TITLE PAGE

GENETIC RISK SCORE BASED ON OBESITY-RELATED GENES AND PROGRESSION IN WEIGHT LOSS AFTER BARIATRIC SURGERY: A 60-MONTH FOLLOW-UP STUDY

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Short title: Genetic risk score on obesity and bariatric surgery

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ABSTRACT:

Background: Obesity is a polygenic multifactorial disease. Recent genome-wide association studies have identified several common loci associated with obesity-related phenotypes. Bariatric surgery (BS) is the most effective long-term treatment for severe obesity. Huge variability in BS outcome between patients, suggests a moderating effect of several factors, including the genetic architecture of the patients.

Objective: To examine the role of a Genetic Risk Score (GRS) based on 7 polymorphisms in 5 obesity-candidate genes (*FTO, MC4R, SIRT1, LEP* and *LEPR*) on weight loss after BS.

Setting: University hospital in Spain.

Methods: We evaluated a cohort of 104 patients with severe obesity submitted to BS (Roux-en-Y Gastric Bypass or Sleeve Gastrectomy) followed up over 60 months (loss to follow-up: 19.23%). A GRS was calculated for each patient considering the number of carried risk alleles for the analyzed genes. During the postoperative period, the percentage of excess weight loss (%EWL), total weight loss (%TWL) and change in Body Mass Index (BMI-change) were evaluated. Generalized Estimating Equation (GEE) models were used for the prospective analysis of the variation of these variables in relation to the GRS.

Results: The longitudinal model showed a significant effect of the GRS on the %EWL (P = 1.5e-05), %TWL (P = 3.1e-08) and BMI-change (P = 7.8e-16) along time. Individuals with low GRS seemed to experience better outcomes at 24 and 60 months after surgery than those with a higher GRS.

Conclusion: The use of GRS considering the polygenic nature of obesity seems to be a useful tool to better understand the outcome of patients with obesity after BS.

Keywords: genetic risk score, bariatric surgery, weight loss, obesity, long- term follow-up

Introduction:

Obesity is a complex multifactorial disease that arises from the interaction between genetic, environmental, and behavioral risk factors. Family, twin, and adoption studies provide strong evidence for a large genetic influence on Body Mass Index (BMI), with heritability estimates ranging from 50% to over 90% [(1)].

Monogenic obesity represents a low proportion of the cases in the population (3-5%), it is inherited in a Mendelian pattern, where single rare variants result in severe and early-onset forms of obesity [(2)]. However, the most common form of obesity is multifactorial, where multiple common genetic variants with a small effect contribute to individual's susceptibility to develop obesity [(3)]. In this regard, clinical candidate gene studies have found different variants of minor effect involved in body weight regulation, obesity-related traits, or associated comorbidities [(4)]. Despite their utility in establishing relationships between disease susceptibility and genetic variation, this approach may not provide full resolution for this complex phenotype. Hence, the emergence of Genome-Wide Association Studies (GWAS) has been key in the identification of an unprecedented number of associated loci over the past decade [(5)].

Therapeutic interventions in obesity aim to induce weight loss and the improvement of comorbidities. Bariatric Surgery (BS) is one highly effective weight loss intervention for clinically severe obesity, when lifestyle intervention and pharmacological therapy are proven ineffective. The most common procedures in BS are Roux-en Y Gastric-Bypass (RYGB) and Sleeve Gastrectomy (SG). Both procedures result in comparable reductions in excess body weight (up to 60% at 1 year) [(6)]. However, this improvement seems to reach the peak at 2 years and then remains relatively stable [(7)], indicating that the effects at short and long term are different. Besides that, it has been observed that there is considerable interindividual variation in the surgery outcome. Some of this

heterogeneity could be explained by a variety of complex factors potentially moderating weight loss outcomes such as sex, age, baseline comorbidities, and BMI among others [8]. Previous studies have also reported that individual genetic variability plays a role in the surgery outcome and could explain why some patients are more likely to gain/lose weight after the intervention. Recent analyses of the moderating effect of different candidate genes in the BS outcome have pointed out different trajectories after surgery relying on genetic variability (see for instance [9-11]).

Some of the most classical candidate genes in obesity (fat mass and obesity-associated [*FTO*], melanocortin 4 receptor [*MC4R*], among others) have also been associated with the outcome in BS. A single nucleotide polymorphism (SNP) in *FTO* (rs9939609) has been associated with different outcomes after BS, where patients carrying the A allele lose less weight after 2 years of surgery (10). Furthermore, the same allele has also been correlated with higher BMI in other previous works (11). Regarding *MC4R*, the C allele of the polymorphism rs17782313 has been related to a higher pre-surgical BMI and lesser variation in BMI after the surgery, as well as with a higher BMI in general (12,13).

Other genes such as sirtuin 1 (*SIRT1*), leptin (*LEP*) or leptin receptor (*LEPR*) are in the spotlight of the studies analyzing different outcomes after surgery, due to their important role in the physiopathology of obesity, especially in monogenic forms. Regarding *SIRT1*, two SNPs have been analyzed in the study of obesity. The C allele of rs7069102 has been considered a protective factor for obesity risk (14) and carriers of the A allele for the SNP rs12413112 in *SIRT1* seem to have lower basal energy expenditure associated with reduced BMI (15).

The *LEP* gene has been one of the most reported genes in obesity due to its implication in food intake regulation, with multiple SNPs associated with obesity-

related phenotypes (16). The A allele of rs12535708 has been related to a healthier BMI in men (17). Another important gene for the regulation of food intake is *LEPR*. The risk allele (G) of the rs1137100 variant has been associated with excess weight in individuals with a low daily frequency of consumption of fat and a high consumption of soft drinks, artificial juice and refined cereals (18).

Besides these specific candidate gene studies, recent research has analyzed surgery outcomes in relation to Genetic Risk Scores (GRS) that jointly consider the effect of different genetic variants in order to consider the polygenic nature of obesity, as well as their impact on weight loss after BS (19).

The present study sought to study the individual effects of 7 SNPs located in 5 obesity-candidate genes (*FTO, MC4R, SIRT1, LEP* and *LEPR*), as well as their joint effect when combined in a GRS on weight loss after BS. To this aim we analyzed a cohort of patients with obesity submitted to RYGB or SG and followed at mid and long term (i.e., 24 and 60 months after BS).

Methods:

Participants

The present study consisted of a prospective cohort of 104 patients with severe obesity submitted to BS at the *Hospital Universitari Parc Taulí* (Sabadell, Spain), who were followed up for 60 months. Inclusion criteria were BMI > 35 kg/m^2 with co-morbidities or BMI > 40 kg/m^2, and older than 18 years. Blood samples were taken from all patients at fasting state at baseline (t0) and were immediately processed in the biochemistry laboratory. Serum glucose (mg/dl) was determined by glucose-oxidase method, serum fasting insulin (µIU/ml) by enzyme-linked immunosorbent

assay (ELISA) and plasma glycated hemoglobin (%) by high pressure liquid chromatography (HPLC). Clinicians performed an exhaustive clinical assessment to discard cases of monogenic obesity. Surgical treatment included either RYGB (n = 68) or SG (n = 36). This cohort was evaluated pre-, peri- and post-operatively by a multidisciplinary team (endocrinologists, clinical nurses, surgeons, and dieticians) in consecutive visits according to the local protocol. This period was divided as follows: before surgery, 1, 3, 6, 12, 24, 36, 48 and 60 months after surgery (i.e., t_0, t_{1m}, t_{3m}, t_{6m}, t_{12m}, t_{24m}, t_{36m}, t_{48m} and t_{60m}, respectively).

Anthropometric assessment

Measurements of weight and height were obtained from physical examination during the evaluated period. BMI was calculated according to the formula: weight (Kg) / height $(m)^2$.

To report weight loss, we calculated for all the assessments (from t_0 to t_{60m}): difference of BMI (BMI-change), percentage of excess weight loss (%EWL), and percentage of total weight loss (%TWL). The 104 patients completed all the assessments up to the 24^{th} month and 84 patients up to 60 months (loss to follow-up at t_{60m}: 19.23%).

The BMI-change was calculated as [(BMI at t_0) – (postoperative BMI)]. The %EWL was calculated as [(weight loss / excess weight) $\times$ 100], where weight loss was the weight in kg lost in the period between the surgery and the current assessment, and excess weight was taken as the weight in kg above the weight corresponding to a BMI of 24.9 kg/m^2 (i.e., the upper threshold of the normal weight range). Finally, the %TWL was calculated as [(weight loss / weight at t_0) $\times$ 100].

Ethics

All patients were informed about our study and invited to participate in this prospective cohort. Informed consent was obtained from all the participants. The Institutional Ethics Committee of *Hospital Universitari Parc Taulí* approved the protocol, and all investigations complied with the Declaration of Helsinki (20).

Genotyping and Calculation of the Genetic Risk Score (GRS)

Genomic DNA was extracted from saliva samples and genotyped by *the GoldenGateR Genotyping Assay for VeraCode*. The genetic predisposition was assessed using 7 SNPs in 5 genes included in the *Nutri inCode (NiC)* (Ferrer inCode, Barcelona, Spain). This product includes SNPs previously associated with susceptibility to weight loss, obesity, abdominal obesity, type 2 diabetes (T2D) and cholesterolemia, among others (10,13,14,17,18,21–26).

The 7 selected polymorphisms were: rs1421085 and rs9939609 in *FTO*, rs17782313 in *MC4R*, rs7069102 and rs12413112 in *SIRT1*, rs12535708 in *LEP* and rs1137100 in *LEPR*. The selection was based on their reported and replicated associations with obesity-related phenotypes and therefore, considered to influence weight loss after BS. For each participant, the genotype of each SNP was coded based on the number of risk alleles carried (i.e., 0 for no risk alleles, 1 for heterozygote carriers, and 2 for individuals carrying two risk alleles). Risk alleles were determined based on previous literature (Supplementary Table 1). The maximum score for each SNP was 2 (i.e., presence of 2 risk alleles for the variant). The GRS was created by adding the number of risk alleles in a patient for the seven genetic markers analyzed. Thus, in total, one individual could present a maximum score of 14.

Statistical analysis

All the statistical analyses were performed using RStudio 4.1.0 software (RStudio, Boston, MA) and $P < 0.05$ was considered statistically significant. Hardy-Weinberg

equilibrium was tested by comparing observed and expected genotype frequencies in the sample using a Hardy-Weinberg calculator (available at: https://gene-calc.pl/hardy-weinberg-page).

The comparison of the baseline characteristics of the sample between risk allele carriers of each of the 7 SNPs *versus* non-carriers were analyzed using the Pearson χ^2 test for contingency tables or the nonparametric Mann-Whitney U test for continuous variables. Differences in age between sexes and differences in preoperative BMI between surgeries were tested with the nonparametric Mann-Whitney U test. Pearson correlations were used to test the correlation between the GRS and preoperative BMI, Fasting plasma glucose, Fasting insulin and Glycated hemoglobin at baseline.

Generalized Estimating Equation (GEE) models were run with the *geeglm* function in the *geepack package* (v1.3.9) for the prospective analysis of the variation of BMI-change, %EWL and %TWL in a follow-up of 60 months after BS. The models followed the formula: $y \sim x_1 + \ldots + x_n$, where y is the response variable (i.e., BMI-change, %EWL and %TWL) and $x_1 + \ldots + x_n$ are the explanatory variables. Apart from the genetic explanatory variables, the models also included the following variables: time, age, sex, type of surgery, and presence or absence of T2D. The effect of the genetics was first analyzed with each SNP separately, and then, the joint effect of all 7 SNPs was analyzed by means of a GRS. Those SNPs located in the same gene (i.e., rs1421085 and rs9939609 in *FTO*; and rs7069102 and rs12413112 in *SIRT1*) were analyzed together in the same model. Analyses were run at 24 and 60 months.

Additionally, in order to visualize the longitudinal effect of the GRS on BMI-change, %EWL and %TWL, the GRS variable was dichotomized using a median-split method of the feasible range of the GRS (i.e., the value of 7) as a cut point to generate two

groups: patients with high GRS and patients with low GRS. From the 104 individuals of our sample, 64 had a high GRS (GRS ≥ 7) and 40 had a low GRS (GRS < 7).

Results:

Characteristics of the sample

The sample consisted of 104 patients with obesity, mainly women (77.9%) between 19–61 years. Males and females differed in terms of age (mean = 42.3, SD = 11.6 and mean = 47.7, SD = 9.2, respectively, W = 10816, P < 2.2e-16). All of them underwent either RYGB (n = 68, 65.4%) or SG (n = 36, 34.6%). Significant differences on preoperative BMI were found between surgeries (mean = 45.3, SD = 4.8 and mean = 45.3, SD = 8.7, respectively, W = 10816, P < 2.2e-16), where patients who underwent RYGB presented higher BMI at baseline than patients who underwent SG. A description of the total sample at baseline is shown in Table 1.

No differences were observed between genotype groups (i.e., risk allele carriers *vs* non-carriers) and the baseline characteristics considered (data not shown). Only the *SIRT1* rs7069102 polymorphism (CC *vs* G carriers) seemed to have an effect on Fasting insulin at baseline (W = 581.5; P = 0.0395).

The GRS was calculated for each patient, with scores ranging from 2 to 10. No significant correlation was found between the GRS and preoperative BMI, Fasting plasma glucose, Fasting insulin and Glycated hemoglobin at baseline.

Longitudinal assessment

All the 104 participants completed the 2-year follow-up (loss to follow-up: 0%) and 84 achieved t_{60m} (loss to follow-up: 19.23%). First, we analyzed the independent effect of each variant on BS outcomes then, the jointly effect of all 7 SNPs by means of a GRS. To this aim we applied GEE models and using t_0 as a reference time point, we

analyzed all repeated measurements included after BS (i.e., t_{1m}, t_{3m}, t_{6m}, t_{12m}, t_{24m}, t_{36m}, t_{48m} and t_{60m}). All GEE models included the following variables: age, sex, type of surgery, presence or absence of T2D, and either the genotype of one (or two) of the SNPs or the GRS.

i) Longitudinal analysis with single variants

Regarding the analysis of single variants, all models for the 24-month follow-up revealed an effect of time on the variation of the three variables analyzed (P = 2.2e-16 for BMI-change, %EWL, and %TWL). An effect of age was also found on BMI-change, %EWL and %TWL (P = 3.3e-08, 2.6e-07 and 2.6e-09, respectively). In the same way, the surgical procedure (i.e., RYGB or SG) was statistically significant for %EWL (P = 0.0006). According to these results, younger patients, women, and patients submitted to SG showed a better outcome 24 months after surgery. In relation to the genetic variants, the *LEP* SNP rs12535708 had a significant effect on %EWL and %TWL (P = 0.0373 and 0.0390, respectively). According to these results, the individuals with the AA genotype had better outcome 24 months after BS. The *SIRT1* SNP rs12413112 was significant for the variable BMI-change (P = 0.0240) for which the A carriers presented a larger change in BMI after 24 months, and the *FTO* SNP rs1421085 was significant for the %EWL (P = 0.0375), where the C carriers had a better outcome.

The model for the 60-month follow-up also revealed an effect of time (P = 2.2e-16 for BMI-change, %EWL, and %TWL) and age (P = 3.3e-08 for BMI-change, P = 2.6e-07 for %EWL and P = 2.6e-09 for %TWL) on the variation of all the variables analyzed. In the same way, sex was significant for the same variables (P = 0.0004 for BMI-change, P = 0.0029 for %EWL and P = 1.9e-06 for %TWL) and the surgical method for %EWL (P = 0.0006), as found at short term. In relation to the genetic variants, the

LEP SNP rs12535708 was also significant for the variables %EWL and %TWL (P = 0.0074 and P = 0.0031, respectively), where individuals with the AA genotype had better outcome 60 months after BS. Likewise, the *SIRT1* SNP rs12413112 had an effect on BMI-change (P = 0.0397), for which the A carriers presented a larger change in BMI after 60 months. However, at 60 months no significant effect was found for the *FTO* SNP rs1421085.

i) Longitudinal analysis with the Genetic Risk Score (GRS)

When studying the longitudinal effects of the GRS on BMI-change, %EWL and %TWL 24 months after BS, the model showed a significant effect of the GRS on %EWL (P = 1.5e-05), %TWL (P = 3.1e-08) and BMI-change (P = 7.8e-16). This result was replicated at 60 months on the %EWL (P = 1.5e-05), %TWL (P = 3.1e-08) and BMI-change (P = 7.8e-16). As in the previous models analyzing the independent effect of each SNP, the other variables seemed to have an effect on the outcome of BS, only being not previously reported the significance of T2D (P = 0.0263 for BMI-change, P = 0.0110 for %TWL).

In order to visualize the effect of the GRS on the outcomes of BS over time, we divided the patients in two groups: individuals with a high GRS (GRS ≥ 7; n = 64) and a low GRS (GRS < 7; n = 40) (Figure 1). Although the largest differences in terms of weight loss were observed between the 12^{th} and 24^{th} month, individuals with a low GRS seemed to lose more weight and to have a healthier BMI than individuals with a high GRS at every point of the follow-up. Mean and Standard Error of the Mean (SEM) of the three anthropometric variables at each assessment according to high and low GRS is reported in Supplementary Table 2.

Discussion:

We studied in a sample of patients suffering from severe obesity and submitted to bariatric surgery (BS) the variation of BMI, %EWL and %TWL during a period of 24 and 60 months. Firstly, we explored the influence of genetic variants located in candidate genes previously associated with obesity-related phenotypes on the outcome of BS. Secondly, we investigated the additive effect of the variability of these genes by means of a Genetic Risk Score (GRS) at short and long term (i.e., 24 and 60 months).

Our analyses revealed an effect of time, age and sex on weight loss after BS, where younger patients and women showed a better outcome along time. This result replicates previously published studies by our group and others (27–29). Additionally, our results revealed that patients submitted to SG had a significantly higher %EWL after BS compared to those who underwent RYGB. Although in the previous literature it is not yet clear if one surgery achieves a better outcome than the other, we hypothesize that this effect may be partially influenced by the different inclusion criteria for each surgery. Patients with a higher preoperative BMI (BMI ≥ 40 kg/m^2) are more likely to be submitted to RYGB, whereas those with a lower BMI (BMI = 35 - 39.9 kg/m^2) are usually submitted to SG. Therefore, patients who undergo SG have in average less excess weight before surgery than those who undergo RYGB, which makes achieving a certain %EWL easier for those submitted to SG, since they have to lose less weight.

When we analyzed the independent effect of the 7 polymorphisms in the outcome of BS, we only found significant effects for three of them. At 24 months, the *SIRT1* SNP rs12413112 had an effect on the variable BMI-change, the *FTO* SNP rs1421085 on the variable %EWL, and the *LEP* SNP rs12535708 on the variables %EWL and %TWL. However, it should be noted the small number of patients in the risk allele non-

carriers group for the *LEP* SNP rs12535708 (n = 5). These results were replicated at 60 months only for the *SIRT1* SNP rs12413112 and the *LEP* SNP rs12535708. Given the polygenicity of obesity, it is not surprising that this approach would not yield more significant results. Each genetic variant alone usually has a small effect and it is the sum of multiple of these effects what could impact the outcome (30–32).

Our second approach used a GRS calculated adding the number of risk alleles carried by each patient in the 7 SNPs. According to our results, patients with a higher GRS had a worse outcome (i.e., less weight loss) after BS at short and long term than patients with a lower GRS. Some previous studies that have calculated a GRS related to BS outcomes in a similar way that ours have found some interesting results. Ciudin and colleagues (19) computed a GRS with nine SNPs located in obesity-related genes and found that combining the information provided by clinical variables such as age, type of surgery and presence of diabetes with the information provided by the GRS was key to increase the predictability of the weight loss response after BS (19). In the same line, Katsareli and colleagues (33) found that their GRS had an effect at both 12 and 24 months after BS procedure, suggesting the genetic background could be a possible modulator of the higher/lower weight loss (33). In our sample, the largest differences between patients with high or low GRS were found 12 months after BS. This effect has also been seen in previous studies [(7)]. One year after surgery, all patients started to recover some weight. At long term (60 months), we observed that patients with a high GRS still had a worse outcome compared to patients with a low GRS, although with smaller differences. It is possible that the smoothening of these differences is partly due to the re-gaining of weight that patients experience 24 months after the surgery. Therefore, the significant loss of weight in these first years could be the subjacent reason for the significance observed in all periods. As far as we know,

this is the first study with a 5-year follow-up so we cannot compare these long-term results with previous studies.

The reason for this weight regain 24 months after the surgery in some cases seems to be procedural failures, but most commonly seems to be due to environmental factors such as failing to follow the recommended diet, returning to previous eating habits, maintaining a sedentary lifestyle, experiencing food cravings, among others (34). This is consistent with the multifactorial nature of the trait, in which not only genetic factors but also environmental influences play a role in its susceptibility.

The findings of the present study should be interpreted in light of some limitations. First, the GRS that we used was not weighted by the effect size of each variant. Thus, this GRS assumes every SNP contributes the same, and this may not be accurate. However, knowing that obesity is a complex trait influenced by multiple genes of small effect, this approach leads to more realistic conclusions than individual candidate gene studies. Therefore, the GRS used in the present study only considers the individual genetic effects of some of the influencing SNPs for BS outcomes and not all of them. In this sense, future studies should include more genetic markers with weighted GRS to confirm this effect. Moreover, to fully study the whole picture, environmental factors such as diet and physical activity should also be included in the assessments, since it is clear that these factors would have an important role on the outcome of the surgery. Furthermore, our cohort has a high percentage of females (77.9%) and a slightly higher percentage of patients submitted to RYGB (65.4%) compared to the SG procedure, which could have introduced certain bias in our analyses. It should be appreciated, however, that this cohort was followed up for 60 months after surgery and, to our knowledge, this is one of the first studies where a genetic score is used to study the outcome of BS at such a long period of time.

Conclusion:

There is a large individual variation in weight loss response after BS and substantial weight loss is known to be achieved primarily during the first 12-18 months post-surgery. Despite this, our results showed that patients with a high GRS composed of SNPs associated with obesity-related phenotypes have a worse outcome at short and long term and that there are other factors such as sex, age or the type of BS that should be considered to understand the multi-causality of both the disease and the outcome. The replication of these results in larger samples and with a larger number of genetic markers could be an important achievement to evaluate the prognosis and effectiveness of bariatric interventions, representing a step further in precision medicine.

Disclosures:

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Table 1. *Characteristics of the study subjects at baseline (t_0)*

Baseline (n = 104)	**mean**	**SD**
Age (years)	46.50	10.01
Weight (kg)	119.37	21.16
Body Mass Index (kg/ m^2)	45.32	6.40
Fasting plasma glucose (mg/dl)	111.63	42.81
Fasting insulin (μIU/ml)	23.19	17.71
Glycated hemoglobin (%)	6.29	1.42

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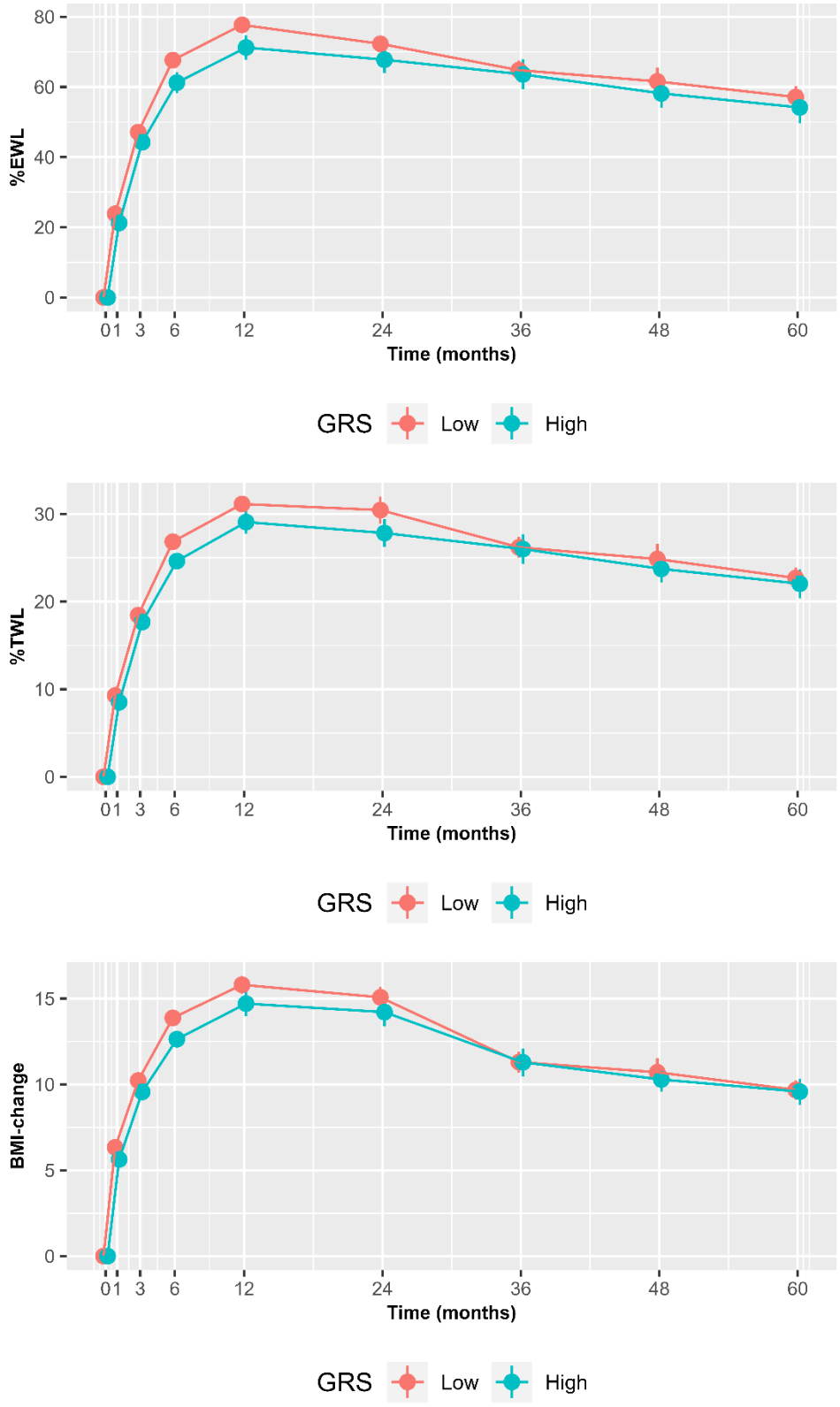
Figure 1. Changes in the variation of body mass index loss (BMI-change), the percentage of excess weight loss (%EWL) and the percentage of total weight loss (%TWL) over time stratified by the GRS (high and low).



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Supplementary Table 1. *Genetic variants included in the calculated Genetic Risk Score*

Gene	SNP	Alleles	Risk allele	Genotype frequency [n (%)]	
MC4R	**rs17782313**	T/C	C	TT TC CC	67 (64.42) 31 (29.81) 6 (5.77)
LEP	**rs12535708**	A/C	C	AA AC CC	5 (4.81) 49 (47.11) 50 (48.08)
LEPR	**rs1137100**	A/G	G	AA AG GG	63 (60.58) 33 (31.73) 8 (7.69)
FTO	**rs1421085**	T/C	C	TT TC CC	25 (24.04) 49 (47.11) 30 (28.85)
	rs9939609	T/A	A	TT TA AA	29 (27.88) 45 (43.27) 30 (28.85)
SIRT1	**rs7069102**	C/G	G	CC CG GG	11 (10.57) 43 (41.35) 50 (48.08)
	rs12413112	G/A	A	GG GA AA	77 (77.04) 27 (25.96) 0 (0)

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Supplementary Table 2. *Mean and Standard Error of the Mean (SEM) of the three anthropometric variables (i.e., %EWL, %TWL and BMI-change) at each assessment according to high and low GRS*

		time	t_0	t_1	t_3	t_6	t_{12}	t_{24}	t_{36}	t_{48}	t_{60}
		n	**104**	**104**	**104**	**104**	**104**	**104**	**91**	**91**	**84**
%EWL	**Low GRS**	**mean**	0	23,84	47,09	67,63	77,68	72,28	64,78	61,57	57,12
		SEM	0	1,47	2,02	2,31	2,17	2,33	2,72	3,88	3,10
	High GRS	**mean**	0	21,23	44,24	61,21	71,23	67,75	63,56	58,15	54,15
		SEM	0	1,16	2,38	2,95	3,43	3,87	4,26	4,00	4,48
%TWL	**Low GRS**	**mean**	0	9,28	18,45	26,84	31,14	30,45	26,19	24,86	22,69
		SEM	0	0,43	0,51	0,63	0,73	1,54	1,19	1,71	1,20
	High GRS	**mean**	0	8,51	17,66	24,62	29,08	27,83	26,00	23,73	22,04
		SEM	0	0,34	0,67	0,90	1,30	1,56	1,69	1,53	1,66
BMI-change	**Low GRS**	**mean**	0	6,33	10,22	13,86	15,79	15,06	11,29	10,70	9,67
		SEM	0	0,29	0,32	0,42	0,52	0,62	0,60	0,81	0,57
	High GRS	**mean**	0	5,63	9,56	12,63	14,70	14,20	11,28	10,28	9,57
		SEM	0	0,21	0,32	0,48	0,73	0,83	0,81	0,70	0,76