

Testing evolutionary theories of aging in wild populations

Anne M. Bronikowski¹ and Daniel E.L. Promislow²

¹Department of Ecology, Evolution, and Organismal Biology, Iowa State University, Ames, IA 50011, USA

²Department of Genetics, University of Georgia, Athens, GA 30602, USA

Classic theories for the evolution of senescence predict that rates of aging should be highest in populations in which extrinsic mortality is high. This predication is called into question in new work by David Reznick and co-workers, who found that guppies *Poecilia reticulata* derived from natural populations with high levels of predation live the longest in the laboratory. This study illustrates that the effect of mortality on aging might depend on how we define aging, and on the particular cause of increased mortality.

In our quest to understand the evolution of senescence, many evolutionary biologists have focused on laboratory-based searches for genes and gene pathways that extend life span (e.g. [1]). Although results from these molecular studies are exciting, a new study on senescence in Trinidadian guppies *Poecilia reticulata* by David Reznick and co-workers [2] reminds us that we still have much to learn from nature. Over the past 15 years, Reznick has established the guppy as one of the best-known species for studies of life-history evolution in the wild. In his latest work, he set out to test classic theories of the evolution of senescence.

Classic theory

Theories for the evolution of senescence are based on the idea that mutations whose effects are confined to late age will have a much lower impact on fitness than will mutations with early-age effects [3]. As Medawar realized [4], late-age deleterious mutations will thus accumulate over evolutionary time, leading to a decrease in physiological and biochemical function with age. Subsequently, Williams pointed out that selection will favor these late-acting deleterious mutations if they have beneficial effects early in life [5]. Both models predicted that deleterious mutations would accumulate at a faster rate in populations with high extrinsic mortality, because fewer individuals would survive to breed at later ages and the force of selection would thus decline more quickly.

Test of classic theory in the wild

To test this prediction directly, Reznick *et al.* collected guppies from both high- and low-predation sites in two separate drainages in the mountains of Trinidad [2]. They bred the fish in the laboratory and, after two generations,

measured age-specific mortality and fecundity, as well as the 'C-start', an anti-predator swimming escape behavior. In marked contrast to theoretical expectation, they found that fish from populations with high extrinsic mortality exhibited longer life span relative to populations from low-mortality environments. Additionally, high-predation guppies began reproducing at an earlier age and had higher age-specific fecundity across their reproductive life span.

This unexpected finding might be due, in part, to the fact that all extrinsic mortality forces are not equal. In guppies, high densities of predators of guppies reduce prey (i.e. guppy) density, which can increase food resources for surviving guppies (e.g. [6]). Greater resource availability might then release guppies from density-dependent regulation, an evolutionary force that is known to operate in low-predation guppy populations [7]. Furthermore, because high-predation populations have high rates of extrinsic mortality [8], high predation could also select for faster, fitter guppies. As the authors suggest, these findings show that we should interpret observations from nature using more-realistic models of senescence that incorporate factors such as density dependence [9] and condition dependence [10,11].

Issues arising

The study by Reznick *et al.* [2] raises three important empirical issues that must be addressed if we are to understand fully the biology of aging in the field and laboratory. First, studies of senescence have used a variety of different demographic parameters to measure aging in addition to maximum life span, including initial mortality rate of young adults, age of onset of increasing mortality and the rate of increase of age-specific mortality. We need to determine which parameter is most appropriate to use when we measure senescence, because different measures could lead to different conclusions. Second, we need to put much greater emphasis on aging in the underlying behavioral and physiological traits that lead to increases in age-specific mortality. Our current focus on age at death as the metric of senescence inevitably limits our ability to understand fully the genetics and evolution of aging. Finally, in thinking about how extrinsic mortality affects senescence, we need to consider not only the rate of extrinsic mortality, but also the source(s) of mortality. From an evolutionary perspective, not all deaths are the same.

Corresponding author: Bronikowski, A.M. (abroniko@iastate.edu).

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Which parameter is most appropriate for measuring senescence?

In studies that compare senescence in different cohorts, one often sees plots of survivorship (the proportion, l_x , of a single cohort alive at each age, x). These plots provide a useful starting point to gain qualitative information about senescence because they show median and maximum life expectancy ($l_x=0.5$ and $l_x=0$, respectively). Unfortunately, l_x values are influenced by deaths that occurred in previous ages, and so are not statistically independent of one another. To obtain independent demographic estimates at each age, demographers turn to intrinsic mortality rates. When plotted against age, these mortality hazards (μ_x =probability of death at age x) often have a characteristic 'bathtub' shape that is consistent with high infant mortality, followed by a period of low mortality, and increasing mortality starting at some (often young) adult age. Mortality analyses provide several variables of interest in studies of aging, including the age at which mortality begins to increase, the rate at which it increases (which can depend on the maximum lifespan), and the constancy of the rate of increase.

Many studies have found that, over a large fraction of the life span, the pattern of increase in instantaneous mortality rate (μ_x) versus age fits the Gompertz equation, $\mu_x=Ae^{bx}$ (Figure 1). The initial mortality (A) and slope (b) are often considered measures of the frailty and rate-of-senescence of the population, respectively [12,13]. Reznick *et al.*'s study suggests that the real world is a great deal more complicated. Consider the possible measures of aging that we have mentioned. We would predict, *a priori*, that high predation should lead to reduced maximum life

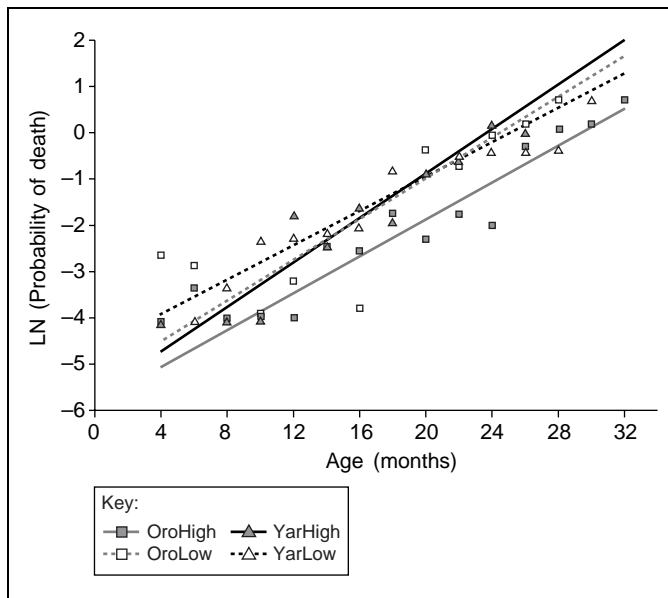


Figure 1. Mortality hazards of Reznick *et al.* [2] from two Trinidadian drainages (Yarra and Oropuche) and two levels of predation (high and low). For the rate of increase in age-specific mortality, Yarra high predation populations had faster senescence than did Yarra low predation populations, but Oropuche high predation populations did not differ from Oropuche low predation populations. For initial mortality rate, Yarra low predation populations had higher frailty than did Yarra high predation populations, and Oropuche low predation populations had higher frailty than did Oropuche high predation populations. If high predation causes faster aging, then we would expect both rate-of-increase and initial mortality rates to be highest in the high predation populations within each drainage area.

span, increased frailty, younger onset and increased rate of senescence [14]. Based on the analyses of Reznick *et al.*, we can compare these measures in the two high-predation sites (YH, Yarra River high predation; OH, Oropuche River high predation) with the two low-predation sites (YL, Yarra River low predation; OL, Oropuche River low predation) when the fish were raised in a common laboratory environment (analytical method of [15]). As expected, the rate of aging (b) was highest in a high predation population in the Yarra drainage (YH>YL), although not in the Oropuche drainage (OH=OL). The age of mortality onset was earliest in the high predation locale in the Yarra drainage, but not in the Oropuche drainage. But surprisingly, frailty (A) was highest in the low-predation site for both drainages (YL>YH) and (OL>OH). Similarly, the longest life spans were observed in fish derived from a high predation pool. Thus, whether we support or reject the claim that high extrinsic mortality rates increase senescence depends on how we define senescence.

Which phenotype is most appropriate for measuring senescence?

Some of the confusion over how to measure aging can be resolved by turning to measures other than mortality. Biogerontologists have traditionally focused on death rates as the definitive measure for the onset and rate of senescence (e.g. [12]). But as Miller pointed out [16], there are plenty of traits to choose from that deteriorate with age, affecting neuronal, immune and musculoskeletal function. Studies of age-related physiological or behavioral changes typically include measures at just two or three ages. However, by incorporating a more demographic approach, Reznick *et al.* demonstrated senescence in other traits, such as reproduction and behavior. By broadening our focus from age-related changes in mortality rate to senescent changes in physiological or behavior traits, we might increase our understanding of the underlying causes of demographic senescence. We might ask if the exponential increase in mortality rate is mirrored by exponential changes in other traits, suggesting similar causes. Consider, for example, the case of menopause in humans. If we treat menopause as a demographic event (Figure 2), the age-related increase in the risk of menopause is described by the same Gompertz equation as is risk of death, but with a doubling time of ~ 3 years, rather than the 8-year doubling time that we see for female mortality [17]. Detailed analysis of other physiological traits (e.g. metabolism [18]) or behavioral traits (e.g. C-start [2] or voluntary exercise [19]) should help reveal the evolutionary genetics of deteriorating phenotypes, which leads to increasing age-specific mortality.

Which sources of mortality matter?

From an evolutionary perspective, not all deaths are the same. When G.C. Williams [5] argued that higher extrinsic mortality should lead to higher rates of senescence, he was referring to random, condition-independent events. Because guppy populations with predators have higher rates of extrinsic mortality [8], Reznick *et al.* point

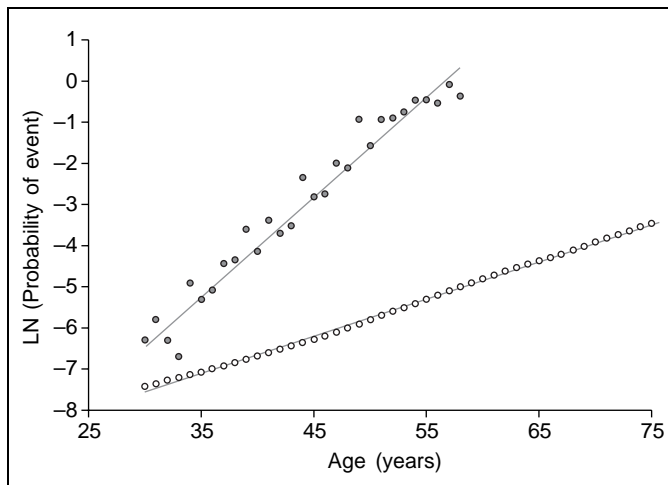


Figure 2. Observed age-specific menopause rate (solid circles) and female mortality rate (open circles) for women from an Australian twin study (data from [20] for menopause) and women from the US vital statistics report (data from [17]). The slope for menopause was 0.23 and for mortality was 0.087, showing that menopause, similar to mortality, follows Gompertz rates of increase with age.

to alternative models that could explain their unexpected findings [11]. Williams and Day [11] note that, if the risk of dying from an extrinsic hazard depends on the condition of an individual, we might see a negative correlation between the extrinsic force of mortality and rate of senescence. This could explain the finding that guppies from high-predation populations have lower mortality rates. It would be interesting to extend this model to include other kinds of mortality hazard. Consider, for example, the difference between predators and pathogens. An individual that escapes a predator today will have the same probability of becoming that the lunch for that predator tomorrow, all else being equal. By contrast, an individual that survives infection by a pathogen might be less likely to die from future infections by this same pathogen, owing to the benefits of acquired immunity. Thus, different types of condition-dependent mortality might have different long-term effects on the evolution of senescence.

Conclusions

That all mortality sources might not have equivalent effects on senescence when their force is changed is a recent realization in studies of the evolution of aging and will be a productive area for future theoretical work. Natural systems, such as the Trinidadian guppies, demonstrate that our understanding of the evolution of aging will benefit from modeling numerous aging

parameters, traits other than age at death and the causes of mortality.

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References

- 1 Tatar, M. *et al.* (2001) A mutant *Drosophila* insulin receptor homolog that extends lifespan and impairs neuroendocrine function. *Science* 292, 107–110
- 2 Reznick, D.N. *et al.* (2004) Effect of extrinsic mortality on the evolution of senescence in guppies. *Nature* 431, 1095–1099
- 3 Hamilton, W.D. (1966) The moulding of senescence by natural selection. *J. Theor. Biol.* 12, 12–45
- 4 Medawar, P.B. (1952) *An Unsolved Problem of Biology*, H.K. Lewis
- 5 Williams, G.C. (1957) Pleiotropy, natural selection and the evolution of senescence. *Evolution* 11, 398–411
- 6 McIntosh, A.R. *et al.* (2004) Predator-induced resource heterogeneity in a stream food web. *Ecology* 85, 2279–2290
- 7 Bronikowski, A.M. *et al.* (2002) Population-dynamic consequences of predator-induced life-history variation in the guppy (*Poecilia reticulata*). *Ecology* 83, 2194–2204
- 8 Reznick, D.N. *et al.* (1996) Life history evolution in guppies (*Poecilia reticulata*). 6. Differential mortality as a mechanism for natural selection. *Evolution* 50, 1651–1660
- 9 Charlesworth, B. (1994) *Evolution in Age Structured Populations*, Cambridge University Press
- 10 Abrams, P. (1993) Does increased mortality favor the evolution of more rapid senescence? *Evolution* 47, 877–887
- 11 Williams, P.D. and Day, T. (2003) Antagonistic pleiotropy, mortality source interactions and the evolutionary theory of senescence. *Evolution* 57, 1478–1488
- 12 Finch, C.E. *et al.* (1990) Slow mortality rate accelerations during aging in some animals approximate that of humans. *Science* 249, 902–905
- 13 Pletcher, S.D. *et al.* (2000) Why do life spans differ? Partitioning mean longevity differences in terms of age-specific mortality patterns. *J. Gerontol.* 55, B381–B389
- 14 Promislow, D.E.L. and Tatar, M. (1998) Mutation and senescence: where genetics and demography meet. *Genetica* 102–103, 299–314
- 15 Pletcher, S.D. (1999) WINMODEST 1.0.2, <http://www.hco.org/scott/softw-winmodest.asp>
- 16 Miller, R.A. (2004) Accelerated aging: a primrose path to insight? *Aging Cell* 3, 47–51
- 17 Bronikowski, A.M. *et al.* (2002) The aging baboon: comparative demographic senescence in a model non-human primate. *Proc. Natl. Acad. Sci. U. S. A.* 99, 9591–9595
- 18 Promislow, D.E.L. and Haselkorn, T.S. (2002) Age-specific metabolic rates and mortality rates in the genus *Drosophila*. *Aging Cell* 1, 66–74
- 19 Bronikowski, A.M. *et al.* (2003) Lifelong voluntary exercise in the mouse prevents age-related alterations in gene expression in the heart. *Physiol. Genomics* 12, 129–138
- 20 Do, K.A. *et al.* (1998) Predictive factors of age at menopause in a large Australian twin study. *Hum. Biol.* 70, 1073–1091