nature portfolio

Corresponding author(s): Jena S. Tronieri

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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	Redcap v.14.9.4
Data analysis	SPSS Statistics v.28.0.1.1; R (v.4.2.2) package miceadds

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

De-identified participant data used in the present analyses will be made available to investigators for research purposes after release of this publication. Data will be provided following the review and approval of a research proposal (including
a statistical analysis plan) by the corresponding author and at least one other doctoral-level researcher at the University of Pennsylvania. The initial review will be completed within 3 months of receipt of the proposal. Completion of a data sharing agreement through the Office of Human Research at the University of

Pennsylvania will then be required before the data can be accessed. Because of privacy restrictions included in the informed consent of the participants, data cannot be made freely available in a public repository. Data request should be addressed to the corresponding author (jena.tronieri@pennmedicine.upenn.edu).

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	SAGER guidance does not apply to RCTs. Sex assigned at birth was collected via self report.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were collected via self-report. For all categorical classifiers (e.g., race), a list of terms was provided by the researchers, but participants could select to write in a different response. Participants could select one or more categories or could decline to respond.
Population characteristics	Adults ages 18-70 years with a BMI ≥31 kg/m² or ≥28 kg/m² with an obesity-related comorbidity
Recruitment	July 2019 - Nov 2021 via print and social media advertisements
Ethics oversight	University of Pennsylvania (PA, USA) Institutional Review Board

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

Behavioural & social sciences study design

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

Study description	single-center, double-blinded, parallel-group design randomized controlled trial
Research sample	147 adults ages 18-70 years with a BMI ≥31 kg/m² or ≥28 kg/m² with an obesity-related comorbidity; 76 of whom were randomized
Sampling strategy	Participants were recruited between July 2019 and November 2021 via print and social media advertisements. We predicted that the BT+AOM group would lose 4.5% more of body weight than the BT+P group from randomization to week 24, with expected standard deviations of 5.5% in both groups (effect size: d = 0.82).20 Assuming a 20% attrition rate, a randomized sample of 50 non-responders (25 per group) was expected to provide 81.5% power to detect between-group differences at week 24 in the primary outcome (2-tailed □ level = 0.05). We anticipated that at least 33% of phase 1 participants would be categorized as early non-responders.5-7 Therefore we planned to enroll 150 participants in phase 1 in order to achieve a randomized sample of □50 early non-responders.
Data collection	In-person assessment at weeks -4, 0, and 24; week 24. Body weight was measured to the nearest 0.1kg by trained staff using a digital scale (Tanita BWB800). Body weights were measured at home for 22 early non-responders and 8 early responders using a uniform procedure and scale due to the suspension of in-person activities due to COVID-19.
Timing	Recruitment occurred between July 2019 - November 2021, and the last participant completed the study in May 2022
Data exclusions	No data were excluded; all 76 randomized participants were included in ITT analyses
Non-participation	795 persons were pre-screened but not enrolled. Of the 147 who enrolled; 16 did not enroll in phase 2 and 55 were early responders who were not eligible for randomization, resulting in 76 who were randomized. Five randomized participants did not provide a body weight at week 24.
Randomization	Early non-responders were randomly assigned 1:1 to phentermine or placebo in permuted blocks of 2 to 4 participants via random number tables. Randomization was performed by Penn's Investigational Drug Services, which provided the study medications in blinded capsules.

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 number NCT03779048
Study protocol	Available at: https://doi.org/10.21203/rs.3.pex-2526/v1
Data collection	Recruitment occurred at the University of Pennsylvania (Philadelphia, PA) between July 2019 - November 2021, and the last participant completed the study in May 2022
Outcomes	Primary: percentage change in initial body weight as measured from randomization (week 0) to week 24 in early non-responders to BT. Secondary: portion of non-responders who achieved a post-randomization loss of ≥5% and ≥10% of body weight, as measured from randomization to week 24, as well as 24-week changes in resting blood pressure, pulse, fasting glucose, triglycerides, lipids, quality of life and mood

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.*