

## Research Paper

# Stochasticity Explains Nongenetic Inheritance of Lifespan and Apparent Trade-Offs between Reproduction and Aging

Elizabeth D. Drake,<sup>1,2</sup> and Mirre J. P. Simons<sup>1,\*</sup>

<sup>1</sup>School of Biosciences, University of Sheffield, Sheffield, United Kingdom

<sup>2</sup>Institute of Ecology and Evolution, Ashworth Laboratories, The King's Buildings, The University of Edinburgh, Edinburgh, United Kingdom

\*Corresponding author: [m.simons@sheffield.ac.uk](mailto:m.simons@sheffield.ac.uk)

<https://doi.org/10.59368/agingbio.20230012>

Stochastic effects are central to the biology and demography of aging. Genetically identical individuals do not all die at the exact same time but show a distribution of lifespan. Although such effects are appreciated, any cascading effects from the stochastic effects of aging are underappreciated. We show here that genetically identical female flies (*Drosophila melanogaster*) that live long produce longer-lived daughters. In line with previous work, we also find that daughters born to older mothers are shorter-lived, also termed the Lansing effect. We further show that longer-lived flies produce less offspring, suggesting an apparent trade-off due to stochastic effects alone. We explain these effects using an extension of the reliability theory of aging by dichotomizing aging physiology in reproduction and lifespan-supporting units. These simple models reproduce the nongenetic inheritance of lifespan, the Lansing effect, and trade-offs between reproduction and lifespan. Our work implies that if nongenetic inheritance of lifespan is widespread, it explains the generally low heritability of this trait. Furthermore, trade-offs between performance, for example, reproduction, and lifespan may be less widespread than predicted by the evolutionary biology of aging, stemming from stochasticity rather than differential investment. Antiaging treatments could therefore come without any unintended costs to other physiology, a perceived risk that limits the translation of these treatments to humans.

## Introduction

Aging is existential but poorly understood in both its evolutionary and mechanistic biology<sup>1–4</sup>. In a population, not all individuals appear to age at the same rate<sup>5</sup> in terms of lifespan and reproduction<sup>6</sup>. Moreover, it is not always evident that these two traits are negatively correlated, as some individuals appear to both show high reproduction and longevity in a population, often termed quality effects<sup>7–9</sup>. Understanding reproduction and lifespan is critical to understand aging at a fundamental level, as they are most closely related to Darwinian fitness. When we understand such variation we can start to understand how selection acts on aging and partition environmental from genetic effects. Surprisingly, however, for both reproductive output and lifespan, a large amount of variation has been observed in individuals of the exact same genotype kept in the exact same environment<sup>10–12</sup>. In the absence of genetic and environmental effects, stochastic and parental effects remain.

Stochastic effects in aging are evident, as the resultant phenotype lifespan is inherently variable. Lifespan follows from a presumed genetically determined mortality risk function with age<sup>13,14</sup>. How reproduction changes with age, often termed reproductive senescence, has also been shown to vary among individuals in human and other animal populations<sup>15,16</sup>. In addition to this, there are mechanistically unexplained effects of parental age on offspring lifespan and reproduction<sup>17,18</sup>. The nongenetic inheritance of

how organisms age is thus documented but not understood. Here, we show the nongenetic inheritance of lifespan using an inbred population of fruit flies (*Drosophila melanogaster*). Mothers that lived the longest produced long-lived daughters.

Differences in Darwinian fitness traits are often explained as differences in quality<sup>7,19</sup>. The term quality encompasses differences in local adaptation or the long-lasting effects of early environmental effects. In line with this, in many animal populations, individuals with high reproductive rates or high lifetime reproductive success are also often the most long-lived<sup>6,7,20</sup>. We find, however, that mothers that are long-lived are not typical high-quality individuals, as longevity was associated with reduced reproductive output. Across genetically identical individuals, we thus find evidence of an apparent trade-off between reproduction and lifespan. Such trade-offs have been fundamental to explaining life-history theory and the evolution of aging<sup>1,21,22</sup>. Here, we provide a novel explanation of the nongenetic inheritance of lifespan and parental age effects, and apparent trade-offs between reproduction and lifespan, using the reliability theory of aging.

## Theoretical Model

Aging can be modeled in various ways. The earliest models described aging as an exponential mortality risk curve<sup>13</sup>, and stochastic effects have been central in models of aging, especially those describing mortality<sup>23</sup>. Mortality in many species can be

accurately described using a simple two-parameter exponential risk model such as the Gompertz equation<sup>24,25</sup>. Perhaps more importantly, treatment effects<sup>24,26,27</sup> and differences between human populations can be similarly captured by these models<sup>28</sup>. Risk, and thus stochasticity within the population, is fundamental to how we understand aging. In the underlying biology of aging, we also find these ideas, with damage accumulation with age as central<sup>29</sup> to all physiology implicated in aging. Although the central role of damage accumulation with age has been challenged by quasi-program and developmental explanations of aging<sup>30</sup>, these theories currently fail to explain why exponentially increasing risk with age appears central to aging.

A theory that has been underappreciated but provides an excellent quantitative embedding of aging-related biology is the reliability theory of aging. This theory states that organisms consist of units that fail at a set pace (termed “failure rate”) and that organisms have a level of redundancy built in (termed “units”)<sup>31,32</sup>, and when all redundancy is lost, the system fails. Importantly, this theory explains why mortality risk plateaus and converges at old age<sup>31</sup>. More recent applications of this theory have explained why biomarkers of physiological system redundancy reduce in explanatory power with age<sup>33</sup>. Here we use the reliability theory of aging to explain the nongenetic inheritance and maternal age effects we find in the fruit fly. In addition, our extension of the reliability theory of aging predicts apparent trade-offs between physiological domains of aging that result from stochasticity rather than differential investment. The latter is assumed in the disposable soma theory and life-history theory, although evidence of such investment is lacking<sup>2,34</sup>.

We assume that physiology consists of units that fail with age, as in the original reliability theory of aging. Of these units of physiology, we now assume some support physiology that prevents mortality and others support reproductive output. Such compartmentalization in physiology, separating aspects that cause mortality from others that decline with age, is probably prevalent. The aging of different aspects of physiology is expected to be related to mortality risk in varying degrees. For example, we believe wrinkles to not be causally linked to mortality, even though the presence of wrinkles is a correlate of age and thus mortality risk. Other physiology, such as immune functioning, might have more of a central role in overall physiology and might thus determine, for example, age-related reproductive performance or endurance, as well as age-related mortality risk. Of interest to us here is how these physiological domains are expected to age in relation to each other in a genetically identical population.

In the original models of aging using reliability theory, each unit of physiology has an independent chance of failing over time. Thus, without any variation in the failure rate of the system’s components and of how much redundancy the system has, each physiological domain will age independently as each failure is an independent chance event. The alternative, not explored in these models before, is one of constant damage to the system but with the damage falling on components of the system in a stochastic fashion. This generates an inverse relationship between physiological domains, as damage falling on one part of physiology will not fall on the other. When such damage is attributed to the system in a draw with replacement, that is, a failed unit that is damaged can absorb damage, this model behaves similarly to the original reliability models of aging. Mortality converges to the risk of the rate of failure divided by all the redundancy in the system.

Reliability theory models incorporating compartmentalization of physiology and constant damage applied through a draw with

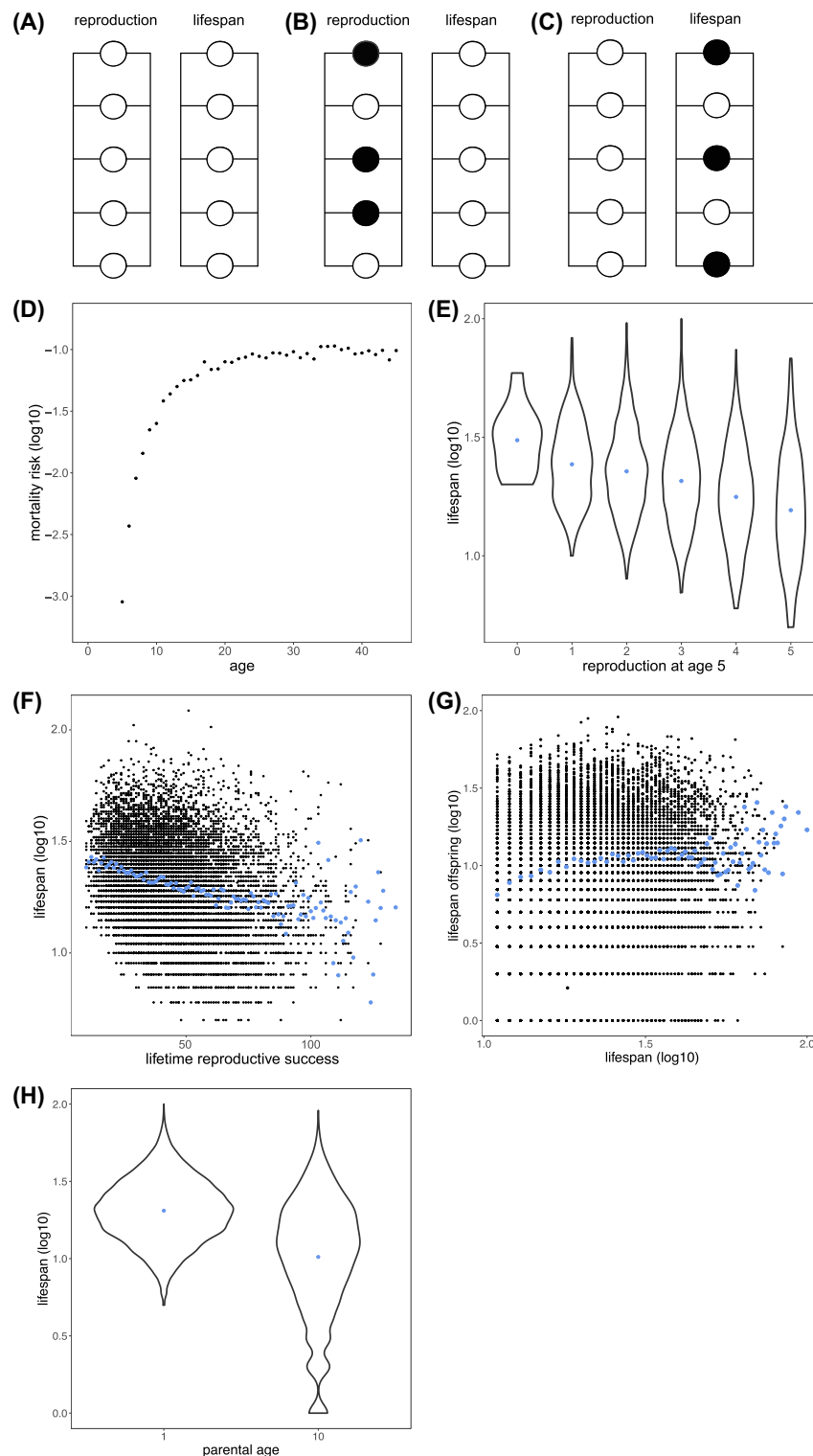
replacement at each timepoint were simulated using R. Our model is intended to aid interpretation of our findings rather than be parameterized to observations. We modeled a system of 10 physiological units, with 5 sustaining reproduction and 5 sustaining lifespan (Fig. 1A), in a population comprising 10,000 individuals with damage of one unit per time (redraw across the 10 units). The level of units left in reproduction, we propose is a metric of the ability to sustain reproduction. When all units are damaged in the lifespan sustaining system, an individual dies (Fig. 1D). The mutual exclusivity of damage distribution on this physiological network with stochastically allocating a constant level of damage on the network means some individuals in the population will age disproportionately in either physiological domain (Fig. 1B,C). Individuals that lose system integrity on the reproduction side more rapidly have a larger proportion of their lifespan sustaining physiology left intact, and vice versa (Fig. 1B,C). Stochasticity thus leads to an apparent trade-off between reproductive output and lifespan across individuals that are intrinsically physiologically identical (Fig. 1E,F).

We can further apply this model to understand the effects of parental age on offspring fitness<sup>35</sup> and lifespan<sup>17</sup>, also termed the Lansing effect. We can hypothesize that either part of physiology, the reproduction or lifespan sustaining component, is passed down through nongenetic inheritance. When organisms would pass on their age-dependent level of life-sustaining redundancy, this generates a relationship between parental age and offspring lifespan because redundancy is lost as a function with age. Furthermore, such a hypothesized nongenetic inheritance mechanism would generate a positive relationship between the lifespan of the parent and the offspring. As the level of redundancy left at a given parental age is a predictor of both parental and offspring survival, these assumptions show that similar physiology could underlie both parental age effects and parental offspring lifespan relationships.

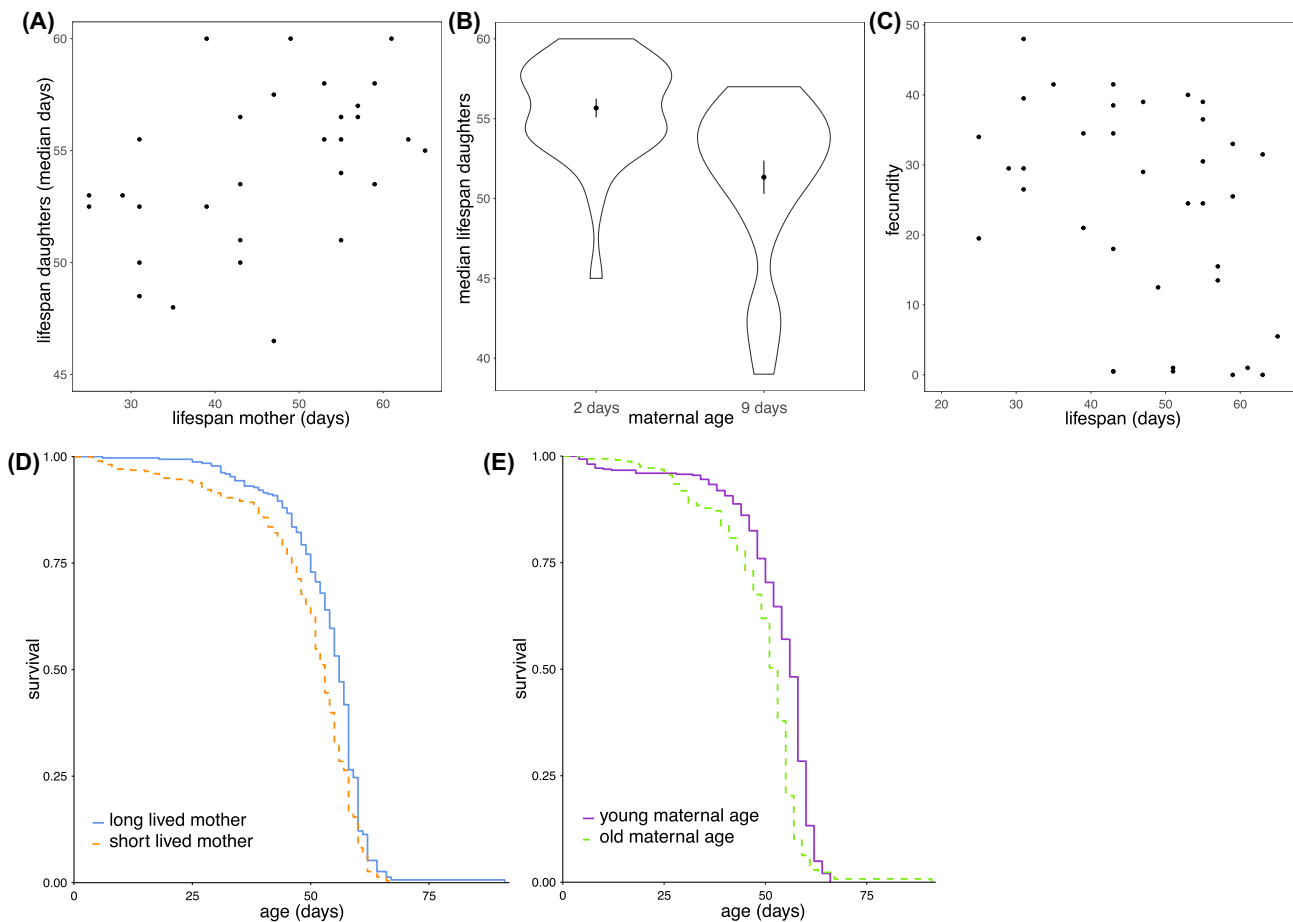
## Results and Discussion

Mothers that lived long produced long-lived daughters ( $r_s = 0.49$ ,  $p = 0.006$ ; Fig. 2A,D;  $HR(coxme) = -0.016 \pm 0.0059$ ,  $p = 0.005$  per day of maternal lifespan). Daughters born to mothers at older ages showed reduced longevity ( $HR(coxme) = 0.11 \pm 0.02$ ,  $p < 0.001$  per day of maternal age; Fig. 2B,E). Mothers that lived long had less reproductive output ( $r_s = -0.49$ ,  $p = 0.028$ , as measured across both ages; Fig. 2C). Note that any of these effects are unlikely due to population size differences in the growing vials, as total pupal case numbers per vial did not correlate to the resulting lifespan of offspring from those vials ( $r_s = 0.048$ ,  $p = 0.74$ ).

The fly experiments indicate that in a highly inbred genetic line, stochastic effects inherent to the aging process can explain several findings that currently lack a mechanistic explanation. Offspring from older mothers show truncated lifespans, also termed the Lansing effect<sup>17,36</sup>. Similarly, parental and offspring lifespan correlations are often interpreted in a genetic context only<sup>37</sup>. Our findings suggest that part of the correlation between parent and offspring lifespan could originate from the same physiology that underlies the Lansing effect. Note that such parental effects would affect twin studies<sup>38</sup> as well as parent-offspring correlation and pedigree-based approaches to heritability of lifespan. When nongenetic inheritance of lifespan is



**Figure 1.** (A) Reliability theory model of aging partitioning physiology between reproduction and longevity. Damage is drawn as one unit failing per time across all ten units (including those that have already been damaged). Some individuals simply due to stochasticity age disproportionately either in (B) reproduction or (C) lifespan sustaining physiology. (D) The model behaves as a standard reliability theory of aging model, with mortality increasing semi-exponentially with age and mortality converging at the oldest ages. (E) The partitioning between reproduction and lifespan but their shared susceptibility of one unit being hit by damage per time generates a negative relationship between reproduction (here number of units left equals reproductive output) and lifespan. This effect is reminiscent of the reproduction, lifespan trade-off central to evolutionary biology and mechanisms of aging, but notably only came about through stochastic effects. (F) Moreover, this relationship extends into total lifetime reproductive success with individuals with long lifespans producing less offspring in total. When nongenetic inheritance is incorporated into this model by assuming lifespan sustaining physiology is inherited somehow additional insight is gained. This simple stochastic model generates (G) a positive relationship between the lifespan of the parent and the lifespan of the offspring and (H) a negative relationship between parental age and offspring lifespan.



**Figure 2. Nongenetic inheritance of longevity in inbred fruit flies.** (A,D) Mothers that were long-lived produced daughters that were long-lived (median). (B,E) Daughters born to mothers of older ages survived less long. (C) Mothers that lived long produced less offspring.

ubiquitous and due not to what is usually interpreted as environmental effects but to stochastic effects alone, the realized heritability of a trait and thus its response to selection reduces<sup>39</sup>.

A final important observation from our work is that trade-offs can emerge from stochastic effects during aging alone. Individuals that age fast in one physiological domain supporting, for example, lifespan, age less fast in another physiological domain, for example, reproduction. Trade-offs between reproduction and longevity are central to life history but, when tested experimentally, lack empirical support, especially in naturalistic settings<sup>7,40</sup>. As an explanation for this, differences in phenotypic quality, allowing some individuals to show both high reproductive output as well as longevity, have been suggested to mask trade-offs and hence limit selection<sup>40,41</sup>. In contrast, we show here that apparent trade-offs between traits can emerge from stochastic aging in inbred flies and in our theoretical models. Thus, in both directions of the fitness landscape, natural selection is limited in its potential to select for sharp trade-offs. The assumed strength of the trade-off between reproduction and longevity, central to the biology of aging, could thus be overstated. We should therefore not be forced to assume the costs of antiaging treatments to other physiological domains, although this is dictated by life-history doctrine. This idea fits with observations of cost-free longevity extension<sup>42</sup>. When the costs of longevity treatments are not presumed, translating findings

from biology of aging research to the clinic increases in feasibility<sup>43,44</sup>.

## Methods

### Experiments in the fly

Fruit flies of the standard inbred laboratory (yw) stock were used for the experiments<sup>45</sup>. All experiments were conducted on our standard lab diet (“rich”), 8% yeast<sup>46</sup>. Mothers were grown together in one bottle to ensure shared environmental effects, and these were mated together for two days after eclosion. Mothers (n = 40) were then single-housed in vials until they died to record their lifespan (three flies were lost to follow-up). Food vials were changed every two days when a census was taken. Daughters of these mothers were collected from vials when mothers were 2 to 3 days old and 9 and 11 days old, were mated in a vial for 2 days (presence of males was confirmed), and then recorded as a population for longevity using demography cages (n = 1–31 per cage, maximum of one cage per collection point). Only intact offspring were used, and individuals were censored if they were stuck to the food or escaped from the cage during handling<sup>2</sup>. Total offspring produced from the individual mothers was recorded by counting the pupal cases at both collection timepoints. Data were analyzed using spearman rank correlations, linear mixed effects models, and cox proportional hazard models that included random terms for cage and mother and right-hand censoring.

Results from the spearman rank correlations and cox models are presented, as the linear mixed effect models gave qualitatively similar results.

## Acknowledgments

M.J.P.S. is supported by a Sir Henry Dale Fellowship (Wellcome and Royal Society; 216405/Z/19/Z) and an Academy of Medical Sciences Springboard Award (the Wellcome Trust, the Government Department of Business, Energy and Industrial Strategy [BEIS], the British Heart Foundation and Diabetes UK; SBF004\1085). For the purpose of Open Access, the author has applied a CC BY public copyright license to any Author Accepted Manuscript version arising from this submission. We thank Laura Hartshorne and Gracie Adams for technical support. We thank Marc Tatar for supplying the fly stock used.

## Author Contributions

E.D.D. designed and conducted the experiments and reviewed this article. M.J.P.S. designed the experiments, produced the model, and wrote the first draft of this article.

Accepted July 2, 2023

Published July 28, 2023

## References

- Cohen A.A., Coste C.F.D., Li X.-Y., Bourq S., & Pavard S. (2020). Are trade-offs really the key drivers of ageing and life span? *Funct. Ecol.* **34**, 153–166. doi: [10.1111/1365-2435.13444](https://doi.org/10.1111/1365-2435.13444).
- McCracken A.W., Adams G., Hartshorne L., Tatar M., & Simons M.J.P. (2020). The hidden costs of dietary restriction: Implications for its evolutionary and mechanistic origins. *Sci. Adv.* **6**, eaay3047. PMID: [32128403](https://pubmed.ncbi.nlm.nih.gov/32128403/); doi: [10.1126/sciadv.aay3047](https://doi.org/10.1126/sciadv.aay3047).
- Schumacher B., Pothof J., Vijg J., & Hoeijmakers J.H.J. (2021). The central role of DNA damage in the ageing process. *Nature* **592**, 695–703. PMID: [33911272](https://pubmed.ncbi.nlm.nih.gov/33911272/); doi: [10.1038/s41586-021-03307-7](https://doi.org/10.1038/s41586-021-03307-7).
- Kowald A., Passos J.F., & Kirkwood T.B.L. (2020). On the evolution of cellular senescence. *Ageing Cell* **19**, e13270. PMID: [33166065](https://pubmed.ncbi.nlm.nih.gov/33166065/); doi: [10.1111/accel.13270](https://doi.org/10.1111/accel.13270).
- Belsky D.W., Caspi A., Houts R., Cohen H.J., Corcoran D.L., Danese A., ... Moffitt T.E. (2015). Quantification of biological aging in young adults. *Proc. Natl. Acad. Sci.* **112**, E4104–E4110. PMID: [26150497](https://pubmed.ncbi.nlm.nih.gov/26150497/); doi: [10.1073/pnas.1506264112](https://doi.org/10.1073/pnas.1506264112).
- Bouwhuys S., Sheldon B.C., Verhulst S., & Charmantier A. (2009). Great tits growing old: Selective disappearance and the partitioning of senescence to stages within the breeding cycle. *Proc. R. Soc. B Biol. Sci.* **276**, 2769–2777. PMID: [19403537](https://pubmed.ncbi.nlm.nih.gov/19403537/); doi: [10.1098/rspb.2009.0457](https://doi.org/10.1098/rspb.2009.0457).
- Winder L.A., Simons M.J.P., & Burke T. (2022). The optimal clutch size revisited: Separating individual quality from the costs of reproduction. 2022.05.30.493969 Preprint at doi: [10.1101/2022.05.30.493969](https://doi.org/10.1101/2022.05.30.493969).
- Nenko I., Hayward A.D., Simons M.J.P., & Lummaa V. (2018). Early-life environment and differences in costs of reproduction in a preindustrial human population. *PLOS ONE* **13**, e0207236. PMID: [30540747](https://pubmed.ncbi.nlm.nih.gov/30540747/); doi: [10.1371/journal.pone.0207236](https://doi.org/10.1371/journal.pone.0207236).
- McLean E.M., Archie E.A., & Alberts S.C. (2019). Lifetime fitness in wild female baboons: Trade-offs and individual heterogeneity in quality. *Am. Nat.* **194**, 745–759. PMID: [31738100](https://pubmed.ncbi.nlm.nih.gov/31738100/); doi: [10.1086/705810](https://doi.org/10.1086/705810).
- Rea S.L., Wu D., Cypser J.R., Vaupel J.W., & Johnson T.E. (2005). A stress-sensitive reporter predicts longevity in isogenic populations of *Caenorhabditis elegans*. *Nat. Genet.* **37**, 894–898. PMID: [16041374](https://pubmed.ncbi.nlm.nih.gov/16041374/); doi: [10.1038/ng1608](https://doi.org/10.1038/ng1608).
- Kirkwood T.B.L., Feder M., Finch C.E., Franceschi C., Globerson A., Klingenberg C.P., ... Westendorp R.G. (2005). What accounts for the wide variation in life span of genetically identical organisms reared in a constant environment? *Mech. Ageing Dev.* **126**, 439–443. PMID: [15664632](https://pubmed.ncbi.nlm.nih.gov/15664632/); doi: [10.1016/j.mad.2004.09.008](https://doi.org/10.1016/j.mad.2004.09.008).
- Spudich J.L., & Koshland D.E. (1976). Non-genetic individuality: Chance in the single cell. *Nature* **262**, 467–471. PMID: [958399](https://pubmed.ncbi.nlm.nih.gov/958399/); doi: [10.1038/262467a0](https://doi.org/10.1038/262467a0).
- Kirkwood T.B.L. (2015). Deciphering death: A commentary on Gompertz (1825) 'On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies'. *Philos. Trans. R. Soc. B Biol. Sci.* **370**, 20140379. PMID: [25750242](https://pubmed.ncbi.nlm.nih.gov/25750242/); doi: [10.1098/rstb.2014.0379](https://doi.org/10.1098/rstb.2014.0379).
- Tatar M., & Carey J.R. (1994). Genetics of Mortality in the Bean Beetle *Callosobruchus maculatus*. *Evolution* **48**, 1371. PMID: [28564469](https://pubmed.ncbi.nlm.nih.gov/28564469/); doi: [10.1111/j.1558-5646.1994.tb05320.x](https://doi.org/10.1111/j.1558-5646.1994.tb05320.x).
- Hayward A.D., Wilson A.J., Pilkington J.G., Clutton-Brock T.H., Pemberton J.M., & Kruuk L.E.B. (2013). Reproductive senescence in female Soay sheep: Variation across traits and contributions of individual ageing and selective disappearance. *Funct. Ecol.* **27**, 184–195. doi: [10.1111/1365-2435.12029](https://doi.org/10.1111/1365-2435.12029).
- Hayward A.D., Nenke I., & Lummaa V. (2015). Early-life reproduction is associated with increased mortality risk but enhanced lifetime fitness in pre-industrial humans. *Proc. R. Soc. B Biol. Sci.* **282**, 20143053. PMID: [25740893](https://pubmed.ncbi.nlm.nih.gov/25740893/); doi: [10.1098/rspb.2014.3053](https://doi.org/10.1098/rspb.2014.3053).
- Ivimey-Cook E., Shorr S., & Moorad J. (2022). The distribution of the Lansing Effect across animal species. 2022.04.27.489689 Preprint at doi: [10.1101/2022.04.27.489689](https://doi.org/10.1101/2022.04.27.489689).
- van Daalen S.F., Hernández C.M., Caswell H., Neubert M.G., & Gribble K.E. (2022). The contributions of maternal age heterogeneity to variance in lifetime reproductive output. *Am. Nat.* **199**, 603–616. PMID: [35472026](https://pubmed.ncbi.nlm.nih.gov/35472026/); doi: [10.1086/718716](https://doi.org/10.1086/718716).
- Wilson A.J., & Nussey D.H. (2010). What is individual quality? An evolutionary perspective. *Trends Ecol. Evol.* **25**, 207–214. PMID: [19897275](https://pubmed.ncbi.nlm.nih.gov/19897275/); doi: [10.1016/j.tree.2009.10.002](https://doi.org/10.1016/j.tree.2009.10.002).
- Lee P.C., Fishlock V., Webber C.E., & Moss C.J. (2016). The reproductive advantages of a long life: Longevity and senescence in wild female African elephants. *Behav. Ecol. Sociobiol.* **70**, 337–345. PMID: [26900212](https://pubmed.ncbi.nlm.nih.gov/26900212/); doi: [10.1007/s00265-015-2051-5](https://doi.org/10.1007/s00265-015-2051-5).
- Stearns S.C. (1989). Trade-offs in life-history evolution. *Funct. Ecol.* **3**, 259–268. doi: [10.2307/2389364](https://doi.org/10.2307/2389364).
- Kirkwood T.B.L., & Austad S.N. (2000). Why do we age? *Nature* **408**, 233–238. PMID: [11089980](https://pubmed.ncbi.nlm.nih.gov/11089980/); doi: [10.1038/35041682](https://doi.org/10.1038/35041682).
- Ricklefs R.E. (1998). Evolutionary theories of aging: Confirmation of a fundamental prediction, with implications for the genetic basis and evolution of life span. *Am. Nat.* **152**, 24–44. PMID: [18811399](https://pubmed.ncbi.nlm.nih.gov/18811399/); doi: [10.1086/286147](https://doi.org/10.1086/286147).
- Garratt M., Nakagawa S., & Simons M.J.P. (2016). M. J. P. comparative idiosyncrasies in life extension by reduced mTOR signalling and its distinctiveness from dietary restriction. *Ageing Cell* **15**, 737–743. PMID: [27139919](https://pubmed.ncbi.nlm.nih.gov/27139919/); doi: [10.1111/accel.12489](https://doi.org/10.1111/accel.12489).
- Jones O.R., Scheuerlein A., Salguero-Gómez R., Camarda C.G., Schaible R., Casper B.B., ... Vaupel J.W. (2014). Diversity of ageing across the tree of life. *Nature* **505**, 169–173. PMID: [24317695](https://pubmed.ncbi.nlm.nih.gov/24317695/); doi: [10.1038/nature12789](https://doi.org/10.1038/nature12789).
- Garratt M., Nakagawa S., & Simons M.J.P. (2017). Life-span extension with reduced somatotropic signaling: Moderation of aging effect by signal type, sex, and experimental cohort. *J. Gerontol. Ser. A* **72**, 1620–1626. PMID: [28207064](https://pubmed.ncbi.nlm.nih.gov/28207064/); doi: [10.1093/gerona/glx010](https://doi.org/10.1093/gerona/glx010).
- Simons M.J.P., Koch W., & Verhulst S. (2013). Dietary restriction of rodents decreases aging rate without affecting initial mortality rate - a meta-analysis. *Ageing Cell* **12**, 410–414. PMID: [23438200](https://pubmed.ncbi.nlm.nih.gov/23438200/); doi: [10.1111/accel.12061](https://doi.org/10.1111/accel.12061).
- Vaupel J.W. (2010). Biodemography of human ageing. *Nature* **464**, 536–542. PMID: [20336136](https://pubmed.ncbi.nlm.nih.gov/20336136/); doi: [10.1038/nature08984](https://doi.org/10.1038/nature08984).



29. Kirkwood T.B.L. (2005). Understanding the odd science of aging. *Cell* **120**, 437–447. PMID: [15734677](#); doi: [10.1016/j.cell.2005.01.027](#).
30. Gems D. (2022). The hyperfunction theory: An emerging paradigm for the biology of aging. *Ageing Res. Rev.* **74**, 101557. PMID: [34990845](#); doi: [10.1016/j.arr.2021.101557](#).
31. Gavrilov L.A., & Gavrilova N.S. (2001). The reliability theory of aging and longevity. *J. Theor. Biol.* **213**, 527–545. PMID: [11742523](#); doi: [10.1006/jtbi.2001.2430](#).
32. Gavrilov L.A., & Gavrilova N.S. (2005). Reliability theory of aging and longevity. *Handb. Biol. Aging* 3–42. doi: [10.1016/B978-012088387-5/50004-2](#).
33. Boonekamp J.J., Simons M.J.P., Hemerik L., & Verhulst S. (2013). Telomere length behaves as biomarker of somatic redundancy rather than biological age. *Aging Cell* **12**, 330–332. PMID: [23346961](#); doi: [10.1111/accel.12050](#).
34. O'Brien D.M., Min K.J., Larsen T., & Tatar M. (2008). Use of stable isotopes to examine how dietary restriction extends *Drosophila* lifespan. *Curr. Biol.* **18**, 155–156. PMID: [18302914](#); doi: [10.1016/j.cub.2008.01.021](#).
35. Schroeder J., Nakagawa S., Rees M., Mannarelli M.-E., & Burke T. (2015). Reduced fitness in progeny from old parents in a natural population. *Proc. Natl. Acad. Sci.* **112**, 4021–4025. PMID: [25775600](#); doi: [10.1073/pnas.1422715112](#).
36. Priest N.K., Mackowiak B., & Promislow D.E. (2002). The role of parental age effects on the evolution of aging. *Evol. Int. J. Org. Evol.* **56**, 927–935. PMID: [12093028](#); doi: [10.1111/j.0014-3820.2002.tb01405.x](#).
37. Pearl R. (1931). Studies on human longevity. IV. The inheritance of longevity. Preliminary report. *Hum. Biol.* **3**, 245–269.
38. Herskind A.M., McGue M., Holm N.V., Sørensen T.I., Harvald B., & Vaupel J.W. (1996). The heritability of human longevity: A population-based study of 2872 Danish twin pairs born 1870–1900. *Hum. Genet.* **97**, 319–323. PMID: [8786073](#); doi: [10.1007/BF02185763](#).
39. Steiner U.K., & Tuljapurkar S. (2012). Neutral theory for life histories and individual variability in fitness components. *Proc. Natl. Acad. Sci.* **109**, 4684–4689. PMID: [22392997](#); doi: [10.1073/pnas.1018096109](#).
40. van Noordwijk A.J., & de Jong G. (1986). Acquisition and allocation of resources: Their influence on variation in life history tactics. *Am. Nat.* **128**, 137–142. doi: [10.1086/284547](#).
41. Hadfield J.D., Nutall A., Osorio D., & Owens I.P.F. (2007). Testing the phenotypic gambit: Phenotypic, genetic and environmental correlations of colour. *J. Evol. Biol.* **20**, 549–557. PMID: [17305821](#); doi: [10.1111/j.1420-9101.2006.01262.x](#).
42. Maklakov A.A., & Immler S. (2016). The expensive germline and the evolution of ageing. *Curr. Biol.* **26**, R577–R586. PMID: [27404253](#); doi: [10.1016/j.cub.2016.04.012](#).
43. Phillips E.J., & Simons M.J.P. (2022). Rapamycin not dietary restriction improves resilience against pathogens: A meta-analysis. *GeroScience*. PMID: [36399256](#); doi: [10.1007/s11357-022-00691-4](#).
44. Bischof E., Siow R.C., Zhavoronkov A., & Kaeblerlein M. (2021). The potential of rapalogs to enhance resilience against SARS-CoV-2 infection and reduce the severity of COVID-19. *Lancet Healthy Longev.* **2**, e105–e111. PMID: [33665645](#); doi: [10.1016/S2666-7568\(20\)30068-4](#).
45. Wessells R.J., Fitzgerald E., Cypser J.R., Tatar M., & Bodmer R. (2004). Insulin regulation of heart function in aging fruit flies. *Nat. Genet.* **36**, 1275–1281. PMID: [15565107](#); doi: [10.1038/ng1476](#).
46. McCracken A.W., Buckle E., & Simons M.J.P. (2020). The relationship between longevity and diet is genotype dependent and sensitive to desiccation in *Drosophila melanogaster*. *J. Exp. Biol.* **223**, jeb.230185. PMID: [33109715](#); doi: [10.1242/jeb.230185](#).