

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 PET-CT was acquired by nanoScan PET/CT (Mediso, Hungary, <https://mediso.com/global/en/product/pre-clinical-products/nanoscanr-petct>) Echocardiography used VisualSonics Fujifilm, Vevo2100 (<https://www.visualsonics.com/>)

Data analysis PET data used imlook4d (<https://github.com/JanAxelsson/imlook4d>) Echocardiography analyses used VevoLab v.3.2.5 (VisualSonics Fujifilm <https://www.visualsonics.com/product/software/vevo-lab>) Data analysis, statistical analysis and visualization were performed in R using the tidyverse, rstatix and ggpubr packages (see supplementary methods).

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](#)

All data generated and/or analysed during this study are either included in this article (and its Supplementary information) or are available from the corresponding author on reasonable request.

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](https://www.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	No sample size calculations were performed. The sample size (n) of each experiment is provided in the corresponding figure captions in the main manuscript and supplementary information files. Sample sizes were chosen to support meaningful conclusions.
Data exclusions	Mice with apparent health problems, such as tumor development, >10% reduction in body weight, or fighting were excluded with no differences between groups.
Replication	All in vivo experiments were successfully replicated 2-3 times. Cohorts of BKS and db/db mice and F1 male off-spring were housed in groups of 4-5 mice/cage. In vitro analysis of tissues were successfully repeated 2-3 times with different cohorts.
Randomization	In the different cohorts, mice were randomly allocated to the cages, ranked based on weight and fasting blood glucose and allocated cage-wise, or if possible individually, to different treatments in order to minimize influence of starting weight and glucose homeostasis. For in vitro analyses such as western blot, qPCR, histology and immuno-histology work samples from 5-9 mice/diet were randomly selected.
Blinding	Plasma analyses were performed by one blinded performer. Calculations using PET data was examined by two blinded evaluators. Echocardiography analyses was performed by one blinded evaluator.

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
☒	☐ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

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

Antibodies

Antibodies used

Primary antibodies used;
 Insulin Guinea pig Dako (A0564)
 Glucagon Rabbit Euro Diagnostica (B31-1)
 Somatostatin Rabbit Abcam (ab111912)
 Pancreatic Polypeptide Guinea pig Linco (4041-01)
 Glut2 Rabbit Produced in house (Goulley et al., Cell Metabolism 5:207–219, 2007)
 Ipf1/Pdx1 Rabbit Produced in house (Ohlsson et al., EMBO J 12:4251–4259, 1993)
 Nkx6-1 Rabbit Produced in house (Öström et al., PloS ONE 3:e2841, 2008)
 MafA Rabbit Nordic Biosite (IHC-00352)
 RaldH3 Rabbit Novus Biologicals (NBP2-15339)
 ACC Rabbit Cell signaling (cat. nr. 3662)
 p-ACC (Ser-79) Rabbit Cell signaling (cat. nr. 3661)
 AMPK Rabbit Cell signaling (cat. nr. 2532)
 p-AMPK Rabbit Cell signaling (cat. nr. 2535)

Raptor Rabbit Cell signaling (cat. nr. 2280)
 p-Raptor Rabbit Cell signaling (cat. nr. 2083)
 S6 Rabbit Cell signaling (cat. nr. 2217)
 pS6 (Ser240/244) Rabbit Cell signaling (cat. nr. 5364)
 TXNIP Rabbit Abcam (cat. nr.188865)

Secondary antibodies used;
 Alexa Fluor® 594 AffiniPure Donkey Anti-Rabbit IgG (H+L) Jackson ImmunoResearch. (711-585-152)
 Alexa Fluor® 488 AffiniPure Donkey Anti-Guinea Pig IgG (H+L) Jackson ImmunoResearch. (706-545-148)
 HRP Goat anti-Rabbit Jackson ImmunoResearch. (111-035-003)

Validation

All antibodies have been used according to manufacturer's instructions. For details of verification, relevant citations or further information; see the manufacturer's website.

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)

Rat insulinoma INS-1E cells were purchased from AddexBio Technologies. The C2C12 myoblast cell line (CRL-1772) were purchased from ATCC.

Authentication

The cells were commercially available and therefore not authenticated following purchase.

Mycoplasma contamination

The cell lines was tested negative for mycoplasma

Commonly misidentified lines (See [ICLAC](#) register)

Name any commonly misidentified cell lines used in the study and provide a rationale for their use.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals

F1 male off-spring from crossing of male CBA/CaCrI (#609, Charles River, UK) and female C57BL/6J (#000664, Jackson Laboratory, US) were used throughout the study.
 Leptin receptor-deficient male BKS.Cg-Dock7m +/- Leprdb/J (db/db), #000642, and C57BLKS/J (BKS), #000662, mice were obtained from The Jackson Laboratory, US

Wild animals

No wild animals were involved in this study.

Field-collected samples

No field-collected samples were collected for this study.

Ethics oversight

Animal experiments were approved by the Animal Review Board at the Court of Appeal of Northern Norrland in Umeå and conducted in accordance with Guidelines for the Care and Use of Laboratory animals.

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