IFSO

REVIEW

A Systematic Review of Genetic Correlates of Weight Loss After Bariatric Surgery

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Abstract

This systematic review synthesized research evaluating the relationship between genetic predictors and weight loss after bariatric surgery. Fifty-seven studies were identified that examined single genes or genetic risk scores. Uncoupling protein (*UCP*) rs660339 was associated with excess weight loss after surgery in 4 of 6 studies. The most commonly assessed genes were fat mass and obesity–associated (*FTO*) gene ($n = 10$) and melanocortin-4 receptor *(MC4R)* ($n = 14$). Both were inconsistently related to weight loss. Genetic risk scores predicted weight loss in 6 of 7 studies. This evidence suggests the potential of using genetic variants and genetic risk scores to predict the amount of weight loss anticipated after bariatric surgery and identify patients who may be at risk for suboptimal weight reduction.

Keywords Bariatric surgery · Genetic · Precision medicine · Weight loss

Introduction

Despite the well-established use of bariatric surgery to treat obesity, significant interindividual variability has been noted in short-term and long-term weight loss [1, 2]. Patients generally achieve a maximum weight loss 1–2 years after surgery [3]. On average, patients who have sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) achieve a 25% or greater

Key Points
• *FTO* and *MC4R* are inconsistently related to weight loss after bariatric surgery.
• Genetic risk scores may be useful to predict the amount of weight loss after surgery.
• *UCP* was associated with excess weight loss after surgery in multiple studies.

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reduction of their initial weight within the first year [4]. However, there is a wide interindividual response to the various types of bariatric surgery, particularly during longer-term follow-up (>2 years). For example, in the Longitudinal Assessment of Bariatric Surgery-2 study, there were 6 distinct patterns of weight change identified in response to surgical treatments [2]. Genetic factors may help to explain these interindividual differences.

Family, twin, and adoption studies have demonstrated heritability estimates of 20–90% for body mass index (BMI) [5]. Multiple obesity-predisposing genetic loci have also been identified. For example, the fat mass and obesity–associated (*FTO*) gene has a well-established role in predisposing one to childhood or adult obesity [6]. Hundreds of additional genetic loci have been established in relation to obesity, such as those coding for apolipoprotein receptors (*APOB*) [7]. These genetic loci may interact with obesity treatments and influence weight loss outcomes. Previous reviews have examined the interaction between genomic information and lifestyle interventions [8–12]. However, the literature on genetic factors in relation to weight loss after bariatric surgery has not been well synthesized.

Identifying genetic factors related to weight loss after bariatric surgery may help to guide weight management strategies pre- and post-surgery and to identify and develop novel interventions. The purpose of this systematic review was to provide a narrative synthesis of research on the association

between genetic factors and weight loss heterogeneity in patients who received bariatric surgery.

Methods

Our study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [13]. Articles were identified using the databases PubMed, Embase, Web of Science, PsycInfo, and Cochrane Library. A research librarian was consulted to create the search strategy (Table S1). The reference lists of selected articles were manually searched. Randomized controlled trials, observational reports, and cohort studies were considered for this review. Eligible journal articles were peer reviewed and published in the English language. Studies that measured changes in gene expression, epigenetics, proteomics, or metabolomics were excluded. The literature search was conducted from inception to July 2, 2020.

Data Extraction

We piloted a data abstraction form. Data were extracted on country, sample size, age, BMI, race/ethnicity, sex, and association between the gene and weight loss outcomes.

Quality Analysis

The Q-Genie tool was used to assess study quality [14]. The tool was developed by collating published guidelines and recommendations for genetic association studies, such as STrengthening the REporting of Genetic Association Studies (STREGA) and Strengthening the Reporting of Genetic Risk Prediction Studies (GRIPS). The Q-Genie tool consists of 11 items including the rationale for the study; classification for the genetic variant; sources of bias and confounding factors; test of genetic assumptions (e.g., agreement with the Hardy Weinberg equilibrium); statistical methods and control; and inferences drawn from the results. Each item was scored on a Likert scale from 1 to 7, with 7 indicating the highest score in the category. Studies with control groups and composite scores >45 indicate good-quality studies, those with 36–45 were of moderate quality, and those with ≤35 indicate poor-quality studies.

Results

The literature search yielded a total of 2598 eligible articles and 3 additional studies were found by checking reference lists of relevant studies (Figure 1). After removing duplicates, 1836 articles remained for title and abstract screening. Of these, 1585 were excluded. The remaining 251 articles were screened at full-text level. After full-text review, 194 were excluded. In total, 57 articles met inclusion criteria. All studies were rated as good-quality studies based on the Q-Genie assessment tool.

Demographics

The sample size ranged from 4 to 1443 participants (Table 1). In most studies, the major inclusion criteria for surgery followed standard guidelines for bariatric surgery: BMI ≥40 or ≥35 kg/m^2 with one or more obesity-related comorbidity. The range of average BMIs reported in studies was 35–55 kg/m^2. The participants in the selected studies had a range of average age from 16 to 52 years old. The range of average percent female of a sample was 50–100%.

FTO

Ten studies explored *FTO* in relation to weight loss after bariatric surgery (Table 2). Of these studies, four studies showed an association between *FTO* and improved weight loss, two demonstrated a lesser weight loss, and the rest showed no significant association. Of the four articles that showed improved weight loss, three specifically studied the rs9939609 variant of *FTO* and found an association between 3 and 24 months. However, Rodrigues et al. found that participants with the rs9939609 polymorphism lost less weight at 24–60 months after RYGB [18]. Thus, there was mixed support that differences in weight change based on *FTO* gene variants were associated with bariatric surgery outcomes.

MC4R

Fourteen articles examined the melanocortin-4 receptor (*MC4R*) gene and weight loss after bariatric surgery, and results were mixed (Table 2). Nine of 14 studies found no association between *MC4R* and weight loss. Four studies concluded that variations in the *MC4R* gene were associated with a poorer weight loss outcome. These studies reported outcomes from 3 to 60 months and included patients who underwent various types of bariatric surgeries including SG, RYGB, and GB. BMI at the start of the study ranged from 43 to 51 kg/m^2. On the other hand, Javanrouh et al. found that patients with the rs17773430 variant of *MC4R* experienced a greater reduction in percent excess weight loss (%EWL) up to 12 months after gastric bypass [21]. Mirshahi et al. also reported improved weight loss in patients with the rs5282087 variant in the *MC4R* promoter region [22]. However, this relationship was only significant up to 36 months post-RYGB and was not sustained thereafter at 48 months.

Figure 1 PRISMA diagram of article inclusion
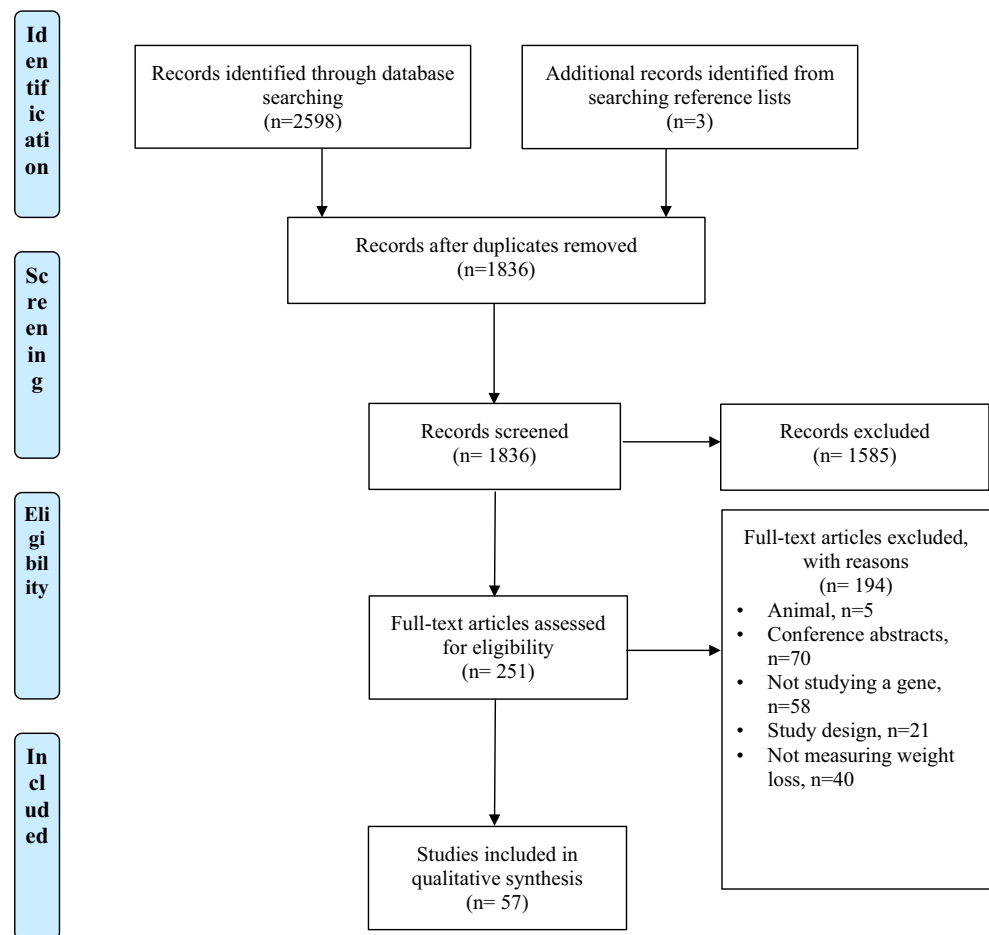
Leptin

Six articles examined the association of either leptin or the leptin receptor genes (*LEP/LEPR*) with weight loss after bariatric surgery (Table 2). Between 12 and 24 months after RYGB, Kops et al. noted that patients with the rs1137101 variant of *LEP223* experienced a greater percent excess weight loss [23]. De Luis et al. also found patients had better weight loss outcomes with a rs1805094 mutation in *LEPR* after BPD [24]. However, the remaining studies did not find an association between genetic variants of leptin and weight loss post-surgery.

Uncoupling Protein

Eight studies explored different variants of the uncoupling protein (*UCP*) gene (Table 2). Four of six studies that examined the rs660339 variant of *UCP2* found that this variant was associated with greater weight loss after bariatric surgery, while two studies found no association with this variant. Of the four articles that highlighted greater weight loss, significant findings occurred between 6 and 12 months after surgery. Liou et al., Chen et al., and Lee et al. measured weight loss after LAGB [16, 25, 26]. Six months after surgery, Liou et al. reported that participants with a

risk genotype of "CT/TT" lost more weight than those without the genotype (-7.5 versus -6 kg/m^2, respectively) [16]. Chen et al. similarly demonstrated a greater weight loss for patients with the risk genotype compared to those with the "CC" genotype, 12.2 versus 8.1 kg/m^2 at 12 months post-surgery and 13.1 versus 9.3 kg/m^2 at 24 months post-surgery, respectively [25]. Nicoletti et al. measured weight loss after RYGB and found improved weight loss with the rs660339 variant [27]. They also found the G866A variant in the *UCP2* gene had a similar, positive association 12 months after RYGB. Finally, 6 months after LAGB, Sesti et al. found that patients with the A866A variant in the promoter region of *UCP2* experienced greater weight loss [28]. The remaining studies did not find an association between variants of the uncoupling protein gene and bariatric surgery outcomes.

Peroxisome Proliferator–Activated Receptor

Five studies explored the association between genetic variations of the peroxisome proliferator–activated receptor (*PPAR*) gene and weight loss after bariatric surgery (Table 2). While Lee et al. found the rs4684846 of *PPAR* to be associated with improved weight loss outcomes 24 months after LAGB, the other four studies revealed there was no association between these two variables.

Table 1 Study characteristics

Title	Country	Sample size	Age (years, mean ± sd or range)	BMI (kg/m², mean ± sd)	Race/ethnicity	% sample female
Bandstein et al. [15]	Switzerland	210	42.8±0.8	45 ± 0.43	NR	72
Liou et al. [16]	Taiwan	520	20–55	35	NR	83
de Luis et al. [17]	Spain	119	42.0±11.8	47.8±6.8	NR	73
Rodrigues et al. [18]	Brazil	146	41.7	53.4	NR	82
Sarzynski et al. [19]	Sweden	1443	37–60	42.2	NR	71
Figueroa-Vega et al. [20]	Mexico	21	38.4±10.0	42.6±6.5	NR	73
Javanrouh et al. [21]	Iran	424	33.8 ± 1.1	45.3	NR	81
Mirshahi et al. [22]	USA	1433	45.8	46.6	White: 99%	80
Kops et al. [23]	Brazil	105	43.2 ± 10.9	48.2 ± 7.2	NR	87
de Luis et al. [24]	Spain	41	42.8 ± 12.9	46.8 ± 6.3	NR	78
Chen et al. [25]	Taiwan	304	32.5 ± 7.8	44.7	NR	62
Lee et al. [26]	Taiwan	74	31.7 ± 9.1	41 ± 7.3	NR	70
Nicoletti et al. [27]	Brazil	150	47.2 ± 10.5	51	NR	80
Sesti et al. [28]	Italy	167	40 ± 10	44.6 ± 6.5	NR	85
di Renzo et al. [29]	Italy	20	42	46.05 ± 8.81	NR	50
di Renzo et al. [30]	Italy	40	NR	44.90 ± 7.81	NR	NR
Vitolo et al. [31]	Italy	79	45 ± 11	48.0 ± 0.7	NR	65
Matzko et al. [32]	USA	657	46.0	48.6	White: 93.3% Black: 2.4% Hispanic: 1.4% Other or unknown: 2.9%	81
Velazquez-Fernandez et al. [33]	USA	249	41.1 ± 11.3	42.5 ± 6.5	Mexican mestizos: 67.5% Other ancestry: 32.5%	64
Hartmann et al. [34]	Brazil	42	43.4 ± 10.1	47.7 ± 5.6	White: 52.4%	88
Peña et al. [35]	Spain	151	46.3 ± 10.0	43.2 ± 6.3	NR	78
Rinella et al. [36]	USA	1143	NR	NR	NR	NR
Ciudin et al. [37]	Spain	96	NR	NR	NR	100
de Toro-Martín et al. [38]	Canada	793	42.4 ± 9.7	50.3 ± 7.2	NR	70
Aasbrenn et al. [39]	Denmark/Norway	577	45.3 ± 10.3	44.4 ± 5.2	NR	74
Katsareli et al. [40]	Greece	47	40.6 ± 11	48 ± 6.9	NR	72
Nicoletti et al. [41]	Brazil	150	47.2 ± 10.5	51.3±7.3	Mixed ethnicity: 100%	80
Käkelä et al. [42]	Finland	163	47.8±8.6	44.9±6.0	NR	63
Scott et al. [43]	England	19	25–54	43–68	NR	NR
Balasar et al. [44]	Turkey	74	19–62	≥40	NR	73
Novais et al. [45]	Brazil	351	20–50	35–75	NR	100
Wang et al. [46]	Taiwan	188	41.13 ± 13.5	40.9 ± 6.5	NR	52
Cooiman et al. [47]	Netherlands	1014	46.2	45.7	NR	65.9
Potoczna et al. [48]	Switzerland	300	42 ± 1	43.5 ± 0.3	NR	77
Resende et al. [49]	Brazil	167	43.6 ± 0.8	51.3 (39.4–82.8)	NR	84.4
Aslan et al. [50]	USA	92	45±10.4	55±8.5	NR	NR
Censani et al. [51]	USA	4	16.5 ± 1.2	54.4 ±8.6	NR	50
Hatoum et al. [52]	USA	928	44.6	50.6	NR	74.8
Moore et al. [53]	USA	1433	NR	NR	NR	79.90
Valette et al. [54]	France	648	42.1	47.3	NR	85
Zechner et al. [55]	USA	1433	45.78	NR	NR	NR
de Luis et al. [56]	Spain	40	42.9 ±13.2	49.7±5.6	NR	77.5
de Luis et al. [57]	Spain	41	42.9 ± 13.2	49.6 ± 5.8	NR	78
Hulsmans et al. [58]	Belgium	21	39 ± 3	44 ± 1	NR	NR
de Luis et al. [59]	Spain	41	42.9 ±10.1	50.6 ± 7.5	NR	78

Table 1 (continued)

Title	Country	Sample size	Age (years, mean ± sd or range)	BMI (kg/m², mean ± sd)	Race/ethnicity	% sample female
Alexandrou et al. [60]	Greece	87	44.3 ± 10.5	50	NR	79
Hatoum et al. [61]	USA	1020	46.2	49.6	NR	72.7
Beisani et al. [62]	Spain	68	49 ± 10	45 ± 7	NR	71
Poitou et al. [63]	France	65	41.3 ± 1.1	50.7 ± 1.2	NR	81
Rasmussen-Torvik et al. [64]	USA	95	47.8 ± 10.9	NR	White: 100%	85
Bandstein et al. [65]	Sweden	251	43±10.7	45.1±6.1	NR	77
de Luis et al. [66]	Spain	67	42.9 ± 13.2	48.9 ± 7.5	NR	76
Leyvraz et al. [67]	Switzerland	30	39 ± 9	44 ± 5	White: 100%	100
Ruiz-Lozano et al. [68]	Spain	252	52 ± 11	46.4 ± 6.0	NR	79
Potoczna et al. [69]	Switzerland	304	42 ± 1	43.9 ± 0.3	NR	81
Goergen et al. [70]	Luxembourg	195	NR	46	NR	83
de Luis et al. [71]	Spain	147	47.0 ± 8.2	47.3 ± 5.2	White: 100%	74

NR, not reported

Other Genes

Several other genes were examined in five or fewer studies (Table 2).

Interleukin-6 Of the four studies reporting findings on interleukin-6 (*IL-6*) gene, two found significant short-term associations. Sesti et al. noted the G174G mutation in the promoter region was associated with greater percent BMI decrease 6 months after LAGB [28]. Di Renzo et al. found those with a G174C to have poorer weight loss outcomes 6 months after LAGB [29, 30].

Ghrelin Three studies examined either the ghrelin gene or ghrelin receptor (*GHRL/GHSR*). Vitolo et al. found the rs696217 variant of *GHRL* was associated with greater percent total weight loss after RYGB at 6, 26, and 52 weeks post-surgery [31]. In a longer-term study, Matzko et al. found the rs490683 variant of *GHSR* to be associated with greater weight loss 30 months after RYGB [32].

Proopiomelanocortin Three articles reported on variations in the proopiomelanocortin (*POMC*) gene. Velázquez-Fernández et al. found the rs1042571 variant to be associated with greater percent excess weight loss after RYGB at 6, 12, 18, and 24 months [33]. The other two studies did not find any association.

FK506-Binding Protein 5 The two studies reporting on the rs1360780 variation of the FK5506-binding protein 5 (*FKBP5*) gene both noted a lower percent excess weight loss after RYGB for individuals who carried the T allele up to 24 months after surgery. In Hartmann et al., the association was significant at the 12–14, 18–20, and 24–26 month time points,

while the association in Peña et al. was significant at the 24-month mark [34, 35].

Estrogen Receptor 1 Significant short-term findings were reported for the rs712221 variant of the estrogen receptor-1 (*ESR1*) gene. Liou et al. found that patients undergoing LAGB or laparoscopic mini-gastric bypass experienced better weight loss 6 months after surgery [16]. Similarly, Velázquez-Fernández et al. found an association between rs712221 and percent excess body weight loss 6 and 12 months after RYGB, with a difference of 10% or more at both timepoints [33].

Genes with no Significant Relationships with Weight Loss Four articles explored adiponectin (*ADIPOQ*), none of which found a significant association between this gene and weight loss (Table 2). These studies ranged in duration from 6 weeks to 6 years with no associations at any of the timepoints. The one article that explored the insulin receptor substrate 1 (*IRS1*) gene did not find an association with weight loss 6 months after bariatric surgery. Two studies explored polymorphisms in the tumor necrosis factor (*TNF*) gene, none of which found a significant association between weight loss and outcomes 1 year and 6 years following bariatric surgery. Three articles reported on variations of the guanine nucleotide–binding protein (*GNBP*) gene. None of the studies had significant findings 6, 12, 18, 24, and 72 months after surgery. Two articles explored the relationship between fatty acid–binding protein-2 (*FABP2*) and weight loss 1 and 2 years after bariatric surgery. Neither study reported a significant association.

Genes Identified in One Study Only We found several genes that were only found in one study but had a significant association with weight loss after bariatric surgery. Serotonin receptor

Table 2 Genetic variants and weight loss after bariatric surgery

FTO (fat mass and obesity associated)		
rs11075986	=	Sarzynski et al. [19]
rs16945088	↑	Sarzynski et al. [19]
	=	Velazquez-Fernandez et al. [33]
rs16952482	=	Sarzynski et al. [19]
rs8050136	=	Velazquez-Fernandez et al. [33]
rs9930506	↓	Figueroa-Vega et al. [20]
rs9939609	↑	Bandstein et al. [15]; Liou et al. [16]; de Luis et al. [17] (up to 3 months, not significant at 9 and 12 months)
	=	Kops et al. [23]; Velazquez-Fernandez et al. [33]; Balsar et al. [44]; Novais et al. [45]
	↓	Rodrigues et al. [18]
MC4R (melanocortin-4 receptor)		
rs11152213	=	Javanrouh et al. [21]
rs17773430	↑	Javanrouh et al. [21]
rs17782313	=	Javanrouh et al. [21]; Velazquez-Fernandez et al. [33]; Valette et al. [54]
	↓	Resende et al. [49]
rs2229616	=	Hatoum et al. [52]; Moore et al. [53]
	↓	Mirshahi et al. [22]
rs476828	=	Javanrouh et al. [21]
rs5282087	↑	Mirshahi et al. [22]
	=	Hatoum et al. [52]; Moore et al. [53]; Valette et al. [54]; Zechner et al. [55]; Goergen et al. [70]
rs9947255	=	Sarzynski et al. [19]
Various additional mutations	=	Aslan et al. [50]; Censani et al. [51]; Moore et al. [53]; Valette et al. [54]; Georgen et al. [70]
	↓	Cooiman et al. [47]; Potoczna et al. [48]
LEP/R (leptin)		
rs10954172	=	Sarzynski et al. [19]
rs1137100	=	Velazquez-Fernandez et al. [33]
rs1137101	↑	Kops et al. [23]
	=	Novais et al. [45]
rs1805094	↑	de Luis et al. [24]
	=	Kops et al. [23]
rs7799039	=	Novais et al. [45]
rs9436740	=	Sarzynski et al. [19]
Various additional mutations	=	Potoczna et al. [48]
UCP (uncoupling protein)		
rs1800849	=	Novais et al. [45]
rs603573	=	Velazquez-Fernandez et al. [33]
rs659366	=	Novais et al. [45]
rs660339	↑	Liou et al. [16]; Chen et al. [25]; Lee et al. [26]; Nicoletti et al. [27]
	=	Velazquez-Fernandez et al. [33]; Novais et al. [45]
A866A	↑	Sesti et al. [28]
G866A	↑	Nicoletti et al. [27]
C55T	=	de Luis et al. [56]
PPAR (peroxisome proliferator–activated receptor)		
rs1801282	=	Sesti et al. [28]; Velazquez-Fernandez et al. [33]
rs1822825	=	Liou et al. [16]
rs2970869	=	Sarzynski et al. [19]
rs2970884	=	Sarzynski et al. [19]
rs4684846	↑	Lee et al. [26]
	=	Liou et al. [16]
IL-6 (interleukin-6)		
G174G	↑	Sesti et al. [28]
G174C	=	Poitou et al. [63]
	↓	di Renzo et al. [29, 30]
GHRL/GHSR (ghrelin)		
rs26802	=	Novais et al. [45]
rs27647	=	Vitolo et al. [31]

Table 2 (continued)

FTO (fat mass and obesity associated)		
rs490683	↑	Matzko et al. [32]
	=	Vitolo et al. [31]
rs572169	=	Novais et al. [45]
rs696217	↑	Vitolo et al. [31]
rs9819506	↓	Matzko et al. [32]
POMC (proopiomelanocortin)		
rs1042571	↑	Velazquez-Fernandez et al. [33]
Various additional mutations	=	Cooiman et al. [47]; Potoczna et al. [48]
FKBP5 (FK506-binding protein 5)		
rs1360780	↓	Hartmann et al. [34]; Peña et al. [35]
ESR1 (estrogen receptor 1)		
rs712221	↑	Liou et al. [16]; Velazquez-Fernandez et al. [33]
ADIPOQ (adiponectin)		
rs17366743	=	Sarzynski et al. [19]
rs2241766	=	Vitolo et al. [31]
rs822396	=	Velazquez-Fernandez et al. [33]
Various additional mutations	=	Poitou et al. [63]
IRS1 (insulin receptor substrate 1)		
rs1801278	=	Sesti et al. [28]
TNF (tumor necrosis factor)		
rs1799964	=	Sarzynski et al. [19]
rs1800629	=	de Luis et al. [59]
rs2229094	=	Sarzynski et al. [19]
rs2844482	=	Sarzynski et al. [19]
GNBP (guanine nucleotide–binding protein)		
rs10744720	=	Sarzynski et al. [19]
rs2071080	=	Sarzynski et al. [19]
rs5443	=	Velazquez-Fernandez et al. [33]; Potoczna et al. [69]
FABP2 (fatty acid–binding protein-2)		
rs1799883	=	Kops et al. [23]; de Luis et al. [57]
Miscellaneous[c]		
ADRB2	=	Velazquez-Fernandez et al. [33]
rs1042714		
ADRB3	=	Velazquez-Fernandez et al. [33]
rs4994		
AGRP	=	Velazquez-Fernandez et al. [33]
rs5030980		
ANGPTL4	↑	Wang et al. [46]
APOB	=	Velazquez-Fernandez et al. [33]
rs693		
BDNF	=	Sarzynski et al. [19]
rs6265		
rs925946		
CB2R	=	de Luis et al. [71]
rs3123554		
CCL2	=	Beisani et al. [62]
CD40L	↓	Vitolo et al. [31]
rs1126535		
CLOCK	=	Ruiz-Lozano et al. [68]
rs1801260		
DUSP1	=	Velazquez-Fernandez et al. [33]
rs7702178	=	Velazquez-Fernandez et al. [33]
rs881150		
FAAH	↑	de Luis et al. [66]
C358A		
FAS	=	Beisani et al. [62]
FASN	=	Beisani et al. [62]
FXR	=	Scott et al. [43]

Table 2 (continued)

FTO (fat mass and obesity associated)			
IFI30	=	Velazquez-Fernandez et al. [33]	
rs11554159			
IRAK3	↑	Hulsmans et al. [58]	
LIPC	=	Velazquez-Fernandez et al. [33]	
rs8034802			
LYPLAL1	↑	Bandstein et al. [65]	
rs4846567			
MTIF3	↑	Rasmussen-Torvik et al. [64]	
rs4771122			
NAMPT	=	Beisani et al. [62]	
NR3C1	=	Sarzynski et al. [19]	
rs2963155	=	Sarzynski et al. [19]	
rs860457			
PCSK1	=	Cooiman et al. [47]	
SH2B1	=	Novais et al. [45]	
rs7498665			
ST8SIA2	↑	Hatoum et al. [61]	
rs17702901			
TAS1R2	=	Novais et al. [45]	
rs35874116	=	Novais et al. [45]	
rs9701796			
VDR	=	Alexandrou et al. [60]	
rs1544410			
5-HT2C	↑	Novais et al. [45]	
rs3813929			
11-HSD1	=	Leyvraz et al. [67]	

[b] ↓: poorer weight loss outcomes, ↑: better weight loss outcomes, =: no association

[c] Additional gene names: β-2 adrenergic receptor (ADRB2); β-3 adrenergic receptor (ADRB3); agouti-related protein (AGRP); brain-derived neurotrophic factor (BDNF); cannabinoid receptor type 2 (CB2R); C-C motif chemokine ligand 2 (CCL2); circadian locomotor output cycles kaput (CLOCK); dual-specificity phosphatase 1 (DUSP1); Fas cell surface death receptor (FAS); fatty acid synthase (FASN); farnesoid X receptor (FXR); lysosomal thiol reductase (IFI30); hepatic lipase (LIPC); nicotinamide phosphoribosyltransferase (NAMPT); nuclear receptor subfamily 3, group C, member 1 (NR3C1); proprotein convertase subtilisin/kexin type 1 (PCSK1); SH2B adaptor protein 1 (SH2B1); taste receptor type 1 member 2 (TAS1R2); vitamin D receptor (VDR); 11β-hydroxysteroid dehydrogenase type 1 (11-HSD1)

(5-HT2C), angiopoietin-like 4 (ANGPTL4), mitochondrial translational initiation factor 3 (MTIF3), lysophospholipase-like 1 (LYPLAL), fatty acid amid hydrolase (FAAH), ST8 sialyltransferase 2 (ST8SIA2), and interleukin-1 receptor–associated kinase-3 (IRAK3) were genes that had polymorphisms associated with them resulting in improved weight loss after bariatric surgery. The associations were significant 12 months, 2 years, 1–9.5 years, 2 years, 1 year, at time of weight nadir, and 3 months after bariatric surgery, respectively. Conversely, a variation in the CD40 ligand (CD40L) gene was associated with poorer weight loss outcomes 6, 26, and 52 weeks after RYGB.

Genetic Risk Score

Seven articles used genetic risk scores to predict the weight loss outcomes over a range of time periods, from 12 to 96 months after bariatric surgery (Table 3). Rinella et al. combined 17 genes into a predictive model that assessed the association with weight loss 24 months after RYGB [36]. After conducting a primary investigation of genes associated with weight loss after RYGB, these 17 single nucleotide polymorphisms (SNP) were identified as having the most potential clinical utility. Ciudin et al. similarly created a predictive model using 57 genes to ascertain the weight regain 60 months after RYGB [37]. The 57 SNPs were found to be associated with obesity, appetite regulation, and weight loss in response to bariatric surgery. The polygenic risk score created by de Toro-Martín et al. combined 186 SNPs and was also found to be helpful to predict weight loss up to 96 months after BPD [38]. BMI-associated SNPs were selected from the GWAS Catalog. Aasbrenn et al. incorporated 77 SNPs into a genetic risk score and found it to be associated with predicting percent excess BMI loss (%EBMIL) 24 months after RYGB but stated it may not be ready for clinical practice yet [39]. Notably, patients in the

highest tertile of the genetic risk score lost 1.7kg more weight than those in the lowest tertile, EBMIL of 81.1% versus 73.9%, respectively. Katsareli et al. found that their models using 108 SNPs were significantly able to predict percent total weight loss (%TWL) 12 and 24 months after RYGB [40]. Specifically, one proposed model found a 4.62% decrease in %EWL at 12 months after surgery. The predisposition score composed of 7 SNPs, by Nicoletti et al., found that patients with a higher score had greater metabolic benefits 1 year after RYGB [41]. Patients with a higher predisposition score were found to have a greater reduction in glycemia, total cholesterol, and triglycerides. Finally, the genetic risk score created by Käkelä et al. using 33 SNPs was not able to predict weight changes 36 months after bariatric surgery [42].

Discussion

Fifty-seven articles were considered in this review to find a genetic association with weight loss after bariatric surgery. The *UCP* variant rs660339 demonstrated significant, positive correlations with excess weight loss after bariatric surgery. Specifically, four studies concluded the rs660339 variant of *UCP2* was associated with greater weight loss after LAGB and RYGB. Both articles exploring *FKBP5* noted lower weight loss for patients with the rs1360780 variant. A combination of various genes, measured by genetic risk scores, was also shown to have significant predictive value after surgery. Our review supports that weight loss is influenced by multiple genetic variants that have modest individual effects, yet together produce a larger aggregate effect. As such, polygenic risk scores may better capture the genetic architecture of weight loss with bariatric surgery.

Although numerous genes have an established association with obesity, our findings show a lack of consistently identifiable genetic factors that can reliably predict weight loss outcomes after bariatric surgery. While genetic risk score evaluations show promise in predicting weight loss, evidence of efficacy in predicting longer-term outcomes (3 years or longer) is needed before such measures can be used by clinicians.

Studies are necessary to determine whether genetic risk score evaluations can provide patients with an accurate anticipated amount of weight loss post-surgery, which holds implications for greater satisfaction with the chosen treatment. However, the feasibility, cost, and added clinical value of these analyses need to be examined. In addition to the relationship of weight loss after surgery, genetic factors and risk scores may be useful in determining postoperative changes, such as response to drug therapies and alterations in dietary habits. Thus, future studies would be useful to further explore this relationship (reviewer #6, comment #2).

The *FTO* and *MC4R* genes were inconsistent in their relationship with the amount of weight loss after surgery, as some articles found a significant change in weight while others did not. This result was noteworthy as these genes have a well-known relationship to obesity [6, 7]. A few explanations may underlie these findings. Firstly, multiple genes explain the interindividual variability in weight loss; thus, it seems that *FTO* and *MC4R* are more useful in a genetic risk score than alone. Additionally, not enough studies have been conducted on the multitude of variants present for the *FTO* and *MC4R* genes. For example, the rs9930506 variant of *FTO* has been identified as a significant marker of BMI and obesity yet only one study explored this SNP [72]. Finally, it is possible that the genetic variants associated with the development of obesity are not involved in weight loss following treatment.

Several limitations are present within this study. First, the variability in sample size and participant characteristics may affect the generalizability to a larger patient population. Second, there was a large amount of heterogeneity in the type of surgery, method of sample collection, length of study, and gene identification. Third, case studies and articles not published in the English language were excluded, possibly missing relevant reports. Furthermore, LAGB, VBG, and BPD currently make up a low percentage of the total number of bariatric procedures performed annually in the USA and worldwide but were included in many of the reviewed studies [73]. Findings from these studies may not translate to more commonly used procedures of sleeve gastrectomy and RYGB.

Table 3   Genetic risk scores and weight loss after bariatric surgery

Title	# of SNPs	Surgery	Longest time after surgery (months)	Association with weight Loss
Rinella et al. [36]	17	RYGB	24	Yes
Ciudin et al. [37]	57	RYGB	60	Yes
de Toro-Martín et al. [38]	186	BPD	96	Yes
Aasbrenn et al. [39]	77	RYGB	24	Yes
Käkelä et al. [42]	33	RYGB, SG	37.2±32.4	No
Katsareli et al. [40]	108	RYGB, SG	24	Yes
Nicoletti et al. [41]	7	RYGB	12	Yes

RYGB, Roux-en-Y gastric bypass; *BPD*, biliopancreatic diversion; *SG*, sleeve gastrectomy

Conclusions

This review suggests some evidence of the importance of *UCP* and *FKBP* variants and genetic risk scores in predicting the weight loss outcomes of bariatric surgery. Our study contributes to the numerous factors that clinicians may consider when discussing surgery with their patients. Nevertheless, more research is needed to explore the interaction between genetic, lifestyle, and environmental factors and their effect on weight loss after bariatric surgery. Given the rise in popularity of sleeve gastrectomy, future studies examining the relationship between genetic predictors and weight loss outcomes would add to the literature. Long-term studies evaluating genetic factors and weight regain beyond the "honeymoon" period of 2–3 years after bariatric surgery are needed.

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Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Participate Does not apply.

Conflict of Interest Ariana M. Chao reports grants and consulting fees from WW International, Inc., outside the submitted work. Thomas A. Wadden discloses serving on advisory boards for Novo Nordisk and WW International, Inc. Robert I. Berkowitz reports receiving funding through grant support from Eisai Inc and Novo Nordisk and scientific consulting fees from WW International. The other authors declare no conflict of interest.

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