Eating Behavior, Low-Frequency Functional Mutations in the Melanocortin-4 Receptor (*MC4R*) Gene, and Outcomes of Bariatric Operations: A Six-Year Prospective Study

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OBJECTIVE

Data on the effects of eating behavior and genetics on outcomes of gastrointestinal surgery for diabesity have been sparse, often flawed, and controversial. We aimed to assess long-term outcomes of bariatric operations in patients characterized for eating behavior and rare mutations in the melanocortin-4 receptor (*MC4R*) gene, which is strongly implicated in energy balance.

RESEARCH DESIGN AND METHODS

Between 1996 and 2005, 1,264 severely obese Swiss patients underwent current laparoscopic adjustable gastric banding, gastroduodenal bypass, or a hybrid operation. Of these, 872 patients were followed for a minimum of 6 years and were screened for *MC4R* mutations. Using regression models, we studied relationships between eating behavior and *MC4R* mutations and postoperative weight loss, complications, and reoperations after 6 years.

RESULTS

At baseline, rare functional *MC4R* mutation carriers exhibited a significantly higher prevalence of binge eating disorder (BED) or loss-of-control eating independent of age, sex, and BMI. Six years after bariatric surgery, the mutation carriers had more major complications than wild-type subjects independent of age, baseline BMI, sex, operation type, and weight loss. Furthermore, high baseline BMI, male sex, BED, and functional *MC4R* mutations were independent predictors of higher reoperation rates.

CONCLUSIONS

Sequencing of *MC4R* and eating typology, combined with stratification for sex and baseline BMI, might significantly improve patient allocation to banding or bypass operations for diabesity as well as reduce both complication and reoperation rates.

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Gastrointestinal bypass operations are the most effective treatment for severe obesity, offering sustained long-term weight reduction with improvement and prevention of comorbidities and reduced mortality rates (1,2). The mechanistically different gastric restrictive (banding) and diversionary (bypass) operations have remained largely unchanged over 40 years, although new approaches and devices have been introduced (3). Nonetheless, they are encumbered by complications in 10–20% of cases, with perioperative mortality rates up to 1% depending on type of operation, surgeon experience, and medical socioeconomics (4,5). Reoperations are serious events in all surgeries, but bariatric surgery is especially prone to late revisions and variable weight loss and mortality rates (6,7), yet guidelines for choosing operations and indications for reoperation are insufficient.

The identification of interindividual variability in response to treatment might allow selective allocation of patients according to eating behavior, energy balance, and genetic background. We and others previously described associations between disordered eating and mutations in the melanocortin-4 receptor (*MC4R*) gene (8,9), the most common cause of monogenic obesity in Europeans. We also reported outcomes of laparoscopic adjustable gastric banding (AGB) in 19 *MC4R* variant carriers, who had poorer outcomes at 3 years than noncarriers (10). This work has been followed by numerous conflicting publications regarding eating behavior and surgical outcomes in patients with rare and common genetic variants in *MC4R* (11–19). Main confounds are short follow-up, absence of stratification for sex and age, and underpowered study designs that impede analyses of mechanisms, potentially affecting outcomes (19). Although *MC4R* variants seem to influence eating behavior and associate with binge eating disorder (BED) (8), the effects of *MC4R* variants and BED on outcomes of bariatric operations are still elusive (19–21).

In the current study, we assessed the contribution of eating behavior and rare functional *MC4R* mutations to long-term surgery outcomes at a minimum of 6 years. Included were weight loss, complications, and reoperations, considering the effect of preoperative characterization, comorbidities, and operation type, in 872 severely obese unrelated Swiss Caucasian patients.

RESEARCH DESIGN AND METHODS

Patients

Between 1996 and 2005, 1,264 severely obese unrelated Swiss Caucasian patients underwent laparoscopic bariatric operations at four academically affiliated, urban hospital centers (Table 1 and Supplementary Fig. 1). Inclusion criteria were age between 16 and 70 years and BMI $\geq$40 or 35 kg/m^2 in the presence of one or more serious comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea syndrome, lower-extremity degenerative joint disease, heart failure). Exclusion criteria were open and obsolete operations (e.g., vertical banded gastroplasty and classic biliopancreatic diversion), prior bariatric surgery, large hiatal hernia, geographic factors encumbering regular follow-up, inability to comprehend necessary perioperative and follow-up procedures, psychosis, alcohol or drug abuse, serum creatinine level $>$200 μmol/L, evidence of liver cirrhosis, and not consenting to genetic testing.

A multidisciplinary team comprising an endocrinologist specializing in obesity, his specialty trained associate physician, a bariatric surgeon, a dietitian, and a psychologist assessed each eligible patient before surgery but were blinded to genotype information. An array of diverse phenotypic data and blood stored for subsequent genetic analysis were routinely obtained at baseline and annually thereafter (22).

A total of 872 patients met the eligibility criteria and were prospectively followed postoperatively for at least 6 years with a 100% in-office clinician follow-up rate. No 30-day deaths occurred, and no patients had reversal of their operation. Complications, reoperations, vital signs, physical examinations, band adjustments, and medications were recorded at each visit.

Patients were fully informed and gave written consent. This study was approved by local ethics committees and complied with the Declaration of Helsinki.

Operations

AGB, a purely restrictive operation, consists of a small proximal gastric reservoir ($\sim$25 mL) and stoma that limit the volume and speed with which solid food empties (Supplementary Fig. 2) (22). Laparoscopic Roux-en-Y gastric bypass (RGB), a metabolic operation, creates a small, stapled proximal gastric reservoir attached to the jejunum, bypassing stomach, pylorus, duodenum, and the first part of the jejunum (Supplementary Fig. 2) (22). The hybrid operation (HYB) combines restrictive AGB with a pylorus-sparing duodenal-jejunal bypass and duodenal switch, dividing and closing the proximal duodenum attaching the postpyloric stomach to the ileum (Supplementary Fig. 2) (23). Both bypass operations exclude the duodenum, altering the sequence and magnitude of nutrient-stimulated responses, digestion, and absorption.

Table 1—Preoperative characterization and eating behavior in 1,264 bariatric surgery patients in total and compared by sex

	Total	Men	Women	*P* value
No. of patients	1,264	316	948	
Age (years)	42 $\pm$ 11	43 $\pm$ 11	42 $\pm$ 11	$<$0.05
Weight (kg)	125 $\pm$ 22	141 $\pm$ 21	119 $\pm$ 19	$<$0.001
Height (cm)	167 $\pm$ 9	177 $\pm$ 7	164 $\pm$ 7	$<$0.001
BMI (kg/m^2)	44.7 $\pm$ 6.5	44.8 $\pm$ 6.3	44.6 $\pm$ 6.6	..
Hypertension	81	91	78	$<$0.001
Dyslipidemia	67	74	65	$<$0.01
Type 2 diabetes	29	40	25	$<$0.001
BED	26	24	27	..
Big eater	60	80	54	$<$0.001
Snacker	36	25	40	$<$0.001
Sweets eater	55	45	58	$<$0.001
Fat eater	66	81	61	$<$0.001
LOC	28	27	28	..

Data are mean $\pm$ SD or %.

Definition of Complications and Reoperations

Major complications were defined as pulmonary (pneumonia, edema, respiratory insufficiency, adult respiratory distress syndrome), cardiovascular (myocardial infarct, congestive heart failure, stroke), renal, psychiatric (depression, psychosis), or abdominal (peritonitis, intestinal obstruction, gastric dilatation, deep wound infection, internal herniae) classified as either gastrointestinal or port/tube related (10). Postoperative complications and insufficient weight loss followed published criteria and governed the choice of reoperation (10,24).

Major reoperations required laparoscopy or laparotomy under general anesthesia, whereas minor reoperations included interventional gastroscopy and port/tube-related abdominal wall procedures not requiring laparotomy or general anesthesia. Reoperations after gastric bypass were mainly limb resections or the addition of restrictive AGB for inadequate weight loss, whereas primary banding and HYB had pouch revisions for fistula or dilatation (24).

Complications and reoperations were operation specific. AGB and HYB had device-related complications not applicable to RGB, which in turn had gastroenterotomies and anastomoses not present in AGB.

Eating Behavior

Eating behavior was comprehensively evaluated as published earlier (8), using the German translation of Spitzer's eating disorder questionnaire (25) and independent semistructured interviews requiring unanimity among three team members making the diagnosis of BED as currently defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (26). In addition, the work-up consisted of 3-day dietary diaries reporting food frequency, which were analyzed for meal composition and calories by Prodi software as described in Kobe et al. (27). For the evaluation of these diaries, each patient had a debriefing interview by a specially trained dietitian using plates and other visual aids.

By combining these food frequency responses and individual items from the BED questionnaire, patients were characterized into four categories as big eaters, snackers, sweets eaters, and fat eaters (28). A similar interview was also conducted with each patient by the obesity specialist, which required consensus with the dietitian. A separate analysis was performed to diagnose loss of control (LOC) reported as a binary item in the BED questionnaire (25,28,29). This characteristic of hyperphagia distinguishes impulsive LOC eating from conscious deliberate choices of macronutrients and eating style exhibited in the four categories.

Sequencing of *MC4R* Gene

The coding exon of *MC4R* (NM_005912.2) was sequenced in the 872 patients followed postoperatively for at least 6 years by using a standard protocol (30). We identified 16 low-frequency or rare nonsynonymous variants, including 5 rare mutations (p.S36T, p.V128L, p.I185F, p.T246A, and p.I251T) that had never been reported (Supplementary Table 1). Among the 11 previously described mutations, nine (p.S94N, p.T112M, p.D126Y, p.S127L, p.R165W, p.A175T, p.299H, p.I301T, and p.Q307*) were known to be rare and associated with loss of function (LOF) of *MC4R*, whereas two low-frequency variants (p.V103I and p.I251 L) were known to be associated with a gain of function (GOF) (Supplementary Table 1) (31–34). Of note, two patients carried homozygous LOF mutations. We analyzed them along with the carriers of heterozygous LOF mutations due to low statistical power.

Functional Characterization of the Novel *MC4R* Mutations

All novel variants (i.e., p.S36T, p.V128L, p.I185F, p.T246A, p.I251F) (Supplementary Fig. 3) were investigated. The effect of each mutation on cAMP activity in human HEK293 cells was assessed as previously described (30). We found that three novel mutations (p.I185F, p.T246A, and p.I251T) decreased cAMP activity and were therefore associated with LOF of *MC4R*, whereas two mutations (p.S36T and p.V128 L) were neutral (Supplementary Fig. 3). Thus, these two variants were excluded from further analyses.

Statistical Analyses

Data are presented as mean ± SD, unless specified otherwise. Linear and logistic regression models were used for the analysis of the outcomes weight loss (BMI decrease), reoperation, and major complications and the predictors sex, baseline BMI (BMI0), age, operation type (AGB, RGB, or HYB), eating behavior (BED, big eater, snacker, sweets eater, fat eater, and LOC), and *MC4R* mutation status. The models were unadjusted, unless specified otherwise, in the RESULTS section.

We used the receiver operating characteristic (ROC) area under the curve (AUC) to assess the potential contribution of screening *MC4R* mutations and eating typology beyond information provided by operation type, BMI0, age, and sex. We used the DeLong test to compare the various ROC curves to predict reoperations (35).

$P < 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.3 or SPSS version 22 software.

RESULTS

At baseline, the 1,264 patients were studied, including 75% women and 25% men (Table 1). Men were older and had more comorbidities, albeit at the same BMI0. Regarding eating behavior, BED prevalence was similar in women and men, whereas the prevalence of big eaters and fat eaters was higher in men. Women were more often snackers and sweets eaters than men. In both sexes, BED or LOC prevalence was inversely associated with the other eating types (big eaters, fat-eaters, sweet-eaters, and snackers; $P < 0.0001$).

Among the 872 patients followed for at least 6 years, the proportion of men who had RGB or HYB was higher than those who had AGB (Table 2). In both sexes, patients with higher BMI0 had RGB or HYB operations, whereas those with lower BMI0 had AGB, reflecting the surgeons' clinical biases. RGB patients had more hypertension and type 2 diabetes than AGB patients; HYB patients were more hypertensive and dyslipidemic. BED and LOC were more frequent in HYB patients than AGB patients, whereas the proportion of big eaters and fat eaters was significantly higher in RGB patients than AGB patients. Carriers of LOF *MC4R* mutations were, on average, 6 years younger with 5 units higher BMI0. After adjusting for age and sex, this last association remained significant ($\beta = 4.5 \pm 1.6$, $P = 5.4 \times 10^{-3}$). BED or LOC was more frequent in carriers of functional *MC4R* mutations compared with wild-type (WT) subjects. When adjusting for age, sex, and BMI0, functional *MC4R* mutations

Table 2—Preoperative characterization, eating behavior, and comorbidity in 872 bariatric surgery patients according to operation type and *MC4R* mutations followed ≥ 6 years

				P value					*P* value	
	AGB	RGB	HYB	AGB vs. RGB	AGB vs. HYB	WT subjects	Carriers of GOF mutation	Carriers of LOF mutation	WT vs. GOF	WT vs. LOF
No. of patients	628	173	71			808	47	17		
Female	81	68	69	<0.001	<0.05	76	70	76	..	..
Age (years)	42 ± 10	44 ± 11	43 ± 9	..	..	43 ± 10	44 ± 11	37 ± 10	..	<0.05
Weight (kg)	119 ± 18	127 ± 19	152 ± 27	<0.001	<0.001	123 ± 21	125 ± 25	132 ± 25	..	..
Height (cm)	166 ± 8	167 ± 10	168 ± 8	..	..	167 ± 9	168 ± 10	165 ± 7	..	..
BMI (kg/m^2)	43 ± 6	46 ± 6	54 ± 10	<0.001	<0.001	44 ± 7	44 ± 7	49 ± 9	..	<0.01
Hypertension	76	90	90	<0.001	<0.01	80	85	76	..	..
Dyslipidemia	65	66	80	..	<0.05	70	77	71	..	..
Type 2 diabetes	23	40	25	<0.001	..	27	28	12	..	..
BED	24	30	48	..	<0.001	26	45	59	<0.01	<0.01
Big eater	54	68	48	<0.001	..	56	57	53	..	..
Snacker	35	40	18	..	<0.01	35	36	18	..	..
Sweets eater	52	60	34	..	<0.01	53	45	47	..	..
Fat eater	59	77	45	<0.001	<0.05	62	60	41	..	..
LOC	27	32	49	..	<0.001	27	68	59	<0.001	<0.01
GOF mutation	5.4	6.4	2.8	..	..	..	..	..	..	..
LOF mutation	1.6	1.7	5.6	..	<0.05	..	..	..	..	..

Data are mean ± SD or %.

were still significantly associated with BED (OR 2.4 [95% CI 1.3–4.4], $P = 5.1 \times 10^{-3}$ for GOF mutations; 2.9 [1.1–7.8], $P = 0.039$ for LOF mutations) or LOC (6.2 [3.3–11.9], $P = 2.4 \times 10^{-8}$ for GOF mutations; 2.8 [1.0–7.7], $P = 0.043$ for LOF mutations). Although the clinical team was blinded to *MC4R* mutation genotypes, HYB was performed as a primary operation significantly more frequently in LOF mutation carriers owing to the patients' greater mean BMI0 at a younger age.

Six years postoperation, the overall complication rate of 7.8% was low, especially for RGB patients (2.7%) but highest in HYB patients (16.4%) (Table 3), which was mainly attributable to the AGB component. We did not find an association between complications and sex, BMI0, or age, whereas weight loss was significantly inversely associated with complications. When we included age, BMI0, sex, operation type, and weight loss in the same logistic regression model, the inverse association between weight loss and complication rates was highly significant (OR 0.89 [95% CI 0.85–0.94], $P = 7.0 \times 10^{-5}$). We did not find associations between metabolic disorders or eating behavior and complications. However, GOF *MC4R* mutation carriers had 2.3 higher odds of major complications than WT subjects, which increased to 2.6 after adjusting for age, BMI0, sex, operation type, and weight loss (2.6 [1.1–6.3], $P = 0.034$).

The reoperation rates were high (35.1% in RGB patients, 38.4% in HYB patients, 40.6% in AGB patients) (Table 3) owing to our strict indications. We did not find associations between reoperation rates and age, sex, or operation type, although patients with higher BMI0 had significantly higher reoperation rates. Patients with BED and LOC also had higher reoperation rates, even after adjusting for age, sex, BMI0, and operation type (OR 1.4 [95% CI 1.0–1.9], $P = 0.026$ for BED; 1.4 [1.1–2.0], $P = 0.016$ for LOC). In contrast, snacking and sweets eating were associated with lower risk of reoperation, even after adjusting for age, sex, BMI0, and operation type (0.7 [0.5–0.9], $P = 0.036$ for snacking; 0.7 [0.5–0.9], $P = 0.010$ for sweets eating). The risk of reoperation was significantly higher in functional *MC4R* mutation carriers, especially the GOF *MC4R* mutation, even after adjusting for age, sex, BMI0, operation type,

Table 3—Effect of preoperative characterization, eating behavior, operation, and *MC4R* mutations on complications, reoperations, and BMI loss in 872 bariatric surgery patients followed ≥ 6 years

	Complications	OR (95% CI)	*P* value*	Reoperations	OR (95% CI)	*P* value*	BMI loss (kg/m^2)†	Effect ± SD	*P* value‡
Sex									
Male	18 (9.7)	..	..	73 (36.9)	..	..	12 (9–15)	0.11 ± 0.05	0.021
Female	49 (7.5)			270 (40.1)			12 (9–16)		
BMI0	NA	..	..	NA	1.03 (1.00–1.05)	6.9×10^{-3}	NA	0.04 ± 0.003	1.7×10^{-52}
Age0	NA	..	..	NA	..	..	NA	−0.004 ± 0.002	0.021
Operation									
AGB	51 (8.3)			255 (40.6)			11 (8–15)		
RGB (vs. AGB)	4 (2.7)	0.3 (0.1–0.9)	0.023	60 (35.1)	..	..	14 (10–18)	0.26 ± 0.05	1.1×10^{-7}
HYB (vs. AGB)	12 (16.4)	2.2 (1.1–4.3)	0.026	28 (38.4)	..	..	19 (15–24)	0.63 ± 0.07	2.4×10^{-17}
BMI loss	NA	0.94 (0.89–0.94)	7.5×10^{-3}	NA	..	..	NA	NA	NA
Complication									
No	NA	NA	NA	299 (38.8)	..	..	12 (9–16)	−0.33 ± 0.076	1.6×10^{-5}
Yes	NA	NA	NA	29 (43.3)			11 (5–15)		
Reoperation									
No	38 (7.5)	..	..	NA	NA	NA	12 (9–16)	..	..
Yes	29 (8.8)			NA	NA	NA	13 (9–17)		
Hypertension									
No	10 (6.0)	..	..	59 (34.3)	..	..	11 (8–15)	0.10 ± 0.05	0.048
Yes	57 (8.5)			284 (40.6)			13 (9–16)		
Dyslipidemia									
No	16 (5.7)	..	..	117 (40.2)	..	..	12 (7–16)	..	..
Yes	51 (9.2)			226 (38.9)			12 (9–16)		
Type 2 diabetes									
No	48 (7.8)		..	253 (39.7)	..	..	12 (9–16)	..	..
Yes	19 (8.4)			90 (38.3)			13 (10–17)		
BED									
No	46 (7.7)	..	..	230 (36.7)	1.4 (1.1–2.0)	0.011	12 (9–16)	..	..
Yes	21 (8.9)			113 (46.1)			13 (9–17)		
Big eater									
No	25 (6.7)	..	..	163 (42.8)	..	..	12 (9–16)	..	..
Yes	42 (9.0)			180 (36.7)			12 (9–16)		
Snacker									
No	47 (8.6)	..	..	240 (42.0)	0.7 (0.5–1.0)	0.025	12 (9–16)	..	..
Yes	20 (6.9)			103 (34.2)			12 (9–16)		
Sweets eater									
No	37 (9.2)	..	..	183 (43.8)	0.7 (0.5–0.9)	0.010	12 (9–16)	..	..
Yes	30 (6.9)			160 (35.2)			12 (9–16)		
Fat eater									
No	25 (7.6)	..	..	131 (39.1)	..	..	12 (9–16)	..	..
Yes	42 (8.3)			212 (39.5)			12 (9–16)		

Continued on p. 6

Table 3—Continued

	Complications	OR (95% CI)	*P* value*	Reoperations	OR (95% CI)	*P* value*	BMI loss (kg/m^2)†	Effect ± SD	*P* value‡
LOC									
No	45 (7.7)	..	..	223 (36.4)	1.5 (1.1–2.0)	7.4×10^{-3}	12 (9–16)	..	..
Yes	22 (8.8)			120 (46.2)			13 (9–17)		
LOF mutation									
WT	64 (7.8)	..	..	335 (39.2)	..	..	12 (9–16)	..	..
Yes	3 (17.6)			8 (47.1)			14 (11–15)		
GOF mutation									
WT	60 (7.6)	2.3 (1.0–5.4)	0.05	314 (38.1)	2.6 (1.4–4.8)	1.6×10^{-3}	12 (9–16)	..	..
Yes	7 (15.6)			29 (61.7)			13 (9–16)		

Data are *n* (%) unless otherwise indicated. Age0, baseline age; NA, not applicable. *According to unadjusted logistic regression model. †Data are median (25th–75th percentile). ‡According to unadjusted linear regression model where ΔBMI was logarithmically transformed before statistical analyses.

and eating behavior (2.9 [1.4–5.7], $P = 2.9 \times 10^{-3}$). Finally, we used the AUC to assess the utility of sequencing *MC4R* and studying eating behavior beyond the information provided by operation type, BMI0, age, and sex to predict reoperation (Fig. 1*A*–*C*). Including genotype and eating behavior significantly improved the AUC from 0.58 (95% CI 0.55–0.62) to 0.63 [0.59–0.66], $P = 0.017$) (Fig. 1*A*), especially in men (from 0.53 [0.45–0.61] to 0.68 [0.60–0.76], $P = 4.9 \times 10^{-3}$) (Fig. 1*B*).

Postoperative weight loss (i.e., units of BMI decrease) differed slightly between men and women; older patients lost less weight, whereas higher BMI0 was strongly associated with greater weight loss (Table 3). RGB and HYB patients lost significantly more weight than AGB patients, even after adjusting for age, sex, and BMI0 ($P = 5.0 \times 10^{-5}$ for RGB vs. AGB, $P = 2.5 \times 10^{-3}$ for HYB vs. AGB). Neither BED nor any of the four eating types were associated with weight loss, regardless of operation, likely owing to our stringent reoperation policy. Hypertension per se was a predictor of weight loss, although not when adjusting for age, sex, BMI0, and operation type. Furthermore, we found significantly less weight loss in patients with postoperative complications, even after adjusting for age, sex, BMI0, and operation type ($\beta = -0.35 \pm 0.065$, $P = 7.5 \times 10^{-8}$). Of note, functional *MC4R* mutations were not associated with weight loss.

CONCLUSIONS

This is a unique prospective study of a homogeneous, severely obese Swiss population retrospectively sequenced for *MC4R* and followed for a minimum of 6 years (with an exceptional 100% follow-up) after undergoing mechanistically different current laparoscopic operations. We demonstrate that rare functional variants in *MC4R* are associated with eating behavior phenotypes and that both *MC4R* mutations and eating behavior types significantly affect outcomes of the surgical treatment of obesity.

Our baseline phenotyping included measures of eating behavior with distinct sexual dimorphism, which independently correlate with both preoperative and postoperative clinical parameters. The relatively large sample size, although limited by strict exclusion criteria, allowed us to detect clinically relevant associations between retrospectively identified functional *MC4R* variants and outcomes of the different operations, including reoperation and complication rates, but not with weight loss. This is important given the relatively high prevalence of adverse outcomes associated with bariatric surgery independent of weight loss, a second-order phenotype (3).

The seemingly paradoxical phenotypic concordance and similar outcomes of the rare LOF *MC4R* variants and GOF *MC4R* variants in the current study accord with our earlier report that lacked in vitro functional assays (36). MC4R, episodically stimulated by acute stress during mobilization of energy stores, is intrinsically anorexigenic, explaining why *MC4R* haploinsufficiency may cause obesity or chronic hyperphagia with LOC (through abrogated prefrontal cortical signaling) and increased responsiveness to food stimuli (37). *MC4R* deficiency is associated with autonomic nervous system effects, such as lower blood pressure and reduced sympathoexcitability (38,39). Thus, enhanced excitability in GOF mutation carriers with increased sympathoadrenal tone may explain the abnormal behavior phenotypes described here, as in stress-induced hyperphagia, as well as the phenotypic similarity with LOF mutation carriers after surgery. Alternatively, GOF of *MC4R* could somewhat reduce appetite, prompting us to speculate that relatively increased α-melanocyte–stimulating hormone signaling might induce physiologic counterregulatory overdrive inhibition or downregulation, mitigating adverse effects of excess signaling with resultant behavior abnormalities similar to those directly attributable to LOF mutations (40,41). We did find inverse correlations between BED or LOC and quantitative/qualitative eating patterns, showing dissociation between impulsive versus deliberate satiety/preference behaviors. In line with the current data, the specific *MC4R* p.V103I GOF mutation was shown to be associated with increased energy and carbohydrate intake in general and in severely obese populations (42).

The eating behavior associated with *MC4R* mutations in the current study is predominantly disordered, as in BED and LOC, and in contrast to others' findings

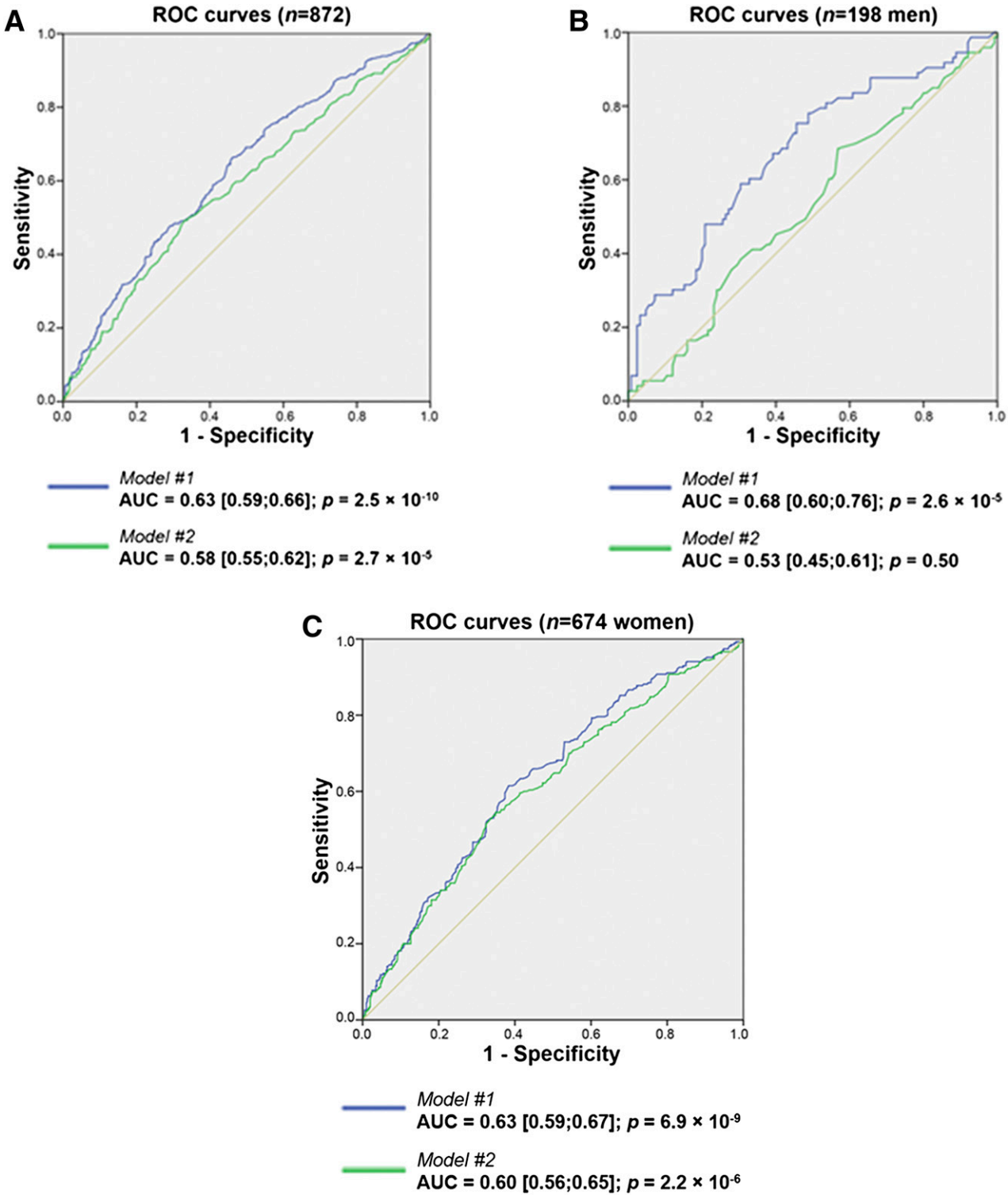

Figure 1—ROC curves for modeling reoperations. AUC (95% CI) reported for each curve, corresponding to models with (model #1) and without (model #2) the inclusion of *MC4R* genotype and eating behavior (BED, big eater, snacker, sweets eater, and fat eater) as predictors, in addition to operation types, sex, BMI0, and age in all participants (*A*), men (*B*), and women (*C*). *P* values show the significance of the tests according to the reference AUC (0.50).

(30,43), exhibited prevalently in both LOF and GOF variants without sex differences. LOF carriers are younger with higher BMI compared with WT subjects, as are patients with BED compared with those without BED. A pilot imaging study of patients with *MC4R* deficiency demonstrated greater responses to visual food cues (37), and other studies showed that women are much more responsive than men (44). *MC4R* variants, eating types, and sex, with increased food-cue

responsiveness, each similarly adversely affected outcomes of the gastric restrictive band operations.

This complex study had several limitations. The Swiss population lacks ethnic diversity, limiting generalization of the findings, and the universal healthcare system in Switzerland might not be applicable to other systems that impose socioeconomic limitations not present here. For consistency, we focused on patients with 6 years of follow-up. Additional follow-up of 7–9 years in 612 patients exhibited similar trends for reoperations over the very long term, with lower reoperation rates and greater sustained weight loss after RYB compared with AGB (data not shown). Patient selection reflected a degree of surgeon bias consistent with real-life medical practice and was mitigated by the relatively small group of surgeons and the consolidating role of one obesity expert and associate without conflicts of interest, such as industry ties or surgical fees, who followed all patients. Again, we emphasize that all genotyping was retrospective and blinded. Owing to the rarity of the functional *MC4R* variants, there were too few male carriers to achieve statistical significance. Nevertheless, the sexual dimorphism of comorbidities, more prevalent in men, is consistent with the literature, as are the eating types influencing the study outcomes. Another limitation is the use of only one in vitro test for the assessment of functional effect of *MC4R* mutation. Indeed, MC4R is a G-protein–coupled receptor that can be linked to several downstream signaling pathways (45). Finally, we did not perform corrections for multiple testing, which might have led to false-positive results, emphasizing a need for further confirmation in a larger phenotypically well-characterized patient population.

To conclude, we established in a European, severely obese population significant sex-specific differences in eating behaviors and differences in rare functional mutations of the *MC4R* gene associated with 6-year outcomes of mechanistically different gastrointestinal bariatric operations consistent with current understanding (46). Careful preoperative studies of eating behavior and *MC4R* screening to identify aggressive overeaters may achieve substantial improvements in outcomes of bariatric operations by selective allocation to bypass or banding.

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