

# Characteristics of Childhood Onset and Post-Puberty Onset Obesity and Weight Regain after Laparoscopic Sleeve Gastrectomy in Japanese Subjects: A Subgroup Analysis of J-SMART

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## Keywords

Obesity · Childhood onset obesity · Weight regain · Bariatric surgery · Laparoscopic sleeve gastrectomy

## Abstract

**Introduction:** The psychosocial background of subjects with severe obesity developed from childhood onset obesity (CO) and their outcomes after bariatric surgery have not been fully investigated. **Methods:** 305 subjects were enrolled in the J-SMART study, which examined the effects of laparoscopic sleeve gastrectomy (LSG) in Japan, and categorized into two

groups: CO defined as onset up to 13 years of age (CO group) and post-puberty onset obesity defined as onset after 13 years of age (PPO group). The subjects were followed up for at least 2 years and up to 5 years after LSG. Changes in physical parameters and remission of obesity-related comorbidities were assessed at 2 years after LSG. Weight regain (WR) was also assessed by evaluating the nadir weight after LSG and maximum weight thereafter during follow-up period.

**Results:** The mean postoperative follow-up period was 3.0 ± 1.1 years. 40.0% of the subjects had CO and these subjects had higher BMI and HOMA-β and lower age, HbA1c, HDL cholesterol, and visceral/subcutaneous fat area ratio com-

pared to those with PPO. The CO group was also characterized by having higher rates of mental retardation, developmental disorders, and obesity in either parent and lower rate of marriage compared to the PPO group. Two years after LSG, there were no differences in total weight loss and remission rates of diabetes, dyslipidemia, and sleep apnea syndrome between the two groups, although remission rate of hypertension was higher in the CO group. The CO group also had a higher rate of WR after LSG than the PPO group, with CO, BMI, mental disorder, and binge eating contributing to WR. **Conclusion:** This study suggests that CO might be associated with genetic and psychosocial factors. CO and PPO probably differ in pathogenesis and may require different treatment strategies.

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## Introduction

Childhood onset obesity (CO) develops into adult obesity, which in turn leads to the development of obesity-related comorbidities such as diabetes, hypertension, dyslipidemia, and obstructive sleep apnea syndrome (OSAS). Obese children were around five times more likely to be obese in adulthood than those who were not obese [1]. Recent studies have shown an acceleration of obesity in children and adolescents due to the increased time spent at home as a result of the COVID-19 pandemic, and this has become a serious problem [2, 3].

Although various factors may contribute to the development of CO, such as heredity, upbringing environment, and intellectual development [4], the contributing factors may be different between CO with onset before/during puberty and post-puberty onset obesity (PPO). Moreover, the effects of bariatric surgery may also be different between CO and PPO. The purpose of this study was to investigate the physical and psychosocial characteristics of CO among patients treated with bariatric surgery and compare the effects of bariatric surgery and the rate of postoperative weight regain (WR) between CO and PPO.

## Methods

This study was a subgroup analysis of the Japanese Survey of Morbid and Treatment-Resistant Obesity (J-SMART) study [5], which retrospectively examined the effects of bariatric surgery on weight loss and remission of diabetes in a representative sample of centers performing bariatric surgery in Japan. The study design was retrospective and observational. The J-SMART study included

322 Japanese subjects who underwent laparoscopic sleeve gastrectomy (LSG) at 10 bariatric surgery facilities accredited by the Japanese Society for the Treatment of Obesity (JSTO) between January 2011 and December 2014, with a follow-up period of at least 2 years. The subjects were followed up for at least 2 years and up to 5 years after LSG. Changes in physical parameters and remission of obesity-related comorbidities were assessed at 2 years after LSG. WR was also assessed by evaluating the nadir weight after LSG and maximum weight thereafter.

In Japan, the percentage of overweight (POW) index is more commonly used for children than the age-percentile body mass index (BMI). The POW index is calculated based on measured weight and standard weight for height as follows:  $POW (\%) = 100 \times (\text{measured weight} - \text{standard weight for height}) / \text{standard weight for height}$  [6]. A POW  $\geq 15\%$  is considered to be mildly obese,  $\geq 20\%$  moderately obese, and  $\geq 30\%$  severely obese in children younger than 6 years of age. For children aged 6 years or older, a POW  $\geq 20\%$  is considered mildly obese,  $\geq 30\%$  moderately obese, and  $\geq 50\%$  severely obese [7, 8]. In the present study, the subjects were asked whether they had been diagnosed with obesity based on the above criteria during annual school health check and were classified as CO if they were obese up to the age of 13 years and PPO if they were obese after the age of 13 years.

The JSTO guidelines adopted the following as indications for bariatric surgery: primary obesity between the ages of 18 and 65 years, inadequate response to medical treatment, and one of the following conditions: (1) BMI of  $35 \text{ kg/m}^2$  or higher for the purpose of weight loss (weight loss surgery), (2) BMI of 32 or higher for the purpose of treating comorbidities (including diabetes, hypertension, dyslipidemia, liver dysfunction, and sleep apnea syndrome). In the present subgroup analysis, 305 subjects who underwent LSG based on these guidelines and whose obesity onset period was known were selected from the J-SMART database. From the subjects' records, the following data were extracted: sex, age, and physical and clinical parameters such as height, body weight, visceral fat area (VFA), subcutaneous fat area (SFA), blood pressure, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), fasting serum connecting peptide immunoreactivity (CPR), and fasting immunoreactive insulin (IRI). The CPR index was calculated by the following formula:  $CPR \text{ index} = 100 \times \text{fasting CPR (ng/mg)} / \text{FPG (mg/dL)}$  [9, 10]. Homeostasis model assessment (HOMA)-beta cell function (HOMA- $\beta$ ) was calculated by the following formula:  $HOMA-\beta = (\text{fasting IRI } [\mu\text{IU/mL}] \times 360) / (\text{FPG [mg/dL]} - 63)$  [11, 12]. HOMA-insulin resistance (HOMA-IR) was calculated as follows:  $HOMA-IR = (\text{fasting IRI } [\mu\text{IU/mL}] \times \text{FPG [mg/dL]}) / 405$  [11, 12]. Other extracted data were lipid level markers, serum creatinine, history of insulin administration, number of medications, and apnea-hypopnea index (AHI). Subjects with AHI  $\geq 5$  and sleep-related symptoms of OSAS were diagnosed as having OSAS. VFA and SFA were measured by computed tomography at the level of the umbilicus with the subject in supine position. Information on mental disorders, intelligence, economic status, and family background collected in the J-SMART was also used in the present analysis. Mental disorders, mental retardation, developmental disorders, and binge eating were diagnosed by skilled psychiatrists in doubtful cases, according to the criteria in Diagnostic and Statistical Manual of Mental Disorders 4th or 5th edition, or International Statistical Classification of Diseases and Related Health Problems 10th Revision. The prevalence of mental disorders was the sum of mental retardation, develop-

**Table 1.** Comparison of baseline physical data between CO and PPO groups

	CO (n = 122)	PPO (n = 183)	p value
Age, years	42.2±9.4	50.5±10.3	0.000*
Male, %	45.9	42.1	0.509
Body weight, kg	125.3±31.4	114.2±26.7	0.002*
BMI, kg/m <sup>2</sup>	43.8 (38.6–50.6)	40.3 (36.7–45.7)	0.000*
FPG, mg/dL	109.0 (98.0–128.8)	115.5 (102.0–139.3)	0.054
HbA1c, %	6.2 (5.5–7.3)	6.7 (5.9–8.2)	0.023*
TC, mg/dL	195.4±45.5	204.0±38.9	0.212
TG, mg/dL	138.0 (98.0–205.0)	160.0 (104.0–218.0)	0.276
HDL-C, mg/dL	44.0 (37.5–50.5)	46.0 (41.0–55.0)	0.013*
Serum creatinine, mg/dL	0.61 (0.55–0.75)	0.69 (0.58–0.85)	0.052
Uric acid, mg/dL	6.6±1.6	6.3±1.6	0.332
SBP, mmHg	140.2±20.0	139.5±19.9	0.870
DBP, mmHg	89.3±19.2	85.7±13.0	0.255
CPR index	2.9 (2.2–4.2)	2.7 (2.0–3.6)	0.068
HOMA-IR	4.2 (3.1–7.9)	4.5 (3.0–7.7)	0.782
HOMA-β, %	155.3 (66.5–263.3)	93.9 (60.6–148.1)	0.023*
VFA, cm <sup>2</sup>	163.2 (133.5–208.8)	198.0 (165.0–244.7)	0.000*
SFA, cm <sup>2</sup>	567.0 (434.4–658.9)	483.3 (430.0–588.6)	0.008*
VFA/SFA ratio	0.37±0.20	0.48±0.23	0.000*
Rate of diabetes, %	60.7	67.2	0.241
Rate of hypertension, %	73.7	81.8	0.098
Rate of dyslipidemia, %	98.4	95.1	0.132
Antidiabetic drugs, n	1 (0–2)	1 (0–2)	0.477
Insulin use, %	4.1	9.8	0.115
Antihypertensive drugs, n	0 (0–1)	1 (0–2)	0.004*
Lipid-lowering drugs, n	0 (0–1)	0 (0–1)	0.439
Rate of OSAS, %	68.9	75.4	0.209

Data are presented as mean±SD or median (interquartile range) or percentage. CO, childhood onset obesity; PPO, post-puberty onset obesity; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; CPR, connecting peptide immunoreactivity; HOMA-IR, homeostasis model assessment (HOMA)-insulin resistance; HOMA-β, HOMA for beta cell function; VFA, visceral fat area; SFA, subcutaneous fat area; OSAS, obstructive sleep apnea syndrome; SD, standard deviation. \* p value ≤0.05.

mental disorders, binge eating, and/or other mental disorders. The Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) was performed as the intelligence test in general practice. WAIS-III was administered and scored by a trained psychiatrist or psychologist. WAIS-III was used to estimate their postsurgical outcomes.

Complete remission and partial remission of diabetes were defined as HbA1c less than 6.0% and 6.5%, respectively, without using antidiabetic drugs [13]. Dyslipidemia remission was defined as total cholesterol level <220 mg/dL, triglyceride level <150 mg/dL, and high-density lipoprotein cholesterol level ≥40 mg/dL without drug treatment for dyslipidemia, based on the criteria of the Japanese Atherosclerosis Society guidelines [14]. Remission of hypertension was defined as systolic blood pressure less than 130 mmHg and diastolic blood pressure less than 80 mmHg in the absence of antihypertensive drugs, based on the normal range of the Japanese Society of Hypertension guidelines [15]. Postoperative WR was evaluated using three major indices in bariatric surgery as follows: (1) WR of more than 25% of lost weight from the nadir weight [16,

17], (2) WR of more than 10 kg from the nadir weight [18–20], and (3) regaining more than 5 BMI points from the BMI at nadir weight [17, 21].

All procedures and data collection were performed in accordance with the ethical standards of the institutional and Japanese research committees and the ethical standards of the 1975 Declaration of Helsinki. This study was approved by the Ethics Committee of Toho University Sakura Medical Center (Approval Number: S16026). Informed consent was obtained in the form of opt-out on the Website.

#### Statistical Analysis

Results were expressed as mean ± SD or median (interquartile range) or percentage. Normal distribution was tested using the Shapiro-Wilk test. For comparisons between the two groups, Student's *t* test was used to analyze parametric data and Mann-Whitney *U* test for nonparametric data. Fisher's exact test was used to detect significant differences between proportions and categorical

**Table 2.** Comparison of baseline psychological and social data between CO and PPO groups

	CO	PPO	<i>p</i> value
Mental disorder, %	18.9	21.3	0.841
Mental retardation and developmental disorders, %	4.4	0.6	0.027*
Full IQ (WAIS-III)	93.8±20.8	98.8±14.0	0.385
Verbal IQ (WAIS-III)	97.2±20.3	98.3±12.7	0.834
Performance IQ (WAIS-III)	93.3±19.6	98.7±16.1	0.364
Economic independence, %	63.9	65.6	0.405
Marriage, %	36.9	63.4	0.000*
History of divorce, %	9.0	11.5	0.726
Living with family, %	80.3	86.9	0.205
Obesity of either parent, %	61.5	28.3	0.001*
Binge eating, %	13.9	10.9	0.540

Data are presented as mean±SD or percentage. CO, childhood onset obesity; PPO, post-puberty onset obesity; IQ, intelligence quotient; WAIS-III, Wechsler Adult Intelligence Scale 3rd edition; SD, standard deviation. \* *p* value ≤0.05.

variables. For analysis of the proportions of CO in various BMI categories,  $\chi^2$  test for trend was used. Simple linear regression analysis was performed using Spearman's rank correlation. Multiple regression analysis was performed to identify factors that contribute to postoperative WR. These analyses were performed using SPSS software version 26 (IBM Corp, Armonk, NY, USA). A *p* value ≤0.05 was considered significant.

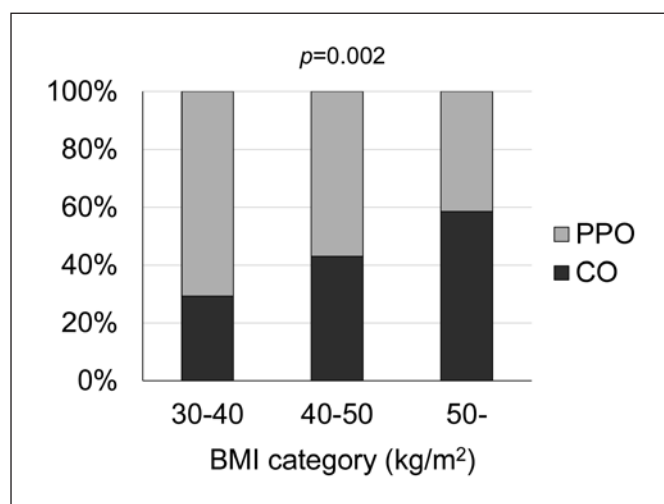
## Results

### Comparison of Baseline Physical Data between CO and PPO Groups

Of 305 subjects, 122 (40.0%) were classified in the CO group and 183 (60.0%) in the PPO group. Compared to the PPO group, the CO group had higher body weight, BMI, HOMA- $\beta$ , and SFA and lower age, HbA1c, high-density lipoprotein cholesterol, VFA, VFA/SFA ratio, and number of antihypertensive drugs (Table 1). There were no differences between the two groups in sex ratio, FPG, total cholesterol, triglyceride, serum creatinine, uric acid, systolic blood pressure, diastolic blood pressure, HOMA-IR, percent diabetes, percent hypertension, percent dyslipidemia, OSAS, number of medications for diabetes and dyslipidemia, and percent insulin use.

### Comparison of Baseline Psychological and Social Data between CO and PPO Groups

Psychological and social baseline data in the CO or PPO groups are shown in Table 2. Compared to the PPO group, the CO group had higher prevalence of mental retardation and developmental disorders and obesity of either parent. They were also less likely to be married. There



**Fig. 1.** Percentage of CO and PPO subjects stratified by BMI category. The proportion of patients with CO increases as BMI increases. BMI, body mass index; CO, childhood onset obesity; PPO, post-puberty onset obesity.

were no differences between the two groups in the prevalence of mental disorder, full/verbal/performance intelligence quotient (IQ) evaluated by WAIS-III, economic independence, history of divorce, living with family, and binge eating.

### Percentage of CO and PPO Subjects by BMI Category

Figure 1 shows the percentage of CO and PPO subjects stratified by BMI category. The percentage of CO subjects increased and the percentage of PPO subjects decreased as BMI increased.

**Table 3.** Comparison of changes in physical parameters and remission rates of obesity-related comorbidities 2 years after LSG

	CO	PPO	p value
ΔBody weight, kg	-38.2±1.7	-35.0±1.4	0.143
ΔBMI, kg/m <sup>2</sup>	-13.9±0.6	-12.9±0.5	0.180
%TWL, %	30.1±11.7	29.7±10.6	0.772
ΔFPG, mg/dL	-15.0 (-37.0 to [-5.0])	-20.0 (-45.0 to [-8.0])	0.234
ΔHbA1c, %	-0.7 (-1.7 to [-0.4])	-1.0 (-2.0 to [-0.5])	0.163
ΔTC, mg/dL	-0.6±6.5	-8.3±4.2	0.298
ΔTG, mg/dL	-57.0 (-110.8 to 1.0)	-61.0 (-106.0 to [-15.0])	0.372
ΔHDL-C, mg/dL	17.5±2.2	14.7±1.3	0.241
ΔSerum creatinine, mg/dL	0.40 (-0.43 to 0.90)	-0.20 (-0.70 to 0.50)	0.014*
ΔUric acid, mg/dL	-0.9±0.2	-0.8±0.1	0.693
ΔSBP, mmHg	-3.2±2.6	1.6±1.6	0.115
ΔDBP, mmHg	0.3±1.9	0.8±1.2	0.819
ΔVFA, cm <sup>2</sup>	-84.7 (-123.9 to [-37.2])	-132.7 (-186.8 to [-82.7])	0.063
ΔSFA, cm <sup>2</sup>	-145.1 (-254.9 to [-92.9])	-108.7 (-274.5 to [-78.9])	0.520
ΔVFA/SFA ratio	-0.07 (-0.17 to [-0.16])	-0.10 (-0.24 to [-0.28])	0.324
CR of diabetes, %	80.0	65.6	0.061
Complete or partial remission of diabetes, %	83.6	77.1	0.337
Remission of dyslipidemia, %	57.7	65.6	0.196
Remission of hypertension, %	47.4	32.1	0.028*
Remission of OSAS, %	58.4	66.2	0.236

Data are presented as mean±SD or median (interquartile range) or percentage. CO, childhood onset obesity; PPO, post-puberty onset obesity; BMI, body mass index; %TWL, percent total weight loss; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; VFA, visceral fat area; SFA, subcutaneous fat area; OSAS, obstructive sleep apnea syndrome; LSG, laparoscopic sleeve gastrectomy; SD, standard deviation; CR, complete remission. \* p value ≤0.05.

### Changes in Physical Parameters and Remission of Obesity-Related Comorbidities

The mean postoperative follow-up period was 3.0 ± 1.1 years. Changes in physical parameters and remission of obesity-related comorbidities were assessed at 2 years after LSG (Table 3). There were no differences between the two groups in body weight, BMI, percent total weight loss (%TWL), FPG, HbA1c, lipids levels, uric acid, blood pressure, VFA, SFA, and VFA/SFA ratio. The amount of change in serum creatinine was different between the CO and PPO groups. Remission rates of obesity-related comorbidities including complete and partial remission of diabetes, dyslipidemia, and OSAS were not significantly different between the two groups, but the remission rate of hypertension was higher in the CO group than in the PPO group. The amount of change in VFA was associated with complete or partial remission of diabetes and remission of dyslipidemia, and the amount of change in SFA was associated with remission of dyslipidemia and hypertension. Being CO or PPO did not contribute to

changes in VFA or SFA (online suppl. Table S1; see [www.karger.com/doi/10.1159/000524941](http://www.karger.com/doi/10.1159/000524941) for all online suppl. material).

### Comparison of WR after LSG between CO and PPO Groups

Table 4 shows the differences in WR after LSG between the CO and PPO groups. There were no significant difference in the percentage of subjects with WR of more than 25% of lost weight from the nadir weight and WR of more than 10 kg from the nadir weight. However, the percentage of subjects who regained more than 5 BMI points from the BMI at nadir weight was significantly higher in the CO group.

### Relationship between WR of More than 5 BMI Points after LSG and Physical and Psychosocial Parameters

Based on the results of Table 4, the relationship between WR of more than 5 BMI points from the BMI at nadir weight after LSG and physical and psychosocial

**Table 4.** Comparison of weight regain after LSG between CO and PPO groups

	CO	PPO	<i>p</i> value
Regain of more than 25% of lost weight from the nadir weight, %	32.1	25.7	0.305
Regain of more than 10 kg from the nadir weight, %	28.6	19.1	0.104
Regain of more than 5 BMI points from the BMI at nadir weight, %	17.9	5.1	0.002*

Data are presented as percentage. CO, childhood onset obesity; PPO, post-puberty onset obesity; LSG, laparoscopic sleeve gastrectomy. \* *p* value ≤0.05.

**Table 5.** Relationship between WR of more than 5 BMI points from the BMI at nadir weight (1) or not (0) and each parameter

	WR of more than 5 BMI points from the BMI at nadir weight (1) or not (0)			
	univariate		multivariate	
	<i>r</i>	<i>p</i> value	β coefficient	<i>p</i> value
CO (1) or PPO (0)	0.206	0.002*	0.132	0.05*
Age, years	-0.164	0.015*	-0.031	0.652
Body weight, kg	0.115	0.089		
BMI, kg/m <sup>2</sup>	0.19	0.005*	0.226	0.001*
FPG, mg/dL	-0.062	0.379		
HbA1c, %	-0.082	0.397		
TC, mg/dL	0.031	0.75		
TG, mg/dL	0.007	0.941		
HDL-C, mg/dL	-0.043	0.663		
Serum creatinine, mg/dL	0.078	0.418		
Uric acid, mg/dL	0.02	0.845		
SBP, mmHg	0.101	0.163		
DBP, mmHg	-0.006	0.938		
OSAS (1) or not (0)	0.062	0.37		
Mental disorder (1) or not (0)	0.18	0.007*	0.149	0.024*
Mental retardation and developmental disorders (1) or not (0)	0.097	0.165		
Economic independence (1) or not (0)	-0.043	0.53		
Marriage (1) or not (0)	0.037	0.589		
History of divorce (1) or not (0)	-0.012	0.863		
Living with family (1) or not (0)	-0.112	0.100		
Obesity of either parent (1) or not (0)	0.011	0.930		
Binge eating (1) or not (0)	0.173	0.011*	0.156	0.018*

*r*, Spearman's rank correlation coefficient; WR, weight regain; CO, childhood onset obesity; PPO, post-puberty onset obesity; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; VFA, visceral fat area; SFA, subcutaneous fat area; OSAS, obstructive sleep apnea syndrome. The multivariate analysis model was  $r^2 = 0.458$ ,  $p = 0.021$ . \* *p* value ≤0.05.

data was analyzed. In simple linear regression analysis, CO, age, BMI, mental disorder, and binge eating were associated with WR. In multiple regression analysis, CO, BMI, mental disorder, and binge eating were extracted as independent contributing factors for WR (Table 5). No significant correlation was found between WR of more than 5 BMI points from the BMI at nadir weight and changes in each parameter in all subjects (online suppl. Table S2).

## Discussion

This study analyzed the physical and psychosocial characteristics, the effects of bariatric surgery, and post-operative WR in CO patients who underwent bariatric surgery compared with PPO patients. In Japan, bariatric surgery has gradually become more widespread in recent years [22], but the number of patients undergoing surgery is still low compared to developed countries in the field

of bariatric surgery. The J-SMART study is one of the largest databases of bariatric surgery in Japan, and the enrolled patients underwent LSG between 2011 and 2014. Although some time has passed since then, the characteristics of CO subjects needed to be clarified, and a sub-analysis of the J-SMART study was conducted in this study. The results suggest that background factors such as genetic predisposition (obesity of either parent), living environment, and mental problems were significantly associated with CO and that CO also contributed to post-operative WR.

Tables 1 and 2 presented the background characteristics of CO. A study of bariatric surgery candidates with obesity onset younger than 20 years showed that early onset of obesity was associated with higher total body fat mass [23], which is consistent with the finding of the CO subjects in our study. HbA1c was significantly lower in the CO group than in the PPO group, and the prevalence of diabetes and hypertension in the CO group tended to be lower, although not significantly different. It is well known that subcutaneous fat is predominant in childhood obesity [24, 25], and the amount of subcutaneous fat in young adults has been reported to be associated with BMI changes during both late childhood and adolescence [26]. Longitudinal studies suggest that excess fat and associated comorbidities persist into adulthood, with approximately 90% of children with severe obesity becoming adults having BMI  $\geq 35$  kg/m<sup>2</sup> [27]. In the present study, the CO group was also obese with predominant accumulation of subcutaneous fat. Study has suggested that subcutaneous fat may have a protective effect against metabolic and cardiovascular diseases [28], which may support the lower HbA1c in the CO group than in the PPO group.

The remission rates of diabetes, dyslipidemia, and OSAS in this study were not different between the two groups, while the rate of hypertension remission was significantly higher in the CO group. In a sub-analysis of the SOS study, there was no difference in the remission of diabetes after bariatric surgery between subjects who were obese at age 20 and those who were not obese [29]. Since one of the purposes of this study was to identify the characteristics of CO, the subjects were classified by the cutoff age of 13 years, and there were no differences in remission rates of diabetes, dyslipidemia, and OSAS between the two groups. The reason for the significantly higher remission rate of hypertension in the CO group was unclear, but the PPO group was older and used a larger number of antihypertensive drugs than the CO group, which may suggest that the PPO subjects had longer du-

ration of hypertension or more severe hypertension before LSG.

Another finding in this study was that CO, BMI, mental disorder, and binge eating were identified as contributing factors to WR after LSG. There are several major criteria for WR after bariatric surgery. In the present study, the prevalence of post-LSG increase in BMI of 5 or more was significantly higher in the CO group. Previous studies have reported a variety of factors associated with WR after bariatric surgery [30–32]. A systematic review reported the factors that contribute to postoperative WR [31], but there are few reports of the relationship between CO and WR. The reason for the association between CO and WR is not clear, but as there are reports about obesity and appetite abnormalities in children [33, 34], the presence of genetic abnormality influencing appetite regulation in the central nervous system in CO is plausible. On the other hand, for obese patients with CO and mental retardation or developmental disorders, genetic abnormalities such as Prader-Willi syndrome, Cohen syndrome, and Bardet-Biedl syndrome should be carefully excluded preoperatively [35]. In addition, in recent years, drugs such as setmelanotide may become a new treatment option for obesity caused by some specific genetic abnormalities [36, 37], and the possibility of genetic abnormalities should always be assumed in the practice of obesity.

BMI is also associated with WR [38], and WR is more likely to occur in patients with BMI over 50 [39]. A review found no association between preoperative BMI and WR [31], but careful interpretation is necessary because of the differences in surgical technique and ethnicity.

The finding of an association between WR and mental disorders and binge eating was also important; especially, depression and binge eating have been reported to be more common in candidates for bariatric surgery [40]. Because the current study focused on the association between CO and LSG, it did not focus on elucidating the factors that make it easier or harder for subjects to lose weight after LSG. On the other hand, the original J-SMART study showed weight trends for the entire cohort and further revealed that there was a higher prevalence of mental disorders in subjects with lower %TWL after LSG (%TWL <15%). Interestingly, subjects with higher %TWL (%TWL  $\geq 45\%$ ) also had a higher prevalence of mental disorders [5]. In other reports, mental disorder and binge eating are also associated with WR after bariatric surgery [41–43]. In our study, there was no difference in the prevalence of mental disorder and binge eating between the CO and PPO groups. However, mental disorder and binge eating were extracted as factors that independently

contributed to WR, confirming the importance of these factors for WR in Japanese subjects. IQ was not different between the CO and PPO groups and was not a contributing factor to WR. Although one report has shown that obese children have lower IQ than normal weight children and that lower IQ in childhood is associated with higher BMI in adulthood [44], there are few studies on the relationship between IQ or intellectual level and postoperative WR. On the other hand, severe mental retardation is often considered a contraindication for bariatric surgery [45]. The finding of no association between IQ and CO or WR in this study may be due to selection bias. It is necessary to examine whether bariatric surgery can be expected to improve the remission of obesity-related comorbidities in CO subjects with low IQ.

This study has several limitations. The retrospective observational study design and missing data in some subjects may have affected the results of the analysis. Furthermore, in dividing the subjects into CO and PPO groups, the original data were based on interviews with them, not on the existence of medical record data on their height and weight. It was also necessary to compare historical weight trends with Z-scores and percentiles based on pediatric growth curves for both the CO and PPO groups, but accurate historical weight data were not available and could not be analyzed. In the current study, most patients underwent LSG in their 40s or 50s; subjects in the CO group had been obese since childhood, but at what point they actually became obese enough to meet the criteria for surgery could not be determined without accurate historical weight records. In addition, since only Japanese subjects were included, the effects of racial differences could not be studied. It should also be noted that the analysis of WR was based on a maximum follow-up of 5 years and that the number of subjects included in this analysis has been decreasing over time.

## Conclusion

In conclusion, this study suggests that severely obese patients with childhood onset tend to have more severe and subcutaneous fat-dominant obesity compared to those with post-puberty onset, and subcutaneous fat predominance may be associated with lower HbA1c in those with childhood onset. Compared to PPO, CO might be associated with genetic and psychosocial factors and shows a tendency to regain weight after bariatric surgery. These findings suggest CO and PPO may involve different pathogenesis, which may require different treatment strategies.

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## Statement of Ethics

This study was performed in accordance with the ethical standards of the institutional and Japanese research committees and the ethical standards of the 1975 Declaration of Helsinki. This study was approved by the Ethics Committee of Toho University Sakura Medical Center (Approval Number: S16026). Informed consent was obtained in the form of opt-out on the Website.

## Conflict of Interest Statement

I.T. received lecture fee from Takeda Pharmaceutical Co., Ltd., and Novartis Pharma Ltd. and honorarium from Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and Bayer Yakuhin, Ltd. T.N. received honorarium from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Medtronic, Inc., Johnson & Johnson, Inc., Olympus Corporation, Terumo Corporation, Sumitomo Bakelite Co., Ltd., Takeda Pharmaceutical Co., Ltd., Merck & Co., MC Medical, Inc., Daiichi Sankyo Co., Ltd., Bayer Yakuhin, Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Eli Lilly Japan K.K., research grant from Japan Society for the Promotion of Science, and Grant-in-Aid for Scientific Research (C) (#17K10575), Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., and Medtronic, Inc. Y.M. received honorarium from Otsuka Pharmaceutical Co., Ltd. and Covidien Japan Inc. M.T. received lecture fee from Eli Lilly Japan K.K., Sumitomo Dainippon Pharma Co., Ltd., and Ono Pharmaceutical Co., Ltd. K.Y. received grant from Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., MSD K.K., Pfizer Japan Inc., Novo Nordisk Pharma Ltd., Taisho Pharmaceutical Co., Ltd., Kao Corporation, Ono Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Sumitomo Dainippon Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Teijin Pharma Limited, Shionogi Co., Ltd., Astellas Pharma Inc., Kowa Co., Ltd., and Bayer Yakuhin, Ltd., consulting fees from Kowa Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Novartis Pharma K.K., Novo Nordisk Pharma Ltd., AstraZeneca K.K., Pfizer Japan Inc., and Bayer Yakuhin, Ltd., and honorarium from Kowa Co., Ltd., MSD K.K., Astellas Pharma Inc., Mitsubishi Tanabe Pharma Corporation, Amgen K.K., Takeda Pharmaceutical Co., Ltd., Sanofi K.K., Ono Pharmaceutical Co., LTD., AstraZeneca K.K., Daiichi Sankyo Co., Ltd., Novartis Pharma K.K., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Kirin Co., Ltd., Pfizer Japan Inc., Novo Nordisk Pharma Ltd., Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Taisho Pharmaceutical Co., Ltd., and Janssen Pharmaceutical K.K. K.K. received lecture fee from Ethicon and Covidien Japan Inc. Y.I. received honorarium from MSD K.K., Novartis Pharma K.K., Novo Nordisk Pharma Ltd., Takeda Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi K.K., and Mitsubishi Tanabe Pharma Corporation. Y.S. received research grant from Medtronic, Inc., Johnson & Johnson, Inc., Nikkiso Co., Ltd., Sunny Health Co., Ltd., and Daiwa Securities Health Foundation.



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## Author Contributions

All authors made significant contributions to the study. A.S. and T.Y. designed the original concept. Y.W. wrote the initial draft of the manuscript. A.S. and I.T. reviewed and edited the manu-

script. All other authors contributed to data collection and interpretation and critically reviewed the manuscript. All the authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Data Availability Statement

Data described in the article will be made available upon reasonable request from the corresponding author.

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