

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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ | 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ | 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	Data were obtained from clinical measurements, imaging platforms, structured questionnaires, and cognitive assessments, and were entered manually into study databases. No specialized software was used for data collection
Data analysis	No custom code or algorithms were developed for this study. All analyses were performed using standard functions from established R packages (version 4.4.1), including: metafor, ggplot2, dplyr, tidyr, lme4, MESS, ggrridge, DiagrammeR, and ggsummary.

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](#)

Data are available from the corresponding author, Prof. Iris Shai. Requests will be reviewed in accordance with institutional guidelines and relevant ethical approvals

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	Sex was used as the relevant variable throughout the study. Sex was determined based on biological attributes as recorded in clinical documentation. Gender was not assessed. All analyses and subgroup characteristics refer to biological sex.
Reporting on race, ethnicity, or other socially relevant groupings	Race, ethnicity, and other socially constructed variables were not collected or analyzed in this study.
Population characteristics	The study included 881 adult participants aged 30–75 years, recruited across four RCTs conducted between 2005 and 2018 in Israel. Inclusion criteria varied by trial and included abdominal obesity (waist circumference or BMI thresholds), type 2 diabetes, and/or dyslipidemia.
Recruitment	Participants were recruited via personal contact among individuals who had previously participated in one of four lifestyle intervention trials (DIRECT, CASCADE, CENTRAL, DIRECT-PLUS). All individuals were approached individually and invited to participate in the current long-term follow-up study
Ethics oversight	The original randomized controlled trials and the long-term follow-up study, were approved by the Institutional Review Board (IRB) and the Helsinki Committee of Soroka University Medical Center, Beer-Sheva, Israel. All participants provided written informed consent in accordance with the Declaration of Helsinki.

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	The analytic sample was drawn from four prior lifestyle intervention trials, yielding 881 participants after excluding duplicates. Of these, 647 completed follow-up assessments in the FIT study, including 533 individuals who underwent brain MRI scans. As the final sample size was dependent on both historical trial enrollment and participants' willingness to take part in long-term follow-up, it could not be pre-specified. Nonetheless, a post hoc power analysis was conducted following data collection. Detailed power calculations are presented in the Supplementary Methods.
Data exclusions	Participants who were deceased, lost to follow-up, or declined participation in the FIT study were excluded from the long-term follow-up.
Replication	Brain MRI scans were acquired using consistent imaging protocols and re-analyzed with the same automated software (NeuroQuant v4.1.2) for both historical and follow-up scans. Blood biomarkers and anthropometric measures were collected using identical protocols as in the original RCTs. VAT quantification showed high reproducibility (inter- and intra-rater $r > 0.96$). Consistency in acquisition and analysis methods supports reproducibility.
Randomization	The FIT study is a non-randomized follow-up of four prior RCTs. No new random allocation was applied;
Blinding	No intervention groups were defined in the FIT follow-up study. All data analyses, including imaging and adiposity assessments, were performed using anonymized identifiers (SNO), and analysts were blinded to participants' identities and clinical history.

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	The FIT is follow-up study and was not registered as a clinical trial. The original intervention trials (DIRECT, CASCADE, CENTRAL, DIRECT-PLUS) were registered; registration numbers are provided in the respective original publications.
Study protocol	The FIT follow-up study is a study following four previously registered lifestyle intervention trials (DIRECT, CASCADE, CENTRAL, and DIRECT-PLUS), with registration numbers provided in the main manuscript. A formal protocol for the FIT study was not published or prospectively registered. However, the study design, data sources, and methodologies are described in detail in Supplementary Methods 1–4.
Data collection	Primary outcome data, including abdominal and brain MRI scans, cognitive testing using the Montreal Cognitive Assessment (MoCA), and lifestyle questionnaires, were collected at Soroka University Medical Center during the FIT follow-up visits. Secondary data, including anthropometric measurements, blood pressure, and fasting blood biomarkers, were collected at two designated clinics: the health clinic of the Negev Nuclear Research Center (NNRC) in Dimona, for participants who were still actively employed, and the Briuta Care Medical Center in Be'er Sheva, for retired participants. Additional methodological details are available in Supplementary Methods 1–4.
Outcomes	Primary outcomes included:(1) Cognitive performance, measured using the Montreal Cognitive Assessment (MoCA; score range: 0–30) and the MoCA Memory Index Score (MoCA-MIS; range: 0–15);(2) Brain volumes assessed using 3D T1-weighted MRI scans and quantified with FDA-approved NeuroQuant® software (version 4.1.2), including total brain volume (TB), cortical gray matter (GM), white matter (WM), total ventricular volume (TV), and hippocampal occupancy score (HOC);(3) Abdominal adipose tissue depots (visceral adipose tissue [VAT], deep and superficial subcutaneous adipose tissue [SAT]), assessed via 3T MRI using standardized anatomical landmarks and semi-automated MATLAB-based software. Secondary outcomes included:Anthropometric indices (e.g., BMI), blood pressure, fasting blood biomarkers (e.g., glucose, lipid profile), and structured lifestyle questionnaire data with dietary adherence evaluated using the 14-item Mediterranean Diet Adherence Screener. Further methodological details are provided in Supplementary Methods 1–4.

Plants

Seed stocks	<i>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.</i>
Novel plant genotypes	<i>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.</i>
Authentication	<i>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, mosaicism, off-target gene editing) were examined.</i>

Magnetic resonance imaging

Experimental design

Design type	No task-related, event-related, or block-design paradigms were used. Structural T1-weighted MRI scans were acquired at rest using standard clinical imaging protocols.
Design specifications	Structural brain scans were acquired using a 3.0-Tesla Philips Ingenia scanner with a 3D T1-weighted turbo field echo (T1-TFE) sequence. Voxel resolution was 1.0 mm ³ isotropic, with TR = 2500 ms and TE = 30 ms. Abdominal fat imaging employed a modified DIXON (mDIXON) sequence without interslice gaps (slice thickness: 2 mm), with echo times of 1.19 ms and 2.3 ms and voxel size of 2 × 1.4 × 1 mm.

Behavioral performance measures

No behavioral or performance measures were collected during the MRI acquisition. Cognitive performance was assessed separately using the Montreal Cognitive Assessment (MoCA) and MoCA Memory Index Score (MoCA-MIS), outside the scanner environment.

Acquisition

Imaging type(s)

Structural (T1-weighted) brain MRI and structural abdominal fat imaging (mDIXON-based fat–water separation)

Field strength

3.0 Tesla

Sequence & imaging parameters

For brain imaging, a T1-weighted 3D sagittal acquisition (T1-3D SAG), compliant with NeuroQuant® specifications, was used. Scans were acquired on a 3.0-Tesla Philips Ingenia scanner using a turbo field echo (T1-TFE) sequence and were saved as DICOM file with the following parameters: voxel size = 1.0 mm³ isotropic; TR = 2500 ms; TE = 30 ms; field of view = 240 × 220 × 150 mm. This sequence is FDA-approved and fully compatible with the NeuroQuant® analysis pipeline. For abdominal imaging: 3D modified DIXON (mDIXON) sequence without interslice gaps; TR = 3.6 ms; TE = 1.19 ms and 2.3 ms; voxel size = 2 × 1.4 × 1 mm; FOV = 520 × 440 × 80 mm. Four phase-encoded images acquired per scan (in-phase, out-of-phase, fat-phase, water-phase). Breath-hold technique used to minimize motion artifacts.

Area of acquisition

Whole-brain coverage was acquired for brain imaging. Abdominal scans focused on two axial slices at standardized vertebral levels: L4–L5 and L5–S1.

Diffusion MRI

☐

Used

☒

Not used

Preprocessing

Preprocessing software

Brain MRI preprocessing was performed using NeuroQuant® Software v4.1.2 (CorTechs Labs, FDA-cleared). The pipeline includes skull stripping, bias correction, segmentation, and volumetric quantification based on atlas registration. Abdominal imaging data were processed using custom MATLAB-based semi-automated software, including manual delineation of anatomical landmarks.

Normalization

Brain region volumes were normalized to intracranial volume (ICV), automatically computed by NeuroQuant based on segmented brain tissues. Volumes are expressed both as raw (cm³) and as %ICV. For abdominal fat data, areas were expressed as absolute values (cm²) and as a proportion of total abdominal fat area, with no normalization applied.

Normalization template

NeuroQuant applies spatial normalization to an atlas-based brain mapping, which supports age- and sex-matched percentile comparisons.

Noise and artifact removal

NeuroQuant includes bias field correction, intensity normalization, and skull removal and automated artifact correction. Abdominal scans were acquired using a breath-hold technique to minimize motion artifacts; structured noise correction was not required due to short scan duration.

Volume censoring

No explicit volume censoring was applied. All brain scans passed automated NeuroQuant quality checks. Poor-quality abdominal scans were excluded by trained raters blinded to condition and time point. Abdominal scans were visually inspected, and poor-quality images were excluded.

Statistical modeling & inference

Model type and settings

Statistical analyses included: (1) Linear regression models for cross-sectional associations; (2) Linear mixed-effects models (LMMs) for repeated measures of brain volume over three time points, with random intercepts for participant ID; and (3) fixed-effect meta-analysis across two trials using summary estimates. All continuous predictors were standardized (Z-scores).

Effect(s) tested

Effects tested included: (a) associations between adiposity depots (VAT, SAT) and MoCA cognitive score, (b) Time × VAT AUC interactions on brain volume slopes, and (c) percent changes in fat depots predicting long-term brain structure and cognition.

Specify type of analysis:

☐

Whole brain

☐

ROI-based

☒

Both

Anatomical location(s)

Brain volume analysis focused on global structural measures, including total brain volume (TB), cortical gray matter (GM), white matter (WM), and total ventricular volume (TV), as well as the hippocampal occupancy score (HOC). These outcomes were quantified using NeuroQuant® (Version 4.1.2), an FDA-cleared automated segmentation software. Abdominal fat depots were manually delineated from axial MRI slices at standardized vertebral levels (L4–L5 and L5–S1) using MATLAB-based semi-automated analysis.

Statistic type for inference

Inference was based on LMM estimates and regression beta coefficients with 95% CI.

(See [Eklund et al. 2016](#))

Correction

Correction for multiple comparisons was applied for models involving multiple testing using false discovery rate (FDR) adjustment.

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☐	☒ Multivariate modeling or predictive analysis

Multivariate modeling and predictive analysis

Outcome variables included structural brain volumes (TB, GM, WM, HOC, and TV). Independent variables included abdominal adipose tissue measures. Analyses were conducted using linear regression and linear mixed-effects models (LMM), accounting for repeated measures over time. No feature extraction, dimension reduction, or model training.