nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Electronic biobank consents were collected via the OmaBiopankki portal (https://omabiopankki.fingenious.fi/login). Study consents and online questionnaire data were collected via RedCap (15.0.30). Self-reported bodyweight data were collected via SMS/email. Diet intervention data were collected via the ViaEsca Oy phone application. Clinical chemistry data were collected via the Fimlab and Tampere Biobank databases.
Data analysis	R version 2026.01.1+403 was used for all the analyses. 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.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

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.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	As this was a biobank-based study that used already available genetic data from FinnGen project, sex (i.e., male and female) was the only variable used and reported in the manuscript. Sex was determined based on both self-reported information and a matching genetic profile.
Reporting on race, ethnicity, or other socially relevant groupings	All participants were Finns.
Population characteristics	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). 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. The flow of the study population through the study is shown in Figure 2.
Recruitment	Participants were recruited from a biobank population based on extreme BMI polygenic score (PS) percentiles (top and bottom 5%), and were invited to participate via a recall consent process. Interested participants self-selected into the study by logging into an online portal, providing electronic informed consent, and completing an eligibility survey. This self-directed recruitment process may introduce self-selection bias, as individuals who chose to engage are likely more health-conscious, digitally literate, and motivated to lose weight than non-responders, and indeed, motivation to lose weight was an explicit eligibility criterion. This may lead to an overestimation of intervention effects compared to a less selected population. The study sample also had a higher proportion of women (74.9%) than men, consistent with known sex differences in volunteer participation. Additionally, 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, which may affect the representativeness of the PS groups. Generalisability may further be limited to populations with the resources, interest, and digital literacy to engage in a structured digital dietary intervention. However, the pre-specified primary outcome, i.e., the PS group by diet interaction is an internal comparison and is less susceptible to these biases than the absolute intervention effects.
Ethics oversight	Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS/583/2022)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	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 6 months, there was 80% power to detect a 15% difference in diet intervention effect by BMI PS group (i.e., whether diet intervention affected weight change between BMI PS groups). This was based on simulations and a 2-sided Wald test at the .05 significance level. 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.
Data exclusions	An intent-to-treat principle was applied, including all randomized participants with baseline data in the analysis according to original

Data exclusions	assignment, regardless of adherence or follow-up. This assumes missing follow-up data are unrelated to unobserved weight values, conditional on treatment assignment and baseline/intermittent weights.
Replication	The study represents a first-in-kind study design combining polygenic score-based participant stratification with a dietary intervention, and exact replication of the trial is not feasible given its unique design and the resource requirements of a prospective randomised controlled trial. Reproducibility was addressed through the following measures: (1) the trial was prospectively registered at ClinicalTrials.gov (NCT06092372) with a pre-specified primary outcome and analysis plan; (2) pseudonymized participant data are made available via the FINBB Fingenious portal to enable independent re-analysis of the reported findings; (3) analysis code is publicly available at [https://github.com/dsgelab/GENEROOS_Public] enabling full computational reproducibility of all statistical analyses; and (4) the manuscript reports all primary and secondary outcomes as pre-specified, with no selective reporting.
Randomization	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.
Blinding	Participants were blinded to their PS group, and outcome assessors were blinded to PS group and lab measures, though not to intervention assignment. Interventionists were blinded to participants' PS group and lab measures.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov Identifier: NCT06092372
Study protocol	The approved study protocol is provided in Supplementary Material as File 1
Data collection	The Role of Genetics in Weight Loss Study (GENEROOS, ClinicalTrials.gov: NCT06092372) was a 6-month, single-site, parallel-arm diet intervention trial, and participants were enrolled from the Finnish Clinical Biobank Tampere between October 2, 2023, and November 8, 2024
Outcomes	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 (Figure 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 month 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 Figure 2). Non-prespecified exploratory outcomes were changes in basic cardiometabolic clinical markers (total cholesterol, LDL, HDL, triglycerides, glucose and HbA1c) as measured at baseline and follow-up from blood.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*