

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	Biotech Gen 5 and BioRad Bioplex Manager for ELISA data for blood serum biomarkers and FAGE quantification, Applied Biosystems Quantstudio Design and Analysis for qRT-PCR data, Instron Bluehill 2 for mechanical test data, Scanco Medical software for microarchitecture data, Leica LASX for quantitative histomorphometry, Horiba LabSpec6 for Raman spectra, MSCConvert and XCMS for metabolite spectra data
Data analysis	Scanco Trabecular Bone Morphometry script, Minitab (v21.2), MATLAB (vR2021b+), Python (V3.9+), ImageJ

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 used for these analyses can be found in the Supplementary Data 2 file.

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 N/A

Reporting on race, ethnicity, or other socially relevant groupings N/A

Population characteristics N/A

Recruitment N/A

Ethics oversight N/A

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 A power analysis was performed using preliminary aging data on bone strength to determine the sample size number per group.

Data exclusions Two aged female mice were excluded from all analyses due to tumor development. Another aged female and male were excluded because they died before the end of the diet intervention.
For ipGTT, body mass, and fat pad mass, there were no excluded samples.
Exclusion criteria: For microCT, samples were excluded if samples were missing a section of analysis (e.g. trabecular region). For mechanical tests, samples were excluded if a bone broke before testing, if there was movement during testing, or if the notch for fracture toughness was not at an appropriately placed for loading. For blood serum biomarkers, samples were from certain markers if they were outside the detectable range. For qRT-PCR, samples were excluded from analysis for genes if they had insufficient RNA yield, had an insufficient R check, or were outside the detectable range. For histology (TRAP, bMAT, TUNNEL), samples were excluded if sample sectioning was torn, folded, or missing regions of interest. For quantitative histomorphometry, samples were excluded because of fragmentation and having missing regions after fracture for polishing and imaging making them incomparable. For FAGEs, excluded samples did not have sufficient bone for analyses. For periosteal and endocortical Raman, approximately half the females were excluded because the samples were not available for hydrated Raman. Additional samples for Raman were excluded if the distal femur was too short for periosteal point spacing or the cross-section was too trabecularized after preparation. More endocortical Raman measures were excluded due to having fewer valid data points causing the mathematical models used to derive properties like RMSD and gradient to act incorrectly. In addition to the excluded samples, outliers for each group were identified by a single Grubb's test and were removed as well. Analyses were run with and without outliers to determine their impact on conclusions.

Replication Well-defined data collection procedures were used in this study (microCT, quantitative histomorphometry, FAGEs, qRT-PCR, cortical bone metabolite data collection, and Raman spectrometry. Blanks were run every 7-10 samples for LC-MS to prevent contamination and drift, calibrations were run for microCT, biomechanical tests, and Raman for each data collection session. Standard curves were used for ELISAs and FAGE quantification. Extracted RNA underwent quality check with spectrophotometry before qRT-PCR. RNA that was not pure enough was cleaned and analyzed again for purity. Data analysis was coded to reduce human error and methods such as ECCO were chosen to reduce bias.

Randomization Cages of mice were randomly assigned high fat diet or low fat diet. Further experiments randomly pulled samples from each group.

Blinding Researchers were not fully blinded to groups for experimental preparation for mechanical tests, microCT, qRT-PCR, ELISAs, quantitative histomorphometry, metabolomics, and Raman spectrometry as they required multiple days of preparation and/or testing samples. Thus, researchers ensured samples from each group were randomly chosen for each session, testing, or preparation to reduce error sources from affecting one group. The samples for each session were then tested and analyzed in a blind manner. Researchers were blinded for all other analyses.

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

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	C57BL/6JN mice (5 months and 22 months of age at the end of the experiment)
Wild animals	N/A
Reporting on sex	Sex was a consideration of this study with n = 9-10 / female group. Results are disaggregated.
Field-collected samples	N/A
Ethics oversight	Montana State University's Institutional Animal Care and Use Committee approved this research

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

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A