

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
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ 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
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ 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	Lipidomics data were acquired using a Thermo Scientific Ultimate 3000 binary HPLC coupled to a Q Exactive Plus Orbitrap mass spectrometer, controlled by Thermo Xcalibur software. C. elegans lifespan data were collected manually and recorded in GraphPad Prism 9.
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Data analysis

An R script to assess lipid length from lipidomics datasets is available on GitHub (<https://github.com/gejanssens/lipidomics-lipid-length-analysis/releases/tag/v1.0>).

R v3.5.1
 ggplot2 R package version 3.2.1
 ggpubr R package version 0.2.5
 RColorBrewer R package version 1.1-2
 segmented R package version 2.1.3
 ieugwasr R package version 0.1.5
 PLINK version 1.90b6.21
 GROMACS version 2025.1
 CHARMM36 simulation software (from Huang 2013)
 Martini 3 force field software (from Pedersen 2025)
 CHARMM-GUI membrane builder (from Wu 2014)
 LiPyphilic Python tool (from Smith 2021)
 insane Python tool (from Wassenaar 2015)
 mstool Python tool (from kim 2023)
 VMD (from Humphry 1996)

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](#)

Published lipidomics datasets can be found in their original publications, and newly generated lipidomics datasets are available in the accompanying Supplemental Tables. See 'Lipidomics datasets' of the methods section. Newly generated data or analyses includes; Supplemental Table 1: Lipidomics of fly aging. Supplemental Table 2: Lipidomics of fly aging replicate 2. Supplemental Table 3: Lipidomics changes of HL-1 mouse cardiac cells with rapamycin. Supplemental Table 4: Lipidomics of old mouse heart; rapamycin treatment. Supplemental Table 5: Lipidomics of young and old mouse heart; dietary restriction. Supplemental Table 6: Lipid remodeling gene list. Supplemental Table 7: Mendelian randomization, gene correlations with blood. Supplemental Table 8: Mendelian randomization, results. Supplemental Table 9: Worm lifespan statistics. Supplemental Table 10: Lipidome of F36A2.9 and elo-1 RNAi. Supplemental Table 11: Lipidome of elo-3 RNAi. Supplemental Table 12: Lipidome of 40 μ M C21:0 treatment of HeLa cells. Supplemental Table 13: Simulations, properties of single component membranes. Supplemental Table 14: Simulations, compositions of multi component plasma membrane models. Supplemental Table 15: Simulations, properties (average $\pm$ standard error) of multi component plasma membrane models

For further clarification; both published and newly generated lipidomics datasets were analyzed in this study. Specifically, published lipidomic datasets (re)investigated in the context of lipid length, in order of appearance in this study, related to: (1) ten tissues in aging mice, lipidome from Janssens et al. (2024), (2) C. elegans worms aging, lipidome from Gao et al. (2017), (3) Human aging skeletal muscle, lipidome from Janssens et al. (2024), (4) human heart aging, lipidome from Schomakers et al. (2025), (5) human heart disease, lipidome from Nollet et al. (2024), and (6) human exercise, lipidome from Janssens et al. (2024). The datasets, as well as sample preparation and lipidomics procedures for these datasets are presented in the associated publications and references. Additionally, newly generated lipidomics datasets were investigated in this study. These include in order of appearance: (i) D. melanogaster aging (Supplemental Table 1), (ii) D. melanogaster aging replicate 2 (Supplemental Table 2) (iii) rapamycin treatment of HL1 cardiac cells (Supplemental Table 3), (iv) rapamycin treatment of mice, heart tissues (Supplemental Table 4), (v) dietary restriction treatment of mice, heart tissues (Supplemental Table 5), (vi) C. elegans RNAi of elo-1 and F36A2.9 (Supplemental Table 10), (vii) C. elegans RNAi of elo-3 (Supplemental Table 11), (viii) C21:0 treatment of HeLa cells (Supplemental Table 12). These datasets are available as supplemental tables accompanying this publication with methods described in this study.

Reference:

Janssens et al. (2024) Nat. Aging, doi:10.1038/s43587-024-00595-2
 Gao et al. (2017) Sci. Rep. 7, 2408, doi:10.1038/s41598-017-02554-1
 Schomakers et al. (2025) bioRxiv, doi:10.1101/2025.04.17.649294
 Nollet et al. (2024) Circ. Genomic Precis. Med. 17, 238–253, doi:10.1161/CIRCGEN.123.004420
 Remie et al. (2021) Diabetologia 64, 2817–2828, doi:10.1007/s00125-021-05556-5
 Baghdadi et al. (2024) Mol. Metab. 81, 101902, doi:10.1016/j.molmet.2024.101902
 Kaeser et al. (2021) Nat. Aging 1, 218–225, doi:10.1038/s43587-021-00028-4

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

This study reanalyzed previously published human lipidomics datasets. Sex was considered in the study design: analyses were performed separately for men and women where possible (human skeletal muscle and cardiac tissue aging datasets). No statistically significant sex-specific differences in age-related lipid lengthening were observed (skeletal muscle: Student's t-test, $p = 0.11$; heart: Student's t-test, $p = 0.33$). Sex-disaggregated data are presented in Figure 2 and Extended Data Figures

3–4. The human exercise study included only postmenopausal women (Janssens et al., 2024; Remie et al., 2021, Diabetologia).

Reporting on race, ethnicity, or other socially relevant groupings

Race/ethnicity data were not analyzed in the original studies from which the lipidomics datasets were derived, and are therefore not reported here.

Population characteristics

Human skeletal muscle cohort: young group (age 20–30) and older group (age 65–80), both men and women, from Janssens et al. (2024). Human heart aging cohort: young men (n=6, age 19–45), young women (n=6, age 24–44), older men (n=6, age 49–71), older women (n=6, age 47–67), control samples from Schomakers et al. (2025). Human heart disease cohort: patients with varying stages of hypertrophic cardiomyopathy, from Nollet et al. (2024). Human exercise cohort: postmenopausal women undergoing 4 days of sedentary behavior or the same plus 1 hour/day vigorous aerobic exercise, from Janssens et al. (2024) and Remie et al. (2021). Full demographic details are available in the original publications.

Recruitment

Recruitment procedures for each cohort are described in detail in the original publications (Janssens et al., 2024; Schomakers et al., 2025; Nollet et al., 2024; Remie et al., 2021). In brief, participants were recruited through clinical centers and community advertisement. Potential biases inherent to each study design are discussed in the respective original publications.

Ethics oversight

All human datasets analyzed in this study were obtained from previously published studies that received ethical approval from their respective institutional review boards.

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](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

For newly generated samples used in the study, sample sizes were determined based on established conventions in the field and from prior published studies using the same lipidomics platform (3–5 independent biological replicates per condition). For samples that came from other studies and publications, the sample sizes were determined for the purposes of those studies.

Mouse aging: n=8 per group (young vs. old, 10 tissues), as in Janssens et al. (2024).

Drosophila aging: n=2 (replicate 1) and n=3 (replicate 2) independent samples of 10 flies each, based on prior experience with fly lipidomics.

C. elegans lipidomics: n=6 biological replicates per condition, consistent with prior publications (Gao et al., 2017).

HL-1 rapamycin treatment: based on prior lipidomics experiments in cell culture, n=5 per condition.

Mouse rapamycin: control old females n=6, control old males n=8, rapamycin-treated old females n=8, rapamycin-treated old males n=8 (Baghdadi et al., 2024).

Mouse DR: n=8 per group (Kaesler et al., 2021).

BXD mouse panel: n=38 strains, as available in the GeneNetwork database.

C. elegans lifespan: all experiments performed at least twice; exact n per experiment in Supplemental Table 9.

HeLa cell experiments: performed on independent biological replicates.

No statistical methods were used to predetermine sample sizes for newly generated lipidomics data, consistent with the exploratory nature of lipidome-wide analyses. For published datasets, sample sizes were as reported in the original studies.

Data exclusions

For lipidomics analyses, no data were excluded except where specific lipid classes had fewer than three detected lipid species, which precluded meaningful correlation analysis (as stated in Methods). For C. elegans lifespan assays, worms that were missing, displayed internal egg hatching, lost vulva integrity, or burrowed into NGM agar were censored, consistent with standard practice in the field. These criteria were pre-established. No other data exclusions were applied.

Replication

Replication was successful for all key experiments report.

- Drosophila aging lipidomics was replicated in an independent cohort.
- All C. elegans lifespan experiments were performed at least twice; summary statistics for all replicates are provided in Supplemental Table 9.
- Membrane simulations: 4 independent replicas per system with different initial velocity seeds.

Randomization

For newly generated experiments:

- Drosophila: flies were randomly sampled from mixed-population cages at each time point.
 - C. elegans: worms were randomly allocated to RNAi treatment groups from synchronized L1 populations.
 - Cell culture: treatment and control wells were randomly assigned within each plate.
 - For lipidomics sample processing, samples were processed in randomized order to minimize batch effects.
- For published datasets reanalyzed here, randomization procedures are described in the original publications.

Blinding

For most experiments, formal blinding was not performed during data collection, as lipidomics data acquisition and processing are automated and objective. For *C. elegans* lifespan assays, scoring was performed by investigators aware of experimental groups, which is standard in the field; however, the objective criterion for death (no response to platinum wire pick) minimizes potential bias. Lipidomics data analysis was performed using automated computational pipelines applied uniformly to all samples. For membrane simulations, analysis was performed using automated scripts applied identically to all trajectories.

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

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	HeLa cells: standard human cervical carcinoma cell line. Cultured under standard conditions at Amsterdam UMC. HL-1 cardiomyocytes: mouse cardiac muscle cell line. Cultured in Claycomb Medium (Sigma-Aldrich) as described in Methods.
Authentication	HeLa and HL-1 cells were obtained from established cell stocks maintained within the Amsterdam UMC. Both cell lines were routinely cultured according to established protocols. The identity of these cell lines was based on their documented provenance within the laboratory. No additional authentication (e.g. STR profiling or species verification) was performed specifically for this study.
Mycoplasma contamination	Mycoplasma testing was not specifically reported for the cell lines used in this study. Cells were maintained under standard aseptic conditions.
Commonly misidentified lines (See ICLAC register)	NA.

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	<i>C. elegans</i> : hermaphrodites, young = day 1, old = day 7, n=6 biological replicates per group N2 Bristol (wild-type) EU-1 [skn-1(zu67)IV] CF1038 [daf-16(mu86)I] All from Caenorhabditis Genetics Center (CGC). Cultured at 20°C on NGM plates with <i>E. coli</i> OP50 or HT115. <i>Drosophila melanogaster</i> : Strain ywR, females; young (day 4±1) and old (day 23±1).
Wild animals	No wild animals were used in this study.
Reporting on sex	<i>Drosophila</i> : females only. <i>C. elegans</i> : hermaphrodites (standard for lifespan assays). Sex is indicated for all experiments and figure legends.
Field-collected samples	No field-collected samples were used.
Ethics oversight	The newly generated <i>C. elegans</i> and <i>D. melanogaster</i> experiments in this study did not require ethics approval under current European regulations.

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

Seed stocks

Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.

Novel plant genotypes

Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.

Authentication

Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.