjustment for age and BMI at 30 years of age. However, there was no significant trend.

The associations between weight-gain percentage and the risk of NIDDM calculated by the relative models are shown in Table 3. There was no significant OR of NIDDM across any category of weight-gain percentage between 20 years of age and the age at lifetime maximum weight, whether adjusted for current age or not. Those with a weight gain >5.0% between 20 and 25 years of age had significantly greater ORs, compared with those with a weight gain of −5.0 to 4.9% (reference), even after adjustment for age, and the trend was significantly positive. Weight gain after 30 years of age showed a lower risk of NIDDM in the moderate weight gain strata (weight-gain percentage, 10.0–19.9% and 20.0–29.9%), compared with the reference (weight-gain percentage, 0.0–9.9%). Although an inverse association (P = 0.03) was found after adjustment for age, a dose-response relationship was not found.

To investigate the independent effect of weight change or weight-gain percentage, multiple logistic regression analysis was employed. Weight gains ≥20.0 kg between 20 and 25 years of age were associated with NIDDM significantly and positively (OR = 3.59, 95% CI 1.29–9.97), and moderate weight gain (5.0–9.9 kg) from the weight at 30 years of age to the maximum weight significantly decreased the risk (OR = 0.34, 95% CI 0.15–0.80) for absolute models, independent of age, BMI at 20 years of age, and weight change in other age strata. Those who gained 20.0–29.9% or ≥30.0% between 20 and 25 years of age demonstrated a significantly high risk (OR = 2.50, 95% CI 1.12–5.58, or OR = 3.56, 95% CI 1.59–8.11, respectively), and moderate weight gains (10.0–19.9 or 20.0–29.9%)

after 30 years of age presented a significantly lower risk (OR = 0.16, 95% CI 0.05–0.48, or OR = 0.42, 95% CI 0.18–0.99, respectively) for the relative model, independent of age and weight-gain percentage in the other age strata. After additional adjustment for current WHR (top quintile, bottom quintile, and others), smoking status (nonsmokers or smokers), and family history of diabetes (present or absent), the associations were not remarkably changed, except for one: the significant association between moderate weight gain (22.0–29.9%) after 30 years of age and the risk of NIDDM disappeared.

CONCLUSIONS — Weight change between 20 years of age and the age at the maximum weight was not associated with a risk of NIDDM. Weight gain (≥10.0 kg or ≥5.0%) between 20 and 25 years of age was significantly and positively associated with a risk of NIDDM. On the other hand, moderate weight gain (5.0–9.9 kg or 10.0–29.9%) after 30 years of age was significantly and inversely associated with

NIDDM. These two opposing relationships may mask a weight-change effect deriving from the long investigation interval in the development of NIDDM.

The literature on the association between weight change and the risk of NIDDM has been inconsistent. Colditz et al. (3) reported that weight gain after 18 years of age was strongly related to the risk of diabetes after controlling for age and BMI at 18 years of age in their large middle-aged female cohort. Chan et al. (4) also stated that weight gain after 21 years of age strongly predicted the risk of diabetes after adjustment for age, smoking, family history, and BMI at 21 years of age in male health professionals aged 40–75 years. Holbrook et al. (5) demonstrated that relative change in weight between 18 years of age, and the 1984–1987 visit ($\geq$50 years of age) was more strongly associated with diabetes than weight change between 40 and 60 years of age, weight maintenance by exercise, and weight at 18 years of age, independent of age, sex, smoking status, and the above-mentioned variables in their population-based cohort study. On the contrary, Noppa et al. (9) found an inverse association between weight gain for 10 years and incident diabetes in a cohort study of 1,302 women. Furthermore, Sicree et al. (10) demonstrated that weight change was not associated with glucose intolerance in a Nauruan cohort study. Our findings were similar to the findings of the last report.

These previous studies obtained weight changes in protocols with various follow-up intervals and unfixed start- and endpoints of age. The difference in body constitutions may affect the findings. Our population was leaner than those of the previous reports (3,5,7,8,10). Thus, it may have been more difficult to reveal a remarkable weight change in our population. However, the values of mean BMI at 20, 25, and 30 years of age in our subjects were comparable with those of the National Nutrition Survey in Japan (15), but were less than that of U.S. men (16).

Although there was no association between the risk of NIDDM and weight change between 20 years of age and the age at maximum weight, a further examination was carried out in this study. We found curious associations between weight change and NIDDM in adulthood, compared with young adulthood. Despite a positive association of the risk of NIDDM with weight gain between 20 and 25 years of age, the association was negative at $\geq$30 years of age.

Table 3—*Crude and age-adjusted ORs and 95% CIs of NIDDM by weight-gain percentage between 20 and 25 years of age, between 25 and 30 years of age, and between 30 years of age and the age at lifetime maximum weight for male employees of a railway company in Japan, 1995 (n = 895)*

Weight-gain percentage	n	Crude OR	Age-adjusted OR
Between 20 years of age and age at lifetime maximum weight*			
0.0 to 9.9%	256	Reference	Reference
10.0 to 19.9%	360	1.44 (0.64–3.26)	1.27 (0.56–2.90)
20.0 to 29.9%	201	1.59 (0.65–3.90)	1.25 (0.48–3.22)
$\geq$30.0%	78	2.29 (0.81–6.50)	1.68 (0.56–5.09)
P for trend		0.13	0.41
Between 20 and 25 years of age			
Less than −5.0%	49	2.18 (0.62–7.64)	1.72 (0.50–5.85)
−5.0 to 4.9%	482	Reference	Reference
5.0 to 9.9%	199	2.34 (1.10–4.97)	2.53 (1.16–5.50)
$\geq$10.0%	165	3.10 (1.49–6.43)	3.73 (1.76–7.91)
P for trend		0.009	0.002
Between 25 and 30 years of age			
Less than −5.0%	41	1.25 (0.28–5.53)	1.33 (0.30–5.79)
−5.0 to 4.9%	507	Reference	Reference
5.0 to 9.9%	221	1.77 (0.90–3.51)	1.94 (0.97–3.87)
$\geq$10.0%	126	1.43 (0.59–3.45)	1.62 (0.66–4.00)
P for trend		0.26	0.14
Between 30 years of age and age at lifetime maximum weight*			
0.0 to 9.9%	396	Reference	Reference
10.0 to 19.9%	236	0.25 (0.09–0.66)	0.15 (0.06–0.39)
20.0 to 29.9%	216	0.69 (0.33–1.46)	0.38 (0.18–0.79)
$\geq$30.0%	47	1.32 (0.44–3.97)	0.49 (0.15–1.65)
P for trend		0.54	0.03

Data are n or OR (95% CI). *Lifetime maximum weight for diabetic subjects was the maximum previous to diagnosis. P value was calculated by Mantel-Haenszel extended test.

There are several potential explanations for our findings. Subjects who had a lower weight at 20 years of age underwent an increase in weight until 25 years of age and showed a high risk of NIDDM. However, there was no positive association between low BMI at 20 years of age and the risk of NIDDM in our population (unpublished data). A fixed interval in young adulthood may be too short to evaluate the following risk of NIDDM. However, any difference between the case and control subjects is important as a potential precursor to the disease, however slight. The different associations of the risk of NIDDM with weight changes in young adulthood from the weight changes in adulthood cannot be neglected. Since the two variables were correlated strongly and inversely, the effects may be contrasted statistically. However, the percentage weight gain from $\geq$30 years of age was inversely associated with the percentage weight gain from 20 to 25 years of

age as strongly as the change from 25 to 30 years of age ($r = -0.13$ and -0.14, respectively). This inverse association between weight change after 30 years of age and the development of NIDDM may indicate that many subjects are already diabetic or prediabetic at 30 years of age. However, the mean age of onset of NIDDM was 42.4 ± 8.2 years and the probability of diabetic state at 30 years of age in many subjects may have attenuated. The independent opposing directions suggest that subjects who are likely to develop NIDDM, such as a patient with a specific genotype, increase weight in young adulthood and that those who gained weight after 30 years of age had a lower risk than subjects with an early weight gain.

We had several advantages in this investigation, compared with the previously reported studies. We used data on weight at each age that was measured and recorded, and we did not use self-reported data. There was no probability of recall

bias. We obtained the exact time for incident NIDDM. Thus, the exposure to risk factor was defined as the weight change before the disease onset. We examined weight change of a relatively short and fixed term (5 years) in young adulthood separately from that in adulthood. This procedure would be necessary to evaluate the effect of weight change in young adulthood on the risk of NIDDM, because a long investigating period includes the variability of risk factors.

We must consider several limitations of this study. Our subjects were Japanese men from 30 to 65 years of age. Generalization to other races and women was difficult. The prevalence of diabetes in our population (4.9%) was less than that of the U.S. (6.9%) and greater than that of the U.K. (0.9–4.7%) (1,18), but the value of our population was comparable with that of other studies conducted in Japan (19–21). Unfortunately, there are no data describing detailed weight changes similar to our investigation, and we cannot compare our results with other Japanese data. The design of this study was case-control, and death, resignation, or retirement from this company may have biased our results. Furthermore, the probability that cases with diabetes that did not fall within our criteria were included in the control cannot be disregarded. To estimate the nonbiased effect of weight change in early life, a prospective study will be needed. Calorie intake was not included as a confounding factor because of insufficient data in this investigation. Although several studies reported a strong association between abdominal obesity and the risk of NIDDM (22,23), we cannot refer to this association because of a lack of data on waist and hip circumference at 20 and 25 years of age. However, weight change in young adulthood was associated with the risk of NIDDM, independent of current WHR, in spite of the positive association between current WHR and NIDDM. The OR among subjects in the top quintile of WHR, compared with the normal level (middle three quintiles), was 2.01 (95% CI 1.02–3.94). If subjects who gained weight extensively between 20 and 25 years of age accumulated adipose tissue in the abdominal area in early adult life, our findings do not conflict with the general opinion that many people tend to have an increase in abdominal adiposity with aging and similarly are likely to have an increased risk of glucose intolerance with advancing age in Western countries. In general, the Japanese are leaner than Western

people, and the association between abdominal obesity and aging among Japanese may be weaker than that among Caucasians. Unfortunately, we have no data on WHR change from 20 years of age, and we cannot address whether our assumption is appropriate or not.

In conclusion, extreme weight gain between 20 and 25 years of age is a significant predictor of NIDDM, independent of current age, BMI at 20 years of age, and weight change according to other age strata. On the other hand, moderate weight gain between 30 years of age and the age at lifetime maximum weight was associated significantly and inversely with the development of NIDDM.

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