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ORIGINAL CONTRIBUTIONS

Genetic Determinants of Weight Loss After Bariatric Surgery

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Abstract

Background The weight loss after bariatric surgery shows considerable individual variation. Twin studies of response to dietary interventions and studies of bariatric surgery patients suggest that genetic differences may play a role. This study aimed to examine the effect of three genetic risk scores on the inter-individual variation in excess body mass index loss (EBMIL) after Roux-en-Y gastric bypass. Furthermore, we searched among known adiposity-related single nucleotide polymorphisms (SNPs) for genetic determinants of the inter-individual variation in EBMIL.

Methods Patients with morbid obesity underwent Roux-en-Y gastric bypass and were genotyped ($n = 577$). Two genetic risk scores for weight loss after bariatric surgery and a genetic risk score for body mass index were calculated. Associations between the genetic risk scores and EBMIL were evaluated. Lasso regression was performed on 126 SNPs known to be associated with adiposity.

Results The average EBMIL was 76.9% (range 21.7–149.2%). EBMIL was 81.1% (SD 20.6) and 73.9% (SD 21.7) in the high and low tertile groups of a genetic risk score for weight loss. Patients with a low genetic risk score for body mass index (in the lowest 5% percentile) had an EBMIL of 68.8% (SD 20.6, $p = 0.018$). Thirteen adiposity-related SNPs were identified to associate with EBMIL through lasso regression.

Discussion A genetic risk score was associated with EBMIL after bariatric surgery, but may not yet be applicable to clinical practice. Patients genetically predisposed to low body mass index had lower weight loss after bariatric surgery.

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Keywords Genetic risk scores · Weight loss · Genetics · Gastric bypass · Bariatric surgery

Introduction

Bariatric surgery is the most effective treatment of morbid obesity with weight loss around 40 kg, improvement in metabolic health, and reduced mortality [1–3]. The responses to bariatric surgery are likely partly heritable traits [4, 5]. A few studies have described specific genetic determinants of the large individual variation in weight loss after bariatric surgery [5–10]. Some of the known genetic determinants of adiposity in populations [11, 12] might also be determinants of the individual variation in surgery-induced weight loss.

Genetic risk scores for adiposity traits are often calculated as the sum of risk alleles at several genomic loci. Genetic risk scores for body mass index (BMI) and excess BMI loss (EBMIL) after bariatric surgery have been created based on single nucleotide polymorphisms (SNPs) in loci identified in large genome-wide association studies (GWAS) [6, 11, 13].

General genetic risk scores for BMI in populations were not associated with EBMIL after surgery in a study from 2014 [13]. In a study by Bandstein et al. from 2016, known adiposity-related SNPs [14, 15] were analyzed in 238 patients operated with Roux-en-Y gastric bypass [6]. The authors used a random forest method to create two genetic risk scores for weight loss after bariatric surgery (GRS-Bandstein$_{wBMI}$ and GRS-Bandstein$_{wWHR}$) based on some of these SNPs.

In 2013, two GWASs for weight loss after bariatric surgery involving 1143 and 1018 individuals reported the SNPs rs728996 (*PKHD1)* and rs17702901 (*ST8SIA2*), respectively, to be strongly associated with surgery-induced weight loss [7, 9]. Concerning genetic determinants of adiposity in the general population, the list of known GWAS hits has increased rapidly [16]. Meta-analyses from 2015 reported 77 BMI susceptibility SNPs and 49 waist-to-hip-ratio-related SNPs in Europeans [11, 12].

This study aimed to examine the effect of genetic risk scores on the inter-individual variation in EBMIL after Roux-en-Y gastric bypass. Furthermore, to improve the basis for a genetic risk score, we searched among known adiposity SNPs for additional genetic determinants of the inter-individual variation in EBMIL following Roux-en-Y gastric bypass, using lasso regression.

Methods

Study Design and Setting

Between June 2009 and April 2013, adult patients with morbid obesity previously referred to a public obesity center at Hvidovre Hospital, Capital Region of Denmark, were invited to participate. Information was collected at visits to Hvidovre Hospital before and 2 years after Roux-en-Y gastric bypass surgery. Between December 2007 and November 2009, adult patients referred to the private Hamlet Hospital, Søborg, Capital Region of Denmark, were invited to participate. At Hamlet Hospital, information was collected at visits to the hospital before and 3 years after Roux-en-Y gastric bypass surgery. The study visits included anthropometric evaluation and retrieval of blood samples.

Participants

Patients with morbid obesity (BMI > 50 kg/m^2 or BMI > 35 kg/m^2 with obesity-related complications) opting for bariatric surgery were included. In patients without complications of obesity, BMI > 50 kg/m^2 was the indication for bariatric surgery in Denmark in this time period, in contrast to the limit of 40 kg/m^2 used in many other countries [17].

Intervention

All included patients underwent laparoscopic Roux-en-Y gastric bypass surgery. The surgery was done with laparascopic Roux-en-Y gastric bypass, with a 25 ml gastric pouch, a 75-cm-long biliopancreatic limb, and a Roux limb of 100 cm [18].

Variables

Anthropometrics

Weight and height were measured, and BMI was calculated as the weight (kg) divided by the height (m) squared (kg/m^2) both at the first visit to the obesity center (initial BMI) and at the clinical control after bariatric surgery presumed to be the time point with nadir weight (nadir BMI) [18]. A BMI > 25 kg/m^2 was considered as excess, and the EBMIL was calculated as (initial BMI − nadir BMI)/(initial BMI − 25 kg/m^2). Excess weight loss was calculated as (initial weight − nadir weight)/(initial weight − 25 × height^2) and %weight loss was calculated as (initial weight − nadir weight)/(initial weight).

Genotyping

Blood was withdrawn at each visit after an overnight fast, centrifuged within 1 h, and plasma and serum were frozen to and kept at − 80 °C until analysis. Whole blood samples for DNA analysis were frozen to – 80 °C within 2 h after sampling. DNA was extracted at LGC Genomics (LGC, Middlesex, UK), and samples from all participants at baseline (n = 690) were genotyped by the Illumina HumanCoreExome

Beadchip (Illumina, San Diego, CA) using Illumina's HiScan system at the Novo Nordisk Foundation Center for Basic Metabolic Research in Copenhagen, Denmark. Genotypes were called using the Genotyping module (version 1.9.4) of GenomeStudio software (version 2011.1, Illumina). During quality control, we excluded samples that were duplicates, ethnic outliers, had extreme inbreeding coefficients, mislabeled gender, or a call rate < 95%, leaving 577 individuals in the main analysis. Additional genotypes were imputed using the haplotype reference consortium reference panel, with only genotyped variants that were in Hardy Weinberg equilibrium ($p > 0.05$). The imputation quality was high (proper_info > 0.95) for all imputed variants.

Genetic Risk Score Construction

The GRS-BMI_{77} for BMI was based on 77 SNPs associated with cross-sectional BMI in European populations [11]. The GRS-$Bandstein_{wWHR}$ and GRS-$Bandstein_{wBMI}$ for EBMIL were based on 3 and 7 SNPs previously associated with EBMIL after bariatric surgery [6].

We constructed the weighted GRS-BMI_{77} by summing the number of BMI-increasing alleles weighted by the effect size of the variants reported by Locke et al. (Supplementary Table 1) [11]. For the GRS-$Bandstein_{wWHR}$ and GRS-$Bandstein_{wBMI}$, genotypes were coded according to the number of alleles associated with EBMIL after bariatric surgery, as reported by Bandstein et al. [6] (Supplementary Tables 2 and 3). Four of the loci included in the GRS-$Bandstein_{wBMI}$ were also part of the GRS-BMI_{77} (Supplementary Table 1). All genotypes were retrieved from the imputed dataset, and genetic risk scores were calculated based on genotype dosage information. We also created a non-weighted GRS_{LASSO} based on SNPs identified in lasso regression in our material. A short description of the four genetic risk scores is given in Table 1.

Statistical Analysis

Data are presented as mean (standard deviation), median (range), or proportion (percentage). GRS-BMI_{77}, GRS-$Bandstein_{wWHR}$, GRS-$Bandstein_{wBMI}$, and GRS_{LASSO} were used as continuous variables in multiple linear regression analyses with EBMIL as the dependent variable, adjusted for age, sex, recruitment center, and baseline BMI. The EBMILs of individuals with GRS-BMI_{77} at the highest and lowest 5% of the distribution (GRS-BMI_{77} > 82.1 weighted BMI-increasing alleles and GRS-BMI_{77} < 64.4 weighted BMI-increasing alleles) were compared with the EBMIL of the rest of the cohort using the Mann-Whitney *U* tests.

For the SNPs, rs728996 and rs17702901 multiple linear regressions with %weight loss and excess weight loss, respectively, as the dependent variables were performed. We chose these phenotypes in this analysis because they were the ones investigated in the original studies of these SNPs [7, 9]. Subsequently, meta-analysis based on the direction of effect and *p* value observed in each study, with weights proportional to the square-root of the sample size for each study, was done in METAL software computing *z*-statistics, summarizing the magnitude and the direction of effect relative to the reference allele [19].

In order to identify new potential genetic determinants of EBMIL, a lasso regression was performed on 126 imputed SNPs known to be associated with BMI or waist-to-hip ratio [11, 12] with EBMIL as the dependent variable, adjusted for age, sex, recruitment center, and baseline BMI. Lasso regression enabled us to identify an additional set of SNPs which we did not have the statistical power to identify when applying usual multiple-testing correction. The size of the set was determined through loss-minimization in a tenfold cross-validation procedure. Because of small sample size and the risk of overfitting to the training data, we stopped the procedure at one loss standard deviation above the minimal loss. By applying this approach, we attempted to find a

Table 1 Genetic risk scores

Genetic risk score	Description	Reference
GRS-BMI_{77}	Genetic risk score for BMI based on SNPs associated with BMI in European populations	Locke et al. 2015 [11]
GRS-$Bandstein_{wWHR}$	Genetic risk score for surgical weight loss created by Bandstein et al. based on known BMI SNPs associated with EBMIL.	Bandstein et al. 2016 [6]
GRS-$Bandstein_{wBMI}$	Genetic risk score for surgical weight loss created by Bandstein et al. based on known WHR SNPs associated with EBMIL.	Bandstein et al. 2016 [6]
GRS_{LASSO}	Genetic risk score for surgical weight loss proposed in this article, based on the genetic determinants for surgical weight loss that were identified in lasso regression in our material	

BMI, body mass index; *WHR*, waist-to-hip-ratio; *EBMIL*, excess BMI loss; *SNP*, single nucleotide polymorphisms

Table 2 Demographics, clinical characteristics, and genetic risk scores

Included patients, *n*	577
Sex, *n* (% cohort)	
Female	429 (74.4%)
Male	148 (25.6%)
Age (years)	45.3 (10.3)
Initial BMI (kg/m^2)	44.4 (5.2)
Nadir BMI (kg/m^2)	29.9 (4.9)
Change in BMI (kg/m^2)	14.5 (4.4)
Excess BMI before surgery (kg/m^2)	19.4 (5.2)
Excess BMI after surgery (kg/m^2)	4.9 (4.9)
Excess BMI loss (EBMIL) (%)	76.9 (21.8)
GRS-BMI$_{77}$ (number of weighted BMI-increasing alleles)	72.5 (5.3)
GRS-Bandstein$_{wBMI}$ (number of weighted EBMIL-increasing alleles)	7.1 (1.8)
GRS-Bandstein$_{wWHR}$ (number of weighted EBMIL-increasing alleles)	2.9 (1.1)
GRS$_{LASSO}$ (number of EBMIL-increasing alleles)	13.6 (2.3)

BMI, body mass index; *GRS*, genetic risk score; *EBMIL*, excess BMI loss. The results are given as the number (proportion in percent) for categorical variables, mean (standard deviation) for continuous variables

small set of SNPs that provided the best possible prediction on unseen data. This approach has the additional effect of producing only independent signals. This lasso regression identified 13 SNPs which subsequently were evaluated individually with linear regression with EBMIL as the dependent variable, adjusted for age, gender, recruitment center, and baseline BMI.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Scientific Ethics Committee of the Capital Region, Denmark, protocol number HD2009-78. Informed consent was obtained from all individual participants included in the study.

Results

A total of 577 patients (26% males) with a mean BMI of 44.4 kg/m^2 (SD 5.2) and mean age 45.3 years (SD 10.3) were included. The average EBMIL was 76.9% (range 21.7–149.2%) (Table 2). GRS-Bandstein$_{wWHR}$ associated with EBMIL (B = 1.48% EBMIL per weight loss–associated allele (95% confidence interval, 0.01% to 2.95%), p = 0.048) (Table 3). Patients in the GRS-Bandstein$_{wWHR}$ tertile with a high expected weight loss had an EBMIL of 81.1% (SD 20.6), while patients in the GRS-Bandstein$_{wWHR}$ tertile with a low expected weight loss had an EBMIL of 73.9% (SD 21.7, p = 0.003) (Table 4).

In the tails of the distribution of GRS-BMI$_{77}$, we found that the 27 patients with a GRS-BMI$_{77}$ value above 82.1 had an EBMIL of 77.0% (SD 19.9, p = 0.25) while the 26 patients

Table 3 Genetic risk scores as determinants of EBMIL after bariatric surgery

	Uncorrected		Corrected (sex, age, and center)		Final corrected (sex, age, center, and baseline BMI)	
	B (95% CI)	*p* value	*B* (95% CI)	*p* value	*B* (95% CI)	*p* value
Sex (male)	− 10.5 (− 14.5 to − 6.5)	< 0.001				
Age	− 0.36 (− 0.53 to − 0.19)	< 0.001				
Center	− 0.48 (− 4.13 to 3.18)	0.80				
Initial BMI	− 1.66 (− 1.97 to − 1.34)	< 0.001				
GRS-BMI$_{77}$	0.15 (− 0.19 to 0.48)	0.40	0.05 (− 0.27 to 0.38)	0.75	0.00 (− 0.30 to 0.30)	1.00
GRS-Bandstein$_{wBMI}$	− 0.15 (− 1.12 to 0.85)	0.78	− 0.01 (− 0.97 to 0.94)	0.98	− 0.20 (− 1.08 to 0.68)	0.66
GRS-Bandstein$_{wWHR}$	2.22 (0.57 to 3.87)	0.008	1.89 (0.28 to 3.48)	0.021	1.48 (0.01 to 2.95)	0.048
GRS$_{LASSO}$	2.40 (1.64 to 3.15)		2.55 (1.82 to 3.27)		2.28 (1.61 to 2.95)	

Analyses with linear regression. In the column "Corrected," gender, age, and inclusion center are included as covariates. In the column "Final corrected," sex, age, inclusion center, and baseline BMI are included as covariates. *EBMIL*, excess BMI loss; *BMI*, body mass index; *CI*, confidence interval.

Table 4 Characteristics, stratified by tertiles of GRS-Bandstein$_{wWHR}$

	Low GRS-Bandstein$_{wWHR}$	Middle GRS-Bandstein$_{wWHR}$	High GRS-Bandstein$_{wWHR}$	*p* values
Male/female	56/192 (29.2%)	50/186 (26.9%)	41/197 (20.8%)	0.15*
Age (years)	47.0 (10.5)	44.0 (10.2)	45.6 (9.9)	0.07
Initial weight (kg)	131.4 (21.1)	130.3 (22.0)	126.9 (20.3)	0.04
Initial BMI (kg/m^2)	44.7 (5.1)	44.7 (5.3)	43.7 (5.1)	0.12
Nadir BMI (kg/m^2)	30.5 (4.8)	30.3 (5.1)	29.0 (4.6)	0.004
Excess BMI loss (%)	73.9 (21.7)	75.5 (22.6)	81.1 (20.6)	0.003
Weight, post-surgery	92.0 (19.9)	88.8 (20.2)	85.8 (17.8)	0.006

Data are presented as mean (standard deviation) or frequency (percentage). Statistical test with chi-squared test (marked with *) or analysis of variance. The group with low GRS-Bandstein$_{wWHR}$ includes patients with 0 to 2.45 imputed risk alleles. The group with middle GRS-Bandstein$_{wWHR}$ includes patients with 2.46 to 3.19 imputed risk alleles. The group with high Bandstein$_{wWHR}$ includes patients with 3.20 to 6 imputed risk alleles. *BMI*, body mass index; *GRS*, genetic risk scores

with a GRS-BMI$_{77}$ value below 64.4 had an EBMIL of 68.8% (SE 20.6, $p = 0.018$). GRS-Bandstein$_{wBMI}$ was not associated with EBMIL (Table 3).

The risk alleles of rs728996 and rs17702901 displayed associations with EBMIL that were directionally consistent with the original findings (Table 5) [5, 7]. Meta-analysis of the present data and the originally reported data showed that rs17702901 is significantly associated with %weight loss (z-score = − 4.73, $p = 2.3 \times 10^{-6}$) and that rs728996 is significantly associated with excess weight loss (z-score = − 4.68, $p = 2.9 \times 10^{-6}$).

Thirteen adiposity-related alleles, seven BMI-related and six related to waist-to-hip ratio, were found to be associated with EBMIL in a lasso regression (Table 5). The GRS$_{LASSO}$ based on SNPs identified in the lasso regression is associated with EBMIL ($B = 2.28\%$ EBMIL per weight loss–associated allele (95% confidence interval, 1.61% to 2.95%)) (Table 3).

Table 5 Association between single SNPs of interest and EBMIL in our cohort

	Related gene	Allele increasing EBMIL	Uncorrected		*p* values	Corrected	*p* values
			B (95% CI)			*B* (95% CI)	
Identified in earlier GWASs							
rs728996	*PKHD1*	C		1.41 (− 1.22 to 4.05)	0.29	1.48 (− 0.87 to 3.82)	0.22
rs17702901	*ST8SIA2/SLCO3A1*	G		6.80 (− 0.12 to 13.7)	0.05	3.21 (− 2.97 to 9.38)	0.31
Identified in lasso regression, BMI-related			Allele increasing BMI				
rs12885454	*PRKD1*	C	C	1.53 (− 1.18 to 4.24)	0.27	1.45 (− 0.96 to 3.85)	0.24
rs17001654	*NUP54/SCARB2*	G	G	5.15 (1.49 to 8.82)	0.006	4.46 (1.18 to 7.73)	0.008
rs3849570	*GBE1*	A	A	1.79 (− 0.81 to 4.38)	0.18	1.32 (− 1.00 to 3.64)	0.26
rs657452	*AGBL4*	G	A	2.43 (− 0.24 to 5.10)	0.08	2.75 (0.37 to 5.12)	0.02
rs7138803	*BCDIN3D*	G	A	1.80 (− 0.83 to 4.42)	0.18	2.12 (− 0.23 to 4.45)	0.08
rs758747	*NLRC3*	C	T	2.78 (− 0.50 to 6.06)	0.10	1.49 (− 1.44 to 4.42)	0.32
rs7903146	*TCF7L2*	T*	C	3.08 (0.21 to 5.94)	0.04	3.05 (0.51 to 5.59)	0.02
Identified in lasso regression, WHRadjBMI-related			Allele increasing WHRadjBMI				
rs12454712	*BCL2*	T	T	2.79 (− 0.50 to 6.09)	0.10	2.30 (− 0.63 to 5.23)	0.12
rs1385167	*MEIS1*	G	G	2.84 (− 1.02 to 6.71)	0.15	3.14 (− 0.28 to 6.57)	0.07
rs1936805	*RSPO3*	C	T	2.47 (− 0.08 to 5.02)	0.058	2.92 (0.65 to 5.19)	0.012
rs224333	*GDF5*	G	G	3.31 (0.55 to 6.07)	0.019	2.67 (0.21 to 5.14)	0.034
rs4765219	*CCDC92*	A	C	2.03 (− 0.63 to 4.69)	0.13	1.76 (− 0.61 to 4.11)	0.15
rs714515	*DNM3-PIGC*	A	G	2.13 (− 0.42 to 4.65)	0.10	1.90 (− 0.07 to 4.43)	0.06

Analysis with linear regression. In the column "Corrected," sex, age, inclusion center, and baseline BMI are included as covariates in addition to the variable written at the start of the row. *SNP*, single nucleotide polymorphism; *EBMIL*, excess BMI loss; *CI*, confidence interval; *GWAS*, genome-wide association study; *BMI*, body mass index; *WHRadjBMI*, waist-to-hip ratio adjusted for body mass index

Discussion

A genetic risk score for surgical weight loss, GRS-Bandstein$_{wWHR}$, was associated with EBMIL after Roux-en-Y gastric bypass. The patients in the highest tertile of the genetic risk score lost 1.7 kg more weight than the patients in the lowest tertile.

Whether the genetic risk of obesity also impairs the ability to lose body weight is a question of clinical and biological interest, in our study, high genetic risk for obesity did not hinder weight loss after bariatric surgery. Patients with very low genetic risk for obesity (GRS-BMI$_{77}$ in the lowest 5% of the distribution) had significantly less weight loss after bariatric surgery than the other patients. It is possible that patients who genetically are disposed to slimness but nevertheless have become morbidly obese more often have non-genetic, including social or cultural, reasons for their obesity that cannot be reversed with surgery.

GRS-Bandstein$_{wBMI}$, another genetic risk score for weight loss after bariatric surgery, was not associated with EBMIL in our study. The explanation could be a false-positive finding arising from construction limitations of the genetic risk score or alternatively a false-negative finding in our cohort. Obviously, the risk score should be tested again in independent cohorts. Replication of one of two earlier genetic risk scores for surgical weight loss highlights that such risk scores may be reproducible but that cross-validation in independent cohorts is crucial. Risk scores for surgical weight loss that can be consistently reproduced may become clinically useful as part of the future indication for bariatric surgery.

We also evaluated two other SNPs that were strongly associated with surgery-induced weight loss in small-scale GWASs [7, 9]: the C allele of rs728996 (*PKHD1*) and the G allele of rs17702901 (*ST8SIA2/SLCO3A1*). These two SNPs were not significantly associated with EBMIL in single SNP analysis in our cohort, but the associations were directionally consistent with the original findings, and when meta-analyzed with the respective earlier studies, our results arguably strengthened the earlier findings [7, 9].

Based on the suspicion that the biology of the BMI distribution in populations and the biology of weight loss are partly overlapping, we also performed lasso regression on a set of 126 known adiposity susceptibility SNPs. The 77 BMI SNPs and 49 WHRadjBMI SNPs described in the recent meta-analyses [11, 12] were pruned down to a set of 13 SNPs that associated with EBMIL. One of these 13 SNPs (rs7903146) is located in the *TCF7L2* gene and is the common genetic variant with the strongest reported association with type 2 diabetes [20]. SNPs at the *TCF7L2* locus are also related to metabolic traits, including the response to non-surgical weight loss interventions [21, 22]. Interestingly, it was the patients homozygous for the *TCF7L2* diabetes-risk allele who had the largest reported weight loss, a finding that remained significant after correction for diabetes (data not shown). It is notable that SNPs at the *MC4R* and *FTO* loci were not selected in our lasso regression. Polymorphisms at the *MC4R* locus have been associated with excess body weight loss after biliopancreatic diversion with duodenal switch [10]. The *FTO* locus contains the SNPs with the highest effect on BMI distribution in populations [16] but was not associated with response to dietary weight loss interventions [23].

The GRS-Bandstein$_{wWHR}$ may be assessed for possible clinical use as an addition to easily available phenotypic variables (e.g., age, sex, and comorbidities). A genetic risk score based on the 13 SNPs identified in the lasso regression, GRS$_{LASSO}$ (Supplementary Table 4) was as expected strongly associated with EBMIL in our cohort and should also be validated in independent cohorts.

Importantly, the main reason for performing bariatric surgery is not only weight loss per se but also improvement of the patient's future health, remission of type 2 diabetes, and reduction of future morbidity and mortality [1]. A genetic risk score that predicts high weight loss following bariatric surgery does not necessarily indicate successful surgery or a long disease-free life for the patient, and future studies of genetic determinants of response to bariatric surgery should take into account a wider range of phenotypes which are important for overall health status.

Strengths and Limitations

Strengths of this study include a considerably larger number of recruited patients than earlier studies examining genetic risk scores for weight loss following bariatric surgery, as well as standardized surgery, high-quality genotyping, and appropriate genotype imputation methods. The cohort is however much smaller than genetic studies in general, and possible associations with SNPs of importance may be missed in our analysis.

Another strength is that the patients were investigated 2 and 3 years after surgery, at a time point where the greatest weight loss has been obtained (nadir). After Roux-en-Y gastric bypass nadir for weight loss is reached after 1 to 2 years after surgery, and from 2 to 3 years, the weight is stable [24, 25].

The SNP effect size estimates of lasso-selected SNPs reported in Table 4 may be subject to the winners' curse selection bias. We did evaluate four different genetic risk scores without correction for multiple testing, and our

findings should be considered as hypothesis-generating. That GRS_{LASSO} would be associated with EBMIL in this cohort was obvious due to the procedure of construction, the genetic risk score is therefore presented without *p*-values but the presentation of the effect sizes is judged relevant (Table 3). We used EBMIL as the weight loss phenotype to be able to test the reproducibility of earlier genetic risk scores, but EBMIL is not necessarily the best measure of weight loss response to bariatric surgery. One replication does not confirm clinical usefulness of the $GRS\text{-}Bandstein_{wWHR}$, and our findings should be reexamined in larger cohorts. Some of the SNPs evaluated are located inside genes, but most of them are not, and the related genes presented in our tables are not necessarily the mediators between the SNPs and the phenotypes: Much work remains to understand how adiposity-related SNPs are related to the biology of adiposity and to the changes herein during weight loss [16].

Conclusions and Perspectives

We found a 1.7-kg difference in weight loss after Roux-en-Y gastric bypass between patients in the lowest and highest tertile of a genetic risk score for surgical weight loss. Patients who genetically were prone to slimness had less weight loss after bariatric surgery than the rest of the patients.

A new 13 SNP genetic risk score GRS_{LASSO} is proposed and should be validated in independent cohorts. Genetic risk scores may become useful in future clinical practice as one of several sources of information when choosing treatment strategies for patients with morbid obesity.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

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