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Reporting Summary

Nature Research 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 Research policies, see Authors & Referees 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	No software was used.
Data analysis	Prism v8 for MacOSX , Prism V 8 for WIndows and Microsoft Excel 13were used for Statistical analysis. CAMERA data analysed using STATA version 15.1. ANCOVA and analysis of data from glucose homeostais experiments was performed using SPSS 25 (IBM).

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the corresponding authors upon request.The CAMERA trial dataset is held at the University of Glasgow and is available on request from the investigators subject to a signed agreement operating within the confines of the original ethics application.

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	Sample sizes were determined on the basis of homogeneity and consistency of characteristics in the selected models and were sufficient to detect statistically significant differences in body weight, food intake and serum parameters between groups, while also ensuring no more animals than necessary were used. These assessments are based on extensive expertise with these models and endpoints. In vitro sample sizes were based on previous extensive experience with reagents and systems used.
Data exclusions	One data point of 25 food intake points collected on day 11 of mouse study 3 was lost due to technical error (see methods). One animal in mouse study 6 which was otherwise well and healthy did not progress to ITT after metformin due to technical and acute behavioural issues at time of study. One blood sample from mouse study 7 was lost due to technical error.
Replication	Acute dosing of metformin to chow fed animals has been replicated and reproduced across two laboratories. Phenfomin data has been replicated. Mouse study 1 has not been replicated exactly but the acute response to metformin in HFD fed animals has been reproduced across two laboratories. Longer term dosing studies of metformin to HFD Gfral and Gdf15 null mice (mouse study 3 and 4) have been replicated; two independent cohorts of Gdf15 null mice appear in the manuscript. ITT post metformin dosing of Gdf15 null has been done once. Mouse study 5 has not been replicated exactly but similar data were generated using anti-GFRAL antibody given over a different time scale but with similar metformin exposure. Mouse studies7 and 8 have been done once. All in vitro and cell based experiments have been replicated successfully and reliably reproduced with replicate numbers reported in legends.
Randomization	Animals were randomised into treatment groups based on body weight such that the mean body weights of each group were as matched as possible but without using excess numbers of animals.
Blinding	Serum/plasma GDF15 measurements were blinded by the investigators. Investigator undertaking ISH analysis of tissue was blinded to treatment during tissue processing and labelling.

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
☐	☒ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data

Methods

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

Antibodies

Antibodies used	ATF4 antibody was obtained from David Ron. CHOP was obtained from Santa Cruz (Cat# sc-7351; RRID: AB_627411). pEIF2a Ser51 was obtained from Abcam (Cat# ab32157; RRID: AB_732117). Calnexin was obtained from Abcam (Cat# ab75801; RRID: AB_1310022). Anti-GFRAL functional blocking antibody generated by NGM.Secondary antibodies used were horseradish peroxidase (HRP)-conjugated anti-rabbit immunoglobulin G (IgG), HRP-conjugated anti-mouse IgG (Cell Signalling Technologies)
Validation	ATF4 and CHOP antibody has been previously validated in KO and siRNA knockdown samples (this study and PMID: 30639358). pEIF2a antibody has been validated previously (PMID: 27297692) and we have independent confirmed this during the course of our studies for PMID: 30639358 (data not shown). Calnexin is a well established commercially available antibody that has been used by numerous investigators and published frequently. Characterization of anti-GFRAL functional blocking antibodies was carried out using a cell-based RET/GFRAL luciferase gene reporter assays, in vitro binding studies (ELISA and Biacore) and in vivo studies as described in patent number; US10174119B2, https://patents.google.com/patent/US10174119B2/en.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Mouse Embryonic Fibroblasts (MEFs) was obtained David Ron (CIMR). The hiPSC line A1ATDR/R was obtained from Ludovic Vallier (Cambridge Stem Cell Institute).
Authentication	MEFs have been previously validated (PMID 12667446 and 12667446) and the hIPS cell line validated (PMID 20739751 and 21993621)
Mycoplasma contamination	MEFs and A1ATDR/R cells were tested negative for Mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	no commonly misidentified lines were used.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mice studied ranged between 2 to 6 months of age. At NGM, animals were kept under controlled light (12hour light and 12hour dark cycle, dark 6:30 pm - 6:30 am), temperature (22 ± 3°C) and humidity (50% ± 20%) conditions. In Cambridge, were maintained in a 12-hour light/12-hour dark cycle (lights on 0700–1900), temperature-controlled (22°C) facility, with ad libitum access to food (RM3(E) Expanded chow, Special Diets Services, UK) and water. Any mice bought from an outside supplier were acclimatised in a holding room for at least one week prior to study. Study diets as outlined in relevant section of "Methods". Age , sex and body weight of mice used as detailed in relevant "Methods" section. Unless otherwise stated, male mice were used a danimals housed singly during studies with environmental enrichment within cages. All drug administration and testing performed during the light cycle. Wild type mice used in Cambridge (C57BL6/J mice) from Charles River, Margate, UK. C57BL/6N-Gdf15tm1a(KOMP)Wtsi/H mice were obtained from the MRC Harwell Institute, UK. Gfral-/- mice were purchased from Taconic (#TF3754) on a mixed 129/SvEv-C57BL/6 background and backcrossed for 10 generations to >99% C57BL/6 background at NGM's animal facility.
Wild animals	The study did not involve wild animals
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	At NGM, all experiments were conducted with NGM IACUC approved protocols and all relevant ethical regulations were complied with throughout the course of the studies, including efforts to reduce the number of animals used. In Cambridge, all mouse studies were performed in accordance with UK Home Office Legislation regulated under the Animals (Scientific Procedures) Act 1986 Amendment, Regulations 2012, following ethical review by the University of Cambridge Animal Welfare and Ethical Review Body (AWERB).

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	CAMERA was a randomized, double-blinded, placebo-controlled trial designed to investigate the effect of metformin on surrogate markers of cardiovascular disease in patients without diabetes, aged 35 to 75, with established coronary heart disease and a large waist circumference (≥ 94cm in men, ≥80 cm in women) . Mean age (yrs)+/-SD; metformin 63(8), placebo 64(8); male sex , metformin 79(81%), placebo 63(72%).Baseline characteristics did not differ substantially between treatment groups. Nine participants completed the study by Konopka and colleagues; 7 had a family history of T2DM and 8 were metformin naïve. One participant had previously used metformin but discontinued more than 2 years before the study commenced.
Recruitment	3000 potential participants were identified from electronic searches of Glasgow general practice databases, supplemented by patients from hospital cardiology clinics. Of those invited, 805 replied and 356 were screened. 173 were enrolled and randomly assigned (86 to metformin, 87 to placebo).Key eligibility criteria included the use of statin therapy, history of coronary heart disease, large waist circumference (≥94cm in men, ≥80cm in women), and no history or biochemical evidence of type 2 diabetes. Eligible participants were randomly assigned to metformin or placebo (1:1) with a randomisation sequence generated independently by computer with permuted blocks of four without stratification. In the study by Konopka and colleagues, inclusion criteria were: obesity (body mass index >30 kg/m2), sedentary (<1 hour of structured activity per week), nonsmoking, and not taking any medication to control blood glucose.
Ethics oversight	All participants in CAMERA study provided written informed consent and were followed up for 18 months. This study was approved by the Medicines and Healthcare Products Regulatory Agency and West Glasgow Research Ethics Committee, and done in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines. The study by Konopka and colleagues was approved by the Mayo Clinic Institutional Review Board and all participants provided written, informed consent .

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

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 CAMERA trial is registered with ClinicalTrials.gov, number NCT00723307. The study by Konopka and colleagues is registered, number NCT01956929.
Study protocol	Trial protocol outlined in PMID: 24622715 and supplied on submission.
Data collection	Participants were randomized 1:1 to 850mg metformin or matched placebo twice daily with meals. Follow up study visits were conducted between 2009 and 2012 at the Glasgow Clinical Research Centre. Participants attended six monthly visits after overnight fasts and before taking their morning dose of metformin. Blood samples collected during the trial were centrifuged at 4 degrees Celsius soon after sampling, separated and stored at -80°C. Bodyweight, body fat (by bio-impedance with a Tanita BIA body fat analyser [Tanita Corporation, Tokyo, Japan]), waist circumference (measured midway between lowest rib and iliac crest), and hip circumference (measured around widest part of the buttocks) were measured at each visit. In the study by Konopka and colleagues, placebo or metformin (week 1, 500mg twice daily; week, 2 1000mg twice daily) were administered following a six week period of washout. Samples were collected in the morning after overnight fasting.
Outcomes	The primary endpoint was progression of mean distal carotid intima-media thickness (cIMT) over 18 months in the modified intention-to-treat population. Further descriptions and results for the pre-specified outcomes for the CAMERA trial are provided in a previous publication PMID: 24622715. As outlined in a previous publication (PMID: 27160898) the study by Konopka and colleagues aimed toi nvestigated whether metformin inhibited glucagon-stimulated endogenous glucose production (EGP) in humans. The study measured EGP using stable isotope methodology under basal, glucagon-deficient, and glucagon-stimulated conditions.