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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.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	No software was used to collect data.
Data analysis	Data in this paper was analysed using R (R development Core Team (2008) version 3.4.1), Graphpad Prism v7.02, Ensembl v54, AxoGraph v1.7.2, Tophat Aligner (v2.0.14), Stringtie tool v1.2.4, ImageLab v5.1, Database for Annotation, Visualisation and Integrated Discovery (DAVID) v6.8, Analyst Software v1.6.2, Multi-Quant v3.0, FIJI Image J v1.52b, Metaboanalyst, KEGG pathway library, v4.0

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 upon request. 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

RNAseq data have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE114855.

Field-specific reporting

Please select 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/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

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

Sample size	Sample size was determined based on our previous work in Solon-Biet et a 2014. Based on a 20 % difference in lifespan (9.6 % standard deviation) observed between the mice on the high protein, low carb (HPLC) diet and low protein, high carb (LPHC) diet in the above published data, the minimum number of mice required is 12. To account for the subset culled at 15 months of age for tissue collection and the risk of euthanasia due to fighting, dermatitis and other unexpected adverse events, each diet treatment had 36-48 animals per sex per diet. For the exome-matched longevity study, only female mice were used (n=60) for lifespan determination. For the calculation of the number of mice required to be euthanized at 15 months for cardiometabolic outcomes and tissue collection, the sample size was based on the reported difference in fasting insulin between the HPLC and LPHC diets. The insulin levels were 30% higher with a standard deviation of 12%. The minimum number of mice required based on this information is 8.
Data exclusions	For lifespan curves in the BCAA longevity study, data exclusions included mice that were culled for assessment of cardiometabolic outcomes at 15 months of age, adverse events related directly to procedures, euthanasia due to fight wounds or cases of dermatitis that affected the face and ears before 12 months of age. Ten animals were also euthanized before 60 weeks of age due weight loss (n=5) or seizures (n=5). Exclusion criteria was pre-established in accordance with animal ethics protocols.
Replication	All attempts at replication were successful. Mice arrived in time-staggered cohorts, with each diet treatment spread evenly across cohorts, ensuring no bias effect of cohort or batches of mice. Cohort, cage and mice were replicated at each stage. In vitro analysis of bio-banked tissues were analysed with sample randomisation using biological and technical replicates.
Randomization	Mice (both males and females) arrived in time-staggered cohorts of 72-96 mice and were randomly allocated to 4 animals per cage. Diet treatments were staggered within and between cohorts to ensure randomization of cohort and diet effects.
Blinding	All samples collected for cardiometabolic analyses were assigned a unique ID number and all analyses were performed using this number, ensuring that sample analyses were performed blind. Longitudinal food intake measurements across life course required the same diet treatments to be added to cages throughout the study. Therefore; for food intake measurements, investigators were required to know treatment allocations at the cage level.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☐	☒ Animals and other organisms
☒	☐ Human research participants

Methods

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

Antibodies

Antibodies used	mTOR, Cell Signaling 2972; phospho-mTOR (Ser 2448), Cell Signaling 2971; UCP1, Cell Signaling 04670; ACLY, Cell Signaling 13390; SCD1, Cell Signaling 2438; FASN, Cell Signaling 3180; ACC, Cell Signaling 3662; β-actin, Cell Signaling 13E5; cyclophilin, Cell Signaling 2175; Polyclonal guinea pig anti-insulin, DAKO A0564 (now Agilent Technologies); Monoclonal mouse anti-glucagon, Sigma G2654; Donkey anti-mouse IgG 594, Invitrogen A-11073; Goat anti-guinea pig IgG 488, Invitrogen A-21202.
Validation	Antibody validations were sourced from company websites. Cell Signaling Technology (CST): Cell Signaling Technology (CST) provides the highest quality primary and secondary antibodies available for western blotting. CST™ antibodies are produced in-house and validated extensively according to a rigorous protocol…Every CST antibody undergoes rigorous application-specific validation testing customized according to the target and needs of the individual antibody. Validation Steps Include: Examination of several cell lines and/or tissues of known expression levels allows accurate

determination of species cross-reactivity and verifies specificity; Treatment of cell lines with growth factors, chemical activators or inhibitors, which induce or inhibit target expression, verifies specificity. Phosphatase treatment confirms phospho-specificity; The use of siRNA transfection or knockout cell lines verifies target specificity; Side-by-side comparison of lots to ensures lot-to-lot consistency; Optimal dilutions and buffers are predetermined, positive and negative cell extracts are specified, and detailed protocols are already optimized, saving valuable time and reagents.
Website reference:
https://www.cellsignal.co.uk/contents/our-approach-antibody-validation-principles/antibody-validation-for-western-blotting/ourapproach-validation-western-blot
Agilent Technologies:
Our immunohistochemistry products provide high staining quality, improved standardization and increased efficiency enabling the ultimate goal of increased patient safety. The broad portfolio of Dako products is continuously enhanced with new generations of carefully selected and clinically relevant reagents and instruments.
Standard staining protocols for our FLEX RTU antibodies combined with integrated instrument and software platforms enable consistent and reliable results. Our immunohistochemistry portfolio is a complete solution with a high focus on quality and service that helps simplify work processes, removes variation and minimizes possible staining imperfections.
Website reference: https://www.agilent.com/en/product/immunohistochemistry
Sigma:
Antibody Standard Validation
Each unique lot of an antibody should be supplied with lot-specific data including the concentration of that lot and validation data for each of the applications in which it has been tested. It should never be assumed, especially in the case of polyclonal antibodies, that every batch of an antibody will show the same pattern of behavior, and it is good practice to test each new lot in-house within the intended application against appropriate controls and alongside the previous antibody lot before using it with precious sample materials.
We are a global company with manufacturing facilities worldwide. Our development and manufacturing processes are subject to rigorous quality control and quality assurance measures, and each of our antibody products is supplied with a comprehensive Certificate of Analysis and Product Information Sheet.
Website reference: https://www.sigmaaldrich.com/technical-documents/articles/biology/antibody-standard-validation.html#lot
We therefore subsequently test in as many additional immunodetection applications as practical in samples chosen to be relevant to the intended use of the product. These include immunohistochemistry, immunocytochemistry (ICC), Western blot, ELISA, immunoprecipitation, and more. This in-depth application testing can help assess the antibody's specificity for the target and provides contextually relevant validation in applications and samples most likely to be used by our customers. This application-specific data should be reviewed by the researcher and appropriately assessed for the researchers intended use. Beyond review of the vendor generated application data, critical review of the epitope, species reactivity, clonality, appropriate host species, and development of appropriate controls are critical responsibilities of the researcher in the selection and use of antibody product.
Website reference: https://www.sigmaaldrich.com/technical-documents/articles/biology/antibody-enhanced-validation.html
Invitrogen
Invitrogen antibodies are currently undergoing a rigorous 2-part testing approach
Part 1: Target specificity verification: Helps ensure the antibody will bind to the correct target, our antibodies are being tested using at least 1 of the following method: Immunoprecipitation/mass spectrometry, knockout, knockdown, independent antibody verification, cell treatment, relative expression, neutralization, peptide array, orthogonal method. Part 2: Functional application validation: These tests help ensure the antibody works in particular application(s) of interest, which may include (but are not limited to): western blotting, immunofluorescent imaging, flow cytometry, ChiP, immunohistochemistry.
Website reference: http://assets.thermofisher.com/TFS-Assets/LSG/brochures/commitment-antibody-performance-flyer.pdf

Animals and other organisms

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

Laboratory animals	For the BCAA longevity study, four week old male and female C57BL/6J mice (Mus musculus) were obtained from the Australian Resource Centre (WA, Australia) in accordance with the University of Sydney Animal Ethics Committee (protocol 2014/752). Mice began dietary treatments at 12 weeks of age. For the exome-matching longevity study, 4 week old C3B6F1 female hybrid mice (Mus musculus) were used for studies using exome-matched diets and generated by a cross between C3H female and C57BL/6J male mice. Body composition data are presented from 12 month old C3B6F1 females hybrid mice. Parental strains were obtained from Charles River Laboratories and experimental animals were bred in in-house animal facility at the Max Planck Institute for Biology of Ageing, Germany. Four-week old female mice were housed in groups of five, in individually ventilated cages under specific-pathogen-free conditions.
Wild animals	This study did not involve wild animals.
Field-collected samples	This study did not involve samples collected from the field.