Table 1—*Background characteristics and dietary intake for 1,414 patients with type 2 diabetes according to quartiles of total dietary fiber*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P_{trend}
N	352	349	353	360	
Total dietary fiber (g/day)	8.7 ± 1.6	12.5 ± 0.9	15.8 ± 1.0	21.8 ± 4.0	<0.01
Soluble dietary fiber (g/day)	2.1 ± 0.4	2.9 ± 0.2	3.7 ± 0.3	5.1 ± 1.2	<0.01
Insoluble dietary fiber (g/day)	6.3 ± 1.2	9.0 ± 0.7	11.4 ± 0.9	15.8 ± 2.9	<0.01
Age (years)	57.5 ± 7.5	58.4 ± 7.2	59.5 ± 6.5	59.0 ± 6.4	<0.01
Women (%)	36.6	46.7	52.4	56.1	<0.01
HbA_{1c} (% in NGSP value)	8.2 ± 1.2	8.3 ± 1.2	8.4 ± 1.5	8.4 ± 1.4	0.03
HbA_{1c} (mmol/mol)	66.0 ± 12.7	66.9 ± 13.3	68.3 ± 16.5	68.1 ± 15.1	0.03
Fasting plasma glucose (mg/dL)	158.1 ± 42.5	158.8 ± 41.0	162.6 ± 46.9	161.9 ± 43.9	0.16
Years after diagnosis	11.1 ± 6.7	11.1 ± 7.1	11.1 ± 7.2	10.6 ± 7.1	0.37
BMI (kg/m^2)	22.8 ± 2.8	22.9 ± 3.1	22.8 ± 2.8	23.2 ± 3.1	0.10
SBP (mmHg)	131.3 ± 16.5	131.1 ± 17.2	132.5 ± 15.2	131.6 ± 15.9	0.57
Diastolic blood pressure (mmHg)	76.3 ± 10.3	76.7 ± 10.0	76.3 ± 9.8	76.7 ± 9.6	0.80
LDL cholesterol (mg/dL)	122.5 ± 31.6	122.7 ± 33.2	123.3 ± 31.5	121.3 ± 32.1	0.69
HDL cholesterol (mg/dL)	53.9 ± 16.8	54.5 ± 16.8	55.3 ± 16.8	55.2 ± 16.9	0.24
Triglycerides (mg/dL)*	101.0 ± 65.0	103.0 ± 71.0	97.0 ± 70.0	98.0 ± 68.0	0.26
Treated by insulin (%)	22.7	22.7	21.0	19.5	0.24
Treated by OHA without insulin (%)	65.6	66.2	66.0	64.2	0.68
Treated by antihypertensive agents (%)	25.6	27.7	26.9	23.1	0.41
Treated by lipid-lowering agents (%)	19.7	25.3	28.0	23.3	0.18
Current smoker (%)	39.6	27.8	23.7	19.9	<0.01
Physical activity (kJ/day)*	424.8 ± 956.3	546.4 ± 1,033.3	600.6 ± 1,041.3	702.9 ± 1,342.2	<0.01
Alcohol intake (%)					
Never	52.1	59.8	63.2	67.1	<0.01
≤1 drink†	40.3	33.9	32.4	27.4	
>1 drink†	7.7	6.3	4.4	5.4	
Grains (g/day)	184.5 ± 51.1	192.0 ± 56.3	194.4 ± 51.1	193.7 ± 49.0	0.02
Vegetables (g/day)	158.6 ± 64.7	258.3 ± 71.2	351.7 ± 86.1	518.3 ± 159.6	<0.01
Fruits (g/day)	70.1 ± 57.0	113.5 ± 74.0	147.3 ± 86.8	203.1 ± 139.3	<0.01
Seafood (g/day)	75.9 ± 44.4	86.2 ± 45.2	106.3 ± 54.5	128.1 ± 73.3	<0.01
Meat (g/day)	40.9 ± 31.2	45.1 ± 34.7	50.1 ± 35.8	59.9 ± 46.3	<0.01
Energy intake (kcal/day)	1,442.3 ± 315.7	1,617.5 ± 300.0	1,787.6 ± 310.0	2,058.9 ± 407.4	<0.01
Protein (% energy)	15.0 ± 2.5	15.3 ± 2.2	16.0 ± 2.3	16.6 ± 2.4	<0.01
Fat (% energy)	26.5 ± 5.3	27.3 ± 5.1	27.5 ± 4.4	28.6 ± 5.1	<0.01
Carbohydrate (% energy)	53.6 ± 6.9	54.2 ± 6.4	53.9 ± 5.9	53.2 ± 7.1	0.36
Saturated fatty acid (% energy)	7.8 ± 2.0	8.0 ± 1.7	7.9 ± 1.5	7.9 ± 1.6	0.35
Dietary cholesterol (mg/day)	260.1 ± 99.7	287.1 ± 90.1	321.4 ± 105.7	371.4 ± 135.8	<0.01
Sodium (g/day)	2.7 ± 0.7	3.7 ± 0.8	4.4 ± 0.9	5.9 ± 1.4	<0.01

Data are means ± SD unless otherwise indicated. OHA, oral hypoglycemic agents. *Median ± interquartile range. †One drink is equivalent to 12.6 g ethanol based on the U.S. Department of Agriculture definition.

Intake of total dietary fiber was positively associated with proportions of protein and fat intake but not with the proportion of carbohydrate intake. Patients in higher quartiles were significantly older and included more women and had preferable lifestyles such as a lower smoking proportion and increased physical activity. However, there were no significant trends in blood pressure, lipids, and medications, and the difference in HbA_{1c} values was only marginal. Total dietary fiber was positively associated with not only intakes of grain, vegetables, and fruits but also intakes of seafood, meat, and sodium.

During the follow-up of a median of 8.1 years, the numbers of incident CVD according to quartiles of total dietary fiber were 21, 24, 27, and 24 for CHD; 22, 15, 13, and 18 for stroke; and 19, 12, 11, and 15 for cerebral infarction, respectively. The 68 stroke events included 58 cerebral infarctions, 5 intracranial hemorrhages, 4 transient ischemic attacks, and 1 stroke of undetermined type in accordance with WHO criteria. The crude incidence rates per 1,000 patient-years for CHD, stroke, and cerebral infarction were 9.70, 6.81, and 5.69, respectively, and the follow-up rate at 8 years was 78%. There was no notable difference in baseline characteristics between patients who completed 8-year follow-up and the other patients (27).

Tables 2 and 3 show HRs for dietary fiber, vegetables, and fruits estimated by Cox regression models unadjusted (top model), adjusted for risk factors (middle model), and further adjusted for total energy intake (bottom model). The energy-adjusted HRs for stroke in the fourth quartile compared with the first quartile were 0.39 (95% CI 0.12–1.29, $P = 0.12$) for total dietary fiber and 0.35 (95% CI 0.13–0.96, $P = 0.04$) for vegetables and fruits (Table 2). There were no significant decreasing trends between grain intake, a

major source of dietary fiber, and incident stroke (data not shown). The HR per 1-g increase was smaller for soluble dietary fiber (0.48 [95% CI 0.30–0.79], $P < 0.01$) than for total (0.82 [95% CI 0.73–0.93], $P < 0.01$) and insoluble (0.79 [95% CI 0.68–0.93], $P < 0.01$) dietary fiber. The HRs for cerebral infarction were similar to those for stroke (Supplementary Table 2). In contrast, both the quartile and linear analyses showed no significant trends toward a decreased incidence rate of CHD (Table 3). Supplementary Fig. 1 shows results of subgroup analysis according to risk factors for CVD. None of these associations indicated significant interactions, suggesting lack of clear evidence of effect modifications.

To explore potentially nonlinear relationships between total dietary fiber and the incidence of stroke, we fitted the energy-adjusted generalized additive models (Fig. 1). As shown graphically, decreasing trends according to higher values for dietary fiber were clearly shown, with the relationships appearing to be nonlinear. Notably, the estimated incidence rate was very low, i.e., <0.90/1,000 patient-years, among patients consuming total dietary fiber >25 g. Indeed, the maximum total dietary fiber in the 68 cases of stroke was 24 g.

CONCLUSIONS—This 8-year follow-up study of Japanese patients with type 2 diabetes revealed an ~60% risk reduction of stroke in the fourth quartile of total dietary fiber and vegetables/fruits compared with the first quartile. The estimated incidence rate of stroke was very low in patients consuming >25 g/day of total dietary fiber, suggesting a potential threshold of ~20–25 g. The association in relation to soluble fiber seemed to be stronger, but there were no significant associations between CHD and any types of dietary fiber. Our findings are in line with results of earlier cohort studies on the incidence of stroke among healthy adults, as summarized in Supplementary Table 1.

In comparison with people in Western countries, diabetic patients in East Asian countries, including Japan, are known to have quite different features such as the much lower incidence rate of CHD than in Western countries (25) and the low prevalence of obesity (20). As expected, the incidence rate of stroke among patients in this cohort, 6.81/1,000 patients-years, was 2–10 times higher than those in earlier studies (14–19)

Table 2—*Cox regression analysis of incidence of stroke* and intake of total, soluble, and insoluble dietary fiber and vegetables and fruits*

	Quartile analysis				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Linear analysis
Total dietary fiber	8.7 ± 1.6	12.5 ± 0.9	15.8 ± 1.0	21.8 ± 4.0	
Age and sex adjusted	Ref.	0.62 (0.32–1.21); 0.16	0.58 (0.29–1.16); 0.12	0.69 (0.36–1.31); 0.26	0.96 (0.91–1.01); 0.09
Adjusted for risk factors†	Ref.	0.46 (0.22–0.98); 0.04	0.41 (0.18–0.95); 0.04	0.45 (0.15–1.35); 0.16	0.86 (0.77–0.95); <0.01
Further adjusted for energy‡	Ref.	0.44 (0.20–0.95); 0.04	0.37 (0.15–0.91); 0.03	0.39 (0.12–1.29); 0.12	0.82 (0.73–0.93); <0.01
Soluble dietary fiber	2.1 ± 0.4	2.9 ± 0.2	3.7 ± 0.3	5.1 ± 1.2	
Age and sex adjusted	Ref.	0.66 (0.34–1.25); 0.20	0.56 (0.27–1.13); 0.10	0.58 (0.30–1.11); 0.10	0.82 (0.66–1.02); 0.08
Adjusted for risk factors†	Ref.	0.47 (0.22–1.00); 0.05	0.41 (0.17–0.95); 0.04	0.37 (0.13–1.09); 0.07	0.57 (0.37–0.87); 0.01
Further adjusted for energy‡	Ref.	0.45 (0.21–0.96); 0.04	0.37 (0.15–0.89); 0.03	0.32 (0.10–1.02); 0.05	0.48 (0.30–0.79); <0.01
Insoluble dietary fiber	6.3 ± 1.2	9.0 ± 0.7	11.4 ± 0.9	15.8 ± 2.9	
Age and sex adjusted	Ref.	0.72 (0.37–1.37); 0.31	0.55 (0.27–1.12); 0.10	0.72 (0.38–1.38); 0.33	0.95 (0.88–1.01); 0.10
Adjusted for risk factors†	Ref.	0.57 (0.27–1.19); 0.13	0.38 (0.16–0.92); 0.03	0.49 (0.17–1.45); 0.20	0.83 (0.72–0.95); 0.01
Further adjusted for energy‡	Ref.	0.55 (0.26–1.16); 0.11	0.36 (0.15–0.89); 0.03	0.44 (0.14–1.40); 0.16	0.79 (0.68–0.93); <0.01
Vegetables and fruits	228.7 ± 84.0	371.9 ± 83.0	499.0 ± 93.8	721.4 ± 197.3	
Age and sex adjusted	Ref.	0.87 (0.47–1.62); 0.65	0.63 (0.31–1.27); 0.19	0.58 (0.29–1.17); 0.13	0.999 (0.997–1.000); 0.04
Adjusted for risk factors†	Ref.	0.72 (0.36–1.45); 0.36	0.45 (0.20–1.05); 0.07	0.36 (0.13–0.97); 0.04	0.997 (0.996–0.999); <0.01
Further adjusted for energy‡	Ref.	0.72 (0.36–1.44); 0.35	0.45 (0.19–1.04); 0.06	0.35 (0.13–0.96); 0.04	0.997 (0.996–0.999); <0.01

Data are means ± SD or HR (95% CI); *P*. HR data for linear analyses are HR per 1-g increase. *The numbers of incident stroke were 22, 15, 13, and 18 in total dietary fiber quartiles; 22, 17, 12, and 17 in soluble dietary fiber quartiles; 21, 17, 12, and 18 in insoluble dietary fiber quartiles; and 21, 20, 13, and 14 in vegetable and fruit quartiles, respectively. †Adjusted for age, sex, BMI, HbA_{1c}, diabetes duration, diabetic retinopathy, treatment by insulin, treatment by oral hypoglycemic agents, SBP, LDL cholesterol, HDL cholesterol, triglycerides, current smoking, physical activity, alcohol intake, and proportions of total fat, saturated fatty acid, n-6 fatty acid and n-3 fatty acid, dietary cholesterol, and sodium intake. ‡Further adjusted for total energy intake.

Table 3—*Cox regression analysis of incidence of CHD* and intake of total, soluble, and insoluble dietary fiber and vegetables and fruits*

	Quartile analysis				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Linear analysis
Total dietary fiber	8.7 ± 1.6	12.5 ± 0.9	15.8 ± 1.0	21.8 ± 4.0	
Age and sex adjusted	Ref.	1.09 (0.61–1.97); 0.77	1.18 (0.66–2.12); 0.57	1.09 (0.60–1.96); 0.78	1.02 (0.98–1.06); 0.36
Adjusted for risk factors†	Ref.	1.06 (0.57–1.97); 0.86	0.91 (0.46–1.80); 0.79	0.62 (0.25–1.58); 0.32	0.97 (0.91–1.05); 0.49
Further adjusted for energy‡	Ref.	1.06 (0.56–2.01); 0.87	0.91 (0.44–1.89); 0.81	0.62 (0.23–1.72); 0.36	0.98 (0.90–1.06); 0.57
Soluble dietary fiber	2.1 ± 0.4	2.9 ± 0.2	3.7 ± 0.3	5.1 ± 1.2	
Age and sex adjusted	Ref.	0.93 (0.51–1.70); 0.82	1.22 (0.68–2.19); 0.50	1.06 (0.59–1.89); 0.85	1.07 (0.93–1.24); 0.36
Adjusted for risk factors†	Ref.	0.90 (0.48–1.71); 0.76	0.94 (0.48–1.85); 0.87	0.62 (0.25–1.51); 0.29	0.88 (0.64–1.21); 0.43
Further adjusted for energy‡	Ref.	0.91 (0.47–1.74); 0.77	0.95 (0.46–1.95); 0.89	0.62 (0.24–1.64); 0.34	0.88 (0.61–1.26); 0.48
Insoluble dietary fiber	6.3 ± 1.2	9.0 ± 0.7	11.4 ± 0.9	15.8 ± 2.9	
Age and sex adjusted	Ref.	0.97 (0.53–1.77); 0.92	1.34 (0.76–2.36); 0.32	0.99 (0.54–1.80); 0.96	1.03 (0.97–1.08); 0.35
Adjusted for risk factors†	Ref.	0.92 (0.49–1.75); 0.81	1.01 (0.52–1.95); 0.99	0.51 (0.20–1.30); 0.16	0.97 (0.87–1.07); 0.49
Further adjusted for energy‡	Ref.	0.92 (0.48–1.77); 0.80	1.00 (0.50–2.02); 1.00	0.50 (0.18–1.38); 0.18	0.97 (0.86–1.08); 0.56
Vegetables and fruits	228.7 ± 84.0	371.9 ± 83.0	499.0 ± 93.8	721.4 ± 197.3	
Age and sex adjusted	Ref.	1.44 (0.80–2.60); 0.23	1.44 (0.79–2.63); 0.24	1.25 (0.68–2.30); 0.47	1.000 (1.000–1.001); 0.28
Adjusted for risk factors†	Ref.	1.23 (0.66–2.29); 0.52	1.31 (0.67–2.55); 0.43	0.79 (0.35–1.76); 0.56	1.000 (0.998–1.001); 0.76
Further adjusted for energy‡	Ref.	1.25 (0.66–2.34); 0.50	1.34 (0.68–2.63); 0.40	0.81 (0.36–1.84); 0.61	1.000 (0.998–1.001); 0.82

Data are means ± SD or HR (95% CI); *P*. HR data for linear analyses are HR per 1-g increase. *The numbers of incident CHD were 21, 24, 27, and 24 in total dietary fiber quartiles; 21, 22, 27, and 26 in soluble dietary fiber quartiles; 21, 22, 31, and 22 in insoluble dietary fiber quartiles; and 19, 27, 25, and 25 in vegetables and fruits quartiles, respectively. †Adjusted for age, sex, BMI, HbA_{1c}, diabetes duration, diabetic retinopathy, treatment by insulin, treatment by oral hypoglycemic agents, SBP, LDL cholesterol, HDL cholesterol, triglycerides, current smoker, physical activity, alcohol intake, and proportions of total fat, saturated fatty acid, n-6 fatty acid and n-3 fatty acid, dietary cholesterol, and sodium intake. ‡Further adjusted for total energy intake.

(Supplementary Table 1). The "metabolically obese" phenotype (20) characterized by normal body weight with increased abdominal adiposity was also common (Table 1). Furthermore, most patients typically had a "low-fat energy-restricted diet," i.e., the proportions of protein, fat, and carbohydrate consumption met the Western guidelines (1–3), which recommended carbohydrate intake ranging from 45 to 65%, fat intake <30–35%, and protein intake from 10 to 20%. On the other hand, despite the possible difference in dietary habits, the distribution of dietary fiber intake substantially overlaps with those in populations of healthy adults except for cohorts in Finland and Sweden (Supplementary Table 1). The current goals for daily intake of total dietary fiber in guidelines are similar between Japan (20–25 g [4]) and the U.S. (14 g/1,000 kcal [1]). We observed a lower incidence of stroke around intake of 20–25 g (Fig. 1), supporting these dietary goals. Achieving such intake would be realistic given the national average in Japanese adults, i.e., 14.6 g (29).

The estimated risk reduction by dietary fiber in this cohort was seemingly stronger than those in the earlier cohort studies (Supplementary Table 1). The HRs of the fifth quintile of total dietary fiber compared with the first quintile ranged from 0.64 (95% CI 0.46–0.88) to 1.05 (0.73–1.51), showing moderate heterogeneity across studies. Data on the effects of dietary fiber in diabetic patients are limited (20–22). The Nurses' Health Study reported that whole-grain and bran intakes were associated with reduced all-cause and cardiovascular mortality among U.S. women with type 2 diabetes (20). Inverse associations with all-cause and cardiovascular mortality were also observed in a study of self-reported diabetes nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study (21). The EURODIAB Prospective Complications Study reported that higher dietary fiber consumption, especially that of soluble fiber, was associated with CVD in type 1 diabetic patients (22). Taken together, high intake of dietary fiber would reduce the incidence of stroke not only in healthy adults but also in patients with type 2 diabetes. However, it is unclear whether dietary fiber is more beneficial for diabetic patients.

The precise mechanisms for our findings cannot be clarified merely from epidemiological studies, but it is important

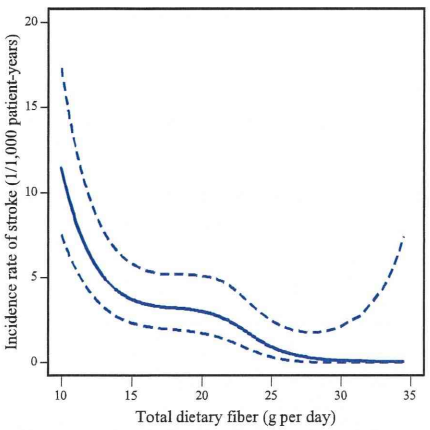

Figure 1—*Incidence rate (solid curve) and 95% CI (broken curve) of stroke in relation to total dietary fiber intake estimated by the generalized additive model.*

to note that the energy-adjusted HR was smaller for soluble dietary fiber (0.48/g) than for total (0.82/g) and insoluble (0.79/g) dietary fiber. Soluble fiber is mainly derived from fruits, vegetables, and legumes in typical Japanese diets. This type of fiber specifically decreases LDL cholesterol by −2.2 mg/dL per 1 g (5) and SBP by −1.32 mmHg (7) if given as supplements. Furthermore, lipids and blood pressure are the leading risk factors for CHD and stroke in Japanese patients, respectively (24). Our observations therefore support the hypothesis that the effects of dietary fiber on some types of stroke are mediated by lipids and blood pressure, but given that the degree of improvement in LDL cholesterol and SBP by dietary fiber is small, the entire risk reduction for stroke does not seem to be attributable to merely the effect on lipids and blood pressure. Other possibilities include reducing postprandial glucose concentration and insulin secretion (6), reducing clotting factors (8), and decreasing inflammation (9). These protective factors against CVD are biologically interrelated, so it may be possible that synergism among them results in the 60% risk reduction of stroke.

Another important finding of this study was that only stroke but not CHD was significantly reduced by dietary fiber. The Japan Public Health Center Study (18) also reported a significant association for only stroke, while dietary fiber was correlated with only CHD—not stroke—in the Japan Collaborative Cohort Study (17) (Supplementary Table 1). However, these three cohorts in Japan consistently reported HRs for CHD of <1 in higher quartiles of dietary fiber, showing weak decreasing trends in CHD (though statistically nonsignificant). Furthermore, our post hoc power calculation suggested that the power of our study may not be sufficient. For example, the observed HR for CHD between the first and fourth quartiles was 0.62, and P = 0.36 (Table 3), but the power to detect a true HR of 0.62 was only 11%, given the 45 CHD incidents in the first and fourth quartiles. Therefore, it is possible that the association between CHD and dietary fiber would become significant by conducting pooled analysis of cohorts.

To the best of our knowledge, this is the first study on dietary fiber and CVD in which patients with type 2 diabetes are prospectively registered based on their HbA_{1c} levels—not retrospectively selected based on self-reported diabetes status. Other strengths include treatment and follow-up plans that were conducted in institutes specializing in diabetes care and adjudication of cardiovascular events by an independent central committee. Our study has several limitations. First, the potential for bias, such as measurement errors in dietary assessments, confounding factors, and informative censoring, cannot be ruled out entirely. However, we found no notable difference in baseline characteristics between patients who completed 8-year follow-up and the other patients (27). Second, in an observational study rather than a randomized trial, it is impossible to conclude whether medical nutritional treatment encouraging dietary fiber or intake of vegetables and fruits would reduce incident stroke in clinical practice. The apparent preferable effects of dietary fiber might be due to a generally healthy lifestyle among high dietary fiber consumers. This possibility cannot be not entirely excluded; patients in higher quartiles of dietary fiber had a relatively low smoking rate and high level of physical activity, although they had adverse dietary behaviors such as increased intake of energy, saturated fatty acid, cholesterol, and sodium. Furthermore, it is difficult, although not impossible under strong assumptions for mediation analysis, to separate the effects specific to dietary fiber and the generic effect mediated by the quantity of energy consumed in this observational study. Finally, our results may not be generally applicable to populations with different lifestyle or genetic factors. For example, BMI and body weight are markedly different between patients in Japan and Western countries (30). Our systematic review found that earlier studies were conducted in U.S., Europe, and Japan and that the findings were moderately heterogeneous. Furthermore, a cohort study suggests that dietary fiber intake may modify the association between TCF7L2 rs7903146 and the incidence of type 2 diabetes, leading to preventive effects of dietary fiber from type 2 diabetes only among non–risk allele carriers (31). The contribution of such ethnic and genetic differences remains uncertain and is worthy of further research. These limitations notwithstanding, we conclude that high intakes of dietary fiber, particularly soluble fiber, and vegetables and fruits reduce incident stroke but not CHD in patients with type 2 diabetes.

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Sh.T. performed statistical analysis and drafted the manuscript. Y.Y. performed the dietary survey. C.K. contributed to the writing of the manuscript. Sa.T. was responsible for statistical analysis and data management. C.H. and R.O. contributed to the writing of the manuscript. H.I. contributed to the design and conduct of the JDCS. Y.O. was responsible for statistical analysis and data management. Y.A. contributed to the design and conduct of the JDCS. N.Y. and H.S. are the principal investigators of the JDCS. H.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Etiology and Pathophysiology/Obesity Comorbidities

Quantitative relationship between body weight gain in adulthood and incident type 2 diabetes: a meta-analysis

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Summary

This meta-analysis quantified the risk of type 2 diabetes mellitus (T2DM) preceded by body weight (BW) gain in the general population. Systematic literature searches retrieved 15 eligible studies. The BW gain was divided into early weight-gain, which was defined as BW gain from early adulthood (18–24 years of age) to cohort entry (≥25 years of age), and late weight-gain, which was defined as BW gain from cohort entry. The pooled relative risk (RR; 95% confidence interval [CI]) of T2DM for an increment of BW gain standardized into a 5-kg m^{-2} increment in the body mass index (BMI) was 3.07 (2.49–2.79) for early weight-gain and 2.12 (1.74–2.58) for late weight-gain. When limiting analysis to studies that concurrently examined T2DM risk for current BMI (defined in both groups as BMI at cohort entry), a larger magnitude of T2DM risk was revealed for early weight-gain compared with current BMI (RR [95% CI], 3.38 [2.20–5.18] vs. 2.39 [1.58–3.62]), while there was little difference between late weight-gain (RR [95% CI], 2.21 [1.91–2.56]) and current BMI (RR [95% CI], 2.47 [1.97–3.30]). The meta-analysis suggested that BW gain was a quantifiable predictor of T2DM, as well as current obesity in adults. Particularly, BW gain in early rather than middle-to-late adulthood played an important role in developing T2DM.

Keywords: Adulthood, type 2 diabetes, weight gain.

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Introduction

It is well known that obesity is a risk factor for type 2 diabetes mellitus (T2DM). In particular, obesity in adulthood rather than childhood obesity is more strongly associated with T2DM (1). The prevalence of obesity gradually increases from 20 years to 60 years of age (2), and a large percentage of T2DM develops from 45 years to 64 years of age (3). These data suggest that body weight (BW) gain in adulthood has an important role in the development of T2DM in middle-to-late adulthood.

While the relationship between body mass index (BMI), an indicator of excess BW, and the risk of T2DM, has been quantified in previous meta-analyses (4,5), the quantitative relationship between BW gain and risk of T2DM remains to be solved because of the variability in study design, such as gender, ethnicity and the period when BW gain occurred. In particular, it remains unclear which of the two periods, i.e. either from early adulthood to middle age or after middle age, during which BW is gained is the more critical for the development of T2DM, and whether background obesity status (i.e. normal or overweight/obese) of the subjects affects future diabetes risk. The aim of this meta-analysis was to quantify the association between BW gain and subsequent T2DM risk in consideration of the period when BW is gained.

Methods

Search strategy

An electronic literature search was conducted for cohort studies that targeted general populations to investigate T2DM risk in relation to BW change using the two databases (MEDLINE [from 1950 to 6 February 2013] and EMBASE [from 1974 to 6 February 2013]) incorporated in ProQuest Dialog™. The search formula was produced by combining the following three components using the Boolean operator 'AND': 'diabetes mellitus', 'weight gain' and 'cohort'. Details of the search terms for each component are shown in the Supporting Information Table S1. Inclusion criteria were as follows (i) studies prospectively followed-up incident T2DM; (ii) the period when weight was gained was followed by the period when incident T2DM was examined; (iii) the two periods were entirely separated but sequential (i.e. there was no gap between them) and (iv) relative risk (RR) as the risk measure of T2DM and its corresponding standard error (SE) for an increment of BW gain could be estimated.

While we *a priori* assumed the log-linearity between BW gain and T2DM risk, it was too difficult to assume the linear relationship between BW change and T2DM risk throughout any BW change because reasons for weight loss were considered to vary among studies and subjects within one study, mainly depending on whether the weight loss was voluntary (e.g. dietary restriction for health) or involuntary (e.g. aging, smoking). If the T2DM risk in relation to weight loss had been elevated (i.e. the relationship between BW change and T2DM risk had been non-linear), the inclusion of data on T2DM risk in relation to weight loss would have underestimated T2DM risk in relation to weight gain.

Therefore, the included studies had to separately estimate T2DM risk for losing BW and for gaining BW. Consequently, two studies (6,7) were excluded because they only provided data on T2DM risk, where BW change was entered as a continuous variable. In one study that investigated T2DM risk for increments of BW change across all BW changes for men, and separately investigated incremental T2DM risks in relation to gaining and losing BW for women (8), we included only the latter data in the analysis.

As previously mentioned, the period when BW change was examined varied among studies and among participants within one study. However, we crudely classified the study-specific period into the following two categories (i) from early adulthood to a definite point (i.e. beginning of the study-specific cohort; early weight-gain) and (ii) during a definite duration in the later phase rather than in early adulthood (late weight-gain). Primarily, BW gain from early adolescence to the beginning of cohort entry was considered as the early weight-gain category. In contrast, we regarded BW gain during an uninterrupted period across all participants in an individual study, after the formation of the cohort, as the late weight-gain category.

Although the two categories inevitably overlapped as to periods when BW change was examined, we discriminated these categories by age at the beginning of the examination of weight change to minimize overlapping: 18–24 years of age for early weight-gain and 25 years or older for late weight-gain. Therefore, we excluded two studies that examined weight change after cohort entry for a subject population that included those less than 25 years of age at cohort entry (9,10) because it was impossible to determine which weight gain in these studies corresponded to early weight-gain or late weight-gain according to our definitions. For late weight-gain, we excluded one study (11) that retrospectively examined weight change from 40 years to 50 years of age, and prospectively followed-up incident T2DM because whether BW at cohort entry was initial or final, significantly affected the study result (10). In one study (12), data on T2DM risk, in relation to weight change both from 50 years of age to cohort entry, and during 3 years from cohort entry, were provided: the latter data were chosen for the same reason. Of the two studies (13,14) having the same study population, we included the study (13) that provided the more updated data. We finally obtained 15 eligible studies (8,12,13,15–26) out of 8,253 papers retrieved from the literature searches (Fig. 1).

Data extraction

For each included study, two authors (SK and HS) extracted the following information relevant to study characteristics as well as several RRs with their corresponding SEs for several weight gain groups vs. a weight-maintenance group: ethnicity, mean age at cohort entry, age when the initial BW was assessed (in early weight-gain), follow-up duration for ascertaining T2DM, duration during which BW changed (in late weight-gain), mean BMI at cohort entry, methods for collecting data on BW and incident T2DM, and study-specific covariates. Inconsistencies were solved by discussion.

Study quality was assessed by modifying the Newcastle Ottawa Quality Assessment Scale (NOS) (27) so that it was applicable to our theme (Supporting Information Table S2). In summary, the NOS scale consists of three major items: S (Selection: three questions), C (Comparability; two questions) and O (Outcome: three questions). For each question that a study could answer with 'yes', 1 point was awarded. We judged study quality by the total score of the awarded points as follows: low (≤5 points); high (>5 points).

If a study provided several RRs, such as unadjusted and adjusted RRs, the most completely adjusted RR was used. Each RR was fundamentally transformed into its logarithm (lnRR) because its corresponding SE was provided for the

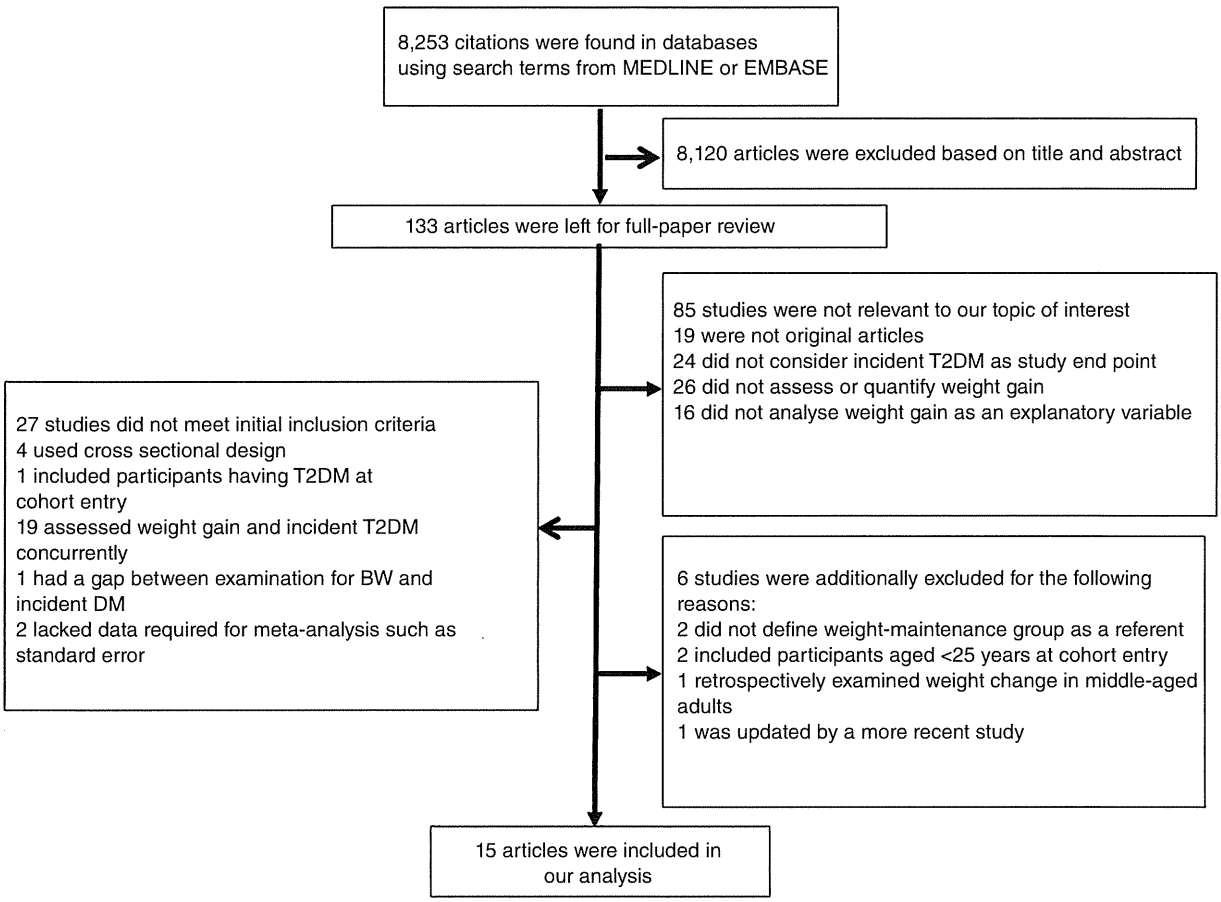


Figure 1 Study flow chart showing the search procedure for eligible studies.

lnRR rather than the RR. If the risk measure was not expressed as RR, but as an odds ratio (OR) (10,23,26), it was transformed into RR using the formula $RR = OR/[(1-P_0) + (P_0 \times OR)]$, in which P_0 is the incidence of the outcome of interest in the reference group (28), where the SE could be calculated by multiplying SE for lnOR by $\sqrt{\ln RR/\ln OR}$; although this method had a potential bias because of some discrepancy between the Mantel-Haenszel OR and the logistic regression OR (29). In one study that did not directly provide data on the RR in relation to weight gain (19), the RR was calculated based on the data on the number of cases and non-cases in referent (i.e. weight-maintenance group) and non-referent groups (i.e. weight gain groups), where the SE was calculated from the confidence interval (CI), or if not provided, was calculated by the following formula:

$$SE^2 = \frac{1}{C_0} - \frac{1}{C_0 + N_0} + \frac{1}{C_1} - \frac{1}{C_1 + N_1}$$

where C_0 and N_0 indicate the number of T2DM cases and non-cases in the referent group, respectively, and C_1 and N_1 indicate the number of T2DM cases and non-cases in the non-referent group, respectively.

Data on BW change were standardized into those in BMI units. If the analysed studies expressed the BW change in kilograms, we estimated BW change in BMI units by dividing the BW change in kilograms by squares of mean height in meter units in the study-specific population. If data on mean height were not provided, they were derived from other papers that shared the same study population as those to be analysed: data from references (15–17,20) were taken from reference (30), while data from references (8,12,18,21,22) were taken from references (31–35), respectively.

Data synthesis

We conducted separate meta-analyses for early weight-gain and late weight-gain. Effect size in an individual study was standardized into lnRR for the incremental gain using the generalized least squares for trend estimation (GLST), where the lnRRs in several BW gain groups in an individual study were regressed on their corresponding mean BW

gain, expressed as the midpoint of the upper and lower boundaries for data on BW change (36). In the open-ended category of BW gain, we estimated the midpoint, assuming that the breadth of BW gain in this category was equal to that of its closest category.

For this estimation, we used the program developed by Orsini *et al.* (37), which can calculate a weighted linear regression of lnRR across categories of BW gain, with consideration of the covariance among the lnRRs if data on the total number of participants (or person-time) and cases are provided. In this regression analysis, we limited the exposure categories to those gaining BW in each study, assuming that not BW change, but BW gain was associated with T2DM risk in a log-linear fashion. The standardized effect size in each study was pooled with a random-effects model. Finally, the T2DM risk in relation to BW gain was obtained as that for an increment of 5 kg m^{-2} in BMI units after exponentiation of the pooled lnRR. Study heterogeneity was assessed by Q-statistics or I-squared overall and within each strata after the stratification (38). The pooled estimates were calculated based on a random-effects model (39).

Sensitivity analysis

To consider the effect of obesity status at baseline (i.e. before BW change) on the significance of BW gain for T2DM risk, we additionally estimated the pooled T2DM risk for studies that examined the T2DM risk in relation to BW gain according to the BMI at cohort entry, limiting the analysis to groups comprised of participants with a normal BMI (BMI <25 kg m^{-2}) or who were overweight or obese (BMI ≥ 25 kg m^{-2}). To compare the magnitude of the association between early weight-gain and late weight-gain, we conducted a multilevel meta-regression analysis where within- and between-study variability in the effect size was considered. For further comparison between early weight-gain and late weight-gain, we compared the magnitude of T2DM risk for a 5-kg m^{-2} increment in the BMI between early weight-gain and current BMI (defined in both groups as BMI at cohort entry), and between current BMI and late weight-gain, limiting the analysis to the 11 studies (8,13,15–23) that investigated T2DM risk in relation to BMI values at cohort entry, as well as BW gain under the condition that the T2DM risk for current BMI and for BW gain was adjusted for similar covariates. For calculation of the T2DM risk for a 5-kg m^{-2} increment in the BMI in each study, we repeated the GLST analysis, where the T2DM risk for one standard deviation (1 SD) was estimated by regressing the lnRRs in several BMI groups in an individual study on their corresponding order statistics in the median of the upper and lower boundaries. If studies did not provide data on the SD of BMI in the study population (12,13,15–18,20–23), it was estimated by regressing several BMI boundary values in each study on their corresponding order statistics (40).

In addition to these sensitivity analyses, the pooled T2DM risk was estimated for subgroups after stratification, on the basis of several pre-specified key study characteristics. Meta-regression analysis was used to test for differences in the magnitude of the effect size among subgroups. Publication bias was assessed for the pooled effect size associated with early weight-gain and late weight-gain: Begg's rank correlation test and Egger's regression asymmetry test (41,42). For statistically suspected publication bias, the trim and fill method was adopted to adjust the pooled T2DM risk, assuming that the asymmetry of the funnel plot is entirely due to publication bias. This method includes detection of unpublished studies that distorted the funnel plot, filling the results of these hypothetical studies to recover the symmetry of the funnel plot, and recalculation of the pooled effect size as if these studies had actually existed (43).

Results

Study characteristics

The characteristics of the included studies that investigated T2DM risk, in relation to early weight-gain and late weight-gain, are described in Tables 1 and 2, respectively. Seven studies (16,17,19,21,22,25,26) consisting of 342,703 participants and 15,397 cases, and 10 studies (8,12,13,15,18,20,23–26) consisting of 305,083 participants and 10,042 cases, were related to early weight-gain and late weight-gain, respectively. One study (25) conducted three separate analyses by ethnicity in both early weight-gain and late weight-gain. Another study (26) stratified the population into two subclasses by gender in early weight-gain and into $2 \times 2 = 4$ subclasses by age and gender in late weight-gain. Finally, 10 and 15 datasets were obtained for early weight-gain and late weight-gain, respectively. The mean age at cohort entry ranged from 38 years to 59 years of age. The mean follow-up duration for ascertainment of T2DM ranged from 3 years to 24 years in studies of early weight-gain and from 4 years to 15 years in studies of late weight-gain. Mean BMI in the study population was relatively homogeneous, ranging from 23.4 kg m^{-2} to 26.7 kg m^{-2} for early weight-gain, and from 23.3 kg m^{-2} to 25.9 kg m^{-2} for late weight-gain. In studies investigating T2DM risk with early weight-gain, data on the age when the initial BW were assessed ranged from 18.5 years to 21 years, and were dependent on self-report in all, but one study (21). In all studies investigating T2DM risk in relation to late weight-gain, the time period during which BW was gained varied among studies, although it was consistent among participants within each study, ranging from 2.3 years to 10 years.

Table 1 Characteristics of the seven included studies that investigated type 2 diabetes risk in relation to early weight-gain*

First author (year)	Dominant ethnicity	Duration (years)†	No.		Age (%)‡			BMI at entry (kg m^{-2}‡)	Methods**		Study covariates
			P	C	Baseline (years)§	Entry (years)¶	Men (%)		BW	T2DM	
Chan (1994) (16)	Caucasian	5	27,983	272	21	56	100	24.7	S	S	Age, gender, FHDM, smoking, baseline BMI
Colditz (1995) (17)	Caucasian	13	114,281	1,804	18	42	0	24	S	S	Age, gender, baseline BMI
McNeely (2001) (19)	Japanese American	5	466	49	20	52	52	24.1	S	D/M	None
Oguma (2005) (21)	Caucasian	24	20,187	1,223	18.5	46	100	24.4	M	S	Age, gender, PA, smoking, HT, FHDM, baseline BMI
Krishnan (2007) (22)	African-American	3	49,766	2,472	18	[38]	0	[26.7]	S	S	FHDM, PA, smoking, education
Morimoto (2011) (25)	Multiple††	14	78,006	8,588	21	59	46	24.9	S	S, R	Gender, ethnicity, education, BMI at baseline and at entry
Nanri (2011) (26)	Japanese American	5	52,014	989	20	56	44.0	23.4	S	S	Age, gender, baseline BMI, smoking, PA, HT, FHDM, coffee consumption

*Early weight-gain was defined in Methods.

†Follow-up duration during which researchers investigated whether the participants developed T2DM.

‡Numerical value in square brackets indicates median value. The remaining values indicate mean value.

§'Baseline' means the point when initial BW was assessed.

¶'Entry' means the point when the cohort began.

**Methods for obtaining data on initial BW (i.e. BW in early adulthood) and whether participants developed T2DM.

††Analyses were stratified by ethnicity.

BMI, body mass index; BW, body weight; C, cases; D/M, doctor diagnosis or medical record; FHDM, family history of diabetes; HT, hypertension; M, measurement; P, participants; PA, physical activity; R, registry; S, Self-report; T2DM, type 2 diabetes mellitus.

Table 2 Characteristics of the 10 included studies that investigated type 2 diabetes risk in relation to late weight-gain*

First author (year)	Dominant ethnicity	Duration		No.		Age (%)		BMI at entry (kg m^{-2})§	Methods		Study covariates
		For T2DM (years)†	For BW‡	P	C	At entry (years)§	Men (%)		For T2DM¶	For BW**	
Colditz (1990) (15)	Caucasian	4	4.0	93,794	512	[38]	0	[23.3]	S	S	Age, gender, BMI at entry
Ford (1997) (18)	Caucasian	9	10.0	8,545	487	45	38	25.2	S	M	Age, gender, race, education, smoking, TC, SBP, HT, medication, BMI at entry, alcohol
Koh-Banerjee (2004) (20)	Caucasian	4	10.0	22,171	305	53	100	25.3	S	S	Age, gender, smoking, alcohol, PA, FHDM, fiber intake, BMI at entry
Wannamethee (2005) (13)	Caucasian	15	5.0	6,194	237	[50]	100	25.4	D/M	M	Age, gender, social class, smoking, PA, alcohol, HT, presence of CHD, FEV1, SBP, TC, BMI
Mishra (2007) (23)	Others than Caucasian	3	2.3	7,239	206	[48]	0	[24.8]	S	S	Age, gender, BMI at entry, PA, smoking, education, menopause
Biggs (2010) (12)	Caucasian	12	3.0	2,807	174	73	41	25.7	D/M	M	Age, gender, race, smoking, PA, diet score, alcohol, BMI at entry
Kataja-Tuomola (2010) (24)	Caucasian	7	3.0	20,952	535	57	100	25.9	R	M	Age, gender, smoking, BMI, BP, TC, HDL-C, alcohol, PA
Berentzen (2011) (8)	Caucasian	5	5.3	15,777	1,027	[56]	100	25.9	R	S	Age, gender, smoking, BMI at entry, WC at entry, diet score, EI, alcohol,
Morimoto (2011) (25)	Multiple††	9	5.5	75,590	5,570	59	46.2	24.9	S, R	M	PA, ethnicity, education, BMI at entry, final BMI
Nanri (2011) (26)	Japanese American	5	5	52,014	989	56	44.0	23.4	S	M	Age, gender, BMI at entry, smoking, PA, HT, FHDM, coffee

*Late weight-gain was defined in Methods.

†Follow-up duration during which researchers investigated whether the participants developed T2DM.

‡Duration during which the BW change was assessed.

§Numerical values in square brackets indicate median value. The remaining values indicate mean value.

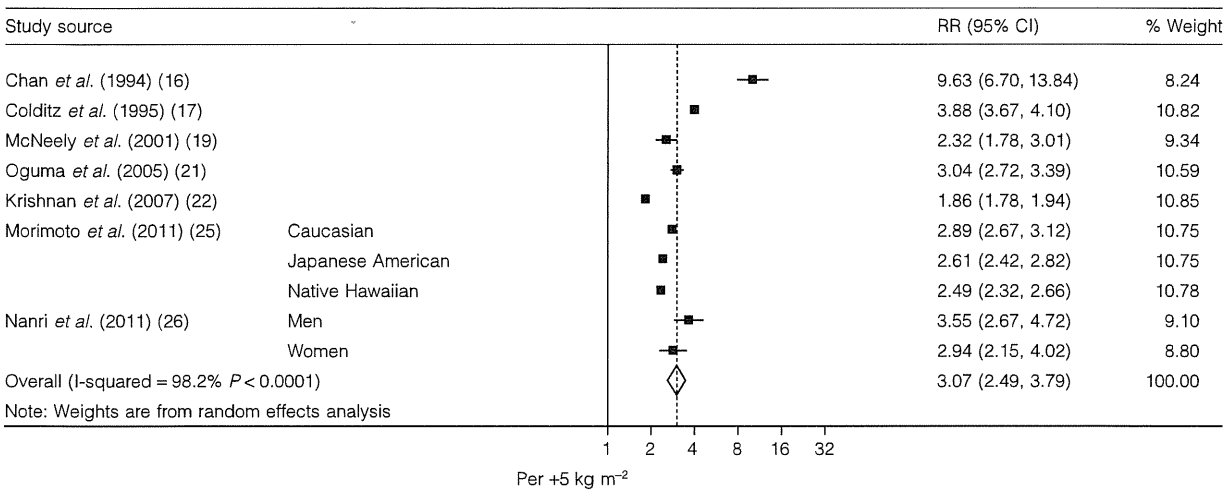
¶Methods for obtaining data on whether participants developed T2DM.

**Methods for obtaining data on initial BMI (i.e. BMI at cohort entry).

††Analyses were stratified by ethnicity.

BMI, body mass index; BP, blood pressure; BW, body weight; C, cases; CHD, coronary heart disease; D/M, doctor diagnosis or medical record; EI, energy intake; FEV1, forced expiratory volume in one second; FHDM, family history of diabetes; HDL-C, HDL cholesterol; HT, hypertension; M, measurement; P, participants; PA, physical activity; R, registry; S, Self-report; T2DM, type 2 diabetes mellitus; TC, total cholesterol; WC, waist circumference.

Table 3 Forest plots of the relative risk (RR) with 95% confidence interval (CI) for risk of type 2 diabetes mellitus (T2DM) with 95% CI in relation to early weight-gain by a 5-kg m^{-2} increment in the body mass index (BMI)



The RRs in each study and the overall RR are indicated by circles and diamonds, respectively. Horizontal lines indicate the range of 95% CI. Areas of the squares are proportional to the study weight expressed as inverse of the square of standard error based on a random-effects model. Early weight-gain was defined in the Methods section.

Supporting Information Table S2 shows the process of assessing study quality for each included study. Two studies (15,17) targeted a specific type of occupation, specifically nurses, and one study (24) exclusively targeted smokers. In the remaining studies, participants were considered to represent the average population. Approximately half of the included studies (eight studies) (8,15–17,20–23) depended on self-report for obtaining data on BW at cohort entry. In all but one study (19), the T2DM risk in relation to BW gain was adjusted for the initial BMI (i.e. before gaining BW; not at cohort entry). As indicated in Tables 1 and 2, only 5 of the 15 included studies (8,12,13,19,24) avoided subjectivity for ascertainment of T2DM by using medical records or registries. Only three studies (15,17,25) allowed participants to be lost to follow-up. Consequently, study quality was *a priori* judged as high in seven studies (8,12,13,18,21,24,26) and as low in eight studies (15–17,19,20,22,23,25).

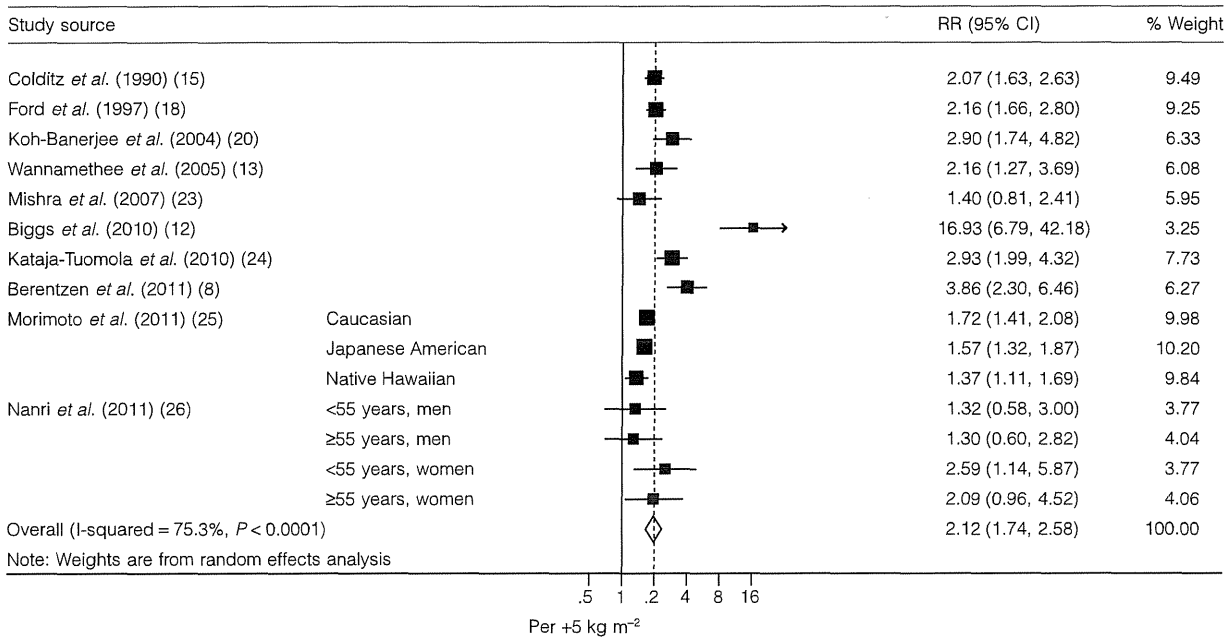
Overall T2DM risk in relation to increment of BW gain

Tables 3 and 4 are forest plots of RR of T2DM with a 95% CI, in relation to early weight-gain and late weight-gain, respectively. The magnitude of T2DM risk for an increment of a 5 kg m^{-2} BMI gain was substantially larger in early weight-gain (pooled RR [95% CI], 3.07 [2.49–2.79]), compared with late weight-gain (pooled RR [95% CI], 2.12 [1.74–2.58]). However, the difference was not significant ($P = 0.09$). All studies revealed positive associations between BW gain and T2DM risk. However, the magnitudes of the associations were highly heterogeneous for both early weight-gain (I-squared = 98.2%, $P < 0.001$) and late weight-gain (I-squared = 75.3%, $P < 0.001$).

There was no study that investigated T2DM risk in relation to early weight-gain by limiting participants to those who were overweight (i.e. ≥25 kg m^{-2} BMI) in early adulthood. Only two studies (19,21) that investigated T2DM risk, in relation to BW gain from early adulthood, limited participants to those who had a normal BMI (<25 kg m^{-2}) before the BW gain. However, the result was controversial; the T2DM risk associated with early weight-gain was significant in one study (21) and non-significant in the other (19). Four studies (13,15,18,26) added a stratified analysis for T2DM risk, in relation to late weight-gain by BMI at cohort entry. The pooled RR (95% CI) for a 5-kg m^{-2} increment in the BMI was 1.87 (1.06–3.31) for those who had normal BMI at cohort entry and 1.98 (2.59–2.47) for those who were overweight at cohort entry. The difference in the magnitude of the T2DM risk was not significant ($P = 0.53$).

Supporting Information Figs S1 and S2 show T2DM risks for increments of early weight-gain and late weight-gain, respectively, compared with those of current BW (i.e. BW at cohort entry). These data were limited to studies that concurrently investigated T2DM risks in relation to the current BW and early or late weight-gain. Although there was little difference in the T2DM risk between late weight-gain and current BMI (RR [95% CI] for a 5-kg m^{-2} increment in BMI, (2.21 [1.91–2.56] vs. 2.47 [1.97–3.10]; *P*

Table 4 Forest plots of the relative risk (RR) with 95% confidence interval (CI) for risk of type 2 diabetes mellitus (T2DM) with 95% CI in relation to late weight-gain by a 5-kg m^{-2} increment in the body mass index (BMI)



The RRs in each study and the overall RR are indicated by circles and diamonds, respectively. Horizontal lines indicate the range of 95% CI. Areas of the squares are proportional to the study weight expressed as inverse of the square of standard error based on a random-effects model. Late weight-gain was defined in the Methods section.

value for difference, 0.65), early weight-gain had a non-significantly stronger association with T2DM risk compared with the current BMI (RR [95% CI] for a 5-kg m^{-2} increment in BMI (3.38 [2.20–5.18] vs. 2.39 [1.58–3.62]; *P* value for difference, 0.09).

Other sensitivity analyses

Supporting Information Table S3 shows the results of stratified analysis of T2DM risk in relation to early weight-gain based on several key items related to study characteristics. Throughout all strata within each item, the T2DM risk in relation to BW gain was positively significant. The magnitude of the T2DM risk was not significantly influenced by the extent to which the study covariates were totally considered ($P = 0.51$) or by study quality ($P = 0.93$). However, differences in the magnitude of T2DM risk were observed among strata in some items, although there was insufficient statistical power to detect a significant difference due to the limited number of data units. Nevertheless, a larger subsequent T2DM risk for an increment of BW gain, as calculated according to a 5-kg m^{-2} increment in BMI, was observed in studies targeting men compared with those including women (RR [95% CI], 5.33 [1.72–16.53] vs. 2.74 [2.18–3.45], *P* value for difference, 0.07) and in studies of a Caucasian-dominant population (≥50% of study population) compared with those of Others than Caucasian dominant populations (>50% of study population; RR [95% CI], 3.91 [3.08–4.99] vs. 2.51 [2.09–3.02], *P* value for difference, 0.08).

Supporting Information Table S4 shows results of the stratified analysis of T2DM risk in relation to late weight-gain. As was observed in the stratified analysis of early weight-gain, the T2DM risk for an increment of BW gain was consistently significant throughout all strata after the stratification. Studies ascertaining T2DM that exclusively used registries or medical records revealed a significantly higher T2DM risk than those dependent upon self-reports (RR [95% CI], 4.06 [2.18–3.74] vs. 1.71 [1.57–7.56]; *P* value for difference, 0.01). In addition, studies with high NOS scores, which indicated high quality, revealed a higher T2DM risk compared with those with lower NOS scores (RR [95% CI] 2.65 [1.87–3.74] vs. 1.70 [1.44–2.01]) although the difference was not significant ($P = 0.12$). Although a gender difference in the magnitude of T2DM risk was not observed, a significantly stronger association in the magnitude of T2DM risk was observed in studies targeting Caucasian-dominant study populations compared with those dominated by other ethnicities (RR [95% CI], 2.69 [2.04–3.56] vs. 1.50 [1.33–1.70], *P* value for

difference, 0.04). Although the effect of the number of study covariates that were considered in the estimation of T2DM risk was not significant ($P = 0.14$), the adjustment for social circumstances or educational level tended to weaken the magnitude of the T2DM risk ($P = 0.06$). Studies that adjusted T2DM risk for alcohol intake revealed a stronger association between BW gain and T2DM risk compared with those without such an adjustment ($P = 0.01$).

Publication bias

Publication bias was statistically suspected in the T2DM risk associated with late weight-gain by Egger's test ($P = 0.05$), but not Begg's test ($P = 0.30$), although there was no evidence of publication bias in T2DM risk associated with early weight-gain ($P = 0.37$ for Begg's test and $P = 0.30$ for Egger's test). We tried to adjust the T2DM risk in relation to early weight-gain using the trim-fill method (Supporting Information Fig. S3). This method detected three hypothetically unpublished datasets, without which the T2DM risk could have been inflated. The recalculation after the inclusion of these hypothetical data slightly weakened the RR (95% CI) for T2DM risk to 1.79 (1.43–2.23).

Conclusions

This meta-analysis showed that there was an elevated T2DM risk associated with incremental increases in BW in adulthood, suggesting a dose–response association between BW gain and subsequent T2DM risk. According to the Evidenced-based Practice Center programme (44), the current meta-analysis might not obtain high strength of evidence for an elevated T2DM risk in relation to BW gain because (i) this meta-analysis was based on observational studies; (ii) the magnitude of the T2DM risk was highly heterogeneous despite consistently positive results across studies and (iii) there was statistically detected publication bias in the estimates of T2DM risk in relation to late weight-gain (Supporting Information Table S5). However, the positive association between BW gain and subsequent T2DM risk was consistent across several study characteristics, in particular, the extent of consideration of study covariates and study quality. Therefore, the overestimation of associations that is often seen in observational studies was unlikely to be the case with this meta-analysis.

The T2DM risk in relation to BW gain has been believed to depend on the initial obesity status; i.e. those who are already obese are susceptible to elevated T2DM risk after additional BW gain (6). However, in the analysis of late weight-gain, when analyses were limited to studies that not only included overweight/obese populations, but also populations with a normal BMI, the difference in the magnitude of the T2DM risk was not significant between the two populations. This result suggested that the association between BW gain and T2DM risk was independent of the initial BW. In other words, BW gain and initial BW could have an additive effect on the elevated risk of T2DM, although future studies are needed to elucidate this factor.

The current meta-analysis indicated that BW at cohort entry (corresponding to those in their 50 s, in general) did not have as strong an association with T2DM risk as BW gain (corresponding to early weight-gain), but was equally predictive of T2DM risk as BW gain after that time (corresponding to late weight-gain). Previous reports (14,45) suggested that the duration of obesity was a primary determinant of T2DM risk, which might be explained by the fact that the failure of glucose homeostasis induced by obesity develops gradually (46). According to this suggestion, it is hypothesized that (i) BW gain is secondary to current obesity, in terms of predicting T2DM risk, because being obese generally has a longer history than becoming obese and (ii) early weight-gain is strongly associated with T2DM risk, compared with late weight-gain, because the earlier BW gain results in a longer duration of obesity. Although the current results were in line with the latter hypothesis, they were inconsistent with the former hypothesis. The reason for the inconsistency is that (i) previous reports (14,45) focused on obesity defined by BMI ≥ 30 kg m^{-2} while our study did not specify the BMI value as a result of BW gain and (ii) the T2DM risk, in relation to the current BMI, could have been underestimated because underweight persons with high risk of T2DM were included (47). Therefore, more caution should be taken in determining whether being obese or becoming obese is more strongly associated with T2DM risk from findings of this meta-analysis.

The positive association between BW gain and T2DM risk was consistent through several stratifications of the specified study characteristics. However, several points need to be addressed regarding the characteristics of study populations that could allow them to be especially susceptible to T2DM risk, in relation to BW gain. Firstly, in the analyses of early weight-gain, studies targeting only men revealed a stronger association between BW gain and T2DM risk, compared with those targeting populations that included women as well as men. However, gender differences in the magnitude of T2DM risk were not observed in late weight-gain. These findings were supported by the following biological mechanisms (i) abdominal adiposity is strongly associated with glucose intolerance (48); (ii) androgen receptors had been identified in greater abundance in intra-abdominal rather than subcutaneous preadipocytes in the cell culture study (49) and (iii) menopause-related testosterone predominance causes the excess fat, resulting from BW gain to be distributed as abdominal adiposity (50). Current results suggested that men, especially, should pay attention to BW change from earlier adulthood and women should avoid BW gain especially after menopause.

Secondly, ethnicity could influence the significance of BW gain in the development of T2DM. The current analysis indicated a tendency for a stronger association with T2DM risk, in relation to BW gain in studies with Caucasian-dominant populations than in those targeting Others than Caucasian dominant populations. The genetic differences according to ethnicity might be suggested by the general finding that a higher proportion of abdominal obesity is present even when BMI values are similar, and that there is a pronounced dysfunction in early insulin secretion in Asian populations, compared with European populations (51). These genetically determined factors could demonstrate a large relative contribution to the development of diabetes in Others than Caucasian people rather than in Others than Caucasian people. However, this does not mean that people having genetic disadvantages with regard to diabetes risk need not pay attention to BW. Rather, it is of note that even a modest BW gain during adulthood substantially increases the risk of diabetes in such people (52). Another explanation for the current finding is that in studies of Others than Caucasian populations, some individuals having such T2DM-susceptible phenotypes had already developed T2DM before cohort entry and were excluded from the study. The ethnic differences in the contribution of BW gain to the development of T2DM may need to be further investigated in future studies.

Several limitations should be addressed in this meta-analysis. Firstly, the effect of some confounders modified the magnitude of T2DM risk in relation to BW gain. For example, among the included studies, while studies with adjustment for alcohol intake revealed a larger RR for late weight-gain, a smaller RR was observed in studies with adjustment for educational or socioeconomical status. It was reported that, compared with non-drinkers, heavy alcohol drinkers had lower insulin concentrations suggesting higher insulin sensitivity (53) despite the higher risk of future BW gain (54). It is possible that among BW gainers, alcohol drinkers had a relatively lower risk of incident T2DM, resulting in the underestimation of T2DM risk in relation to BW gain. Other reports indicated that socioeconomic disadvantages, including low educational status and economic difficulties, were associated with elevated risk of BW gain (55) and T2DM (56). Socioeconomic factors might have partially explained the elevated risk of T2DM in relation to BW gain, which was suggested by the sensitivity analyses in the current meta-analysis: the smaller magnitude of T2DM risk in studies with adjustment for education or some other socioeconomic factors, compared with that in studies not having such adjustments (Supporting Information Tables S3 and S4). Moreover, the possibility of other residual confounders that could not be specified in this meta-analysis could not be ruled out.

Secondly, BW assessments or the ascertainment of T2DM depended on self-reports in several studies. Current studies indicated that a lower RR was observed in studies that completely or partially used self-reports for the ascertainment of T2DM, compared with those that did not use self-reports in the stratified analysis of T2DM risk in relation to late weight-gain. If undiagnosed T2DM had been overlooked, especially among individuals with BW gain because those individuals with unaware of having T2DM, the association between BW gain and T2DM risk would have been weakened. Similarly, underestimation of BW by overweight or obese persons (57) might distort the association between BW gain and T2DM risk, although the stratified analysis indicated no statistically significant evidence that the method for collecting BW information modified the strength of the association. Thirdly, this meta-analysis was limited to studies that separated the duration when BW was gained and when T2DM was ascertained to clarify that T2DM developed as a result of BW gain. This method for selecting studies resulted in ignoring BW change during the follow-up period for ascertaining T2DM, although weight fluctuation was suggested to be diabetogenic in some studies (24,58). In particular, studies with a short duration for assessing BW change would have been susceptible to the effect of the BW change during the follow-up period for ascertaining T2DM. However, the duration for assessing BW change did not affect the study result in the sensitivity analysis of the T2DM risk in relation to late weight-gain.

Fourthly, as previously mentioned, in this meta-analysis we deleted several BW-reduction groups in each study. However, obese persons who had experienced a large weight loss during the recent history of the cohort study, although overall experiencing a total weight gain, might have been included. Many such persons would have already developed diabetes and been excluded from the analysis. However, considering that weight loss often delays the onset of diabetes, some of those individuals might not have been excluded at the beginning of the cohort study and would be diagnosed as having diabetes during the follow-up period. In this case, the quantitative association between BW gain and diabetes might be biased if the total weight gain had been modest. Some cross-sectional studies indicated that weight change between early adulthood and the age at maximum BW had a stronger association with T2DM risk than that between early adulthood and the age at the beginning of the study (59,60). For more accurate estimation of the association between BW gain and subsequent T2DM risk, it is proposed that longitudinal studies investigate T2DM risk in relation to maximal BW gain.

We suggest one important issue that is expected to be solved through future investigations. Some studies (61,62) indicated that body fat distribution, such as waist circumference and waist-to-height ratio, rather than BMI, had a stronger association with T2DM risk although others

(63,64) did not. In the current meta-analysis, a few of the included studies (8,12,20) investigated T2DM risk in relation to the change in waist circumference or waist-to-hip ratio as well as change in BMI. However, no study focused on comparing the strength of the associations with T2DM risk between the two types of changes. Future studies are expected to focus on whether change in fat distribution or BW is more important in predisposing an individual to T2DM.

In conclusion, BW gain in adulthood was a quantifiable predictor of T2DM as well as current obesity. Although the strength of the association varied among studies, BW gain in early adulthood was suggested to play a more important role in developing T2DM compared with that in middle-to-late adulthood.

Author contributions

Conceived and designed the study: SK. Selected studies that met the inclusion criteria and reviewed them: CH, KF, SY. Designed the study's analytic strategy and carrying out the statistical analyses: ST. Gave various opinions on interpretation of the study results: YY, NO, SM, TY, OH. Drafted the paper: SK. Supervised the study and revised the draft critically for important intellectual content; HS.

Conflict of interest statement

No conflict of interest was declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12129

Figure S1. Comparison of the magnitude of type 2 diabetes (T2DM) risk for a 5-kg m^{-2} increment in the body mass index (BMI) between early weight-gain and current body weight (i.e. body weight at cohort entry). Analyses were limited to studies that concurrently investigated T2DM risks in relation to the two exposures. Relative risks (RRs) in each study and the overall RR are indicated by circles and diamonds, respectively. Horizontal lines indicate the range of the 95% confidence interval (CI). Areas of squares are proportional to study weight (i.e. inverse of square of standard error). Early weight-gain was defined in the Methods section.

Figure S2. Comparison of the magnitude of type 2 diabetes (T2DM) risk for a 5-kg m^{-2} increment in the body mass index (BMI) between late weight-gain and current body weight (i.e. body weight at cohort entry). Analyses were limited to studies that concurrently investigated T2DM risks in relation to the two exposures. Relative risks (RRs) in each study and the overall RR are indicated by circles and diamonds, respectively. Horizontal lines indicate the range of 95% confidence interval (CI). Areas of squares are proportional to study weight (i.e. inverse of square of standard error). Late weight-gain was defined in the Methods section.

Figure S3. Funnel plot indicating the adjustment of risk of type 2 diabetes mellitus (T2DM) in relation to late weight-gain for publication bias using the trim and fill method. The standard error of the logarithm of the relative risk (lnRR) of T2DM in relation to a 5-kg m^{-2} increment in the body mass index (BMI) is plotted against the lnRR. The asymmetrical funnel plot (i.e. number of data points is fewer in lower region of the vertical symmetrical line than in upper region) suggests publication bias. Based on the assumption that the funnel plot is symmetrical in the absence of publication bias, data points indicated in the filled squares are filled to recover the symmetry of the funnel plot. Late weight-gain was defined in the Methods section.

Table S1. Details of search terms in this meta-analysis.

Table S2. Study quality assessment according to the modified Newcastle Ottawa Quality Assessment Scale (NOS).

Table S3. Stratified analyses by several study items related to study characteristics of pooled relative risk (RR) of type 2 diabetes mellitus (DM) for each 5 kg m^{-2} of early weight-gain.

Table S4. Stratified analyses by several study items related to study characteristics of pooled relative risk (RR) of type 2 diabetes mellitus (DM) for each 5 kg m^{-2} of body mass index (BMI) gain in relation to late weight-gain.

Table S5. Summary of strength of evidence (SOE) for the association between body weight gain and subsequent type 2 diabetes risk.

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Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

Early Changes of Abdominal Adiposity Detected with Weekly Dual Bioelectrical Impedance Analysis during Calorie Restriction

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Objective: To elucidate early change of intra-abdominal fat in response to calorie restriction in patients with obesity by weekly evaluation using a dual bioelectrical impedance analysis (Dual BIA) instrument.
Design and Methods: For 67 Japanese patients with obesity, diabetes, or metabolic syndrome, intra-abdominal fat area (IAFA), initially with both Dual BIA and computed tomography (CT), and in subsequent weeks of calorie restriction, with Dual BIA were measured.
Results: IAFA by Dual BIA (Dual BIA-IAFA) correlated well with IAFA by CT (CT-IAFA) in obese patients ($r = 0.821$, $P < .0001$, $n = 67$). Ten males and 9 females (age 49.0 ± 14.4 years, BMI 33.2 ± 7.3 kg/m^2) lost more than 5% of baseline body weight (BW) in 3 weeks, and their Dual BIA-IAFA, BW, and WC decreased by 18.9%, 5.3%, and 3.8%, respectively ($P < .05$, ANCOVA).
Conclusion: Dual BIA instrument could detect the weekly change of Dual BIA-IAFA under calorie restriction in obese patients and demonstrated a substantially larger change of IAFA compared with changes of BW and WC in early weeks. This observation corroborates the significance of evaluating IAFA as a biomarker for obesity, and indicates the clinical usefulness of the Dual BIA instrument.

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Introduction

Abdominal adiposity is associated with development of obesity and metabolic abnormalities in obesity-related diseases (1-3). The adipose tissue distribution has been quantitatively evaluated by computed tomography (CT) (4) or magnetic resonance imaging (MRI) (5), and intra-abdominal fat area (IAFA) is used as a clinical parameter of abdominal adiposity (6). Although waist circumference (WC) is casually employed to evaluate abdominal adiposity (7), WC is known to reflect both the intra-abdominal and the subcutaneous abdominal adiposity. In addition, the correlation of WC with intra-abdominal adiposity is influenced by age and sex as shown in epidemiological studies (5). Thus, WC does not necessarily provide the precise information about abdominal fat distribution. Therefore, a new practical method for detecting early change in abdominal adiposity is needed to elucidate its consequence during acute phase of calorie restriction in obesity treatment (8). There have been a few proposals of methods (9,10) that assess IAFA as alternatives to CT (4) or MRI (5). However, there has been no report on clinical application of these methods analyzing the weekly change of IAFA during calorie restriction. We have developed the dual bioelectrical impedance analysis (Dual BIA) instrument that can determine IAFA by measuring truncal impedance and surface impedance at the abdomen separately, each of which reflects the truncal adiposity and the subcutaneous adiposity respectively (11-13). The Dual BIA instrument has been optimized with aims at robustness for use in a wide range of human variation by analyzing the size of effect that each parameter, such as age and gender, can have on the calculation outcomes utilizing information technology (11-13). In this study, we report on application of the Dual BIA instrument to compare the weekly change in IAFA and body weight (BW) of obese patients with the metabolic syndrome or diabetes mellitus resulting from calorie restriction.

Methods

Dual BIA method and instrumentation

Dual BIA instrument calculates the cross-sectional area of intra-abdominal fat at the level of umbilicus based on the measurement of electrical potentials resulting from applying small electrical currents in two different body space. Principles of IAFA determination by Dual BIA instrument have been described previously (11-13) in detail. Briefly, the Dual BIA instrument consists of bioelectrical impedance

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component that measures truncal and surface impedance of the body, and a device that measures physical size of the abdomen. The two sets of electrodes are for limb and truncal placement. The limb electrodes consist of four clip-on electrodes placed on wrists and ankles. The truncal electrodes are eight pairs of electrodes 6 cm apart longitudinally that are fixed to a belt where four pairs each for front and back are positioned at an equal inter-electrode distance. The belt is adjustable so that the electrodes are positioned centered on mid-sagittal line at the level of umbilicus in supine position. The truncal impedance is measured by applying electrical currents between upper and lower limb leads and reading voltage from the electrodes around the abdominal circumference. The surface impedance is measured by applying and reading voltage from the abdominal circumferential electrodes. IAFA by Dual BIA (Dual BIA-IAFA) is calculated as follows.

$$\text{Dual BIA} - \text{IAFA} = \alpha_1 A + \alpha_2 B^2 - \alpha_3 \left(A^2 + B^2\right)^{1/2} Z_s - \alpha_4 / Z_t + \varepsilon \quad (1)$$

A: abdominal antero-posterior diameter, B: abdominal transverse diameter, Z_s: surface impedance, Z_t: truncal impedance, ε: residual constant.

There was a good agreement of Dual BIA-IAFA and IAFA measured by CT (CT-IAFA) with the correlation coefficient of 0.888 ($n = 98$, $P < .001$) (13).

Patient selection

The study was performed according to the protocol approved by Kyoto University Medical Ethics Review Board (no. 080116). The patient gave a written consent to participate in this study which took place at the endocrinology and metabolism ward of Kyoto University Hospital. We collected data from 67 Japanese patients (36 males and 31 females; mean ± SD age, 54.7 ± 14.7 years, BMI 29.3 ± 6.5 kg/m^2) with obesity ($n = 56$), diabetes mellitus ($n = 45$), or the metabolic syndrome ($n = 38$) who were hospitalized for calorie restriction therapy or diet education, and had measurement of IAFA by both Dual BIA method and CT method at the start of calorie restriction. Obesity was diagnosed as BMI 25.0, and metabolic syndrome was diagnosed according to 2005 Japanese criteria of metabolic syndrome (14). Average daily calorie intake was 1437.3 ± 201.4 kcal/day (19.3 ± 4.3 kcal/ideal BW). Out of 67 patients, 35 patients could be followed for longer than 3 weeks, while the other patients were discharged earlier after examination of complications and diet and lifestyle education. Total daily energy was varied individually during hospitalization based on consultation between the patient, a dietician, and a physician. Out of 35 patients who had their Dual BIA-IAFA monitored every week for at least 3 weeks (four times), 19 patients lost more than 5% of baseline BW, and were included in the analysis of weekly change in Dual BIA-IAFA, WC, and BW during weight reduction.

Measurement of Dual BIA, CT, and anthropometric parameters

Dual BIA-IAFA was measured every week in the morning before breakfast depending on individual patient's treatment schedule (Figure 1A). Abdominal CT was performed for calculation of CT-IAFA within 7 days before the initial Dual BIA-IAFA measurement. CT-IAFA was calculated at umbilical level by the software, Virtual Place Lexus (AZE of Japan, Ltd). BW was measured to the nearest 0.1 kg in the morning of the Dual BIA-IAFA measurement.

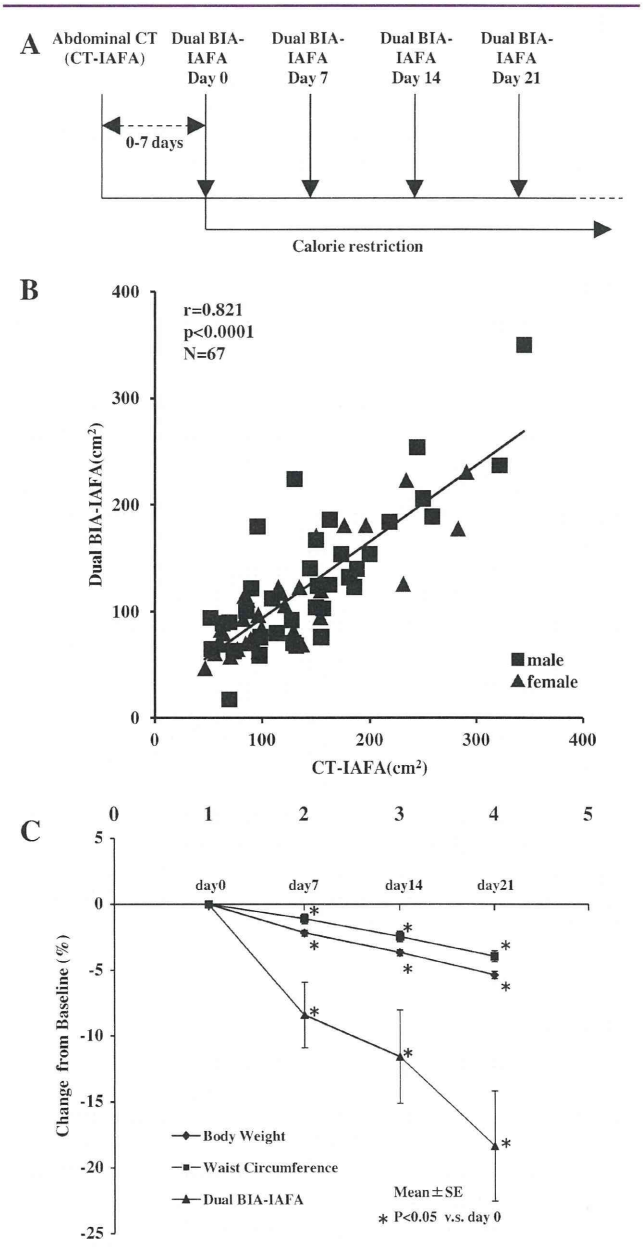

FIGURE 1 **A**: Diagram of IAFA assessment schedule during the calorie restriction. Patients started fixed calorie diet within 7 days of taking the abdominal CT image. Dual BIA-IAFA assessment took place in the morning before meal every week. CT imaging took place either in the morning or in the afternoon. **B**: Correlation between CT-IAFA and BIA-IAFA in 67 patients who were with obesity-related disorders. Square symbols: male, Triangle symbols: female. $r = 0.821$, $P < .001$ by Pearson's analysis. **C**: Weekly change of Dual BIA-IAFA plotted along with BW and WC during weight loss. Nineteen patients who underwent the calorie restriction and had abdominal CT examined at baseline were monitored for their anthropometric parameters and Dual BIA-IAFA weekly for at least 3 weeks. They lost more than 5% of BW during the period. Size of the change from baseline values (mean ± SE) is expressed as %. *$P < .05$ by Student's paired t-test.

WC was measured at the level of the umbilicus to the nearest 0.1 cm in the standing position at the end of expiration while breathing gently at the time of Dual BIA measurement.