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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	All data were collected and analyzed using Excel (Microsoft) and Prism 8 (GraphPad) software. Micro-CT images of femoral bones were obtained by using high-resolution μCT (Skyscan 1172, Bruker MicroCT, Kontich, Belgium), NRecon image reconstruction software (version 1.6), and CTVol 3-dimensional model visualization software (Bruker MicroCT, version 2.0). mRNAs were reverse-transcribed and then amplified using a real-time PCR system (Applied Biosystems). For flow cytometry, stained cells were collected by BD FACS Diva software v9.0 and BD flow cytometry Canto II system. The protein levels were visualized using Image Lab (BioRad,Version 6.1) and ChemiDoc XRS imaging system (BioRad).
Data analysis	For μCT analysis of femoral bones, data analysis software (CT Analyser, version 1.9) were used to analyze the trabecular bone parameters. For flow cytometry analysis, data were analyzed by FlowJo V10 (BD Biosciences).The size and concentration of EVs were analyzed with a Nanoparticle Tracking Analysis. The images of staining and western blot data were quantified using ImageJ 1.52 software.All data were analyzed using Excel (Microsoft) and Prism 8 (GraphPad) software. In bar graphs, data are presented as mean values +/- SEM. Statistical significance ($P<0.05$) was computed using two-tailed Student's t-test, Welch's t-test or one-way ANOVA followed by Tukey's multiple comparisons test.n represents the number of samples used in the experiments.

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

Raw data of metabolomic analysis have been deposited in the Genome Sequence Archive in the National Genomics Data Center, China National Center for Bioinformation, under accession code OMIX006114. Here is a link: https://ngdc.cncb.ac.cn/omix/releaseList. Raw data of RNA sequencing have been deposited in the Sequence Read Archive (SRA), under accession code SRR28495907~ SRR28495911. Here is a link: https://www.ncbi.nlm.nih.gov/sra.Scientific and ethical approval of human data, and statement are described below. The scientific review committee for the IMRD and the institutional review board at Xiangya Hospital approved this study with a waiver of informed consent (23SRC020, 2018091077). THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA. This work uses de-identified data provided by patients as a part of their routine primary care. Source data are available with this paper. All other data are available from the corresponding author upon reasonable request.

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	Men and women.
Reporting on race, ethnicity, or other socially relevant groupings	We used data from IMRD, incorporating data from The Health Improvement Network (THIN), a Cegedim database from general practitioners (GPs) in the UK. IMRD contains anonymized medical records from 839 general practices with approximately 19 million patients.
Population characteristics	The details were listed in Tables of population cohort. We included individuals who were aged 40 to 90 years old, diagnosed with pre-diabetes, and had at least one year of active enrolment with the general practice from January 2000 to December 2022.Pre-diabetes was defined by baseline impaired fasting blood glucose (5.6-6.9 mmol/L), impaired glucose tolerance (glucose tolerance test result 7.8-11.0 mmol/L), HbA1c of 5.7% to 6.4%, or a combination of these results
Recruitment	The details were listed in the METHODS.We used data from IMRD, incorporating data from The Health Improvement Network (THIN), a Cegedim database from general practitioners (GPs) in the UK. IMRD contains anonymized medical records from 839 general practices with approximately 19 million patients. Health care information is recorded at each practice on socio-demographics, anthropometrics, lifestyle factors, visits to GPs, diagnoses from specialists and hospital admissions, and laboratory test results. A previous study has demonstrated the validity of the IMRD database in clinical and epidemiological research
Ethics oversight	The scientific review committee for the IMRD and the institutional review board at Xiangya Hospital approved this study with a waiver of informed consent (23SRC020, 2018091077).

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	No statistical methods were used to predetermine sample size. The sample sizes chosen are consistent with previously published works. Here are references: 1. Li, C.J., et al., Senescent immune cells release grancalcin to promote skeletal aging. Cell Metab, 2021. 33(10): p. 1957-1973.e6. 2. Zou, N.Y., et al., Age-related secretion of grancalcin by macrophages induces skeletal stem/progenitor cell senescence during fracture healing. Bone Res, 2024. 12(1): p. 6
Data exclusions	No data were excluded from the analyses.
Replication	All experiments were performed at at least 3 times, and all attempts at replication were successful.
Randomization	The mice used to 1) treat vehicle or senolytics, 2) to receive young, old, old treated with vehicle or old treated with vehicle or DQ groups, 3) inject senescent or young cells, 4) treat vehicle or fenofibrate were randomly allocated. Further, the mice in evaluation for senescence as well

as aging related tissue phenotypes, aging related gene/protein expression and behavior tests were also randomly assigned. In ex vivo, experiments control and test wells were randomly assigned for each experimental repeat.

Blinding: The investigators were not blinded to allocation during experiments and outcome assessments, but the experiments were performed in appropriate biological replication by independent personal to avoid bias.

Behavioural & social sciences study design

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

Study description	n/a.
Research sample	n/a.
Sampling strategy	n/a.
Data collection	n/a.
Timing	n/a.
Data exclusions	n/a.
Non-participation	n/a.
Randomization	n/a.

Ecological, evolutionary & environmental sciences study design

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

Study description	n/a.
Research sample	n/a.
Sampling strategy	n/a.
Data collection	n/a.
Timing and spatial scale	n/a.
Data exclusions	n/a.
Reproducibility	n/a.
Randomization	n/a.
Blinding	n/a.

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	n/a.
Location	n/a.
Access & import/export	n/a.
Disturbance	n/a.

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

Antibodies

Antibodies used

The detailed information of all antibodies used in the study: Mouse monoclonal anti-p-γH2AX (Santa Cruz, sc-517348, clone: Ser 139, 1:100 dilution); Mouse monoclonal anti-p21 (Santa Cruz, sc-6246, clone: F-5, 1:100 dilution); Mouse monoclonal anti-p53 (Cell signaling Technology, 2524s, clone: 1C12, 1:500 dilution); Rabbit monoclonal anti-p-IR (Cell signaling Technology, 3024s, clone: 19H7, 1:1000 dilution); Rabbit monoclonal anti-IR (Cell signaling Technology, 3025s, clone: 4B8, 1:1000 dilution); Rabbit polyclonal anti-p-AKT (Cell signaling Technology, 9271s, 1:1000 dilution); Rabbit polyclonal anti-AKT (Cell signaling Technology, 9272s, 1:1000 dilution); Rabbit polyclonal anti-p-GSK3β (Cell signaling Technology, 9336s, 1:1000 dilution); Rabbit monoclonal anti-GSK3β (Cell signaling Technology, 9315s, clone: 27C10, 1:1000 dilution); Mouse monoclonal anti-PPARα (Santa Cruz, sc-398394, clone: H-2, 1:100 dilution); Mouse monoclonal anti-PSD95 (Santa Cruz, sc-32290, clone: 7E3, 1:100 dilution); Mouse monoclonal anti-GluR-1 (Santa Cruz, sc-55509, clone: G-12, 1:100 dilution); Rabbit polyclonal anti-IBA1 (Proteintech, 10904-1-AP, 1:100 dilution); Rat monoclonal anti-F4/80 (Abcam, ab6640, clone: CI:A3-1, 1:200 dilution); Mouse monoclonal anti-Osteocalcin (Takara, M188, Clone: R21C-01A, 1:300 dilution); fluorescence-conjugated secondary antibodies Alexa Fluor 488 conjugated anti-rabbit (Invitrogen, A21206, 1:200) or Alexa Fluor 555 conjugated anti-Rabbit (Invitrogen, A21428, 1:200) or Alexa Fluor 555 conjugated anti-mouse (Invitrogen, A31570, 1:200).

Validation

The details validation is listed below. Mouse monoclonal anti-p-γH2AX, RRID: AB_2783871; Mouse monoclonal anti-p21, RRID: AB_628073; Mouse monoclonal anti-p53, RRID: AB_331743; Rabbit monoclonal anti-p-IR, RRID: AB_331253; Rabbit monoclonal anti-IR, RRID: AB_2280448; Rabbit polyclonal anti-p-AKT, RRID: AB_329825; Rabbit polyclonal anti-AKT, RRID: AB_329827; Rabbit polyclonal anti-p-GSK3β, RRID: AB_331405; Rabbit monoclonal anti-GSK3β, RRID: AB_490890; Mouse monoclonal anti-PPARα, RRID: AB_2885073; Mouse monoclonal anti-PSD95, RRID: AB_628114; Mouse monoclonal anti-GluR-1, RRID: AB_629532; Rabbit polyclonal anti-IBA1, RRID:AB_2224377; Rat monoclonal anti-F4/80, RRID:AB_1140040; Mouse monoclonal anti-Osteocalcin, RRID: AB_2935810. Alexa Fluor 488 conjugated anti-rabbit, RRID: AB_2535792; Alexa Fluor 555 conjugated anti-Rabbit, RRID: AB_2535849; Alexa Fluor 555 conjugated anti-mouse, RRID: AB_2536180.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)

The details were listed in key resources table.These cells were validated by the company.Mouse bone marrow macrophages were isolated as described previously. Briefly, Wild-type male mice were sacrificed, and femurs and tibias were removed and flushed with α-MEM essential medium (Gibco). Bone marrow cells were cultured overnight in α-MEM medium containing 10% fetal bovine serum. Then, we discarded the adherent cells and cultured the floating cells with 30ng/ml M-CSF (Proteintech, HZ-1192)) to obtain monocytes and macrophages. Primary mouse hepatocytes were harvested as previously described. Briefly, male mice were anesthetized with pentobarbital, and the digestive solution was perfused into the inferior vena cava to obtain primary hepatocytes. Primary hepatocytes were cultured in DMEM medium containing 10% fetal bovine serum (Gibco).
Mouse myoblast cell line C2C12 and mouse preadipocyte cell line 3T3-L1 were purchased from the Procell Life Science & Technology Co. Ltd. (Wuhan, China, CL-0006 and CL-0044).

Authentication

Mouse bone marrow macrophages were isolated using standard published protocols and validated by flow analysis. Primary mouse hepatocytes were isolated by using standard published protocols.
The STR profiling authentication procedures of C2C12 and 3T3L1 cells were performed by the Procell Life Science & Technology Co. Ltd. (Wuhan, China)

Mycoplasma contamination

Cells were tested for mycoplasma and all cells tested negative.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell line was used in this study.

Palaeontology and Archaeology

Specimen provenance

n/a.

Specimen deposition	n/a.
Dating methods	n/a.

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	

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

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	Wild type (WT) male C57BL/6 mice were purchased from SLAC Laboratory Animal Company of Hunan Province and maintained in SPF environment until the age of 16-24 months. For D+Q treatment, sixteen-month-old WT mice were randomly divided into 2 groups and were given Vehicle (PEG 400) or Dasatinib (5 mg/kg, LC labs, D-3307) plus Quercetin (50 mg/kg, Sigma-Aldrich, Q4951) by gavage twice a week for 5months. For fenofibrate treatment, aged WT mice (23m) were given Vehicle or fenofibrate (100 mg/kg/d, Sigma-Aldrich, F6020) by gavage daily for 5 weeks. MiR-378a floxed heterozygous mice were generated by Nanjing GemPharmatech CO., Ltd, and homozygous mice were obtained by crossing.All animal care protocols and experiments were reviewed and approved by the Animal Care and Use Committee of Laboratory Animals Research Center, Xiangya Medical School, Central South University. Mice were kept at 20 to 24°C with a 12-h light/dark cycle, and all mice were provided with food and water ad libitum. Room temperature: 20~26°C; Daily temperature difference: ≤4°C; Relative humidity: 40%~70%.
Wild animals	The study did not involve wild animals.
Reporting on sex	Male.
Field-collected samples	The study did not involve samples collected from the field.
Ethics oversight	All animal care protocols and experiments were reviewed and approved by the Animal Care and Use Committee of Laboratory Animals Research Center, Xiangya Medical School, Central South University, under the active protocol 2019030214.

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 scientific review committee for the IMRD and the institutional review board at Xiangya Hospital approved this study with a waiver of informed consent (23SRC020, 2018091077).
Study protocol	The details were listed in the METHODS. We included individuals who were aged 40 to 90 years old, diagnosed with pre-diabetes, and had at least one year of active enrolment with the general practice from January 2000 to December 2022. Pre-diabetes was defined by baseline impaired fasting blood glucose (5.6-6.9 mmol/L), impaired glucose tolerance (glucose tolerance test result 7.8-11.0 mmol/L), HbA1c of 5.7% to 6.4%, or a combination of these results. To improve the robustness of observational analysis, we followed the target trial emulation design framework and adopted a prevalent new user design to compare the risk of incident type 2 diabetes between fenofibrate initiators and active comparators (i.e., simvastatin users). We assembled a study cohort including patients initiating therapy with fenofibrate or receiving simvastatin during the study period and then stratified the fenofibrate users into two types: those who switched to fenofibrate (also called prevalent new users) and those who were incident new users. We considered the switching date or date of incident use as the index date. For each prevalent new user, we matched up to five people who continued simvastatin and had used the simvastatin for the same duration at the time of the index date. For each incident new user, we matched up to five incident new users of simvastatin. We excluded patients who were diagnosed with diabetes before the index date. To assess the extra benefits of fenofibrate, we also examined the relation of fenofibrate initiation to the risk of several secondary outcomes, including all-cause mortality, incident major osteoporotic fracture (hip, vertebral, wrist, and humerus fracture), and incident dementia among individuals who were diagnosed with either pre-diabetes or type 2 diabetes.
Data collection	The details were listed in the METHODS. We used data from IMRD, incorporating data from The Health Improvement Network (THIN), a Cegedim database from general practitioners (GPs) in the UK. IMRD contains anonymized medical records from 839 general practices with approximately 19 million patients. Health care information is recorded at each practice on socio-demographics, anthropometrics, lifestyle factors, visits to GPs, diagnoses from specialists and hospital admissions, and laboratory test results. A previous study has demonstrated the validity of the IMRD database in clinical and epidemiological research. The scientific review committee for the IMRD and the institutional review board at Xiangya Hospital approved this study with a waiver of informed consent (23SRC020, 2018091077).
Outcomes	The details were listed in the METHODS. The primary outcome was incident type 2 diabetes. We defined type 2 diabetes using Read codes. This approach has been used in the previous study. The event date is defined by the date of diagnosis. Secondary outcomes included all-cause mortality, incident major osteoporotic fracture (hip, vertebral, wrist, and humerus fracture), and incident dementia. The death date recorded in THIN is linked to the National Health Service; thus, a change in vital status to “dead” is

immediately updated in the individual's electronic health record. Major osteoporotic fracture (hip, vertebral, wrist, and humerus fracture) and dementia were identified by the Read codes, respectively, which have been used in previous studies by using the IMRD database.
Additionally, we estimated life expectancy for patients diagnosed with either pre-diabetes or type 2 diabetes who initiated therapy with fenofibrate or received simvastatin using Abridged period life tables based on the Chiang II method. Life tables were constructed from 2000 to 2022, aggregating death and population data into 5-year age intervals up to 90 years. The difference in life expectancy was calculated as the estimated life expectancy in patients treated with simvastatin minus that in patients treated with fenofibrate.

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☒	☐	Public health
☒	☐	National security
☒	☐	Crops and/or livestock
☒	☐	Ecosystems
☒	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☒	☐	Demonstrate how to render a vaccine ineffective
☒	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☒	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☒	☐	Increase transmissibility of a pathogen
☒	☐	Alter the host range of a pathogen
☒	☐	Enable evasion of diagnostic/detection modalities
☒	☐	Enable the weaponization of a biological agent or toxin
☒	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	n/a.
Novel plant genotypes	n/a.
Authentication	n/a.

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	n/a.
Files in database submission	n/a.

Genome browser session (e.g. UCSC)	n/a.

Methodology

Replicates	n/a.
Sequencing depth	n/a.
Antibodies	n/a.
Peak calling parameters	n/a.
Data quality	n/a.
Software	n/a.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Mouse blood was taken from the tail vein, and approximately 100 μL of peripheral blood was collected in EDTA tubes. The collected blood was resuspended in 10 times the volume of red blood cell lysis buffer and lysed for 10 minutes.
Instrument	Stained cells were collected by BD FACS Diva software v9.0 and BD flow cytometry Canto II system
Software	Data were analyzed by FlowJo V10 (BD Biosciences)
Cell population abundance	The collected blood was resuspended in 10 times the volume of red blood cell lysis buffer and lysed for 10 minutes. The abundance of the cell population is 10*6.
Gating strategy	First, FSC-A/ FSC-H gating was used to group the cells to evaluate the live or dead status of the cells, and then the gate (CD45.1: FITC, CD45.2: APC) was set according to the group of the target cells. Further analysis of the target cells was performed.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	n/a.
Design specifications	n/a.
Behavioral performance measures	n/a.

Acquisition

Imaging type(s)	n/a.
Field strength	n/a.
Sequence & imaging parameters	n/a.
Area of acquisition	n/a.

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software: n/a.

Normalization: n/a.

Normalization template: n/a.

Noise and artifact removal: n/a.

Volume censoring: n/a.

Statistical modeling & inference

Model type and settings: n/a.

Effect(s) tested: n/a.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference: n/a.

(See Eklund et al. 2016)

Correction: n/a.

Models & analysis

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

Functional and/or effective connectivity: n/a.

Graph analysis: n/a.

Multivariate modeling and predictive analysis: n/a.