ARTICLE | VOLUME 35, ISSUE 5, P807-820.E5, MAY 02, 2023

Download Full Issue

# Biological age is increased by stress and restored upon recovery

Jesse R. Poganik • Bohan Zhang • Gurpreet S. Baht • ... Steve Horvath • James P. White • Vadim N. Gladyshev [15] • Show all authors • Show footnotes

Published: April 21, 2023 • DOI: https://doi.org/10.1016/j.cmet.2023.03.015 • Check for updates

PlumX Metrics

## Highlights

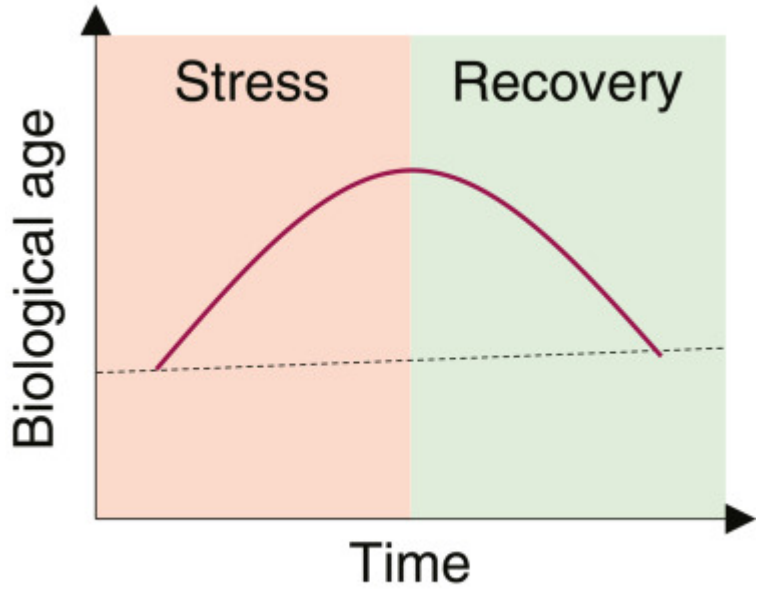
- Biological age undergoes rapid fluctuations in mice and humans
- Severe stress induces increases in biological age that are reversed upon recovery
- Parabiosis, surgery, pregnancy, and COVID-19 transiently elevate biological age
- Biological age recovery rate may predict gerotherapeutics

## Summary

Aging is classically conceptualized as an ever-increasing trajectory of damage accumulation and loss of function, leading to increases in morbidity and mortality. However, recent *in vitro* studies have raised the possibility of age reversal. Here, we report that biological age is fluid and exhibits rapid changes in both directions. At epigenetic, transcriptomic, and metabolomic levels, we find that the biological age of young mice is increased by heterochronic parabiosis and reversed following surgical detachment. We also identify transient changes in biological age

during major surgery, pregnancy, and severe COVID-19 in humans and/or mice. Together, these data show that biological age undergoes a rapid increase in response to diverse forms of stress, which is reversed following recovery from stress. Our study uncovers a new layer of aging dynamics that should be considered in future studies. The elevation of biological age by stress may be a quantifiable and actionable target for future interventions.

## Graphical abstract




View Large Image | Download Hi-res image

## Keywords

aging • biological age • stress • recovery • dynamics • epigenetic aging clocks

## References

1. Zhang B. • Gladyshev V.N.
**How can aging be reversed? Exploring rejuvenation from a damage-based perspective.**
*Adv. Genet. (Hoboken).* 2020; **1**e10025
https://doi.org/10.1002/ggn2.10025

View in Article

PubMed • Crossref • Google Scholar

2. Horvath S. • Levine A.J.
**HIV-1 infection accelerates age according to the epigenetic clock.**
*J. Infect. Dis.* 2015; **212**: 1563-1573
https://doi.org/10.1093/infdis/jiv277

View in Article

Scopus (346) • PubMed • Crossref • Google Scholar

3. Wang T. • Tsui B. • Kreisberg J.F. • Robertson N.A. • Gross A.M. • Yu M.K. • Carter H. • Brown-Borg H.M. • Adams P.D. • Ideker T.
**Epigenetic aging signatures in mice livers are slowed by dwarfism, calorie restriction and rapamycin treatment.**
*Genome Biol.* 2017; **18**57
https://doi.org/10.1186/s13059-017-1186-2

View in Article
Scopus (177) • Crossref • Google Scholar

4. Quach A. • Levine M.E. • Tanaka T. • Lu A.T. • Chen B.H. • Ferrucci L. • Ritz B. • Bandinelli S. • Neuhouser M.L. • Beasley J.M. • et al.
**Epigenetic clock analysis of diet, exercise, education, and lifestyle factors.**
*Aging.* 2017; **9**: 419-446
https://doi.org/10.18632/aging.101168

View in Article
Scopus (376) • PubMed • Crossref • Google Scholar

5. Nwanaji-Enwerem J.C. • Colicino E. • Trevisi L. • Kloog I. • Just A.C. • Shen J. • Brennan K. • Dereix A. • Hou L. • Vokonas P. • et al.
**Long-term ambient particle exposures and blood DNA methylation age: findings from the VA normative aging study.**
*Environ. Epigenet.* 2016; **2**: 74510-74525
https://doi.org/10.1093/eep/dvw006

View in Article
Scopus (63) • Crossref • Google Scholar

6. Horvath S.
**DNA methylation age of human tissues and cell types.**
*Genome Biol.* 2013; **14**R115
https://doi.org/10.1186/gb-2013-14-10-r115

View in Article
Scopus (3197) • PubMed • Crossref • Google Scholar

7. Hannum G. • Guinney J. • Zhao L. • Zhang L. • Hughes G. • Sadda S. • Klotzle B. • Bibikova M. • Fan J.B. • Gao Y. • et al.
**Genome-wide methylation profiles reveal quantitative views of human aging rates.**
*Mol. Cell.* 2013; **49**: 359-367
https://doi.org/10.1016/j.molcel.2012.10.016

View in Article
Scopus (1851) • PubMed • Abstract • Full Text • Full Text PDF • Google Scholar

8. Horvath S. • Oshima J. • Martin G.M. • Lu A.T. • Quach A. • Cohen H. • Felton S. • Matsuyama M. • Lowe D. • Kabacik S. • et al.
**Epigenetic clock for skin and blood cells applied to Hutchinson Gilford progeria Syndrome and ex vivo studies.**
*Aging.* 2018; **10**: 1758-1775
https://doi.org/10.18632/aging.101508

View in Article
Scopus (234) • PubMed • Crossref • Google Scholar

9. Mozhui K. • Lu A. • Li C.Z. • Haghani A. • Sandoval-Sierra J.V. • Williams R.W. • Horvath S.
**Genetic analyses of epigenetic predictors that estimate aging, metabolic traits, and lifespan.**
2021
https://doi.org/10.1101/2021.06.23.449634v2

View in Article
Crossref • Google Scholar

10. Meer M.V. • Podolskiy D.I. • Tyshkovskiy A. • Gladyshev V.N.
**A whole lifespan mouse multi-tissue DNA methylation clock.**
*eLife.* 2018; **7**e40675
https://doi.org/10.7554/eLife.40675

View in Article
Scopus (70) • Crossref • Google Scholar

11. Petkovich D.A. • Podolskiy D.I. • Lobanov A.V. • Lee S.G. • Miller R.A.

Gladyshev V.N.
**Using DNA methylation profiling to evaluate biological age and longevity interventions.**
*Cell Metab.* 2017; **25**: 954-960.e6
https://doi.org/10.1016/j.cmet.2017.03.016

View in Article
Scopus (184) • PubMed • Abstract • Full Text • Full Text PDF • Google Scholar

12. Stubbs T.M. • Bonder M.J. • Stark A.K. • Krueger F. • von Meyenn F. • Stegle O. • Reik W. • BI Ageing Clock Team
**Multi-tissue DNA methylation age predictor in mouse.**
*Genome Biol.* 2017; **18**68
https://doi.org/10.1186/s13059-017-1203-5

View in Article
Scopus (218) • Crossref • Google Scholar

13. Thompson M.J. • Chwiałkowska K. • Rubbi L. • Lusis A.J. • Davis R.C. • Srivastava A. • Korstanje R. • Churchill G.A. • Horvath S. • Pellegrini M.
**A multi-tissue full lifespan epigenetic clock for mice.**
*Aging.* 2018; **10**: 2832-2854
https://doi.org/10.18632/aging.101590

View in Article
Scopus (82) • PubMed • Crossref • Google Scholar

14. Levine M.E. • Lu A.T. • Quach A. • Chen B.H. • Assimes T.L. • Bandinelli S. • Hou L. • Baccarelli A.A. • Stewart J.D. • Li Y. • et al.
**An epigenetic biomarker of aging for lifespan and healthspan.**
*Aging.* 2018; **10**: 573-591
https://doi.org/10.18632/aging.101414

View in Article
Scopus (898) • PubMed • Crossref • Google Scholar

15. Lu A.T. • Quach A. • Wilson J.G. • Reiner A.P. • Aviv A. • Raj K. • Hou L • Baccarelli A.A. • Li Y. • Stewart J.D. • et al.

**DNA methylation GrimAge strongly predicts lifespan and healthspan.**
*Aging.* 2019; **11**: 303-327
https://doi.org/10.18632/aging.101684

View in Article
Scopus (633) • PubMed • Crossref • Google Scholar

16. Belsky D.W. • Caspi A. • Arseneault L. • Baccarelli A. • Corcoran D.L. • Gao X. • Hannon E. • Harrington H.L. • Rasmussen L.J. • Houts R. • et al.
**Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm.**
*eLife.* 2020; **9**e54870
https://doi.org/10.7554/eLife.54870

View in Article
Scopus (139) • PubMed • Crossref • Google Scholar

17. Belsky D.W. • Caspi A. • Corcoran D.L. • Sugden K. • Poulton R. • Arseneault L. • Baccarelli A. • Chamarti K. • Gao X. • Hannon E. • et al.
**DunedinPACE, a DNA methylation biomarker of the pace of aging.**
*eLife.* 2022; **11**e73420
https://doi.org/10.7554/eLife.73420

View in Article
Scopus (58) • PubMed • Crossref • Google Scholar

18. Fahy G.M. • Brooke R.T. • Watson J.P. • Good Z. • Vasanawala S.S. • Maecker H. • Leipold M.D. • Lin D.T.S. • Kobor M.S. • Horvath S.
**Reversal of epigenetic aging and immunosenescent trends in humans.**
*Aging Cell.* 2019; **18**e13028
https://doi.org/10.1111/acel.13028

View in Article
Scopus (212) • PubMed • Crossref • Google Scholar

19. Conboy I.M. • Rando T.A.
**Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches.**

*Cell Cycle.* 2012; **11**: 2260-2267
https://doi.org/10.4161/cc.20437

View in Article
Scopus (168) • PubMed • Crossref • Google Scholar

20. Zhang B. • Lee D.E. • Trapp A. • Tyshkovskiy A. • Lu A.T. • Bareja A. • Kerepesi C. • Katz L.H. • Shindyapina A.V. • Dmitriev S.E. • et al.
**Multi-omic rejuvenation and lifespan extension upon exposure to youthful circulation.**
*Preprint at bioRxiv.* 2021;
https://doi.org/10.1101/2021.11.11.468258

View in Article
Scopus (0) • Crossref • Google Scholar

21. Arneson A. • Haghani A. • Thompson M.J. • Pellegrini M. • Kwon S.B. • Vu H. • Maciejewski E. • Yao M. • Li C.Z. • Lu A.T. • et al.
**A mammalian methylation array for profiling methylation levels at conserved sequences.**
*Nat. Commun.* 2022; **13**783
https://doi.org/10.1038/s41467-022-28355-z

View in Article
Scopus (32) • PubMed • Crossref • Google Scholar

22. Lu A.T. • Fei Z. • Haghani A. • Robeck T.R. • Zoller J.A. • Li C.Z. • Zhang J. • Ablaeva J. • Adams D.M. • et al. • Mammalian • Methylation Consortium
**Universal DNA methylation age across mammalian tissues.**
2021
https://doi.org/10.1101/2021.01.18.426733

View in Article
Crossref • Google Scholar

23. Tyshkovskiy A. • Bozaykut P. • Borodinova A.A. • Gerashchenko M.V. • Ables G.P. • Garratt M. • Khaitovich P. • Clish C.B. • Miller R.A. • Gladyshev V.N.
**Identification and application of gene expression signatures associated with lifespan extension.**

*Cell Metab.* 2019; **30**: 573-593.e8
https://doi.org/10.1016/j.cmet.2019.06.018

View in Article
Scopus (62) • PubMed • Abstract • Full Text • Full Text PDF • Google Scholar

24. Wolf E.J. • Maniates H. • Nugent N. • Maihofer A.X. • Armstrong D. • Ratanatharathorn A. • Ashley-Koch A.E. • Garrett M. • Kimbrel N.A. • Lori A. • et al.
**Traumatic stress and accelerated DNA methylation age: A meta-analysis.**
*Psychoneuroendocrinology.* 2018; **92**: 123-134
https://doi.org/10.1016/j.psyneuen.2017.12.007

View in Article
Scopus (133) • PubMed • Crossref • Google Scholar

25. Zannas A.S. • Arloth J. • Carrillo-Roa T. • Iurato S. • Röh S. • Ressler K.J. • Nemeroff C.B. • Smith A.K. • Bradley B. • Heim C. • et al.
**Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling.**
*Genome Biol.* 2015; **16**: 266
https://doi.org/10.1186/s13059-015-0828-5

View in Article
Scopus (273) • PubMed • Crossref • Google Scholar

26. Sadahiro R. • Knight B. • James F. • Hannon E. • Charity J. • Daniels I.R. • Burrage J. • Knox O. • Crawford B. • Smart N.J. • et al.
**Major surgery induces acute changes in measured DNA methylation associated with immune response pathways.**
*Sci. Rep.* 2020; **10**: 5743
https://doi.org/10.1038/s41598-020-62262-x

View in Article
Scopus (21) • PubMed • Crossref • Google Scholar

27. Levett D.Z.H. • Edwards M. • Grocott M. • Mythen M.
**Preparing the patient for surgery to improve outcomes.**
*Best Pract. Res. Clin. Anaesthesiol.* 2016; **30**: 145-157

https://doi.org/10.1016/j.bpa.2016.04.002

View in Article

Scopus (81) • PubMed • Crossref • Google Scholar

28. Higgins-Chen A.T. • Thrush K.L. • Wang Y. • Minteer C.J. • Kuo P.L. • Wang M. • Niimi P. • Sturm G. • Lin J. • Moore A.Z. • et al.
**A computational solution for bolstering reliability of epigenetic clocks: implications for clinical trials and longitudinal tracking.**
*Nat. Aging.* 2022; **2**: 644-661
https://doi.org/10.1038/s43587-022-00248-2

View in Article

Scopus (23) • PubMed • Crossref • Google Scholar

29. Houseman E.A. • Accomando W.P. • Koestler D.C. • Christensen B.C. • Marsit C.J. • Nelson H.H. • Wiencke J.K. • Kelsey K.T.
**DNA methylation arrays as surrogate measures of cell mixture distribution.**
*BMC Bioinformatics.* 2012; **13**86
https://doi.org/10.1186/1471-2105-13-86

View in Article

Scopus (1983) • PubMed • Crossref • Google Scholar

30. Hill C.C. • Pickinpaugh J.
**Physiologic changes in pregnancy.**
*Surg. Clin. North Am.* 2008; **88**: 391-401
https://doi.org/10.1016/j.suc.2007.12.005

View in Article

Scopus (90) • PubMed • Abstract • Full Text • Full Text PDF • Google Scholar

31. Giller A. • Andrawus M. • Gutman D. • Atzmon G.
**Pregnancy as a model for aging.**
*Ageing Res. Rev.* 2020; **62**101093
https://doi.org/10.1016/j.arr.2020.101093

View in Article

Scopus (12) • PubMed • Crossref • Google Scholar

32. White W.M. • Brost B.C. • Sun Z. • Rose C. • Craici I. • Wagner S.J. • Turner S. • Garovic V.D.
**Normal early pregnancy: a transient state of epigenetic change favoring hypomethylation.**
*Epigenetics.* 2012; **7**: 729-734
https://doi.org/10.4161/epi.20388

View in Article
Scopus (16) • PubMed • Crossref • Google Scholar

33. Guintivano J. • Arad M. • Gould T.D. • Payne J.L. • Kaminsky Z.A.
**Antenatal prediction of postpartum depression with blood DNA methylation biomarkers.**
*Mol. Psychiatry.* 2014; **19**: 560-567
https://doi.org/10.1038/mp.2013.62

View in Article
Scopus (118) • PubMed • Crossref • Google Scholar

34. Knight A.K. • Conneely K.N. • Kilaru V. • Cobb D. • Payne J.L. • Meilman S. • Corwin E.J. • Kaminsky Z.A. • Dunlop A.L. • Smith A.K.
**SLC9B1 methylation predicts fetal intolerance of labor.**
*Epigenetics.* 2018; **13**: 33-39
https://doi.org/10.1080/15592294.2017.1411444

View in Article
Scopus (13) • PubMed • Crossref • Google Scholar

35. Gruzieva O. • Merid S.K. • Chen S. • Mukherjee N. • Hedman A.M. • Almqvist C. • Andolf E. • Jiang Y. • Kere J. • Scheynius A. • et al.
**DNA methylation trajectories during pregnancy.**
*Epigenet. Insights.* 2019; **12**2516865719867090
https://doi.org/10.1177/2516865719867090

View in Article
Scopus (19) • PubMed • Crossref • Google Scholar

36. Smew A.I. • Hedman A.M. • Chiesa F. • Ullemar V. • Andolf E. • Pershagen G. • Almqvist C.
**Limited association between markers of stress during pregnancy and fetal growth in 'Born into Life', a new prospective birth cohort.**
*Acta Paediatr.* 2018; **107**: 1003-1010
https://doi.org/10.1111/apa.14246

View in Article
Scopus (24) • PubMed • Crossref • Google Scholar

37. Mavrikaki M. • Lee J.D. • Solomon I.H. • Slack F.J.
**Severe COVID-19 is associated with molecular signatures of aging in the human brain.**
*Nat. Aging.* 2022; **2**: 1130-1137
https://doi.org/10.1038/s43587-022-00321-w

View in Article
Scopus (6) • Crossref • Google Scholar

38. Santesmasses D. • Castro J.P. • Zenin A.A. • Shindyapina A.V. • Gerashchenko M.V. • Zhang B. • Kerepesi C. • Yim S.H. • Fedichev P.O. • Gladyshev V.N.
**COVID-19 is an emergent disease of aging.**
*Aging Cell.* 2020; **19**e13230
https://doi.org/10.1111/acel.13230

View in Article
Scopus (81) • PubMed • Crossref • Google Scholar

39. CDC
**Cases, data, and surveillance. Cent. Dis. control prev.**
2020
https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html

View in Article
Google Scholar

40. Ying K. • Zhai R. • Pyrkov T.V. • Shindyapina A.V. • Mariotti M. • Fedichev P.O. • Shen X. • Gladyshev V.N.
**Genetic and phenotypic analysis of the causal relationship between aging and COVID-19.**
*Commun. Med. (Lond).* 2021; **1**: 35
https://doi.org/10.1038/s43856-021-00033-z

View in Article
PubMed • Crossref • Google Scholar

41. Kuo C.L. • Pilling L.C. • Atkins J.L. • Masoli J.A.H. • Delgado J. • Tignanelli C. • Kuchel G.A. • Melzer D. • Beckman K.B. • Levine M.E.
**Biological aging predicts vulnerability to COVID-19 severity in UK Biobank participants.**
*J. Gerontol. A Biol. Sci. Med. Sci.* 2021; **76**: e133-e141
https://doi.org/10.1093/gerona/glab060

View in Article
Scopus (15) • PubMed • Crossref • Google Scholar

42. Franzen J. • Nüchtern S. • Tharmapalan V. • Vieri M. • Nikolić M. • Han Y. • Balfanz P. • Marx N. • Dreher M. • Brümmendorf T.H. • et al.
**Epigenetic clocks are not accelerated in COVID-19 patients.**
*IJMS.* 2020; **22**9306
https://doi.org/10.3390/ijms22179306

View in Article
Scopus (11) • Crossref • Google Scholar

43. Pang A.P. • Higgins-Chen A.T. • Comite F. • Raica I. • Arboleda C. • Mendez T. • Schotsaert M. • Dwaraka V. • Smith R. • Levine M.E. • et al.
**Longitudinal study of DNA methylation and epigenetic clocks prior to and following test-confirmed COVID-19 and mRNA vaccination (infectious diseases (except HIV/AIDS)).**
2021
https://doi.org/10.1101/2021.12.01.21266670

View in Article

Crossref • Google Scholar

44. Cao X. • Li W. • Wang T. • Ran D. • Davalos V. • Planas-Serra L. • Pujol A. • Esteller M. • Wang X. • Yu H.
**Accelerated biological aging in COVID-19 patients.**
*Nat. Commun.* 2022; **13**2135
https://doi.org/10.1038/s41467-022-29801-8

View in Article
Scopus (30) • Crossref • Google Scholar

45. Peckham H. • de Gruijter N.M. • Raine C. • Radziszewska A. • Ciurtin C. • Wedderburn L.R. • Rosser E.C. • Webb K. • Deakin C.T.
**Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission.**
*Nat. Commun.* 2020; **11**: 6317
https://doi.org/10.1038/s41467-020-19741-6

View in Article
Scopus (732) • PubMed • Crossref • Google Scholar

46. Sanders J.M. • Monogue M.L. • Jodlowski T.Z. • Cutrell J.B.
**Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review.**
*JAMA.* 2020; **323**: 1824-1836
https://doi.org/10.1001/jama.2020.6019

View in Article
Scopus (1838) • PubMed • Crossref • Google Scholar

47. Chen R. • Xia L. • Tu K. • Duan M. • Kukurba K. • Li-Pook-Than J. • Xie D. • Snyder M.
**Longitudinal personal DNA methylome dynamics in a human with a chronic condition.**
*Nat. Med.* 2018; **24**: 1930-1939
https://doi.org/10.1038/s41591-018-0237-x

View in Article
Scopus (36) • PubMed • Crossref • Google Scholar

48. Lu Y. • Brommer B. • Tian X. • Krishnan A. • Meer M. • Wang C. • Vera D.L. • Zeng Q. • Yu D. • Bonkowski M.S. • et al.
**Reprogramming to recover youthful epigenetic information and restore vision.**
*Nature.* 2020; **588**: 124-129
https://doi.org/10.1038/s41586-020-2975-4

View in Article
Scopus (219) • PubMed • Crossref • Google Scholar

49. Pyrkov T.V. • Avchaciov K. • Tarkhov A.E. • Menshikov L.I. • Gudkov A.V. • Fedichev P.O.
**Longitudinal analysis of blood markers reveals progressive loss of resilience and predicts human lifespan limit.**
*Nat. Commun.* 2021; **12**2765
https://doi.org/10.1038/s41467-021-23014-1

View in Article
Scopus (30) • PubMed • Crossref • Google Scholar

50. Avchaciov K. • Antoch M.P. • Andrianova E.L. • Tarkhov A.E. • Menshikov L.I. • Burmistrova O. • Gudkov A.V. • Fedichev P.O.
**Unsupervised learning of aging principles from longitudinal data.**
*Nat. Commun.* 2022; **13**6529
https://doi.org/10.1038/s41467-022-34051-9

View in Article
Scopus (2) • PubMed • Crossref • Google Scholar

51. Komaki S. • Ohmomo H. • Hachiya T. • Sutoh Y. • Ono K. • Furukawa R. • Umekage S. • Otsuka-Yamasaki Y. • Minabe S. • Takashima A. • et al.
**Evaluation of short-term epigenetic age fluctuation.**
*Clin. Epigenet.* 2022; **14**76
https://doi.org/10.1186/s13148-022-01293-9

View in Article
Scopus (2) • PubMed • Crossref • Google Scholar

52. Rebo J. • Mehdipour M. • Gathwala R. • Causey K. • Liu Y. • Conboy M

Conboy I.M.
**A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood.**
*Nat. Commun.* 2016; **7**13363
https://doi.org/10.1038/ncomms13363

View in Article
Scopus (150) • PubMed • Crossref • Google Scholar

53. Gonzalez-Armenta J.L. • Li N. • Lee R.L. • Lu B. • Molina A.J.A.
**Heterochronic parabiosis: old blood induces changes in mitochondrial structure and function of young mice.**
*J. Gerontol. A Biol. Sci. Med. Sci.* 2021; **76**: 434-439
https://doi.org/10.1093/gerona/glaa299

View in Article
Scopus (9) • PubMed • Crossref • Google Scholar

54. Kiss T. • Nyúl-Tóth Á. • Gulej R. • Tarantini S. • Csipo T. • Mukli P. • Ungvari A. • Balasubramanian P. • Yabluchanskiy A. • Benyo Z. • et al.
**Old blood from heterochronic parabionts accelerates vascular aging in young mice: transcriptomic signature of pathologic smooth muscle remodeling.**
*GeroScience.* 2022; **44**: 953-981
https://doi.org/10.1007/s11357-022-00519-1

View in Article
Scopus (6) • PubMed • Crossref • Google Scholar

55. Le Manach Y. • Collins G. • Bhandari M. • Bessissow A. • Boddaert J. • Khiami F. • Chaudhry H. • De Beer J. • Riou B. • Landais P. • et al.
**Outcomes after hip fracture surgery compared with elective total hip replacement.**
*JAMA.* 2015; **314**: 1159-1166
https://doi.org/10.1001/jama.2015.10842

View in Article
Scopus (122) • PubMed • Crossref • Google Scholar

56. Kankaanpää A. • Tolvanen A. • Heikkinen A. • Kaprio J. • Ollikainen M.

Sillanpää E.
**The role of adolescent lifestyle habits in biological aging: A prospective twin study.**
*eLife.* 2022; **11**e80729
https://doi.org/10.7554/eLife.80729

View in Article
PubMed • Crossref • Google Scholar

57. Raffington L. • Belsky D.W.
**Integrating DNA methylation measures of biological aging into social determinants of Health Research.**
*Curr. Environ. Health Rep.* 2022; **9**: 196-210
https://doi.org/10.1007/s40572-022-00338-8

View in Article
Scopus (10) • PubMed • Crossref • Google Scholar

58. Ryan C.P. • Hayes M.G. • Lee N.R. • McDade T.W. • Jones M.J. • Kobor M.S. • Kuzawa C.W. • Eisenberg D.T.A.
**Reproduction predicts shorter telomeres and epigenetic age acceleration among young adult women.**
*Sci. Rep.* 2018; **8**11100
https://doi.org/10.1038/s41598-018-29486-4

View in Article
Scopus (43) • Crossref • Google Scholar

59. Kresovich J.K. • Harmon Q.E. • Xu Z. • Nichols H.B. • Sandler D.P. • Taylor J.A.
**Reproduction, DNA methylation and biological age.**
*Hum. Reprod.* 2019; **34**: 1965-1973
https://doi.org/10.1093/humrep/dez149

View in Article
Scopus (20) • PubMed • Crossref • Google Scholar

60. Whitten W.K.
**Modification of the oestrous cycle of the mouse by external stimuli associated with the male.**

*J. Endocrinol.* 1956; **13**: 399-404
https://doi.org/10.1677/joe.0.0130399

View in Article
Scopus (318) • PubMed • Crossref • Google Scholar

61. Paynter N.P. • Balasubramanian R. • Giulianini F. • Wang D.D. • Tinker L.F. • Gopal S. • Deik A.A. • Bullock K. • Pierce K.A. • Scott J. • et al.
**Metabolic predictors of incident coronary heart disease in women.**
*Circulation.* 2018; **137**: 841-853
https://doi.org/10.1161/CIRCULATIONAHA.117.029468

View in Article
Scopus (127) • PubMed • Crossref • Google Scholar

62. Aryee M.J. • Jaffe A.E. • Corrada-Bravo H. • Ladd-Acosta C. • Feinberg A.P. • Hansen K.D. • Irizarry R.A.
**Minfi: a flexible and comprehensive Bioconductor package for the analysis of Infinium DNA methylation microarrays.**
*Bioinformatics.* 2014; **30**: 1363-1369
https://doi.org/10.1093/bioinformatics/btu049

View in Article
Scopus (2198) • PubMed • Crossref • Google Scholar

63. Danbelsky. Dunedin PACE. 2022. https://github.com/danbelsky/DunedinPACE.

View in Article
Google Scholar

64. Anders S. • Huber W.
**Differential expression analysis for sequence count data.**
*Genome Biol.* 2010; **11**R106
https://doi.org/10.1186/gb-2010-11-10-r106

View in Article
Scopus (10564) • Crossref • Google Scholar

65. Robinson M.D. • McCarthy D.J. • Smyth G.K.
**edgeR: a Bioconductor package for differential expression analysis of digital gene expression data.**
*Bioinformatics.* 2010; **26**: 139-140
https://doi.org/10.1093/bioinformatics/btp616

View in Article
Scopus (21906) • PubMed • Crossref • Google Scholar

66. Benjamini Y. • Hochberg Y.
**Controlling the false discovery rate: A practical and powerful approach to multiple testing.**
*J. R. Stat. Soc. B.* 1995; **57**: 289-300
https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

View in Article
Crossref • Google Scholar

67. Subramanian A. • Tamayo P. • Mootha V.K. • Mukherjee S. • Ebert B.L. • Gillette M.A. • Paulovich A. • Pomeroy S.L. • Golub T.R. • Lander E.S. • et al.
**Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles.**
*Proc. Natl. Acad. Sci. USA.* 2005; **102**: 15545-15550
https://doi.org/10.1073/pnas.0506580102

View in Article
Scopus (27802) • PubMed • Crossref • Google Scholar

68. Pang Z. • Chong J. • Zhou G. • de Lima Morais D.A. • Chang L. • Barrette M. • Gauthier C. • Jacques P.É. • Li S. • Xia J.
**MetaboAnalyst 5.0: narrowing the gap between raw spectra and functional insights.**
*Nucleic Acids Res.* 2021; **49**: W388-W396
https://doi.org/10.1093/nar/gkab382

View in Article
Scopus (1206) • PubMed • Crossref • Google Scholar

69. Zhou W. • Triche T.J. • Laird P.W. • Shen H.

**SeSAMe: reducing artifactual detection of DNA methylation by Infinium BeadChips in genomic deletions.**

*Nucleic Acids Res.* 2018; **46**e123

https://doi.org/10.1093/nar/gky691

View in Article

Scopus (120) • Crossref • Google Scholar

## Article info

### Publication history

Published: April 21, 2023

Accepted: March 20, 2023

Received in revised form: December 22, 2022

Received: June 7, 2022

### Identification

DOI: https://doi.org/10.1016/j.cmet.2023.03.015

### Copyright



### ScienceDirect

Access this article on ScienceDirect

## Related Articles

**The content on this site is intended for healthcare professionals and researchers across all fields of science.**

## RESEARCH JOURNALS

Cell

Cancer Cell

Cell Chemical Biology

Cell Genomics

Cell Host & Microbe

Cell Metabolism

Cell Reports

Cell Reports Medicine

Cell Reports Methods

Cell Reports Physical Science

Cell Reports Sustainability

Cell Stem Cell

Cell Systems

Chem

Chem Catalysis

Current Biology

Developmental Cell

Device

Heliyon

Immunity

iScience

Joule

Matter

Med

Molecular Cell

Neuron

One Earth

Patterns

STAR Protocols

Structure

## TRENDS REVIEWS JOURNALS

Biochemical Sciences

Biotechnology

Cancer

Cell Biology

Chemistry

Cognitive Sciences

Ecology & Evolution

Endocrinology & Metabolism

Genetics

Immunology

Microbiology

Molecular Medicine

Neurosciences

Parasitology

Pharmacological Sciences

Plant Science

## PARTNER JOURNALS

AJHG

Biophysical Journal

Biophysical Reports

HGG Advances

Molecular Plant

Molecular Therapy Family

Nexus

Plant Communications

Stem Cell Reports

The Innovation

## COLLECTIONS

Best of Cell Press

Cell Press Reviews

Cell Press Selections

Consortia Hub

Nucleus Collections

SnapShot Archive

## BEYOND THE JOURNAL

Cell Career Network

Cell Mentor

Cell Symposia

LabLinks

Webinars

## EVOLVING THE ARTICLE

Community Review

Figure360

Sneak Peek

STAR Methods

## SCIENCE IN SOCIETY

Cell Picture Show

Cell Press Podcast

Cell Press Videos

Coloring and Comics

Research Arc

## CONNECT

About Cell Press

Careers

Contact

Help & Support

Newsroom

Publication Alerts

## ACCESS

Subscribe

Read-It-Now

Recommend to Librarian

## INFORMATION

For Advertisers

For Recruiters

For Librarians

Terms & Conditions

Privacy Policy

Accessibility