Abdominal Obesity Genetic Variants Predict Waist Circumference Regain After Weight Loss

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Although many individuals are able to achieve weight loss, maintaining this loss over time is challenging. We aimed to study whether genetic predisposition to general or abdominal obesity predicts weight regain after weight loss. We examined the associations between genetic risk scores for higher BMI and higher waist-to-hip ratio adjusted for BMI (WHR_{adjBMI}) with changes in weight and waist circumference up to 3 years after a 1-year weight loss program in participants (*n* = 822 women, *n* = 593 men) from the Look AHEAD (Action for Health in Diabetes) study who had lost ≥3% of their initial weight. Genetic predisposition to higher BMI or WHR_{adjBMI} was not associated with weight regain after weight loss. However, the WHR_{adjBMI} genetic score did predict an increase in waist circumference independent of weight change. To conclude, a genetic predisposition to higher WHR_{adjBMI} predicts an increase in abdominal obesity after weight loss, whereas genetic predisposition to higher BMI is not predictive of weight regain. These results suggest that genetic effects on abdominal obesity may be more pronounced than those on general obesity during weight regain.

ARTICLE HIGHLIGHTS

- Nearly all individuals who intentionally lose weight experience weight regain.
- Individuals with a higher genetic risk for abdominal adiposity experience increased regain in waist circumference after weight loss.
- Genetic predisposition to higher BMI does not predict weight regain after weight loss.

Obesity is a global epidemic and a major contributor to the increasing incidence of type 2 diabetes worldwide (1). It is estimated that more than one billion people will have obesity by 2030 (2). Treatment options for obesity include behavioral changes, pharmaceuticals, and bariatric surgery. Lifestyle interventions typically result in an average weight loss of 7–10% within 6 months (3); however, maintaining the weight loss is a significant challenge: participants often regain an average of 33% of the lost weight within 1 year and 50–100% of it within 5 years (4–7).

Independent of overall body fat, abdominal obesity is associated with an increased risk of cardiometabolic diseases, such as type 2 diabetes and coronary heart disease (8–11). Waist circumference (WC) or waist-to-hip ratio (WHR) can serve as proxies for abdominal adiposity, and these measures can also be adjusted for overall adiposity (WC_{adjBMI} and WHR_{adjBMI}, respectively). Abdominal fat tissue is metabolically active, releasing metabolites such as free fatty acids, inflammatory molecules, and hormones directly to the liver, which can cause damage (12). Conversely, fat deposits in the gluteofemoral area are less metabolically active (13), act as a metabolic sink for lipid storage (14) and offer protection against cardiometabolic diseases (14), glucose intolerance (15), and type 2 diabetes (16). Therefore, abdominal obesity may be a better predictor of type 2 diabetes and cardiovascular diseases than BMI (17,18).

Genome-wide association studies (GWAS) have identified hundreds of genetic variants that predispose to higher BMI (19) and higher WHR_{adjBMI} (20). These variants are primarily associated with gene expression in the central

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nervous system and adipose tissue, respectively. Prior research on weight loss and weight regain has focused on individual variants associated with BMI (21–25). The impact of genetic risk scores for either BMI and WHR_{adjBMI} on overall and abdominal obesity after initial weight loss has not yet been evaluated, to our knowledge.

In this study, we assessed the impact of polygenic scores for higher BMI and WHR_{adjBMI} on changes in general and abdominal obesity after weight loss in the Look AHEAD (Action for Health in Diabetes) trial.

RESEARCH DESIGN AND METHODS

Study Participants

We conducted a secondary analysis of the Look AHEAD trial (26,27), a multicenter, randomized controlled study that examined the impact of an intensive lifestyle intervention (ILI) compared with a control group (Diabetes Support and Education [DSE]) on health outcomes among participants with type 2 diabetes and overweight or obesity. Both groups received an educational session on diabetes and cardiovascular risk factors, and the DSE group also had the option to attend three additional sessions on nutrition, physical activity, and social support. The ILI group received a plan for diet and physical activity modification with the goal of achieving and maintaining a weight loss of approximately 7%. In the first 6 months, the ILI participants had one individual and three group meetings per month, with decreasing frequency over the course of the trial (26,28). Medications were prescribed by personal physicians not affiliated with the trial (27). All participants provided informed consent for the Look AHEAD study and the use of genetic data, and the study was approved by the University of Connecticut Institutional Review Board. Race and ethnicity were self-reported using questions from the 2000 U.S. Census questionnaire (27).

Anthropometric Measures

Weight was measured twice at each clinical examination using a calibrated digital scale, with participants wearing light, indoor clothing. WC was measured three times, at the midway point between the bottom of the ribs and the top of the hips, using a tape measure (21). Height was measured twice using a stadiometer. The average of the weight, WC, and height measures was calculated at each time point. The measurement of weight and WC was performed annually (21).

Genetic Data

All participants were genotyped using the Illumina Infinium Global Screening Array-24 version 1.0 BeadChip platform. The quality control (QC), performed on 3,160 samples, included a call-rate threshold of 97%, removal of duplicates and mismatches for sex check, and exclusion of participants with an estimated homozygosity outside the core sex cluster. The QC was also performed on 642,824 markers aligned to Genome Reference Consortium Human Build 37 (GRCh37), which included a call-rate threshold of 97%, a Hardy-Weinberg equilibrium threshold of 0.0004 in each ethnicity group, and the exclusion of duplicates. After the QC, whereby a total of 13,038 markers were removed, 629,788 markers were imputed for each race by MiniMac V3 (29) using the 1000Genomes reference panel (30). Monomorphic variants (minor allele frequency = 0 or 1) and variants with an imputation score <0.7 were excluded.

Genetic Risk Score

We constructed effect size–weighted genetic risk scores for BMI and WHR_{adjBMI}. To construct the genetic risk score for BMI, we used summary statistics from a GWAS meta-analysis of BMI of approximately 700,000 individuals of European ancestry, which identified 656 loci containing 941 independent signals, using a significance threshold of $P < 1 \times 10^{-8}$ (19). For WHR_{adjBMI}, we also used data from a GWAS meta-analysis of approximately 700,000 individuals of European ancestry, which identified 346 loci containing 463 independent signals, using a significance threshold of $P < 5 \times 10^{-9}$ (20). We used a threshold of $P < 5 \times 10^{-8}$ to select independent loci within ± 500 kb of the index variant for both BMI and WHR_{adjBMI}. The final genetic risk scores included 894 independent single nucleotide polymorphisms (SNPs) for BMI and 481 for WHR_{adjBMI} (Supplementary Tables 5 and 6). The scores were normally distributed among all ancestries (Supplementary Fig. 2).

We aligned each SNP based on the trait-increasing allele. The effect size of each trait-increasing allele was multiplied by the number of risk alleles carried by an individual, and the genetic risk score was calculated as the sum of the weighted alleles carried by the individual. The genetic risk scores for BMI and WHR_{adjBMI} were significantly associated with the respective baseline traits in Look AHEAD (for BMI, $P = 4.61 \times 10^{-7}$; for WC_{adjBMI}, $P = 4.55 \times 10^{-6}$) (Supplementary Tables 1 and 2). The genetic risk scores were also correlated with their respective traits (for BMI, $r = 0.12$; for WC_{adjBMI}, $r = 0.04$). The scores explained 1.41% and 0.38% of the variance in BMI and WC_{adjBMI}, respectively, when adjusting for age, age squared, sex, and the first four genetic principal components.

We examined whether using a threshold of $P = 0.00001$ or $P = 0.0001$ for variant selection could improve the performance of the WHR_{adjBMI} genetic score. However, our findings showed that the performance of the score was not improved. When using thresholds of $P < 0.00001$ and $P < 0.0001$, the association between the WHR_{adjBMI} genetic score and the outcome trait had P values of 9.1×10^{-4} and 0.021, respectively.

Statistical Analysis

We investigated the impact of genetic variants on weight change in individuals who successfully lost ≥3% of their initial body weight during the first year of the intervention (n = 822 women and n = 593 men) (31). The outcome measures were weight loss and WC reduction during the

1-year weight loss, as well as change in weight and WC from year 1 to year 2 and year 1 to year 4. Data are reported as mean ± SD. Linear regression models were used to test genetic associations, using *R* version 4.1.2 (32). All analyses were adjusted for age, self-reported sex, height, and baseline values of the outcome traits.

Because the majority of participants in this study were of White ancestry and the genetic variants being studied were originally identified in primarily White European populations, a separate analysis was conducted for this group. The analyses of combined ancestries were further adjusted for the first four genetic principal components (PC) to account for differences in genetic ancestry (Supplementary Fig. 1).

We also examined the outcomes separately in the two intervention arms and in the subset of participants who regained weight from years 1 to 2 and years 1 to 4.

In the analyses of weight change, we additionally adjusted for the year 1 value of body weight as well as the intervention type (ILI/DSE) when examining the full study population. In the analyses of changes in WC, we adjusted for the year 1 value of WC, as well as corresponding changes in body weight. Before the analyses, we confirmed that the outcome traits followed a normal distribution, by visual inspection of the residuals from each model.

Data and Resource Availability

The code is available upon request to the authors. The Look AHEAD data are available in the National Institute of Diabetes and Digestive and Kidney Diseases repository. The genetic data are not available, because of limitations in consent.

RESULTS

Characteristics of the Study Population

The baseline characteristics of individuals who lost ≥3% of their initial body weight during the first year of the intervention were similar between the ILI and DSE groups (Table 1). On average, the ILI group lost 10.94 ± 6.91 kg of body weight (9.02 ± 7.87 cm of WC) and the DSE group lost 6.81 ± 4.45 kg (5.04 ± 5.68 cm) during the first year of the intervention. From year 1 to year 2, ILI participants regained, on average, 2.76 ± 4.68 kg (2.48 ± 5.62 cm of WC) and DSE participants regained 0.64 ± 5.96 kg of weight (0.44 ± 5.83 cm of WC). From year 1 to year 4, the weight for the ILI participants changed by an average of 5.01 ± 7.84 kg of body weight (4.88 ± 7.61 cm of WC) and 1.47 ± 7.77 kg (1.92 ± 7.76 cm of WC) for the DSE.

Genetic Associations With Weight and WC Loss and Regain

We first examined whether there were differences in the effect of the BMI and WHR_{adjBMI} genetic risk scores on weight and WC loss and regain between the ILI and DSE groups by testing for the significance of the interaction term between the genetic risk score and study group (Supplementary Table 4). We found no significant interaction between the BMI or WHR_{adjBMI} genetic risk score and the study group in any of the analyses, so we combined the ILI and DSE groups in all analyses and adjusted for the study group as a covariate.

The BMI and WHR_{adjBMI} genetic scores were not associated with weight loss during the 1-year intervention (Supplementary Table 1). The BMI score was also not associated with the loss in WC (Supplementary Table 2). However, a higher WHR_{adjBMI} genetic score was associated with a smaller 1-year loss in WC, adjusted for weight loss, in all ancestries (P = 0.022) (Supplementary Table 2) except White ancestry (P = 0.166) (Supplementary Table 3).

The BMI and WHR_{adjBMI} genetic scores were not associated with the change in body weight from year 1 to 2 or years 1 to 4 (Table 2). The BMI score was also not associated with the change in WC from year 1 to 2 or years 1 to 4 (Table 3). However, the WHR_{adjBMI} score was associated with a greater increase in WC after year 2 and year 4 in all ancestries ($P = 6.8 \times 10^{-4}$ and P = 0.012, respectively) (Table 3) and in the White ancestry (P = 0.002 and P = 0.037, respectively), independent of weight change (Supplementary Table 3). We performed sex- and age-stratified (≤60 or >60 years) analyses and examined the interaction between the genetic score and sex or age (Supplementary Tables 7 and 8). No significant interactions were found, indicating that the genetic effects on weight loss or weight regain were not dependent on sex or age.

Of the study participants who lost ≥3% of their initial body weight, a total of 1,009 participants (71.3%) regained weight from year 1 to year 2 and 1,044 participants (73.8%) regained weight from years 1 to 4, whereas other participants either maintained or continued to lose weight. To test genetic associations specifically with weight regain, we conducted additional analysis of the subset of participants who regained weight. The WHR_{adjBMI} genetic score was significantly associated with WC regain from year 1 to 2 in all ancestries (P = 0.002) (Table 4) and White ancestry (P = 0.008) (Supplementary Table 3) and was also associated with WC regain in all ancestries from years 1 to 4 (P = 0.019), independent of changes in body weight (Table 4). The BMI and WHR_{adjBMI} genetic scores were not associated with weight regain from year 1 to 2 or years 1 to 4 in the White ancestry group (Supplementary Table 3). The BMI score was also not associated with WC regain from year 1 to 2 or years 1 to 4 (Supplementary Table 3). Hence, genetic predisposition to higher BMI was not associated with either weight loss or weight regain.

Our sample size was limited for identifying SNPs associated with weight loss and weight regain. None of the 894 independent SNPs for BMI reached a false discovery rate threshold of <0.01 for association with weight loss or weight regain (Supplementary Table 6). Similarly, none of the 481 independent SNPs for WHR_{adjBMI} reached a false discovery rate <0.01 for WC loss or regain (Supplementary Table 5).

Table 1—Baseline characteristics (mean ± SD) of the individuals who lost ≥3% of their initial body weight during the 1-year weight loss

	Combined	ILI	DSE	$P_{Difference}$*
Baseline				
Participants, *n*	1,415	1,088	327	
Race/ethnicity, *n* (%)				
White	952 (67.28)	729 (67.00)	223 (68.20)	0.6883
Black	187 (13.22)	147 (13.51)	40 (12.23)	0.5223
Hispanic	233 (16.47)	180 (16.54)	53 (16.21)	0.9822
Other	43 (3.04)	32 (2.94)	11 (3.36)	0.8246
Age, years	59.48 ± 6.63	59.41 ± 6.65	59.73 ± 6.59	0.4568
Weight, kg	101.30 ± 19.86	100.76 ± 19.77	103.10 ± 20.06	0.0713
Height, cm	167.51 ± 9.66	167.51 ± 9.60	167.49 ± 9.87	0.8376
WC, cm	113.97 ± 14.08	113.63 ± 14.16	115.09 ± 13.74	0.0934
WHR_{adjBMI} GRS	466.18 ± 11.14	466.12 ± 11.21	466.39 ± 10.92	0.7062
BMI GRS	864.77 ± 18.12	864.96 ± 18.17	864.12 ± 17.96	0.4560
Change baseline to year 1				
Participants, *n*	1,414	1,088	326	
Weight, kg	−9.99 ± 6.66	−10.94 ± 6.91	−6.81 ± 4.45	5.95×10^{-34}
Weight change, %	−9.76 ± 5.72	−10.72 ± 5.84	−6.56 ± 3.84	3.69×10^{-41}
WC, cm	−8.10 ± 7.61	−9.02 ± 7.87	−5.04 ± 5.68	1.75×10^{-22}
WC, %	−6.99 ± 6.30	−7.80 ± 6.46	−4.30 ± 4.81	2.28×10^{-24}
Change year 1 to year 2				
Participants, *n*	1,377	1,059	318	
Weight, kg	2.27 ± 5.08	2.76 ± 4.68	0.64 ± 5.96	6.93×10^{-9}
Weight change, %	2.57 ± 5.29	3.09 ± 5.03	0.83 ± 5.75	3.82×10^{-10}
WC, cm	2.01 ± 5.73	2.48 ± 5.62	0.44 ± 5.84	5.16×10^{-8}
WC, %	2.01 ± 5.38	2.45 ± 5.34	0.53 ± 5.27	2.12×10^{-8}
Year 2				
Weight, kg	93.71 ± 19.10	92.70 ± 19.08	97.07 ± 18.81	2.90×10^{-4}
WC, cm	107.84 ± 14.42	107.05 ± 14.55	110.48 ± 13.68	1.02×10^{-4}
Change year 1 to year 4				
Participants, *n*	1,382	1,063	319	
Weight, kg	4.19 ± 7.96	5.01 ± 7.84	1.47 ± 7.77	4.96×10^{-12}
Weight change, %	4.83 ± 8.31	5.75 ± 8.27	1.77 ± 7.70	1.27×10^{-14}
WC, cm	4.19 ± 7.75	4.88 ± 7.61	1.92 ± 7.76	3.89×10^{-9}
WC, %	4.21 ± 7.30	4.90 ± 7.23	1.907 ± 7.09	9.43×10^{-11}
Year 4				
Weight, kg	95.41 ± 19.64	94.83 ± 19.75	97.37 ± 19.15	0.0361
WC, cm	109.91 ± 14.60	109.39 ± 14.62	111.66 ± 14.44	0.0113

*Intergroup *P* values between ILI and DSE are derived from two-sample *t* test if the data followed a normal distribution, determined by examining histograms. For nonnormal distributed traits (weight loss from baseline to year 1 and relative weight loss), the Wilcoxon test was used. For ancestries, the χ^2 test was applied due to the categorical variables. GRS, genetic risk score.

DISCUSSION

In the present analyses of 1,415 participants from the Look AHEAD trial, individuals with a genetic predisposition to a higher WHR_{adjBMI} experienced a smaller reduction in abdominal obesity weight loss during the first year of a weight loss intervention and a larger regain in WC over the following 3 years. Genetic predisposition to higher BMI was not associated with either weight loss or weight regain.

Weight loss and maintenance are controlled by a complex interplay of biological and behavioral mechanisms, and genetic diversity in these mechanisms can affect the effectiveness of weight loss and maintenance efforts (33). Despite this, there is a lack of research on how genetic variation affects weight regain. Furthermore, to our knowledge, there have been no studies that have examined the relationship between genetic factors and changes in abdominal obesity after weight loss interventions. One study found that a higher WHR_{adjBMI} genetic risk score was associated with less weight loss (34), but no influence was found for a BMI genetic risk score. Another study found that a higher WHR_{adjBMI} genetic risk score was associated with a smaller loss of abdominal obesity during the first year of weight loss interventions (21). In the present study, we replicate these associations with a more comprehensive genetic risk score and, additionally, we show that a higher WHR_{adjBMI} genetic risk score also was associated with a higher regain of abdominal fat in the years that follow weight loss. Furthermore, our findings indicate that the detrimental effect of the WHR_{adjBMI} genetic risk score on WC during the

Table 2—Associations of BMI and WHR_{adjBMI} genetic scores with weight change from year 1 to 2 and years 1 to 4 in individuals who initially lost ≥3% of their initial body weight

Associations by outcome and group	Beta	Standard error	*P*	*N*	Adjustments
ILI+DSE					
Weight change years 1 to 2					
WHR_{adjBMI} GRS	0.019	0.012	0.127	1,386	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.006	0.008	0.428	1,386	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
Weight change years 1 to 4					
WHR_{adjBMI} GRS	−0.014	0.018	0.448	1,388	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.009	0.012	0.446	1,388	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
ILI					
Weight change years 1 to 2					
WHR_{adjBMI} GRS	0.009	0.013	0.475	1,067	Sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.001	0.008	0.932	1,067	Sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
Weight change years 1 to 4					
WHR_{adjBMI} GRS	−0.007	0.020	0.735	1,068	Sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.006	0.013	0.657	1,068	Sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
DSE					
Weight change years 1 to 2					
WHR_{adjBMI} GRS	0.049	0.030	0.107	319	Sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.026	0.019	0.164	319	Sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
Weight change years 1 to 4					
WHR_{adjBMI} GRS	−0.034	0.040	0.398	320	Sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.021	0.025	0.394	320	sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight

GRS, genetic risk score; PC, (genetic) principal component.

weight loss and weight maintenance periods leads to a compounded effect on abdominal adiposity.

Previous research on the association between individual BMI risk variants and weight loss or regain has yielded mixed results, with some studies finding an association and others reporting a weak or no association (25,35,36). In the present study, we included 894 variants in the BMI score and did not observe an association between them and weight loss during a lifestyle intervention. Additionally, this study is one of the first to examine whether BMI-associated variants predict weight gain after weight loss. We did not find any associations between BMI-associated variants and change in weight after initial weight loss. Furthermore, we found that the BMI-increasing genetic risk score was not associated with the change in abdominal obesity during the 1-year weight loss intervention or after. Overall, our results suggest that obesity risk variants identified in cross-sectional studies may not influence longitudinal changes in body weight during weight loss interventions. This finding suggests that biological mechanisms regulating weight change during such interventions may differ from those that determine body weight in a stable state.

Table 3—Associations of BMI and WHR_{adjBMI} genetic scores with WC change from year 1 to 2 and years 1 to 4 in individuals who initially lost ≥3% of their initial body weight

Associations by outcome and group	Beta	Standard error	*P*	*N*	Adjustments
ILI+DSE					
WC change years 1 to 2					
WHR_{adjBMI} GRS	0.033	0.010	6.78×10^{-4}	1,367	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
BMI GRS	−0.004	0.006	0.529	1,367	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
WC change years 1 to 4					
WHR_{adjBMI} GRS	0.026	0.010	0.012	1,372	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight
BMI GRS	0.006	0.007	0.409	1,372	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight
ILI					
WC change years 1 to 2					
WHR_{adjBMI} GRS	0.030	0.011	6.60×10^{-3}	1,050	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
BMI GRS	−0.003	0.007	0.685	1,050	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
WC change years 1 to 4					
WHR_{adjBMI} GRS	0.032	0.011	5.86×10^{-3}	1,054	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight
BMI GRS	0.004	0.007	0.565	1,054	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight
DSE					
WC change years 1 to 2					
WHR_{adjBMI} GRS	0.039	0.019	0.045	317	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
BMI GRS	−0.007	0.012	0.571	317	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
WC change years 1 to 4					
WHR_{adjBMI} GRS	−0.002	0.024	0.926	318	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight
BMI GRS	0.002	0.015	0.901	318	Sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight

GRS, genetic risk score; PC, (genetic) principal component.

Table 4—Associations of BMI and WHR_{adjBMI} genetic scores with weight and WC regain from years 1 to 2 and years 1 to 4 in the subset of individuals who lost ≥3% of initial body weight and regained weight

ILI+DSE	Beta	Standard error	*P*	*N*	Adjustments
Weight change years 1 to 2					
WHR_{adjBMI} GRS	0.008	0.009	0.388	1,010	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.000	0.006	0.970	1,010	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
Weight change years 1 to 4					
WHR_{adjBMI} GRS	−0.002	0.014	0.913	1,045	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
BMI GRS	0.002	0.009	0.825	1,045	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, year-1 weight
WC change years 1 to 2					
WHR_{adjBMI} GRS	0.035	0.012	1.77×10^{-3}	995	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
BMI GRS	0.001	0.007	0.937	995	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-2 weight
WC change years 1 to 4					
WHR_{adjBMI} GRS	0.028	0.012	0.019	1,032	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight
BMI GRS	0.005	0.008	0.559	1,032	Intervention arm, sex, baseline age, PC1–PC4, baseline weight, baseline height, baseline WC, year-1 weight and WC, year-4 weight

GRS, genetic risk score; PC, (genetic) principal component.

Consequently, there is a need for GWAS to identify genetic variants specifically associated with weight loss and weight regain to enable the design of appropriate polygenic scores and elucidate the underlying biology.

After weight loss, a coordinated decrease in energy expenditure and an increase in appetite contribute to weight regain. Previous research has identified many other potential mechanisms for weight regain, such as decreased resting metabolic rate and lowered leptin levels (37,38). Adding a genetic association, or the lack thereof, to the broader context of weight regain can contribute to our understanding of the mechanisms behind the regain of WC and guide future research. The distinct effects of the BMI and WHR_{adjBMI} genetic risk scores likely reflect their distinct biological effects: genetic variants associated with BMI primarily influence central nervous system–related pathways, whereas WHR_{adjBMI} variants have been implicated in adipose tissue biology and insulin resistance (39), and this seems to be an important factor for abdominal fat mass change during weight loss (40). The role of these variants associated with WHR_{adjBMI} requires further investigation to determine whether they overlap with the mechanisms previously associated with weight regain, such as leptin or resting metabolic rate, or if they are independent of them. This study adds new insights into the function of the variants associated both with overall adiposity and body fat distribution, an important perspective for understanding the significance of this research.

We found no interaction between the genetic risk scores and intervention arms on changes in weight and WC after weight loss. This implies that the results may not be specific to lifestyle intervention and might also apply to other types of weight loss interventions, such as pharmaceutical treatment or obesity surgery. More research is needed to determine if these results hold for different intervention modalities. Currently, genetic variations for BMI and WHR do not appear to influence weight loss or regain after obesity surgery (41,42), although there may be potential in combining clinical markers with genetic risk scores to improve the predictability of weight loss response after surgery (43).

Abdominal obesity is a major risk factor for cardiometabolic disease and type 2 diabetes (8,44). Previous studies in the Look AHEAD trial have revealed that individuals who

experienced the least favorable change in WC during weight loss had an increased risk of cardiovascular morbidity and mortality, regardless of the amount of weight loss (45). The negative impact of the WHR_{adjBMI} genetic risk score on abdominal obesity during weight loss and weight maintenance may undermine the benefits of the weight loss intervention (44).

The present study has several strengths, including the use of data from the large and well-documented Look AHEAD study, which resulted in significant weight loss and reduction in WC during the first year of the intervention, with annual follow-up of the participants. The use of a polygenic approach with hundreds of SNPs improved our ability to detect associations compared with previous studies. However, the study also has limitations. The Look AHEAD trial consisted of middle-aged and older (ages 45–76 years) participants with type 2 diabetes and overweight or obesity (>25 kg/m^2). Thus, the results may not be applicable to younger or nondiabetic populations. The weight change in older participants in Look AHEAD may have been influenced by aging and reduced lean mass (46). Furthermore, some participants continued to lose weight after the 1-year intervention. However, we conducted a sensitivity analysis of those participants who regained weight from years 1 to 2 or years 1 to 4 to ensure the robustness of our findings.

Our study was limited to analyzing the associations between genetic variants and obesity in combining races and ethnicities and in individuals of White ancestry, due to lack of sufficient sample sizes for other races and Hispanic ethnicity. Despite this, some of the associations in the White ancestry did not reach statistical significance, which may have been due to the reduced sample size. Additionally, the genetic variants used in the BMI and WHR_{adjBMI} genetic risk scores were primarily identified in populations of European ancestry, which may not be optimal for studying diverse ancestries. More research is needed to investigate potential differences in the genetic effects on general and abdominal obesity across different ethnicities. Additionally, it would have been valuable to include WHR as an abdominal obesity outcome, but hip circumference was not measured in the Look AHEAD study. However, WC has been suggested to be a better predictor of abdominal fat and type 2 diabetes than WHR (47–49), and WC and WHR are strongly correlated (39).

The key goal in managing obesity is to enhance the long-term health outcomes of the individual. Although there is genetic diversity in the biological and behavioral mechanisms that control weight maintenance, interventions and therapies are typically applied on the basis of their effectiveness in general populations. However, to effectively address obesity, it is essential to personalize interventions and target specific populations. In this study, we found that a genetic predisposition to higher WHR_{adjBMI} was associated with a smaller reduction in WC during a 1-year weight loss and a greater increase in WC during the subsequent 3-year follow-up, regardless of changes in body weight. Over a 4-year period, the WHR_{adjBMI} score was consistently associated with increased WC, whereas the BMI score was not associated with WC, indicating that WC change is regulated by a separate pathway from overall obesity during weight change. To our knowledge, these findings are the first of their kind and provide new insights into the mechanisms of weight regain.

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