nature communications

Article

https://doi.org/10.1038/s41467-026-75224-0

Dietary intervention and BMI reduction in individuals at the extremes of genetic predisposition to higher BMI: a randomized controlled trial

Received: 7 August 2025

Accepted: 22 June 2026

Published online: 13 July 2026

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Genetic susceptibility substantially contributes to inter-individual variation in body mass index (BMI), yet it remains unclear whether genome-wide polygenic risk modifies response to dietary weight loss interventions. We conducted a prospective, randomized controlled trial (GENEROOS) to test whether a BMI polygenic score (PS) interacts with a six-month dietary intervention on BMI change, which was the primary outcome. Using a genetic-first recontact strategy within 38,621 genotyped individuals, we recruited overweight or mildly obese, non-diabetic adults from the top and bottom 5% of the BMI PS distribution. A total of 223 participants (mean age 51.1 years; 74.9% women; mean BMI 30.3 kg/m^2) were randomized to structured dietary coaching or control. At baseline, individuals in the top 5% of the BMI PS distribution had a BMI 3.0 kg/m^2 higher than those in the bottom 5%. The diet intervention reduced BMI at six months (−1.51 kg/m^2, 95% CI − 1.72 to −1.31) compared with controls (−0.01 kg/m^2, 95% CI − 0.22 to 0.19). However, we observed no evidence of a BMI PS by intervention interaction on BMI change ($\beta = 0.06$, 95% CI − 1.33 to 1.44; $P = 0.94$). These findings suggest that, in this population, genetic susceptibility to higher BMI, as captured by current genome-wide polygenic scores, does not substantially modify short-term weight loss response to dietary intervention. However, given the study's sample size, modest interaction effects cannot be excluded, and larger studies are needed to clarify the role of polygenic scores in stratifying lifestyle-based weight loss interventions. ClinicalTrials.gov Identifier NCT06092372.

The prevalence of overweight and obesity is increasing globally, and it is a major public health concern. By 2035, 54% of the global adult population is estimated to be either overweight (body mass index (BMI) ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2)[1]. High BMI is a major risk factor for

several chronic diseases, including cardiovascular disease[2], diabetes mellitus, chronic kidney disease[3], and certain cancers[4], which can lead to premature mortality.

Overweight and obesity are complex, multifactorial conditions influenced by both genetic and environmental factors. Environmental factors contributing to a high BMI include unhealthy diet, low physical activity, and sedentary behaviors[5,6]. Despite environmental factors playing an important role, the heritability of BMI is estimated to be moderate to high, ranging from 0.23–0.90 depending on study design, age group, and population[7–9]. Twin and family studies consistently demonstrate substantial genetic contribution to BMI variability, with

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https://doi.org/10.1038/s41467-026-75224-0

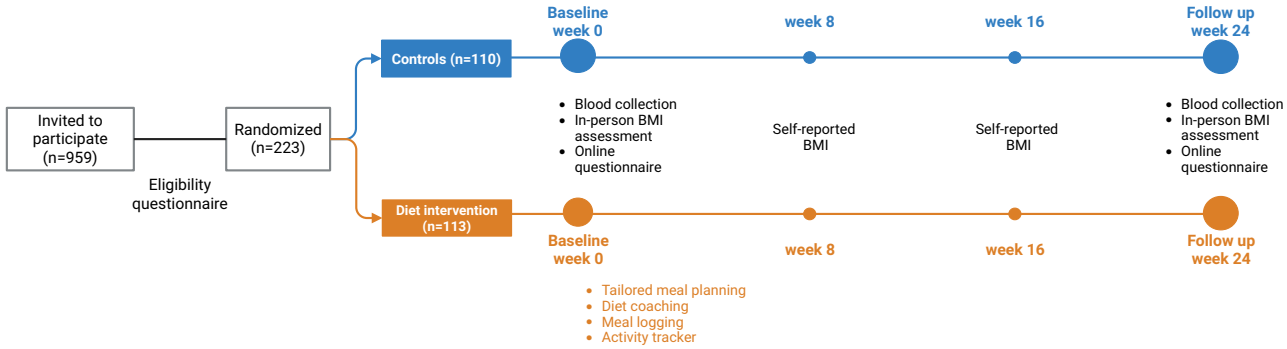

Fig. 1 | Study design and assessment timeline for the GENEROOS study. Schematic overview of participant screening, randomization, intervention, and outcome assessments conducted from baseline to the 24-week follow-up.

higher heritability estimates in children compared to adults, suggesting that genetic factors may exert a stronger influence early in life[7]. While rare monogenic forms of obesity exist, most genetic susceptibility arises from the cumulative effects of common single-nucleotide polymorphisms (SNPs). To date, over a thousand SNPs have been associated with BMI[10–12]. Polygenic scores (PS), which aggregate the effects of thousands of SNPs, explain approximately 8.4% of BMI variation[8], capturing only a fraction of the heritability estimated from twin and family studies[7]. In the UK Biobank, individuals in the top PS decile had a 25-fold higher risk of severe obesity (BMI > 40 kg/m^2) compared to those in the bottom decile[8]. However, PS is not deterministic, emphasizing that while genetic susceptibility plays a significant role, the interplay with the environment is crucial in shaping BMI over a lifetime.

Numerous dietary intervention studies have aimed to reduce body weight in overweight and obese individuals. A meta-analysis of clinical trials reported a mean weight loss of 5–8.5 kg (5% to 9%) during the first six months following reduced-energy diet interventions[13]. While the role of genetic variation in diet response remains unclear, some studies have suggested that genetic factors may influence individual responses to dietary and lifestyle interventions, while others not[14]. For example, a meta-analysis including retrospective analysis of diet interventions found that individuals carrying the homozygous FTO obesity-predisposing allele experienced greater weight loss through diet and lifestyle changes compared to non-carriers[15]. On the contrary, a meta-analysis by Livingstone et al. found that carriers of the FTO minor allele had a similar response to diet, drug, or lifestyle interventions compared to non-carriers[16]. To the best of our knowledge, the DIETFITS study is the only randomized trial that prospectively tested whether a three-SNP genetic score modified weight change in response to a healthy low-fat versus a healthy low-carbohydrate diet, but no significant differences were observed[17].

Genome-wide PS offers a substantially more powerful measure of genetic risk for BMI than individual SNPs such as those in the FTO gene. Two large behavioral intervention trials have investigated BMI polygenic scores or obesity-associated SNPs in relation to weight loss outcomes. Papandonatos et al. evaluated 91 BMI-associated SNPs from the Diabetes Prevention Program and Look AHEAD trials, finding no consistent evidence that genetic risk predicted weight loss or regain[18]. More recently, the ONTIME study by Dashti et al. employed a genome-wide polygenic score and identified that higher BMI PS was associated with a slower rate of weight loss during a structured behavioral intervention, though no association with total weight loss or interaction with intervention intensity was found[14]. However, existing studies have been limited by observational designs, the absence of control groups, or a lack of targeted recruitment based on genetic risk.

The GENEROOS study was designed to fill this gap by prospectively testing whether BMI polygenic risk affects weight loss following a dietary intervention. To further maximize power, we used a biobank-based genetic-first recontact strategy, recruiting participants at the extremes of BMI genetic risk from a pool of 38,621 already-genotyped individuals as part of the FinnGen study (Fig. 1). The primary objective of the GENEROOS study was to test whether overweight or mildly obese non-diabetic individuals in the top and bottom 5th percentile of BMI PS show differential response to BMI change after a six-month dietary intervention, compared to controls.

Results

Among 38,621 genotyped participants, 959 met initial eligibility criteria and were invited to the study, 529 in the Top 5% and 430 in the Bottom 5% of the BMI PS. Out of those invited, 642 (66.9%) did not respond, 79 (8.2%) responded but did not meet the study eligibility criteria, and 15 (1.6%) did not enroll in the study, resulting in 223 participants (23.3%) completing the first in-person visit and being randomized (mean age, 51.1 [SD, 10.4] years; 74.9% women; mean body mass index, 30.3 [SD, 3.2]). The study enrolment rate was very similar to the 23.1% we observed in a recent biobank-based recall study in Finland[19,20]. The flow of the study population through the study is shown in Fig. 2.

While we observed overall more individuals belonging to the top 5% of BMI PS than in the bottom 5% (N = 141 [63.2%] vs N = 82 (36.8%)), the distribution of the two groups was similar between study arms (Fig. 2). As expected at baseline, individuals in the top 5% of BMI PS had, on average, 3.0 kg/m^2 (95% CI, 2.2–3.8 kg/m^2) higher BMI and 8.4 kg (95% CI, 5.1–11.7 kg) higher body weight than those in the bottom 5% of BMI PS (Supplementary Fig. 1). There were no differences in other demographic, anthropometric, and biomarker characteristics between the study arms at baseline (Table 1).

Primary outcome

Of all individuals who participated in the baseline visit, 13 (5.8%) did not return to the six-month follow-up visit. The proportion of lost at follow-up was similar between the diet intervention and control group (6.2% vs 5.5%). In the diet intervention group, the adjusted mean change in BMI (kg/m^2) at two months was −1.18 (95% CI, −1.38−−0.97, n = 109), at four months was −1.61 (95% CI, −1.82−−1.40, n = 108), and at six months (end of study) was −1.51 (95% CI, −1.72−−1.31, n = 106), whereas in the control group the mean change in BMI (kg/m^2) at two months was −0.31 (95% CI, −0.52−−0.11, n = 107), at four months was −0.24 (95% CI, −0.45−−0.04, n = 106), and at six months (end of study) was −0.01 (95% CI, −0.22–0.19, n = 104). The difference in BMI change between the diet intervention and control groups was −0.87 (95% CI, −1.15−−0.58) at two months, −1.37 (95% CI, −1.66−−1.08) at four months, and −1.50 (95% CI, −1.79−−1.21) at six months.

The adjusted mean change in BMI (kg/m^2) in the top 5% BMI PS group at two months was −0.67 (95% CI, −0.84, −0.49, n = 109), at four months was −0.85 (95% CI, −1.03, −0.67, n = 108) and at six months was −0.69 (95% CI, −0.86, −0.51, n = 106), whereas in the bottom 5% BMI PS group at two months was −0.82 (95% CI, −1.03, −0.61, n = 109), at four

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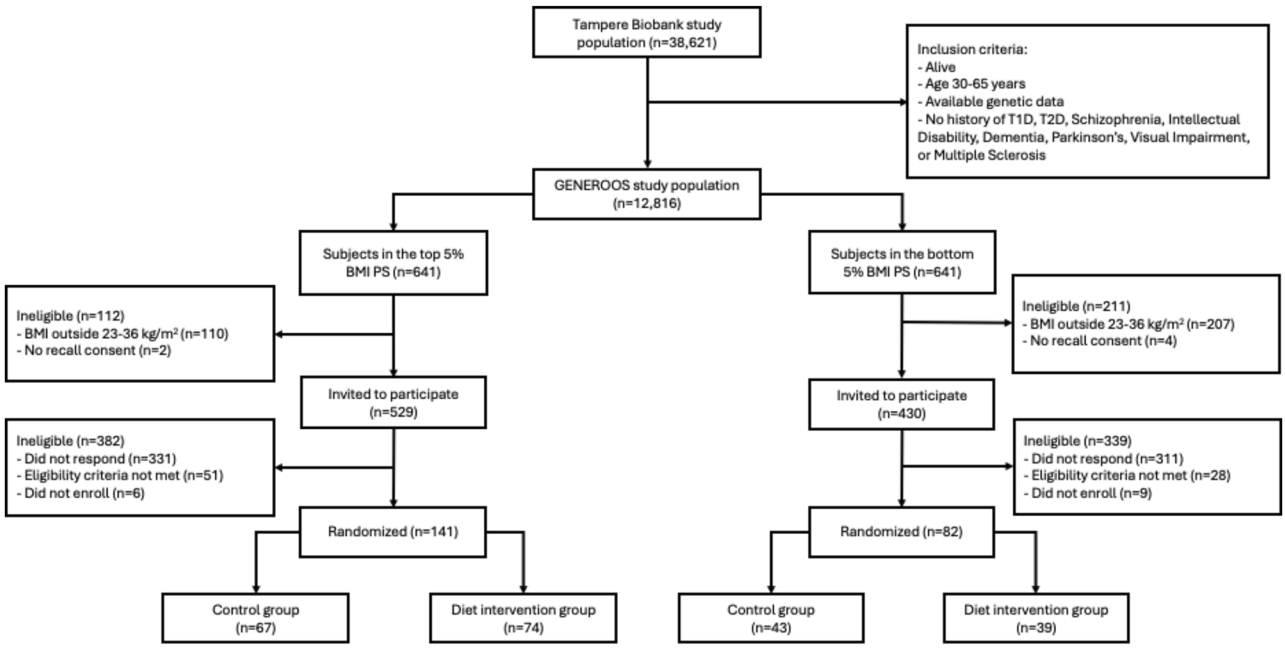

Fig. 2 | CONSORT flow diagram for GENEROOS study participants. Flow diagram showing participant inclusion, exclusion, and eligibility by BMI polygenic score group and trial arm (intervention or control).

Table 1 | Baseline descriptive characteristics of the GENEROOS study participants (*n* = 223)

Variable	Control (*n* = 110)		Diet intervention (*n* = 113)	
	Top 5% (*n* = 67)	Bottom 5% (*n* = 43)	Top 5% (*n* = 74)	Bottom 5% (*n* = 39)
Age, years [mean (SD)]	50.65 (11.21)	53.65 (9.94)	50.10 (10.88)	51.43 (8.55)
Sex, female [*n* (%)]	52 (77.6)	30 (69.8)	54 (73.0)	31 (79.5)
Weight, kg [mean (SD)]	89.74 (11.62)	80.56 (11.89)	88.58 (13.27)	80.89 (12.11)
Height, cm [mean (SD)]	168.06 (8.65)	169.19 (8.69)	168.56 (8.72)	167.51 (8.54)
Body mass index (BMI), kg/m^2 [mean (SD)]	31.72 (2.86)	28.05 (2.79)	31.06 (3.00)	28.73 (2.78)
Total cholesterol, mean (SD), mmol/l	4.91 (1.03)	4.91 (0.75)	4.69 (0.97)	5.15 (1.0)
High-density lipoprotein cholesterol, mean (SD), mmol/l	1.45 (0.40)	1.49 (0.37)	1.39 (0.40)	1.61 (0.41)
Low-density lipoprotein cholesterol, mean (SD), mmol/l	3.01 (0.90)	2.94 (0.78)	2.87 (0.85)	3.15 (0.86)
Triglycerides, mean (SD), mmol/l	1.60 (1.22)	1.51 (0.95)	1.48 (0.98)	1.56 (0.79)
Fasting glucose, mean (SD), mmol/l	5.64 (0.86)	5.60 (0.74)	5.69 (0.79)	5.67 (0.61)
Hemoglobin A1c, mean (SD), mmol/l	37.86 (5.17)	36.95 (4.15)	37.48 (3.84)	37.05 (2.89)

months was −1.00 (95% CI, −1.21, −0.79, $n = 108$) and at six months was −0.84 (95% CI, −1.05, −0.63, $n = 106$). The difference in BMI change between the Top 5% and Bottom 5% BMI PS groups was 0.15 (95% CI, −0.12–0.42) at two months, 0.15 (95% CI, −0.13–0.43) at four months, and 0.15 (95% CI, −0.12–0.42) at six months. The trajectory of BMI change (kg/m^2) between the control and diet intervention by the BMI PS groups is shown in Fig. 3.

We did not observe a statistically significant interaction between the BMI PS group and the diet intervention when using linear mixed models, which leveraged BMI estimates from both in-person visits (baseline and end-of-study) and self-reported weight measurements at months two and four. The interaction remained null in the additional models we ran as sensitivity analyses, which included only individuals with a baseline BMI of 25–35 kg/m^2 and 30–35 kg/m^2, compared to the 23.78–37.45 kg/m^2 used in the primary analysis (Table 2). The full model results from the primary analysis are shown in Supplementary Table 1. The three-way interaction between BMI measurement time, BMI PS group, and randomized intervention group was not statistically significant ($P = 0.42$), and inclusion of this term did not change the estimated BMI PS-by-intervention interaction. No adverse events related to the dietary intervention were reported during the study period.

Non-prespecified exploratory analysis

Participants logged meals on a mean of 64.2 (SD, 66.8) days during the six-month intervention, and their activity data were recorded on a mean of 125.0 (SD, 72.8) days. Greater meal logging adherence was significantly associated with greater BMI reduction ($\beta_{BMI_change} = -0.011$, 95%CI [−0.017, −0.007]). Similarly, greater activity data logging adherence was significantly associated with greater BMI reduction ($\beta_{BMI_change} = -0.006$, 95%CI [−0.011, −0.001]). However, although statistically significant, the estimated effect sizes were small relative to the overall mean BMI reduction of −1.5 kg/m^2 observed during the intervention, indicating that logging adherence alone explains only a limited portion of the total weight loss.

By the end of the study, individuals in the diet intervention group ($n = 106$) compared to controls ($n = 104$) had a change (mean, 95% CI, mmol/l) in total cholesterol of −0.21 (95% CI: −0.33–−0.08) vs −0.009 (95% CI: −0.14–0.12), LDL cholesterol −0.24 (95% CI: −0.35–−0.12) vs −0.06 (95% CI: −0.17–0.06), HDL cholesterol −0.02 (95% CI:

https://doi.org/10.1038/s41467-026-75224-0

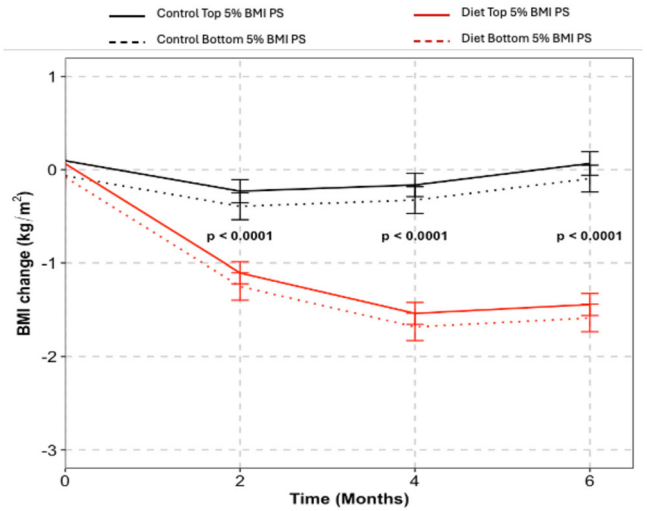

Fig. 3 | This figure shows the trajectory of BMI change (kg/m²) between the control and diet intervention stratified by BMI polygenic score (PS) group (*N* = 223). Data are presented as adjusted means (center) with standard errors (error bars), derived from the fully adjusted model. Participants in the diet intervention exhibited greater BMI reduction compared with controls at two, four, and six months (all $P < 0.0001$). At each time point, BMI change was compared between the diet intervention and control groups using a two-sided Mann-Whitney U (Wilcoxon rank-sum) non-parametric test. The effect of the diet did not differ by BMI PS group over time, as indicated by a non-significant treatment-by-time-by-PGS interaction ($P = 0.42$).

Table 2 | Interaction between BMI polygenic score group and diet intervention on BMI change

Model	PS Group * Diet Interaction Estimate[a]	95% CI	*P* Value
Model 1[b]	−0.02	−0.45, 0.42	0.94
Model 2[c]	−0.006	−0.45, 0.44	0.98
Model 3[d]	−0.08	−0.88, 0.72	0.85

[a]Estimates represent adjusted differences in BMI change comparing polygenic score groups between randomized diet intervention and control derived from linear mixed-effects models including fixed effects for age at baseline, sex, BMI at baseline, time, intervention group, BMI polygenic score group, time and intervention group interaction, and a random intercept for each participant. To model within-subject correlation over time, the compound symmetry was selected.

[b]Model 1 includes data from all individuals ($N_{individuals} = 223$ and $N_{observations} = 863$) with a BMI of 23.78–37.45 kg/m².

[c]Model 2 includes data from overweight/obese individuals ($N_{individuals} = 196$ and $N_{observations} = 760$) with a BMI of 25–35 kg/m².

[d]Model 3 includes data from obese individuals ($N_{individuals} = 101$ and $N_{observations} = 390$) with a BMI of 30–35 kg/m².

−0.05–0.02) vs −0.008 (95% CI: −0.04–0.03), triglycerides −0.22 (95% CI: −0.36–−0.08) vs −0.08 (95% CI: −0.24–0.08), HbA1C −0.62 (95% CI: −0.99–−0.26) vs −0.06 (95% CI: −0.69–0.58), and glucose −0.14 (95% CI: −0.26–−0.03) vs −0.003 (95% CI: −0.11–0.11). The between groups difference in total cholesterol was −0.20 mmol/l (95% CI: −0.38–−0.02), LDL cholesterol −0.18 mmol/l (95% CI: −0.34–−0.02), HDL cholesterol −0.01 mmol/l (95% CI: −0.06–0.04), triglycerides −0.14 mmol/l (95% CI: −0.35–0.07), HbA1c − 0.56 mmol/l (95% CI: −1.29–0.17), and glucose −0.14 mmol/l (95% CI: −0.30–0.02). Changes in all abovementioned laboratory values by intervention and BMI PS groups are shown in Supplementary Table 2. Missing baseline and follow-up laboratory values were low (5.8%) and similarly distributed across intervention and PS BMI groups. Logistic regression including intervention, PS BMI group, age, sex, and baseline BMI showed no significant associations with missingness (all $P > 0.2$), supporting the assumption that missing data were not systematically related to observed characteristics.

Discussion

It remains unclear whether genetic predisposition influences individual response to dietary weight loss interventions. In this prospective randomized study of overweight and mildly obese, non-diabetic individuals selected from the extremes of the BMI polygenic score distribution, a six-month dietary intervention led to significant reductions in BMI. Improvements in key cardiometabolic biomarkers, including total and LDL cholesterol, suggest that the weight loss achieved was sufficient in magnitude and duration to produce detectable and meaningful changes in cardiometabolic risk factors across genetic risk groups. We observed no statistically significant evidence that the BMI polygenic score modified the effect of diet intervention on BMI change. Within the limits of the study's power, these findings suggest that genetic susceptibility to higher BMI, as captured by current genome-wide polygenic scores, does not substantially alter response to dietary intervention.

Two previous meta-analyses[15,16] have reported conflicting results on the differential impact that diet interventions have on FTO risk allele carriers. BMI PS captures a substantially larger proportion of genetic risk for BMI compared to single variants such as FTO, which is also included in the PS, providing greater power to detect differential dietary effects. In our study, the differences in BMI between high and low PS groups (31.3 kg/m² vs. 28.4 kg/m²) were substantially larger than what was reported between carriers and non-carriers of the homozygous FTO risk allele (an increase of 0.31 kg/m² (0.14–0.47); $P < 0.001$) for each additional copy[16]. It remains possible, however, that the biological pathways linked to specific variants like FTO may influence diet responsiveness differently from the broader genetic effects captured by BMI PS.

Our findings are concordant with prior large-scale studies suggesting limited or no influence of genome-wide BMI polygenic scores on weight loss response to dietary and behavioral interventions. In the Look AHEAD and Diabetes Prevention Program trials, only one of 91 known BMI-associated variants (MTIF3-rs1885988) showed an association with total weight loss, underscoring a minor role of individual genetic variants in modifying intervention outcomes[18]. Similarly, in the ONTIME study—a genome-wide analysis of behavioral weight loss in over 1200 individuals—a higher BMI polygenic score was associated with a slightly attenuated rate of weight loss, but not with total weight loss or final outcomes[14]. In contrast, recent bariatric surgery studies have reported that BMI polygenic scores are associated with post-surgical weight loss trajectories, with lower genetic risk linked to greater long-term weight reduction[14,21–24]. These studies typically involve individuals with severe obesity undergoing profound anatomical and metabolic alterations. By design, our study excluded individuals with extreme obesity, prior bariatric surgery, or diabetes and evaluated a non-surgical dietary intervention producing more modest weight changes. It is therefore plausible that genetic influences on weight loss are more detectable in the context of the large physiological perturbations induced by bariatric surgery than in lifestyle-based interventions, where behavioral and environmental factors may play a comparatively greater role. Notably, the mean BMI reduction achieved through the dietary intervention (−1.5 kg/m²) was half of the baseline difference in BMI between BMI polygenic score extremes (3 kg/m²). While the intervention was similarly effective across genetic risk groups, the magnitude of BMI reduction was modest relative to the baseline differences in BMI associated with polygenic score groups.

Our study has several limitations. First, there was a higher proportion of women (74.9%) than men, likely due to known sex differences in volunteer participation, though sex was not a statistically significant predictor of BMI change in the adjusted model. Second, only 36.8% of participants were from the bottom 5th percentile of BMI

PS, as many were excluded for having a BMI below 23 kg/m² at screening. Third, we did not collect detailed data on calorie intake, which limited our ability to examine the behavioral mechanisms underlying weight loss and BMI reduction. Using data on adherence to meal and activity logging, we observed that greater adherence was associated with larger reductions in BMI, though effect sizes were relatively small. Engagement with the intervention application was variable across participants (mean 64.2, SD 66.8 days logged), which should be considered when interpreting these exploratory analyses. Importantly, BMI was directly and systematically measured in all participants, independent of logging behavior, and the variability in app engagement does not affect the reliability of our primary BMI-based findings. Fourth, although we used the most advanced BMI PS available at the time, it does not fully capture genetic contributions to BMI. Future studies should test whether newer, more predictive scores replicate these findings. Finally, generalizability may be limited to populations with the resources, interest, and digital literacy to engage in a structured dietary intervention focused on nutritional coaching and meal planning without a physical activity component.

A major strength of this study is its prospective, randomized design, in contrast to retrospective analyses often used to evaluate genetics in dietary response. Using a genetic-first recontact strategy from a cohort of over 38,000 genotyped individuals, we recruited participants at the extremes of BMI genetic risk with a 23.3% successful enrollment rate, maximizing power to detect differential effects. Although our hypothesis was not supported, we showcase how biobank-based studies can leverage existing genetic data to recall and prospectively enroll individuals into future precision medicine trials. Despite the potential for higher dropout in control groups, the dropout rate was 5.8% and similar across the intervention groups, highlighting strong participation retention and supporting the robustness of our findings. Finally, whereas most weight loss and BMI reduction trials target individuals with obesity and co-morbidities (e.g., type 2 diabetes), we focused on overweight participants without diabetes (BMI 23–36), a population more representative of those who might benefit from preventive interventions.

In conclusion, this prospective randomized dietary intervention study found no statistically significant evidence that BMI polygenic scores modified the intervention effect on BMI change among overweight and mildly obese non-diabetic individuals. Modest interaction effects cannot be excluded given the sample size, and larger studies are needed to evaluate smaller effects. Our findings suggest that, in this population, current genome-wide BMI polygenic scores have limited utility for identifying individuals most likely to benefit from dietary interventions aimed at reducing body weight, underscoring the importance of critically evaluating genetic tools before their integration into clinical decision-making.

Methods

Study design

The Role of Genetics in Weight Loss Study (GENEROOS, ClinicalTrials.gov: NCT06092372) was a six-month, single-site, parallel-arm diet intervention trial (Fig. 1, created in BioRender. Rodosthenous, R. (2025) https://BioRender.com/y4ujzed). The approved protocol, including the study design and statistical analysis plan, can be found in **Supplementary Material File 1**. In brief, participants were enrolled between October 2, 2023, and November 8, 2024. Under the Finnish Biobank Act (688/2012), biobanks may recontact individuals who have consented to such contact. Eligible individuals for recontact had to be alive, have consented to recontact via the Finnish Clinical Biobank Tampere, have genetic data from FinnGen release 11, be in the top or bottom 5th percentile of the BMI PS distribution, aged 30–65 years, and have a BMI of 23–36 based on their latest electronic health record (EHR) from Tampere University Hospital. Those without a recorded BMI were also eligible. Using nationwide inpatient and outpatient registers, we excluded individuals with a diagnosis of Type I or II Diabetes (ICD-10: E10–E14), prior bariatric surgery (Operation codes: JDF00–01, JDF10–11, JDF20–21, JDF96–97, JFD03–04, JFD20, JFD96), schizophrenia or intellectual disability (ICD-10: F20–F29, F70–F79), dementia or Parkinson's (ICD-10: F00–F09, G20, G30), visual impairment (ICD-10: H54), or multiple sclerosis (ICD-10: G35).

Ethics statement

The GENEROOS study was approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS/583/2022). No adverse effects, risks, or significant discomfort were anticipated for participants, aside from minor discomfort from blood draws. In accordance with Ethics Committee requirements, participants were informed about procedures for addressing any significantly abnormal laboratory findings that might require medical attention. Study subjects were also included in FinnGen and provided informed consent for biobank research, based on the Finnish Biobank Act. Details on the FinnGen study ethical approvals can be found in **Supplementary Material File 2**.

Re-contacting approach

Eligible individuals were invited via a physical letter from the Finnish Clinical Biobank Tampere. Interested participants logged into the study portal (https://omabiopankki.fingenious.fi/login), provided electronic informed consent, and completed an eligibility survey in RedCap[25], which collected self-reported height, weight (for BMI calculation), pregnancy status, motivation to lose weight, and smartphone ownership (**see Supplementary Material File 3**). Those with a BMI between 23–36, a smartphone, interest in weight loss, and—if female—not pregnant or breastfeeding, were eligible to enroll and book a clinical lab visit.

All eligible participants were randomized to the control or diet intervention group using computerized randomization (randomizeR package, R version 2024.12.0 + 467). Group assignment was revealed by the research nurse only after the baseline lab visit. Participants were blinded to their PS group, and outcome assessors were blinded to PS group and lab measures, though not to intervention assignment. Participants who were assigned to the control group were informed by the research nurse that no nutritional coaching or similar advise will be given to them during the study and that the team would be reaching out to them to report their body weight two more times, at months two and four, and to book their end-of-study in-person visit at the clinic for blood collection and body weight measurement six months after their enrollment that will successfully conclude their participation.

Blood sample collection and biomarker analysis

Fasting whole blood samples (3 × 3 mL) were collected by a trained bioanalyst in EDTA tubes (BD Vacutainer, catalog number 368499), heparin tubes (BD Vacutainer, catalog number 368497), and Vacuette glucose tubes (Greiner Bio-One, catalog number 454514), both at baseline and follow-up visits and shipped to Fimlab (Tampere, Finland) for biomarker analyses (i.e., total cholesterol, LDL, HDL, triglycerides, glucose and HbA1c). A non-prespecified exploratory analysis compared changes in all measured biomarkers between the diet and control groups. The results of biomarker analyses from both baseline and follow-up were returned to all study participants who provided informed consent and agreed to receive them at the end of the study.

Assessment of the primary outcome

We calculated the participants' BMI four times during the study: at baseline, two months, and four months from enrollment, and at the end of the study (Fig. 1). At baseline and end of the study, participants' BMI was calculated using the body weight and height as measured by a trained nurse in the clinic, whereas at months two and four was calculated using self-reported body weight and height via a text message.

Participants were advised to weigh themselves in the morning, before breakfast, and after emptying their bladder. To ensure the validity of self-reported BMI data at months two and four, we compared the baseline self-reported BMI collected from the online eligibility survey and in-person BMI measurements. The correlation between the two BMI measurements was high (Spearman's rho = 0.93, Supplementary Fig. 2).

Polygenic score for body mass index

We derived a polygenic score (PS) for BMI using summary statistics from two sources: (1) Yengo et al., which performed a GWAS of BMI in approximately 700,000 genotyped individuals[12], and (2) a GWAS of BMI in 315,152 individuals from FinnGen release 11, excluding participants from the Tampere biobank. The summary statistics from these two studies were meta-analyzed using METAL[26]. We then applied PRS-CS[27], following the pipeline available at https://github.com/FINNGEN/CS-PRS-pipeline, to generate the PS weights from the meta-analyzed summary statistics. The PS was based on 1,097,993 SNPs. The polygenic scores were calculated for individuals in the Finnish Clinical Biobank Tampere using the --score function in PLINK v2.00a4LM[28]. Among the 25,941 genotyped individuals with available BMI from the Finnish Clinical Biobank Tampere, the BMI PS explained 12.7% of the variance in BMI as measured by the coefficient of determination (R^2).

Diet intervention

The diet intervention coaching program, provided by ViaEsca Oy (Helsinki, Finland, viaesca.com), supported participants in reducing body weight and adopting a sustainable, balanced approach to healthy eating. It emphasized calorie intake and expenditure, using guidance based on official dietary recommendations. Interventionists were blinded to participants' PS group and lab measures. A standardized approach ensured all participants began from the same baseline, based on the principle that behavioral change is required for outcomes like body weight reduction. The diet intervention program was purely focused on nutritional coaching and meal planning, which addressed eating rhythm, portion control, balanced meals, caloric needs tied to activity levels, and preparation of nutritious, simple meals. There was no formal physical activity coaching, aside from using activity data to estimate each participant's caloric needs. Participants received through the application structured meal plans of five daily meals, personalized to individual caloric needs and set to 500 kcal/day below estimated energy expenditure. Plans followed macronutrient targets of 45–60% carbohydrates, 25–35% fat (at least two-thirds unsaturated), and 15–25% protein, including at least 35 g fiber and 500–800 g of vegetables and fruits daily. Caloric needs were estimated from registration data (age, height, weight, gender, and activity level) and refined with linked activity trackers using a rolling 7-day calorie average whenever possible. Participants could follow or adapt the plan to meet their energy target by voluntarily logging meals in the ViaEsca mobile app to monitor intake. A food diary allowed adjustments for meals outside the plan. An example of a rotating five-day meal plan is provided for reference in **Supplementary Material File 4**. Adverse events were monitored throughout the study by the coaches during the interaction with participants. Two automated messaging types supported participants: time-based messages with daily tips, educational content, and progress check-ins, and activity-based messages providing real-time feedback on intake and prompting coach interaction if targets weren't met. Participants also had online coaching access via chat for support and guidance, if needed. Adherence to the nutritional intervention was quantified using app-derived engagement metrics. Meal logging adherence was defined as the number of days participants logged dietary intake in the mobile application during the six-month intervention period. Activity tracking adherence was defined as the number of days during which step counts were recorded via the wearable device. Both metrics were analyzed as raw counts and as proportions relative to the total study duration.

Statistical analysis

Based on the original study design with 62 participants in each of the 4 relevant groups (Top/Bottom 5% BMI PS and dietary intervention), and assuming normally distributed weight change at six months, there was 80% power to detect a 15% difference in diet intervention effect by BMI PS group (i.e., whether diet intervention affected BMI change between BMI PS groups). This was based on simulations and a 2-sided Wald test at the .05 significance level. The primary outcome was body mass index change (kg/m^2) at six months; all other measures were non-specified exploratory outcomes. Outcomes are presented as means and 95% confidence intervals (CI). An intent-to-treat principle was applied, including all randomized participants with baseline data in the analysis according to original assignment, regardless of adherence or follow-up. This assumes missing follow-up data are unrelated to unobserved BMI values, conditional on treatment assignment and baseline/intermittent weights.

Linear mixed-effects models for repeated measures were used to assess the effects of diet intervention, PS group, and their interaction, using the *lme* function from the *nlme* package in R. Participants had random intercepts to account for individual-level variability. The model included a randomized intervention group (diet or control), BMI PGS group (top or bottom 5%), and their interaction, and was adjusted for age, sex, baseline BMI, and BMI measurement time. To model within-subject correlation over time, unstructured, compound symmetry (CS), first-order autoregressive, and Toeplitz structures were evaluated. The final covariance structure (i.e., CS) was selected based on convergence and the lowest Bayesian Information Criterion (BIC), indicating the optimal balance between goodness of fit and model parsimony. Missing outcome data were handled using likelihood-based estimation in linear mixed-effects models fitted by restricted maximum likelihood (REML). Under the assumption that data were missing at random (MAR), this approach allows all available observations to contribute to parameter estimation without requiring imputation, with within-subject correlation accounted for through the specified covariance structure. The *na.exclude* option was used to ensure appropriate alignment of fitted values and residuals while excluding missing observations from the likelihood. Sensitivity analyses were conducted by refitting the primary mixed-effects model in restricted samples defined by baseline BMI. Specifically, analyses were repeated among participants with baseline BMI 25–35 kg/m^2 to align with the trial protocol, and among obese participants only with baseline BMI 30–35 kg/m^2 to assess the robustness of the primary findings to the BMI range included. Standard diagnostics assessed normality and homoscedasticity of residuals. Differences in body weight and BMI, between Top 5% vs Bottom 5% BMI PS at baseline, were compared using a two-sided Mann-Whitney U (Wilcoxon rank-sum) test. While the prespecified, primary outcome was the change in BMI from baseline to six months, linear mixed-effects models incorporating repeated measurements at months two and four were used to estimate BMI change trajectories and improve precision of effect estimates; these longitudinal analyses are considered exploratory with respect to trial outcome specification. In a sensitivity analysis, we additionally tested a three-way non-prespecified exploratory interaction between BMI measurement time, BMI PS group, and randomized intervention group to assess whether the BMI PS-by-intervention interaction varied over time.

Non-prespecified exploratory analyses comparing changes in total cholesterol, LDL, HDL, triglycerides, glucose, and HbA1c between diet and control groups were conducted using a two-sided Mann-Whitney U (Wilcoxon rank-sum) test. The number and proportion of missing laboratory values were tabulated by intervention and PS BMI group. Associations between missingness and baseline covariates were assessed using logistic regression. Meal logging and activity logging were each modeled separately in univariate regression models against

BMI change, with the predictor unit being the number of days logged during the six-month intervention. All analyses were conducted in RStudio (version 2026.01.1+403).

Changes compared to the registered trial protocol

Compared to the submitted trial protocol, there have been two major changes. First, we originally planned to recruit 300 participants per PS group across three biobanks. Due to logistical challenges, we instead focused on a single biobank and recruited fewer participants than originally planned. The updated power calculations reflect this revised scenario, and post hoc power calculations based on the achieved sample sizes indicate that power remained >80% for detecting the prespecified interaction effect. To maintain our statistical power as high as possible, we kept all individuals who enrolled in the study with a BMI ranging from 23.78–37.45 kg/m^{2,} and instead of removing those outside the 25–35 kg/m^2 range before enrollment, we excluded them in the analysis by performing sensitivity analyses. Second, while the original protocol stated that we would measure clinical biomarkers, we did not explicitly specify them as a "secondary outcome." Because of this, we refer to these analyses in the manuscript as a "non-prespecified exploratory analysis".

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Pseudonymized individual participant data underlying the results reported in this article have been deposited in the CSC Fairdata IDA repository (https://doi.org/10.23729/fd-3410f4a3-79bc-3773-a590-24629494ede6) under restricted access. Access can be obtained through the Finnish Biobank Cooperative's Fingenious® portal (https://fingenious.fi/en/), which provides access to data held at Finnish biobanks, including the Finnish Clinical Biobank Tampere. Access requests must include a methodologically sound proposal and are subject to review and approval in accordance with Finnish biobank legislation and the terms of the original informed consent of the study participants. Secondary users must agree not to attempt re-identification of participants and must cite the original trial (ClinicalTrials.gov: NCT06092372) and specify how their analyses differ from previously reported findings.

Code availability

R code used for data preparation and analysis can be found at the GENEROOS GitHub repository: https://github.com/dsgelab/GENEROOS_Public, as well as in Zenodo https://doi.org/10.5281/zenodo.20441193.

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Acknowledgements

Following biobanks are acknowledged for delivering biobank samples to FinnGen: Auria Biobank (www.auria.fi/biopankki), THL Biobank (www.thl.fi/biobank), Helsinki Biobank (www.helsinginbiopankki.fi), Biobank Borealis of Northern Finland (https://www.ppshp.fi/Tutkimus-ja-opetus/Biopankki/Pages/Biobank-Borealis-briefly-in-English.aspx), Finnish Clinical Biobank Tampere (https://www.pirha.fi/en/web/english/for-professionals/finnish-clinical-biobank-tampere), Biobank of Eastern Finland (www.ita-suomenbiopankki.fi/en), Central Finland Biobank (www.ksshp.fi/fi-FI/Potilaalle/Biopankki), Finnish Red Cross Blood Service Biobank (www.veripalvelu.fi/verenluovutus/biopankkitoiminta), Terveystalo Biobank (www.terveystalo.com/fi/Yritystietoa/Terveystalo-Biopankki/Biopankki/) and Arctic Biobank (https://www.oulu.fi/en/university/faculties-and-units/faculty-medicine/northern-finland-birth-cohorts-and-arctic-biobank). All Finnish Biobanks are members of BBMRI.fi infrastructure (https://www.bbmri-eric.eu/national-nodes/finland/). Finnish Biobank Cooperative -FINBB (https://finbb.fi/) is the coordinator of BBMRI-ERIC operations in Finland. The Finnish biobank data can be accessed through the Fingenious® services (https://site.fingenious.fi/en/) managed by FINBB.

Author contributions

Drs Rodosthenous and Ganna had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. R.S.R., E.W., S.R., and A.G. contributed to the concept and design of the study. R.S.R., L.E.V., A.C., S.J., E.B., E.M., M.V., and N.K. contributed to the acquisition, analysis, or interpretation of data. A.M.C., L.E.V., E.M., M.V., and N.K. provided administrative, technical, or material support. R.S.R. and E.B. performed the statistical analysis. R.S.R., T.C., E.B., and A.G. drafted the manuscript. A.G. obtained funding. E.W., S.R., and A.G. supervised the study. All authors critically reviewed the manuscript for important intellectual content and gave final approval of the version to be published.

Funding

This study has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant number 945733). We also want to acknowledge the participants and investigators of the FinnGen study. The FinnGen project is funded by two grants from Business Finland (HUS 4685/31/2016 and UH 4386/31/2016) and the following industry partners: AbbVie Inc., AstraZeneca UK Ltd, Biogen MA Inc., Bristol Myers Squibb (and Celgene Corporation & Celgene International II Sàrl), Genentech Inc., Merck Sharp & Dohme LCC, Pfizer Inc., GlaxoSmithKline Intellectual Property Development Ltd., Sanofi US Services Inc., Maze Therapeutics Inc., Janssen Biotech Inc, Novartis AG, and Boehringer Ingelheim International GmbH.

Competing interests

The authors declare the following competing interests: Dr. Andrea Ganna is the founder of Real World Genetics Oy, Finland. Ettore Brenna is an employee of Eli Lilly and Company, Indianapolis, Indiana, USA. All other authors declare no potential conflicts of interest.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-026-75224-0.

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Peer review information *Nature Communications* thanks Akl Fahed, Min Kim, Ulf Risérus and the other anonymous reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

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