# Messages from mortality: the evolution of death rates in the old

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**Ageing is an increase in mortality and/or decline in fertility with advancing age. Evolutionary theories predict that ageing will evolve in response to the pattern of externally imposed hazards to survival and fertility; a prediction confirmed in new empirical studies. Recent studies of large cohorts of experimental animals and of humans have revealed that mortality rates do not continue to accelerate at very advanced ages. It has been suggested that evolutionary theories cannot account for these mortality patterns; however, this challenge is more apparent than real. Heterogeneity between individuals can shape mortality trajectories for populations, and recent evolutionary theory can both account for such heterogeneity and accommodate late-age mortality patterns.**

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Long-term studies of natural populations have revealed the presence of ageing, in the form of an increase in probability of death and a decline in fertility with advancing adult age[1,2]. Only a small proportion of individuals survive to become aged in nature[3], and the effects of ageing are much more obvious in captive populations living in benign conditions[4] and in many human groups[3]. It has long been recognized that ageing is, in itself, maladaptive[5] but that its rate can nonetheless evolve. Even where there is no ageing, death will occur from extrinsic causes, such as disease, predation and accidents. Any new, harmful mutation that affects the survival or fertility of the young will be expressed in most individuals that carry it, and thus will be subject to strong selection. By contrast, a mutation that affects only the old will be expressed solely in the few carriers that survive to old age; up until then carriers die and become less fertile at a rate no different from non-carriers. Therefore, selection will be weaker and the intensity of the natural selection maintaining viability and fertility will decline at later ages (Box 1). Growth and learning can both lead to a decrease in the mortality rate over at least part of the adult period, but the intensity of selection maintaining survival and fertility must sooner or later decline with age[6,7]. Selection will therefore be less able to eliminate new mutations with effects at later ages[5,6], and such mutations will rise to a higher frequency under mutation–selection balance; this is called the 'mutation accumulation' theory of ageing.

Ageing can also evolve as a side-effect of life-history optimization (Box 1). Organisms can achieve only certain combinations of survival and fertility at different ages, as a result of their own biology and the ecological conditions that they encounter[8–11]. If a new mutation arises that increases fitness at young ages (e.g. because it increases fertility at those ages), but at the expense of lowered fitness later in life (e.g. because survival or fertility are reduced), natural selection can incorporate the mutation into the population despite its adverse effects later in life, because selection will be stronger on the early, beneficial effect; this is called the 'pleiotropy' theory of ageing[12].

Therefore, evolutionary theories of ageing predict that the intrinsic rate of ageing will evolve in response to the rate at which the intensity of selection on survival and fertility declines with age, as a result of the impact of extrinsic hazards. Organisms that inhabit hazard-prone environments are expected to evolve more rapid rates of intrinsic decline. New comparative demographic studies have confirmed this prediction for the age-related increase in mortality rates in social insects[13], and in birds and mammals[4]. Recent experimental measurements of age-specific genetic variance[14–16] and inbreeding depression[17] in *Drosophila* have produced some evidence for the importance of mutation accumulation in ageing. Artificial selection experiments have produced strong evidence for the importance of pleiotropy[18–20]. Ageing is caused by physiological wear and tear, but the extent to which damage is avoided, prevented or repaired evidently evolves as predicted by evolutionary theory. However, recent work on age-related mortality has produced a challenge to evolutionary biologists to make their predictions more precise.

## Mortality rates at late ages

Gerontologists and demographers have typically paid attention to the effect of ageing on mortality. An increase in age-specific mortality rate (Box 2) is only one aspect of ageing, but it is an important one, from both biomedical and evolutionary viewpoints. Several mathematical functions can be used to describe the increase in death rate with age, and the one in most frequent use is the Gompertz equation, which recognizes the common empirical finding that death rates increase exponentially with age[1,21] (Box 2). The Gompertz equation does not fit all cases. The deteriorative effects of the ageing process occur against a background of programmed changes, such as increase in size, and mortality rates can drop over some periods of adult life[7,22]. Furthermore, in recent years, some striking deviations from Gompertz fits have been found late in life in large cohorts of experimental animals and in humans[21,23]. In the nematode *Caenorhabditis elegans*[24], the fruitfly *Drosophila melanogaster*[25], the medfly *Ceratitis capitata*[26] and the beetle *Callosobruchus maculatus*[27] mortality rates increased more slowly, and reached a plateau or even declined at late ages (Fig. 1) (these findings will be collectively referred to hereafter as 'mortality deceleration'). Small sample sizes could be part of the reason that late-life mortality deceleration was not observed in previous studies. A typical laboratory or field study is concerned with tens or, at the most,

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### Box 1. Life-history theory

Life histories are closely related to fitness, because they describe the way in which reproduction is scheduled in relation to age. In the absence of density dependence, genetic variation and environmental variation, the life history can be characterized by a schedule of survival to age $x$, $l_x$, and fecundity at age $x$, $m_x$. In this case, a measure of fitness is provided by the rate of growth $r$ of the population, determined by solution of the Euler–Lotka equation[6]:

$$\sum_{x=x_r}^{x_{max}} l_x m_x e^{-rx} = 1$$

where $x_r$ and $x_{max}$ are the ages of first and final reproduction. Life-history optimization, in this context, involves selection of the schedules of survival and fecundity that maximize $r$, subject to appropriate physiological constraints. Survival to age $x$ is the product of survivals $s_i$ between age $i$ and $i + 1$, for $i = 0$ to $x_{max}-1$.

Life history theory[6,47] allows the evaluation of how changes in either survival or fecundity at a particular age affect the fitness of the population. In particular:

$$\frac{\partial r}{\partial s_x} = \frac{\sum_{y=x+1}^{x_{max}} l_y m_y e^{-ry}}{s_x \sum_{y=x_r}^{x_{max}} y l_y m_y e^{-ry}}$$

and

$$\frac{\partial r}{\partial m_x} = \frac{l_x e^{-rx}}{T}$$

where $T = \Sigma x e^{-rx} l_x m_x$ is the mean age of the mothers of a newly born set of individuals.

In words, the intensity of selection on fertility at age $x$ depends on the probability of survival to age $x$. The intensity of selection on survival at age $x$ depends on the expected future reproduction after age $x$. Therefore, the intensity of selection on survival remains constant from birth until the age of first reproduction, and then declines.

### Box 2. The rate of ageing

Age-specific mortality is the fraction of individuals alive at age $x$ that die before age $x + 1$. If a population experiences a constant rate of mortality $q$ per unit time, then the fraction of individuals surviving to age $x$ will be $l_x = e^{-qx}$. In a population without ageing, a plot of mortality rate versus age is a horizontal line. Deviations from this line that increase as age increases indicate ageing.

The deviations from constant mortality rate associated with ageing have in general been described using the Gompertz equation, in which survival is $l_x = e^{-q(x)}$ where:

$$q(x) = \frac{m_0}{\gamma}\left(e^{\gamma x} - 1\right)$$

(Note that if $\gamma << 1$, $e^{\gamma x} - 1$ is approximately $\gamma x$, so that $q(x)$ is approximately $m_0 x$.) The Gompertz relationship is a useful empirical approximation to some data sets (another useful approximation is provided by the Weibull relationship[4]). However, these relationships await a theoretical derivation from evolutionary theory, and an optimality approach to the pleiotropy theory produced mortality trajectories of greatly different shape[54]. There are an infinite number of ways that a deviation from constant death rate can occur, and they all represent valid biology. Productive activity is likely to focus on this biology as much as on the mathematical details of the deviation. Mortality deceleration is used here to refer to a less than Gompertzian increase in death rate with age.

The evolutionarily appropriate measure of the rate of ageing is the change in residual reproductive value with age, which is the prospects for future reproduction viewed at successive ages after birth[29]. Residual reproductive value ($V_x$) is given by the quantity:

$$V_x = \frac{e^{rx}}{l_x} \sum_{y=x+1}^{x_{max}} l_y m_y e^{-ry}$$

This quantity gives the amount of expected future reproduction at age $x$, given that age $x$ has been reached, and adjusted appropriately for any subsequent changes in population size. It is a measure of the intrinsic state of an organism.

hundreds of individuals, whereas most studies showing deceleration relied on data from thousands and millions. Such sample sizes are needed to estimate mortality rates accurately at the advanced ages when most individuals are already dead.

Deceleration of late-life mortality rates has been suggested to challenge evolutionary theories of ageing, on the grounds that these predict a monotonic increase in mortality rates to 100% at late ages[3,28]. This claim has forced a reappraisal of exactly what these theories do, and do not, predict.

## Evolutionary theories of ageing revisited

The apparent challenge to evolutionary theories of ageing has come from data on mortality rates. However, the rate of ageing for mortality cannot be predicted by evolutionary theories without taking the fertility schedule into account (Box 1). The two traits evolve together, and together produce a decline in state, the real hallmark of ageing. Recent work has pointed out that the evolutionarily appropriate measure of ageing is the rate of decline in residual reproductive value, which is a description of the current potential of an organism to produce further offspring[29] (Box 2). Decelerations in mortality rate are typically observed in the post-reproductive period and, therefore, will be selectively neutral. Mortality deceleration will not result in a greater potential to produce progeny and, except in organisms where post-reproductive survival has some bearing on the fitness of relatives, will not contribute to fitness. Therefore, it is likely to have evolved, at least in part, as a correlated response to selection on other traits earlier in life[3]. We need to understand how, and why, late-life mortality rates might be genetically correlated with traits that determine fitness at earlier ages.

Theoretically, the effects of mutation accumulation on late-life mortality rates depend crucially on the assumptions made about the genetic correlations between mutational effects on different age classes. If the effects of deleterious mutations are confined to a narrow range of age classes, and are not correlated across age classes, the theory suggests that mortality rates will increase with age and reach 100% at late ages[30–33]. The reason is that, if the post-reproductive mortality rate is free to evolve independently of survival and fertility earlier in life, the lack of selection maintaining it will mean that mutation pressure will be free to drive deleterious alleles affecting it to fixation in the population. However, if mutational effects are correlated across age classes (and there is some empirical evidence for such correlations for different adult age classes in *Drosophila*[34,35]), adult mortality rates will not accelerate so sharply because of selection against the correlated effects on mortality earlier in life[32]. To understand fully the role of mutational effects at different ages in producing mortality trajectories, there is a need for fuller data sets and for information from organisms other than *Drosophila* on the correlations between mutational effects on late adult ages and those during the juvenile and early adult periods. Theoretical understanding of the reasons for the patterns of genetic correlations observed is also required; a similar deceleration of mortality has been observed in motor vehicles[23], and might reflect fundamental features of the dynamics of wear and tear in complex machines. The mutation accumulation theory of ageing does not necessarily predict a Gompertzian mortality trajectory, and theoretical work is needed to define the circumstances under which it might do so.

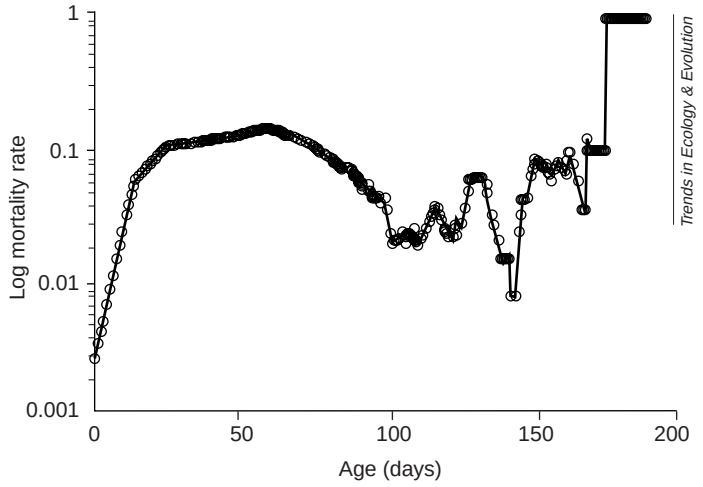


**Fig. 1.** Mortality rates (five-day geometric means) for a cohort of 1 203 646 Mediterranean fruitfly (*Ceratitis capitata*) adults. Plotted from data in Ref. 26.

The predictions of the pleiotropy theory of ageing for late-age mortality trajectories again depend on the pattern of potential genetic correlations between effects, positive and negative, on mortality and fertility at different ages. Optimality modelling has been used to explore the consequences for mortality rates of a tradeoff between the allocation of resources to somatic repair (which was assumed to increase subsequent survival) and to reproduction (which was assumed to reduce the amount of repair). Depending on the precise shape of the tradeoff, this type of model can predict deceleration of mortality at late ages[1]. However, the assumptions of the model await empirical justification, and mortality rates did eventually reach 100%. Explicit genetic models of the pleiotropy theory produce mortality trajectories with shapes that depend crucially on the precise assumptions made about possible patterns of pleiotropy[25,31].

New mutations with a net beneficial effect are rare, and it is not feasible to measure the patterns of genetic correlation relevant to the pleiotropy theory by examining the effects of new mutations as they arise. However, empirical findings from experimental manipulations of life history might cast some light on these matters. Mortality deceleration typically sets in at ages where reproduction has almost, or recently, ceased. A cost of reproduction, where increased reproductive rate decreases survival, is taxonomically widespread[8–11]. A reduction in reproductive costs could therefore contribute to mortality deceleration at late ages. Experimental work is needed to determine the timing of the impact of reproduction on mortality. Both instantaneous[36] and delayed[37] costs of reproduction have been reported. For humans, a new analysis of data on aristocrats (for whom there are good historical records) suggested that old-age (over 60 years) mortality rates in both sexes were related directly to the total number of offspring that had been produced earlier in life, and negatively related to age at first birth[38]. Delayed effects can have different forms of impact, sometimes raising the overall mortality rate, and sometimes the rate at which mortality increases with age[27]. Understanding the reasons for these different patterns, and their quantitative contribution to mortality rate deceleration, presents a challenge for experimental investigation.

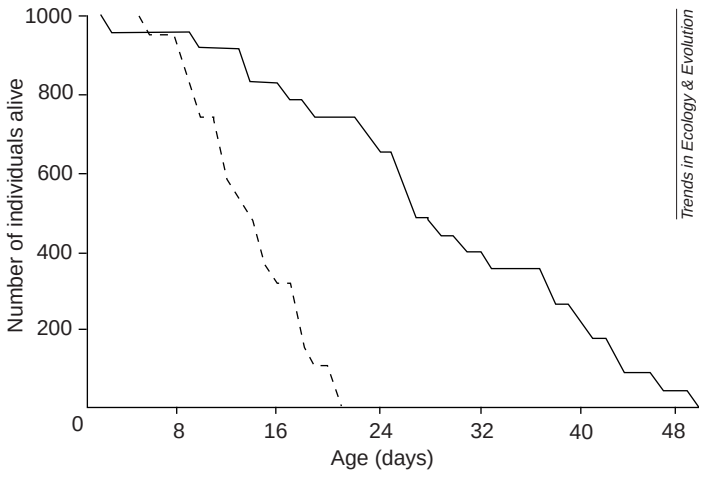


**Fig. 2.** Survival data for *Rhagoletis basiola* as reported by Roitberg[43] for mated flies that were allowed to lay eggs or were prevented from laying. From these data, and comparison with unmated flies, Roitberg concluded that it was the act of egg laying itself that increased ageing. Layers, broken line; non-layers, solid line.

The evolutionary theories of ageing predict that mortality rates after reproduction has ceased can be held below 100% only if costs of earlier reproduction continue to decline indefinitely, or if there exists a substantial class of genes with positive effects on survival late in life, the functions of which are also required at some range of earlier ages[39].

## A missing piece: individual variation

An individual can die only once, and a mortality curve for a population represents differences between individuals in vulnerability to mortality (frailty), as well as intrinsic changes over time within the individuals comprising the population. If the original cohort is heterogeneous, consisting of a mixture of frailty types each with a different Gompertzian mortality trajectory, the frailest subgroups will die first leaving the more robust alive, and there will be a deceleration of mortality rate as death proceeds[25,26,40]. Heterogeneity between individuals could be genetic in origin. A genetically uniform line of *C. elegans* showed less levelling of mortality than a genetically mixed population[24]. But genetic variation cannot be the whole story, because in *Drosophila* the deceleration of mortality was seen in genetically uniform (although non-inbred) cohorts of flies[25].

Environmental sources of variation between individuals might be as, or more, important than genetic variation, but they are harder to identify and quantify. Differences in nutritional and reproductive history and status are known to have an impact on frailty. Dietary restriction decreases mortality rates in a wide variety of taxa[41], and resumption of normal feeding can produce subsequent mortality and fertility schedules little different from those of much younger animals that are fully fed throughout life[42]. The importance of reproductive status was examined in a study of the rose hip fly *Rhagoletis basiola*[43]. Populations of mated and unmated ('spinsters') individuals were maintained, and the mated individuals were divided into a group that was allowed to lay eggs ('layers') and one that was not allowed to lay eggs ('non-layers'). Non-layers had much longer lifetimes (Fig. 2) than layers. Indeed, spinsters had a mortality rate similar to the non-layers; hence, it was the egg-laying event itself, rather than mating, that caused the mortality rate to increase. Although both laying and non-laying subpopulations experienced ageing, the increase in mortality rate

of laying individuals was greater. Imagine a population in which 80% of the individuals laid eggs at any opportunity and, for some reason, 20% of the individuals never did. The individuals laying eggs would experience higher mortality rates and ultimately decline at a much faster rate than the nonlayers. The net effect would be a slowing of mortality at later ages.

Experiments have revealed important potential sources of environmental heterogeneity; the challenge is to understand their role in natural populations. An evolutionary approach can potentially help provide a theory for patterns of environmental heterogeneity in life histories[44]. For example, the typical response of many organisms to dietary restriction is to cease reproduction, and it has been suggested that this response is an evolutionary adaptation that would enable the organism to survive times of food shortage in nature[23]. The widely reported effect of dietary restriction on survival rates might therefore be an example of adaptive phenotypic plasticity[45,46]. Such plastic responses to environmental heterogeneity might in part be responsible for mortality deceleration.

The role of environmental heterogeneity can be examined in models that allow environmental influences to be altered systematically, and that also allow incorporation of stochastic effects. For example, in the case of insects, environmental conditions (e.g. encounter rates with suitable oviposition sites, food availability and mortality rates), physiological state (e.g. mature eggs, oocytes, reserves for producing oocytes, egg maturation rate and somatic maintenance costs) and expected reproductive success can be linked by the use of dynamic state variable models based on stochastic dynamic programming[48–50]. Clearly, genetic variation in the value of the initial physiological state and in the parameters is likely, but stochastic encounter rates can introduce variation into external influences on internal states. These internal and external sources of variation will then lead to different patterns of behaviour and mortality. Because dynamic-state-variable models make explicit the roles of environmental conditions, physiological state and organismal behaviour in determining the rates of mortality and reproduction, they will be a useful tool for understanding ageing[51].

## Interactions and medical implications

An additional source of variation between individuals that could influence mortality trajectories and that has been scarcely explored is gene–environment interaction; individuals with different genotypes can react differently to the same change in the environment. These interactions might be particularly important in humans that inhabit an environment very different from that in which they evolved. Many of the old-age ailments of industrialized societies reflect environmental changes in factors such as diet, but it is also clear that genetics play a role in the responses[52]. Interactions between environmental effects at different ages might also be crucial to determining frailty in humans; the environment experienced in foetal life can interact strongly with conditions experienced in adulthood[53]. An evolutionary approach has much to offer in understanding this variation in human frailty, as well as mortality dynamics in experimental populations and in nature.

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