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Genetic variants of *LEAP2* are associated with anthropometric traits and circulating insulin-like growth factor-1 concentration: A UK Biobank study

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Abstract

Aim: To test the hypothesis that liver-expressed antimicrobial peptide 2 (*LEAP2*) genetic variants might influence the susceptibility to human obesity.

Methods: Using data from the UK Biobank, we identified independent *LEAP2* gene single nucleotide polymorphisms (SNPs) and examined their associations with obesity traits and serum insulin-like growth factor-1 (IGF-1) concentration. These associations were evaluated for both individual SNPs and after combining them into a genetic risk score (GRS_{LEAP2}) using linear and logistic regression models. Sex-stratified analyses were also conducted.

Results: Five SNPs showed positive associations with obesity-related traits. rs57880964 was associated with body mass index (BMI) and waist-to-hip ratio adjusted for BMI (WHRadjBMI), in the total population and among women. Four independent SNPs were positively associated with higher serum IGF-1 concentrations in both men and women. GRS_{LEAP2} was associated with BMI and WHRadjBMI only in women and with serum IGF-1 concentration in both sexes.

Conclusions: These findings reveal sex-specific associations between key *LEAP2* gene variants and several obesity traits, while also indicating a strong independent association of *LEAP2* variants with serum IGF-1 concentration.

KEYWORDS
IGF-1, *LEAP2* genetic variants, obesity traits

1 | INTRODUCTION

The liver-expressed antimicrobial peptide 2 (LEAP2) was recognized as a novel hormone in 2018.[1] The LEAP2 peptide is encoded by the

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LEAP2 gene and is mainly secreted by hepatocytes and specialized cells localized to the jejunum epithelium.[2–4] Functionally, LEAP2 operates through the growth hormone secretagogue receptor (GHSR), a G-protein-coupled receptor predominantly found in the central nervous system, pituitary gland, and pancreas. This receptor was initially identified as the receptor for the stomach-derived hormone ghrelin, which is the only gastrointestinal hormone known to increase appetite.[1,5,6] Moreover, studies in rodents have demonstrated a unique antagonistic effect of LEAP2 on ghrelin actions, inhibiting not only its stimulatory impact on food intake but also on growth hormone (GH) secretion and glucose metabolism.[1,7] Strikingly, plasma LEAP2 concentration is markedly higher than ghrelin concentration in lean individuals, suggesting that LEAP2 may display greater control over GHSR activity than ghrelin. In line with this possibility, in vitro studies have shown that LEAP2 can abrogate some ghrelin-independent actions of GHSR, including the receptor's constitutive activity[8] or its ability to regulate other G-protein-coupled receptors.[9] Studies in mice indicating that ghrelin exhibits limited accessibility to the brain have led to the hypothesis that LEAP2 may differentially affect certain central effects of GHSR that are marginally influenced by plasma ghrelin.[2,10] Currently, the specific anatomical location and physiological implications of the putative role of LEAP2 beyond its function as a ghrelin antagonist are under investigation.

LEAP2 plays a pivotal role in the regulation of energy balance in humans. LEAP2 infusion in healthy individuals reduces food intake, glycaemia, GH secretion, and lipolysis.[7] Plasma LEAP2 concentration decreases in the fasting state and it has been proposed that the upregulation of GHSR signalling, associated with the fall of LEAP2, is crucial for the short-term regulation of energy balance.[11] In contrast, plasma LEAP2 concentration is higher in individuals with obesity,[12] but whether elevated LEAP2 concentration has a primary role in the onset of obesity or whether it increases as a consequence of fat accretion is not clear. Notably, the circulating LEAP2 concentration demonstrates a direct correlation with body mass index (BMI), fat mass, blood glucose and serum triglycerides (TG), while having an inverse association with hunger.[12] Some of these characteristics of LEAP2 parallel those observed in other peptide hormones crucial for modulating energy homeostasis in humans, such as leptin[13] and insulin.[14] These hormones are known to increase in the context of obesity and contribute to controlling appetite and glycaemia, among other effects.[13,14] Consequently, LEAP2 emerges as another unique potentially crucial adaptive response in obesity, aimed at mitigating increases in glycaemia, appetite, and fat gain.

To the best of our knowledge, a comprehensive exploration of the genetic variants within the *LEAP2* gene is currently lacking. A genome-wide study, conducted by Volkov et al.[15] in 2016, uncovered an association between methylation quantitative trait loci of the *LEAP2* gene and traits linked to the adverse metabolic consequences of obesity, such as elevated fasting glycaemia.[15] Furthermore, the genetic variant rs57880964 within the *LEAP2* gene was reported to impact LEAP2 plasma concentration,[16] while rs10491278 was found to be associated with its gene expression level in the liver.[17] Notably, the role of the *LEAP2* gene in encoding a peptide hormone was unknown before 2018 and these observations remained overlooked. Given the current recognition of LEAP2 as a key metabolic player,[1,2,8] and as a possible target for novel drug treatments, it is reasonable to postulate that genetic variants within *LEAP2* may influence susceptibility to obesity development. Remarkably, the T2D Knowledge Portal (https://t2d.hugeamp.org), a resource for exploring genetic associations related to type 2 diabetes,[18] reveals that different genetic variants of the *LEAP2* gene are associated with various obesity traits. However, weighing the implications of these associations for the *LEAP2* gene is challenging, as genetic variants within this gene that exhibit associations with traits independently of each other (i.e., independent single-nucleotide polymorphisms [SNPs]) have not been reported.

The UK Biobank is a detailed prospective study with deep genetic, physical, and health data collected from ~500 000 individuals across the United Kingdom.[19] This initiative is a groundbreaking opportunity to understand the genetic basis of obesity. Although extensive research has been conducted on the association of SNPs with obesity-related traits such as BMI, fat mass, and waist-to-hip ratio (WHR),[20,21] the associations of the genetic variants of the human *LEAP2* gene with obesity traits remain unexplored. Notably, UK Biobank data include serum insulin-like growth factor-1 (IGF-1) concentration, which provides a reliable measure of GH activity status because, unlike GH concentration, it lacks daily pulsatility.[22] GH status strongly depends on the counterregulatory effects of LEAP2 and ghrelin.[23] Indeed, it has been proposed that reduced GHSR tone mediates the reduction in GH secretion and serum IGF-1 concentration observed in individuals with obesity.[24] In turn, several studies have shown that serum IGF-1 concentration displays a negative association with BMI and central adiposity independently of race/ethnicity or sex factor.[25–29]

In this study, we aimed to map the genetic variants of the human *LEAP2* gene, identify the independent SNPs, and evaluate their associations, individually as well as combined in a genetic risk score (GRS_{LEAP2}), with several obesity traits (BMI, WHR, serum TG concentration) using data from the UK Biobank. We also evaluated the associations of the independent SNPs of *LEAP2* and the GRS_{LEAP2} with serum IGF-1 concentration. Since certain aspects of LEAP2 biology,[12,30,31] as well as obesity traits such as WHR,[31] display sexual dimorphism, all association analyses were separately performed in men and women.

2 | METHODS

2.1 | Study population

The UK Biobank cohort recruited approximately 500 000 participants aged 40 to 69 years from England, Scotland and Wales between 2006 and 2010. The cohort has been described elsewhere,[19] and detailed information is available on the UK Biobank website (www.ukbiobank.ac.uk). Baseline data collection included a large range of data from sociodemographic and lifestyle information, medical history,

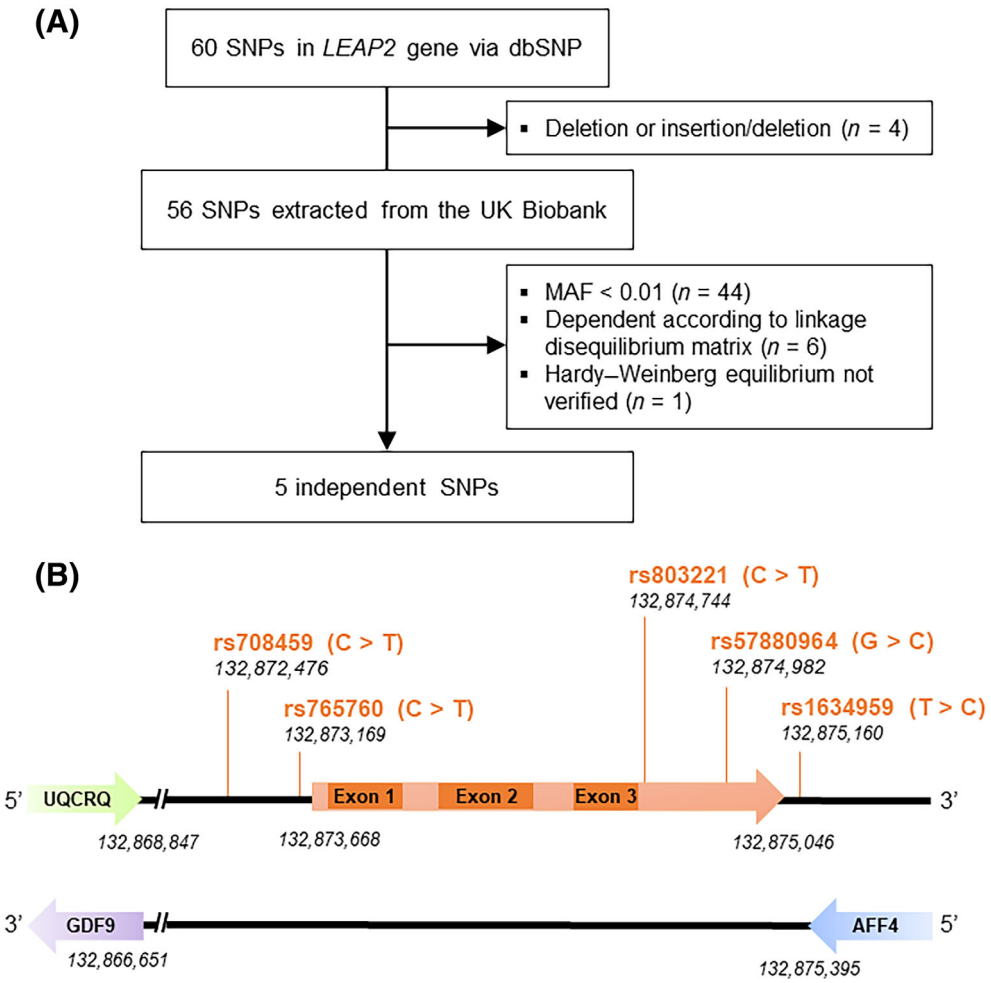

FIGURE 1 *LEAP2* genetic variants. (A) *LEAP2* genetic variants selection process. (B) Representation of the location of the five independent single-nucleotide polymorphisms (SNPs) selected for the *LEAP2* gene. MAF, minor allele frequency.

medication use, physical measurements, and biological samples. The North West Multi-Centre Research Ethics Committee approved the UK Biobank study protocol and the Regional Ethics Committee of Uppsala (Sweden) further approved the data use. All participants provided written informed consent. We excluded participants with withdrawn consent ($n = 231$), missing genetic data ($n = 15\,208$), failed quality control of the genotyped data ($n = 80\,153$), non-European ancestry ($n = 69\,624$), high heterozygosity or high missing rate ($n = 265$), and missing data either for WHR or BMI outcomes ($n = 1183$). Consequently, the current study included 335 955 participants (Supplementary Figure S1).

2.2 | Genotyping and *LEAP2* genetic variant selection

Genotyping was performed using the UK BiLEVE and UK Biobank Axiom arrays.[32] Sixty genetic variants spanning the *LEAP2* gene were identified using the dbSNP database (NCBI-National Institutes of Health [NIH]). Five independent SNPs of the *LEAP2* gene (rs803221, rs57880964, rs1634959, rs708459 and rs765760 [Figure 1]) were selected after excluding deletion or insertion/deletion genetic variants ($n = 4$), SNPs with a minor allele frequency <1% ($n = 44$, Supplementary Table S1), dependent SNPs according to linkage disequilibrium (LD matrix, LDlink platform, National Cancer Institute, NIH; $r^2 > 0.8$, $n = 8$) and SNPs which did not verify Hardy–Weinberg equilibrium ($p < 1 \times 10^{-6}$, $n = 1$).

2.3 | Genetic risk score

For each independent SNP, the risk allele was defined as the allele significantly associated with higher WHR or BMI in our study population. For rs765760, no risk allele could be defined. Hence, rs765760 was not included in the *LEAP2* genetic risk score (GRS_{LEAP2}). Genetic variants rs57880964 (risk allele: G), rs1634959 (risk allele: T), rs708459 (risk allele: C) and rs803221 (risk allele: C) were coded 0 for no risk allele, 1 for one risk allele (heterozygous), and 2 for two risk alleles (homozygous). Then, the GRS_{LEAP2} was calculated by summing the score of the four genetic variants. The GRS_{LEAP2} ranged from 0 to 8 and was categorized as low (0–2), medium (3–5) and high (6–8). These categories were established due to the uneven distribution of participants across different score ranges to ensure comparable groups.

2.4 | Anthropometric outcomes

The WHR was calculated by dividing waist circumference (cm) by hip circumference (cm). WHR was then dichotomized due to non-normal distribution using the sex-specific cut-offs: 0.9 for men and 0.85 for women according to the World Health Organization criteria.[33] BMI was calculated from measured weight/height^2 (kg/m^2) and used as a continuous variable.

2.5 | Blood samples

Triglycerides were quantified using routine enzymatic methods. Serum IGF-1 concentrations were measured by chemiluminescent immunoassay. Details regarding the assay methods and quality control procedures are described elsewhere.[34,35]

2.6 | Sociodemographic information

Age, sex, and education level were collected at the baseline of the study. Education level was recoded from the education qualifications data as having obtained a college or university degree as done in previous studies.[36,37] The Townsend deprivation index (TDI) was used as a proxy of socioeconomic status.[38,39]

2.7 | Statistical analysis

Associations between *LEAP2* genetic variants and WHR were evaluated using logistic models due to non-normal distribution. The regression model was additionally adjusted for BMI to investigate the association between *LEAP2* genetic variants and WHR independent of BMI (this analytical model is referred to as WHRadjBMI hereafter). The same approach has been adopted previously.[40] Furthermore, associations of *LEAP2* genetic variants with BMI, TG or IGF-1 were evaluated using linear models. All models were adjusted for assessment centre, age, sex, and SNP chip (i.e., UK BiLEVE or UK Biobank Axiom arrays). The same models were performed with GRS_{LEAP2} as the exposure. Since earlier studies and some biological characteristics of LEAP2 point towards sex-specific effects,[12,30,31] additional analyses were performed separately in men and women to explore sex-specific associations. Finally, sensitivity analyses were conducted after further adjusting all models for education and TDI, knowing that these confounding factors may affect the outcomes. All *p* values were corrected for multiple testing with false discovery rate correction,[41] and a *p* value <0.05 was considered statistically significant. Statistical analyses were carried out with R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org).

3 | RESULTS

Table 1 shows the characteristics of the total sample as well as the separated characteristics of men and women. The mean (standard deviation) age of the study participants was 57 (8) years and 53.71% of the participants were women. A total of 42.75% of the participants were overweight, and 24.11% had obesity. Supplementary Table S2 shows the characteristics of the sample stratified by sex and WHR classification.

3.1 | *LEAP2* genetic variants are associated with WHR, BMI and serum TG and IGF-1 concentrations

Table 2 and Figure 2 show the association of *LEAP2* genetic variants with WHR, WHRadjBMI, BMI, and TG and IGF-1 concentration. Being heterozygous for rs765760 was associated with higher WHR and WHRadjBMI in the total sample, however, no significant association was found in homozygotes for the rs765760 T allele. Conversely, being homozygous for rs57880964 G or rs803221 C alleles was associated with a high WHR and WHRadjBMI in the total sample. Furthermore, the rs57880964 G, rs1634959 T and rs708459 C alleles were associated with higher BMI in the total sample. After stratification by sex, the rs57880964 G allele was associated with higher WHR, WHRadjBMI, and BMI in women, and being homozygous for the rs803221 C allele was associated with higher WHR also only in women. No significant associations were found in men.

Regarding blood biomarker measurements, being homozygous for the rs57880964 G allele was associated with an increased TG concentration. Carrying the rs1634959 T, rs708459 C or rs803221 C allele was associated with higher serum TG concentration in the total sample. In addition, the rs57880964 G, rs1634959 T, rs708459 C and rs803221 C alleles were associated with higher serum IGF-1 concentration in the total sample. After stratification by sex, being homozygous for the rs57880964 G allele was associated with an increased TG concentration in women, while the rs803221 C allele was associated with higher serum TG concentration in men. The rs57880964 G, rs1634959 G, rs708459 C and rs803221 C alleles were associated with higher serum IGF-1 concentration in both men and women.

The results of the sensitivity analysis performed after additionally adjusting for education and TDI were comparable to those of the main analysis (Supplementary Table S3). Overall, the rs57880964 G allele was consistently associated with higher WHR, WHRadjBMI, BMI, and TG and IGF-1 concentrations. Most of the significant associations were driven by women except for IGF-1 concentration, which was associated with rs57880964 G, rs1634959 G, rs708459 C and rs803221 C alleles in both men and women.

3.1.1 | GRS comprising *LEAP2* genetic variants is associated with obesity traits and serum IGF-1 concentration

As shown in Table 3, compared to participants with no or a lower number of risk alleles (0–2), participants with three or more risk alleles had significantly higher odds for greater WHR measurements. Moreover, a GRS_{LEAP2} > 5 was associated with an overall 4% increased odds of having a WHR greater than 0.9 (men) or 0.85 (women). After

TABLE 1 Characteristics of the study sample.

Characteristics	Total $n = 335\,955$	Men $n = 155\,491$	Women $n = 180\,464$
Age,[a] years	56.88 (7.99)	57.12 (8.09)	56.67 (7.9)
Education (college or university degree)[b]	105 930 (31.53)	51 530 (33.14)	54 400 (30.14)
Townsend Deprivation Index[a]	−1.58 (2.93)	−1.54 (2.99)	−1.61 (2.88)
Height,[a] cm	168.84 (9.24)	175.95 (6.75)	162.71 (6.21)
Weight,[a] kg	78.31 (15.87)	86.21 (14.24)	71.51 (13.93)
WHR ≥0.90 (men)[b] WHR ≥0.85 (women)[b]	165 902 (49.38)	110 965 (71.36)	54 937 (30.44)
BMI,[a] kg/m^2	27.39 (4.75)	27.02 (5.13)	27.83 (4.22)
TG,[a,c] mmol/L	1.76 (1.02)	1.98 (1.14)	1.56 (0.86)
IGF-1,[a,c] nmol/L	21.41 (5.66)	21.94 (5.52)	20.95 (5.73)

Abbreviations: BMI, body mass index; IGF-1, insulin-like growth factor-1; TG, triglycerides; WHR, waist to hip ratio.
[a]Data are presented as mean (SD).
[b]Data are presented as *n* (%).
[c]5% missing values.

adjustment for BMI (WHRadjBMI), only participants with higher number of risk alleles (GRS_{LEAP2} ≥6), showed a significant 3% increase in the odds of having a higher WHR. Furthermore, a GRS_{LEAP2} >2 was associated with increased BMI and higher serum concentrations of TG and IGF-1 in the total sample. In the sex-stratified analyses, the associations between GRS_{LEAP2} and WHR, WHRadjBMI, BMI, and serum TG concentration were observed only among women, while the association between GRS_{LEAP2} and serum IGF-1 concentration was observed among both men and women. Similar results were obtained after further adjustment for education and TDI (Supplementary Table S4).

4 | DISCUSSION

To the best of our knowledge, this is the first study to show that *LEAP2* genetic variants are differentially associated with obesity traits and serum IGF-1 levels (Figure 2). Among the independent SNPs studied, the rs57880964 variant showed the strongest association with BMI, WHR and circulating TG, particularly in women. The associations reflected by this variant as well as the combined impact of all SNPs in GRS_{LEAP2} suggest a potential contribution of *LEAP2* genetic variants, mainly rs57880964, in enhancing certain features of obesity, such as body size and fat distribution, in a sexually dimorphic manner.

The relationships identified in this study strongly indicate that *LEAP2* variants are associated with overall body size (i.e., BMI) and abdominal obesity (i.e., WHRadjBMI). The analysis of the *LEAP2* variants for the total population revealed that the rs57880964 G allele is the only allele positively associated with obesity-related traits and serum TG concentration. Moreover, the rs1634959 T allele and rs708459 C allele (population frequencies of 53.8% and 53.8%, respectively) are positively associated with BMI without being associated with WHRadjBMI. Conversely, the rs803221 C allele (population frequency = 74.5%) was positively associated with WHRadjBMI without being associated with BMI. This denotes the specificity of the genetic variants of *LEAP2* regarding these obesity traits. Notably, the rs57880964 G allele (population frequency 83.4%), was identified in a large proteomics study connecting genes and proteins as a cis-acting genetic variant inversely associated with serum LEAP2 concentration.[16] Thus, it can be hypothesized that individuals carrying the rs57880964 G allele are more susceptible to obesity due to their limited ability to exhibit an obesity-induced increase in plasma LEAP2 concentration. Recently, the plasma proteomic profiles have been analysed for some UK Biobank participants, however, the LEAP2 peptide was not included in the initial analysis, which hindered our ability to assess the implications of other genetic variants of LEAP2 on its plasma concentration.[42] Given that the independent genetic variants of LEAP2 identified here are situated outside the coding region, they do not affect peptide sequence or length. Thus, the biological mechanisms through which they influence certain traits remain to be elucidated. It can be hypothesized that these variants modulate protein levels by affecting regulatory regions of the *LEAP2* gene, such as promoters or enhancers, altering the binding affinity of transcription factors and thereby influencing transcription initiation rates. Moreover, they could impact RNA stability or processing, leading to variations in mRNA levels available for translation. Additionally, non-coding variants might influence epigenetic modifications, such as DNA methylation or histone modifications, which in turn can regulate chromatin accessibility and gene expression. Future studies will be instrumental in exploring and validating these potential mechanisms.

In this study, we report a robust and sex-independent positive association between four out of the five independent SNPs of the *LEAP2* gene and serum IGF-1 levels. IGF-1, a protein hormone primarily synthesized in the liver, plays pivotal roles in growth regulation during childhood and anabolism in adults.[43,44] GH is the most sensitive physiological response to GHSR activation,[1,7,23,45] and IGF-1 serves as the principal peripheral mediator of GH activity. LEAP2 infusion in humans decreases GH levels,[7] while LEAP2 blockage or LEAP2

TABLE 2 Association between *LEAP2* genetic variants and waist-to-hip ratio, body mass index, triglycerides and insulin-like growth factor-1 in the total population and in men and women.

				WHR[a]		WHRadjBMI[a]		BMI[b]		TG[b]		IGF-1[b]	
SNP	**Sample**	**Genotype**	***n***	**OR (CI)**	***p* value***	**OR (CI)**	***p* value***	**β (SE)**	***p* value***	**β (SE)**	***p* value***	**β (SE)**	***p* value***
rs765760	Total	CC	213 407	Reference		Reference		Reference		Reference		Reference	
		TC	108 519	1.02 (1–1.04)	**0.0288**	1.03 (1.01–1.05)	**0.0056**	−0.031 (0.018)	0.1179	0.004 (0.004)	0.3034	−0.001 (0.021)	0.9540
		TT	13 894	1.01 (0.97–1.05)	0.7084	1.03 (0.99–1.07)	0.2865	−0.086 (0.041)	0.063	−0.010 (0.009)	0.3079	−0.011 (0.049)	0.8835
	Men	CC	98 357	Reference		Reference		Reference		Reference		Reference	
		TC	50 535	1.02 (1–1.04)	0.2651	1.04 (1.02–1.06)	0.0949	−0.024 (0.023)	0.6143	0.003 (0.006)	0.7852	0.008 (0.030)	0.9183
		TT	6532	0.97 (0.92–1.03)	0.5579	0.99 (0.93–1.05)	0.9614	−0.124 (0.054)	0.1083	−0.022 (0.015)	0.4167	0.001 (0.071)	0.9847
	Women	CC	115 050	Reference		Reference		Reference		Reference		Reference	
		TC	57 984	1.02 (1–1.04)	0.133	1.03 (1.01–1.05)	0.0553	−0.039 (0.026)	0.1887	0.005 (0.004)	0.3654	−0.008 (0.029)	0.8444
		TT	7362	1.04 (0.98–1.1)	0.1863	1.06 (1–1.13)	0.1088	−0.054 (0.061)	0.42	-8e-04 (0.01)	0.9356	−0.019 (0.068)	0.8444
rs57880964	Total	CC	9260	Reference		Reference		Reference		Reference		Reference	
		CG	92 868	1.06 (1.02–1.1)	**0.0288**	1.04 (0.98–1.1)	0.2471	0.125 (0.051)	**0.0309**	0.012 (0.011)	0.3157	0.184 (0.061)	**0.0114**
		GG	233 792	1.09 (1.05–1.14)	**0.0023**	1.06 (1–1.13)	**0.0307**	0.125 (0.05)	**0.0288**	0.024 (0.011)	**0.0470**	0.403 (0.059)	**<0.0001**
	Men	CC	4323	Reference		Reference		Reference		Reference		Reference	
		CG	43 210	1.03 (0.95–1.11)	0.7248	1.02 (0.94–1.1)	0.8532	0.044 (0.067)	0.7248	0.003 (0.019)	0.9614	0.188 (0.089)	0.1309
		GG	107 939	1.03 (0.97–1.09)	0.6499	1.03 (0.95–1.11)	0.7248	0.029 (0.065)	0.8214	0.012 (0.018)	0.7248	0.396 (0.086)	**0.0002**
	Women	CC	4937	Reference		Reference		Reference		Reference		Reference	
		CG	49 658	1.08 (1.02–1.15)	0.0519	1.06 (0.98–1.15)	0.1609	0.196 (0.076)	**0.0425**	0.022 (0.013)	0.1415	0.177 (0.084)	0.089
		GG	125 853	1.13 (1.06–1.2)	**0.003**	1.11 (1.04–1.17)	**0.0346**	0.2077 (0.074)	**0.0346**	0.034 (0.013)	**0.0346**	0.408 (0.082)	**<0.0001**
rs1634959	Total	CC	71 999	Reference		Reference		Reference		Reference		Reference	
		CT	166 299	1.01 (0.99–1.03)	0.2471	1.00 (0.98–1.02)	0.8835	0.063 (0.021)	**0.0121**	0.012 (0.005)	**0.0194**	0.056 (0.025)	**0.047**
		TT	97 539	1.01 (0.99–1.03)	0.2826	1.00 (0.98–1.02)	0.9341	0.063 (0.023)	**0.0194**	0.016 (0.005)	**0.0113**	0.166 (0.028)	**<0.0001**
	Men	CC	33 621	Reference		Reference		Reference		Reference		Reference	
		CT	77 047	1.00 (0.98–1.02)	0.9615	0.99 (0.95–1.03)	0.7248	0.036 (0.027)	0.4853	0.017 (0.008)	0.1128	0.033 (0.036)	0.6697
		TT	44 768	1.01 (0.97–1.05)	0.7585	1.00 (0.96–1.04)	0.9614	0.044 (0.03)	0.4167	0.019 (0.008)	0.1083	0.145 (0.04)	**0.0037**
	Women	CC	38 378	Reference		Reference		Reference		Reference		Reference	
		CT	89 252	1.03 (1.01–1.05)	0.1088	1.01 (0.99–1.03)	0.3887	0.084 (0.031)	**0.0346**	0.008 (0.005)	0.1887	0.076 (0.034)	0.0721
		TT	52 771	1.01 (0.99–1.03)	0.4200	1.00 (0.96–1.04)	0.9218	0.079 (0.034)	0.0709	0.011 (0.006)	0.1088	0.185 (0.038)	**<0.0001**
rs708459	Total	TT	71 908	Reference		Reference		Reference		Reference		Reference	
		TC	166 305	1.01 (0.99–1.03)	0.2471	1.00 (0.98–1.02)	0.8835	0.061 (0.021)	**0.0141**	0.012 (0.005)	**0.0194**	0.058 (0.025)	**0.0396**
		CC	97 662	1.01 (0.99–1.03)	0.2826	1.00 (0.98–1.02)	0.9235	0.061 (0.023)	**0.0231**	0.015 (0.005)	**0.0114**	0.168 (0.028)	**<0.0001**
	Men	TT	33 589	Reference		Reference		Reference		Reference		Reference	
		TC	77 041	1.00 (0.98–1.02)	0.9615	0.99 (0.95–1.03)	0.7248	0.034 (0.028)	0.4983	0.017 (0.008)	0.1128	0.035 (0.036)	0.6532

TABLE 2 (Continued)

SNP	Sample	Genotype	*n*	WHR[a]		WHRadjBMI[a]		BMI[b]		TG[b]		IGF-1[b]	
				OR (CI)	*p* value*	OR (CI)	*p* value*	β (SE)	*p* value*	β (SE)	*p* value*	β (SE)	*p* value*
		CC	44 825	1.01 (0.97–1.05)	0.7738	1.00 (0.96–1.04)	0.9614	0.042 (0.030)	0.4445	0.020 (0.008)	0.1083	0.148 (0.04)	
	Women	TT	38 319	Reference		Reference		Reference		Reference		Reference	
		TC	89 264	1.03 (1.01–1.05)	0.1088	1.01 (0.99–1.03)	0.3817	0.083 (0.031)	**0.0346**	0.008 (0.005)	0.2003	0.079 (0.035)	0.0709
		CC	52 827	1.01 (0.99–1.03)	0.4189	1.00 (0.96–1.04)	0.8888	0.076 (0.034)	0.0721	0.011 (0.006)	0.1102	0.188 (0.038)	**<0.0001**
rs803221	Total	TT	21 791	Reference		Reference		Reference		Reference		Reference	
		TC	127 466	1.03 (0.99–1.07)	0.0631	1.02 (0.98–1.06)	0.2663	0.071 (0.035)	0.0640	0.020 (0.008)	**0.0194**	0.112 (0.04)	**0.0194**
		CC	186 562	1.05 (1.01–1.09)	**0.0113**	1.04 (1.00–1.08)	**0.0309**	0.055 (0.034)	0.1514	0.026 (0.007)	**0.0036**	0.225 (0.04)	**<0.0001**
	Men	TT	10 077	Reference		Reference		Reference		Reference		Reference	
		TC	59 168	1.02 (0.98–1.06)	0.7248	1.02 (0.96–1.08)	0.7585	0.040 (0.045)	0.6767	0.034 (0.013)	0.0605	0.123 (0.06)	0.1426
		CC	86 186	1.03 (0.99–1.07)	0.4874	1.04 (0.98–1.1)	0.4167	0.016 (0.044)	0.8532	0.035 (0.012)	**0.0397**	0.224 (0.058)	**0.003**
	Women	TT	11 714	Reference		Reference		Reference		Reference		Reference	
		TC	68 298	1.04 (1–1.08)	0.1088	1.03 (0.99–1.07)	0.2157	0.097 (0.05)	0.1088	0.008 (0.009)	0.3887	0.103 (0.056)	0.1173
		CC	100 376	1.06 (1.02–1.1)	**0.0346**	1.05 (1.01–1.09)	0.0721	0.087 (0.0498)	0.1330	0.016 (0.008)	0.1088	0.228 (0.055)	**0.0004**

Abbreviations: BMI, body mass index; CI, confidence interval; IGF-1, insulin-like growth factor-1; OR, odds ratio; TG, triglycerides; WHR, waist to hip ratio; WHRadjBMI, waist to hip ratio adjusted for body mass index.

[a]Logistic model adjusted for center, age, sex (total sample only) and single-nucleotide polymorphism (SNP) chip.

[b]Linear model adjusted for center, age, sex (total sample only) and SNP chip.

*p values after false discovery rate correction.

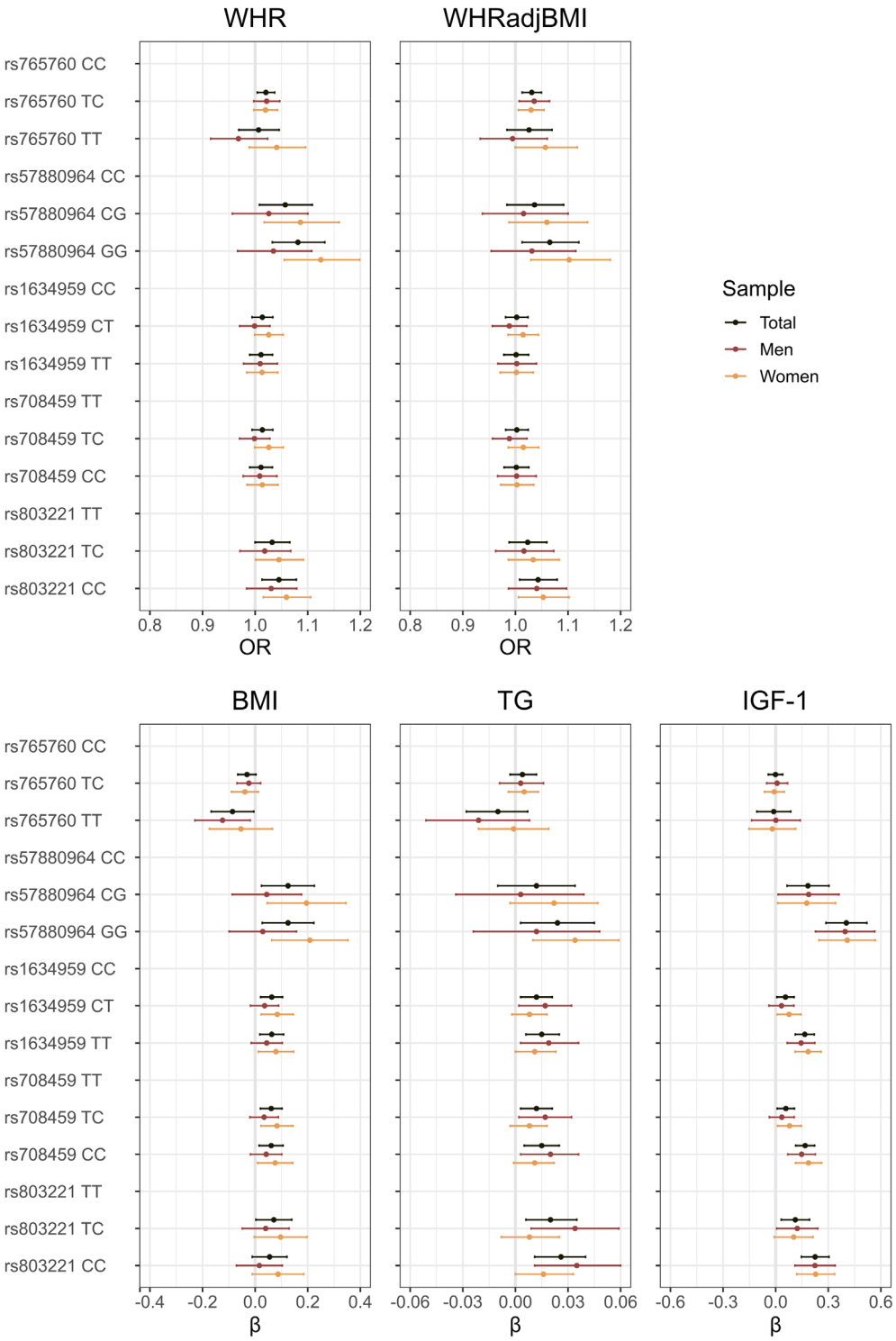

FIGURE 2 Forest plot representing the associations between *LEAP2* genetic variants and waist-to-hip ratio (WHR), body mass index (BMI), triglycerides (TG) and insulin-like growth factor-1 (IGF-1) in the total population and men and women. WHRadjBMI, waist-to-hip ratio adjusted for body mass index.

knockout mice show increased GH levels.[1,46] Given that genetic variants of *LEAP2* may impact its gene expression and plasma concentration, it is plausible that these alterations could ultimately influence GH activity and affect serum IGF-1 concentration. Alternatively, *LEAP2* and *IGF-1* genes may be subject to similar regulatory mechanisms in the liver. Notably, plasma concentrations of IGF-1 and LEAP2 increase during the pubertal growth spurt, and show a positive correlation in girls.[31] However, serum concentrations of LEAP2 and IGF-1 are not correlated in adults,[47,48] indicating that the link between these peptide hormones is dynamic and depends on the life stage. In this regard, it is interesting to mention that IGF-1 concentration is significantly associated with BMI in young (20–58 years) and old (67–86 years) individuals, but not in middle-aged (58–66 years) individuals,[29] while LEAP2 is positively correlated with age in subjects over 60 years

TABLE 3 Association between *LEAP2* genetic risk score and waist to hip ratio, body mass index, triglycerides and insulin-like growth factor-1 in the total population and in men and women.

		WHR[a]		WHRadjBMI[a]		BMI[b]		TG[b]		IGF-1[b]	
	n	OR (CI)	*p* value*	OR (CI)	*p* value*	β (SE)	*p* value*	β (SE)	*p* value*	β (SE)	*p* value*
Total											
0-2	45 009	Reference		Reference		Reference		Reference		Reference	
3–5	118 676	1.03 (1.01–1.05)	**0.0424**	1.02 (1–1.04)	0.2359	0.067 (0.026)	**0.0210**	0.013 (0.006)	**0.0319**	0.109 (0.031)	**0.0017**
6–8	172 056	1.04 (1.02–1.06)	**0.0070**	1.03 (1.01–1.05)	**0.0275**	0.056 (0.025)	**0.0319**	0.020 (0.005)	**0.0015**	0.207 (0.030)	**<0.0001**
Men											
0–2	20 963	Reference		Reference		Reference		Reference		Reference	
3–5	55 061	1.00 (0.96–1.04)	0.9427	1.00 (0.96–1.04)	0.9137	0.023 (0.034)	0.7180	0.016 (0.009)	0.253	0.138 (0.045)	**0.0110**
6–8	79 371	1.02 (0.98–1.06)	0.4220	1.02 (0.98–1.06)	0.4220	0.018 (0.033)	0.7303	0.021 (0.009)	0.063	0.217 (0.043)	**<0.0001**
Women											
0–2	24 046	Reference		Reference		Reference		Reference		Reference	
3–5	64 615	1.05 (1.01–1.09)	**0.0164**	1.03 (0.99–1.07)	0.0596	0.104 (0.039)	**0.0164**	0.010 (0.007)	0.1397	0.083 (0.043)	0.0596
6–8	92 685	1.05 (1.01–1.09)	**0.0115**	1.04 (1.00–1.08)	**0.0260**	0.087 (0.037)	**0.0264**	0.016 (0.006)	**0.0164**	0.201 (0.041)	**<0.0001**

Abbreviations: BMI, body mass index; CI, confidence interval; IGF-1, insulin-like growth factor-1; OR, odds ratio; TG, triglycerides; WHR, waist to hip ratio; WHRadjBMI, waist to hip ratio adjusted for body mass index.

[a]Logistic model adjusted for centre, age, sex (total sample only) and single-nucleotide polymorphism (SNP) chip.

[b]Linear model adjusted for centre, age, sex (total sample only) and SNP chip.

*p values after false discovery rate correction.

old.[49] Unfortunately, we are unaware of studies reporting plasma concentrations of LEAP2 and IGF-1 only in patients aged between 40 and 69 years, corresponding to the age range of UK Biobank participants. Thus, potential increases in LEAP2 and IGF-1 concentrations in the elderly and age-related differences in anthropometric features may condition the associations of the genetic variants of *LEAP2* with serum IGF-1 and obesity-related traits. Notably, the associations uncovered in the current study for the newly identified independent SNPs of the *LEAP2* gene with various obesity traits and serum IGF-1 levels display a high degree of agreement with the associations found in the T2D Knowledge Portal for those SNPs, further confirming the accuracy of our analysis.

In this study, we found that the rs57880964 G allele displayed a strong sexual dimorphism, as it was positively associated with both body size and fat distribution in women but not in men, indicating that this genetic variant might mediate susceptibility to obesity in a sex-specific manner. This association was unexpected because genetic loci that show sexual dimorphism are usually associated with body fat distribution, rather than body size, and are located near genes expressed in adipose tissue.[50] Furthermore, plasma LEAP2 concentration is known to display a strong sexually dimorphic effect, with higher levels observed in women compared to men.[12] Thus, it is evident that the LEAP2 system, at both peptide and genetic levels, exerts sexually dimorphic effects. Indeed, we were unable to identify any association between the genetic variants of the *LEAP2* gene and anthropometric variables or plasma TG concentration in the male population, despite the sample size of the UK Biobank dataset. These observations emphasize the more significant role of LEAP2 in women than in men.

To study the combined effect of the independent genetic variants of the *LEAP2* gene, we calculated a GRS_{LEAP2} based on the alleles that were significantly associated with higher WHR or BMI in the four SNPs. This investigation is not only important to help assess an individual's genetic predisposition to gain weight but also for personalized medicine, to guide tailored interventions. In this study, the proposed GRS_{LEAP2} highlights the robust positive associations of the studied *LEAP2* genetic variants with body size and fat mass distribution and emphasizes that such associations are significant in women but not in men. Overall, we observed very small effect sizes for these associations, which are consistent with previous reports investigating the distribution of effect sizes across susceptible genetic variations. The report suggests that there is an increasing number of susceptibility loci with decreasing effect sizes for complex traits, regardless of the trait being studied.[51] Therefore, the combination of *LEAP2* risk alleles could modestly affect the obesity risk through its possible impact on increased WHR, BMI, and circulating TG concentrations, especially among women.

This study has several strengths. The UK Biobank is a large-scale cohort with deep phenotypic information that allowed us to account for detailed confounding factors, and conduct sex-stratified and sensitivity analyses. Nevertheless, the study also has some limitations that need to be acknowledged. Since UK Biobank participants were aged between 40 and 69 years, caution is needed when extending our results to other age groups, especially considering that anthropometric and metabolic traits as well as IGF-1 concentration are age-dependent. Moreover, our analysis was limited to data on people of European descent as they represent approximately 90% of the UK Biobank population and the remaining ancestry groups are too small to be stratified. It would be necessary to continue research in different populations in order to extend the role of *LEAP2* genetic variants to other ethnic groups.

In conclusion, this study identifies the most relevant *LEAP2* genetic variants and reveals their significant and sex-specific associations with anthropometric variables linked to obesity. Additionally, the study highlights a very strong association of the genetic variants of *LEAP2* with serum IGF-1 concentrations, which seems to be independent of the anthropometric factors.

AUTHOR CONTRIBUTIONS

All authors conceptualized and designed the study. María F. Andreoli, Mario Perello, Gull Rukh and Mélissa Gentreau are responsible for the statistical analyses and writing, original draft. All authors contributed to the data interpretation and writing, review and editing and approved the final version of manuscript as submitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Materials described in this manuscript, including all relevant raw data, will be freely available to any researcher wishing to use them for non-commercial purposes, without breaching participant confidentiality.

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