Measuring senescence in human populations

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INTRODUCTION TO PART I

Age patterns of mortality

Humans die at any moment in their lives. As a result of senescence, the risk of death increases with chronological age.

The Panel on the next page shows three manners in which a population's senescence can be visualised with age patterns of mortality.[1,2] Firstly, the number of individuals that have survived from birth decreases with age until the entire population has died and this decrease quickens with age (Figure A in the Panel). Secondly, the number of individuals that have died is greater at higher than at lower ages (Figure B in the Panel). Thirdly, the mortality rate increases with age (Figure C in the Panel). As explained in the Panel, the age patterns of a population's survival, deaths, and mortality rate are directly related and can be derived from each other.

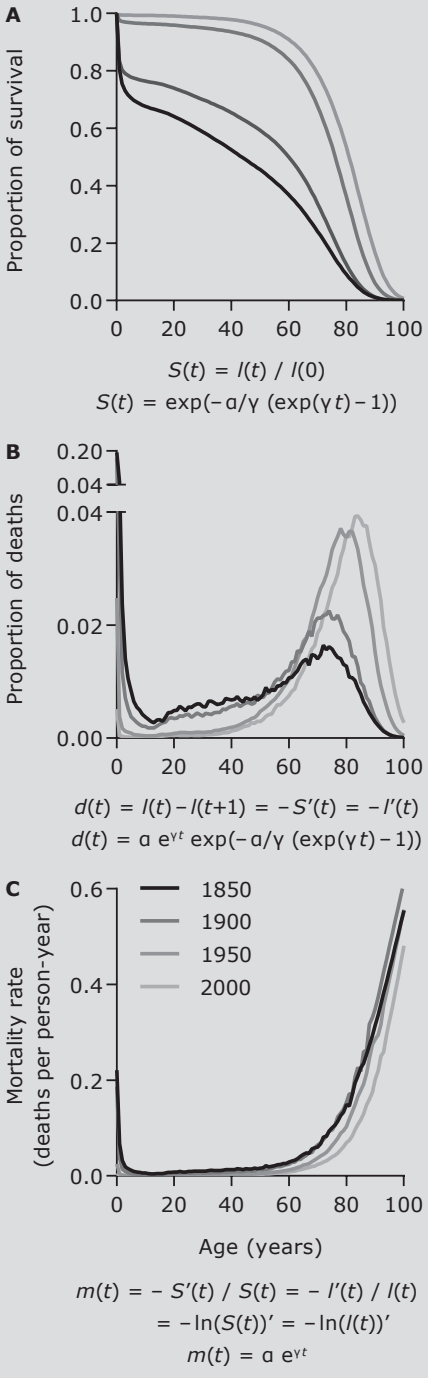
If senescence is the consequence of an accumulation of damage during life, it is plausible that senescence starts at conception. However, only from adolescence onward can senescence be discerned in age patterns of mortality. Early in life, the decline in survival slackens, the number of deaths decreases, and the mortality rate falls (Panel). Age patterns of mortality are the net result of senescence together with its opposing forces of growth, development, and regeneration. The balance between these processes determines whether an age pattern displays senescence. Early in life, growth, development, and regeneration dominate senescence and are of main influence on mortality.[3-6] During life, growth and development regress or derail and the body's capacity to regenerate diminishes.[7] When sufficient time has elapsed and enough damage has accumulated, a deterioration in the body's structures and functions becomes visible as an increase in the risk of death. This is schematically shown in Figure 2.1.

Although some gerontologists have drawn attention to the importance of early-life mortality for research on senescence,[4,5] we depart from the customary approach to leave out of consideration that mortality is high immediately after birth and decreases during childhood to its lowest levels in adolescence. Senescence is, in that manner, studied from adolescence onward, when mortality starts to increase with age. We will discuss the relevance of patterns of early-life mortality in Chapter 4 of this thesis.[8]

Modelling age patterns of mortality

Age patterns of mortality are commonly described using parametric models. Such models suit analytical purposes that are not or not well served by non-parametric models: they are capable of estimating age patterns of mortality continuously, thus for each specific age or age category, their estimated age patterns are precise and smooth, they can be used to assess the effects of measured variables on age patterns of mortality, and they enable the extrapolation and prediction of mortality beyond the observed ages and along alterations in these variables.[16,17]

A wide variety of parametric models exists that describe age patterns of mortal-



Panel • A population's senescence visualised with age patterns of mortality

Age patterns of mortality are shown for different years in the Netherlands.[14] The proportion of individuals that have survived from birth to a given age (A) and the proportion of individuals that have died at a given age (B) are shown relatively to the total number of individuals that have died at any age during life. The age pattern of deaths can be derived from the age pattern of survival, because the number of deaths at any age is the difference in the number of survivors between that age and the consecutive age, which equals the negative derivative function of the age pattern of survival. An age-specific mortality rate (C) can be interpreted as the rate at which individuals die at a given age. It describes the number of deaths per person-year, which is the number of deaths per period of time lived by the individuals in the population of that age. It can be derived from the age pattern of survival as the number of deaths relative to the number of survivors at any age, which equals the negative derivative function of the logarithmically transformed age pattern of survival.

Equations are given that describe the age patterns of survival S, deaths d, and mortality rate m non-parametrically[1] as dependent on the number of living individuals l at age t and according to the Gompertz model[9-13] as dependent on the model's parameters α and γ.

ity, among which the exponential model, gamma model, log-logistic model, Weibull model, and Gompertz model.[17] The Gompertz model is most commonly used in research on senescence.[11,13,18,19]

The British mathematician and actuary Benjamin Gompertz (1779–1865) was the first to observe that mortality rates increase exponentially with age in human populations and captured his observation mathematically as the model that was later named after him.[19,20] The Gompertz model describes the age pattern of a population's mortality rate as dependent on two parameters α and γ (see the Panel). The mortality rate equals α at age t = 0. An age in adolescence, around which mortality is lowest during life, is chosen as t = 0, because the Gompertz model cannot account for the decrease in early-life mortality. From this age onward, the mortality rate is modelled to increase exponentially from the minimal level α to the extent of γ.

The Gompertz model can be extended with a third parameter β that adds to the exponential increase in mortality in an age-independent manner. This model is known as the Gompertz-Makeham model.[9,11,13] As the parameter β is negligible in human populations, the Gompertz model is preferred over the Gompertz-Makeham model.[13,21,22]

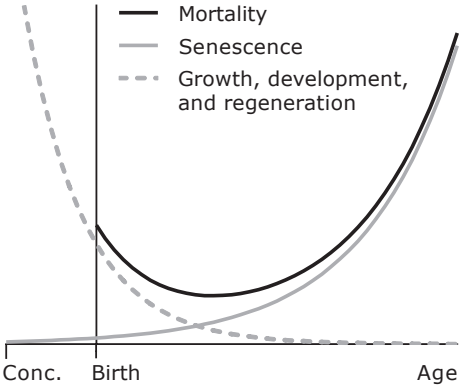


Figure 2.1 • Schematic illustration of the age pattern of mortality as a net result of senescence as well as growth, development, and regeneration. Similar schemes have been proposed by others.[15] Conc.: conception.

Measuring senescence through age patterns of mortality

A population's senescence can be measured through its age patterns of mortality in various manners. From the age pattern of survival, the mean, median, and maximal lifespan can be calculated. From the age pattern of deaths, the mean, median, and modal age at death can be calculated. The mean lifespan equals the mean age at death; both are more commonly referred to as the life expectancy.[23] These measures of senescence each represent a different aspect of a population's age pattern of survival or deaths and should be applied in a supplementary manner. However, as these measures summarise the varying levels of mortality throughout life in a single age-independent constant, they are little informative about its age pattern.[23,24]

Since senescence manifests in human populations as an increase in mortality rate with age, senescence is preferably and commonly measured through age patterns of mortality rates. This can be achieved by evaluating the age pattern of a population's

mortality rate, by graphically comparing the age patterns of different populations, and by calculating the age-specific differences of their mortality rates.[2,25-27]

The classical measure of a population's senescence rate

The Gompertz model is often preferred for modelling age patterns of mortality rates because it has the following advantage. When the Gompertz model is transformed logarithmically, the mortality rate increases linearly with age from adolescence onward. This linear increase is described by the model as: $\ln m(t) = \ln \alpha + \gamma t$ (compare with the Panel). The visual assessment of linear age patterns is much easier than that of exponential age patterns, as illustrated by Figure 2.2. Moreover, the linear increase in the mortality rate, thus the slope of the straight curve, is solely described by the model's parameter γ, as this parameter equals the derivative function of the aforementioned logarithmically transformed model. Differences in the slope of the straight curves are easily discernible on a logarithmic scale (Figure 2.2B).

The linear increase in the mortality rate on a logarithmic scale, thus the slope of the straight curve described by γ, is classically equated with the population's senescence rate. Both consciously and unconsciously this interpretation is widely used to interpret research on senescence.

From the linear increase in the mortality rate on a logarithmic scale, the period of time can be calculated during which a population's mortality rate doubles. This mortality rate doubling time (MRDT) is directly related to the slope of the straight curve described by γ: $\text{MRDT} = \ln 2 / \gamma$. The MRDT has been proposed as a more comprehensible variant of the slope of the straight curve as the measure of a population's senescence rate.[28]

Critique of the classical measure of a population's senescence rate

Although originally the Gompertz model is a purely empirical model, it has acquired the status of a law or dogma that is thought to apply universally to the age patterns of mortality rates of human populations.[19,21,29,30] Yet, the use of the linear increase in the mortality rate on a logarithmic scale, described by the model's parameter γ, as a measure of a population's senescence rate is a theoretical assumption that has never been empirically tested. Meanwhile, it has been objected that this measure of a population's senescence rate may be false.[31-35]

The critique concerns the logarithmic transformation of the Gompertz model, which is necessary for the model to adopt a linear age pattern.[35] This can be illustrated by the following observation.

At the end of the Second World War, civilians in Indonesia were caught as prisoners of war in a Japanese concentration camp. The conditions of life, which were similar for all prisoners, were harsh. They slept in crowded barracks on a small mattress, a couple of planks, or bare stones. Infectious diseases thrived. Hunger was commonplace with estimated average rations of

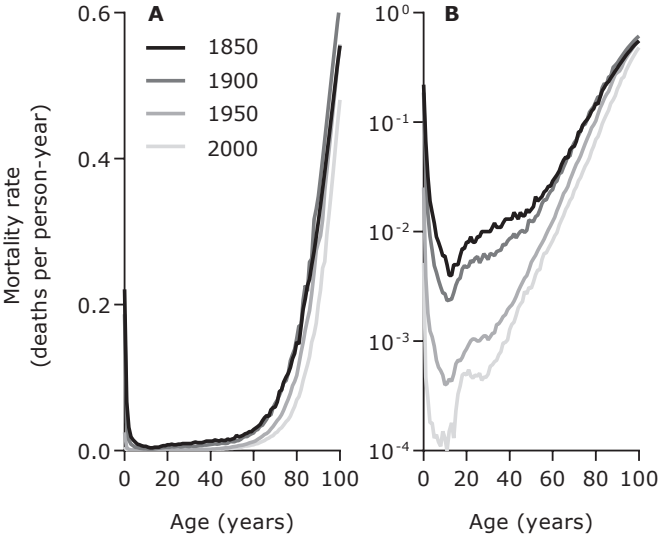
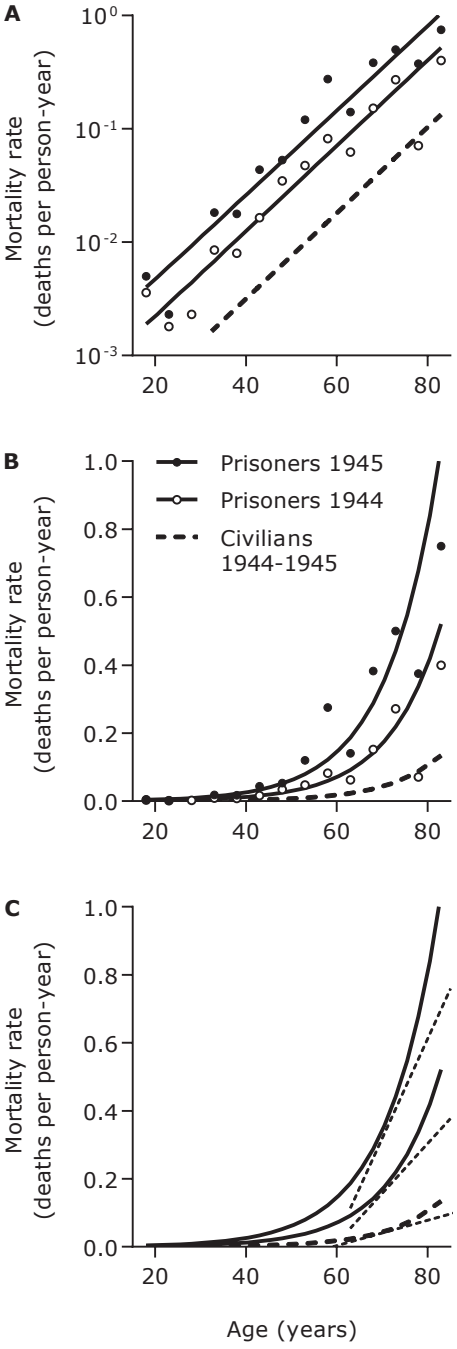


Figure 2.2 • Visualisation of mortality rates on an absolute scale and on a logarithmic scale. Identical mortality rates for different years in the Netherlands are shown on an absolute (A) and on a logarithmic scale (B). According to the Gompertz model, mortality rates increase exponentially with age on an absolute scale, but linearly with age on a logarithmic scale.

1250 kcal per day.[36] When the age pattern of their mortality rate is compared with that of Australian civilians in the same years on a logarithmic scale, the age patterns increase linearly with age and the increases of both populations are equal, as shown in Figure 2.3A. The parallel logarithmic age patterns are classically interpreted to demonstrate that the senescence rate of a human population is equal in adverse and affluent environments.[2,37,38]

However, as shown in Figure 2.3B, when the same age patterns of mortality rates are examined on an absolute scale, they increase exponentially and the difference in mortality rate between both populations grows with age. Interestingly, the comparison of these populations was originally made without any logarithmic transformation. The crude age patterns of the mortality rates were reported to diverge and interpreted as follows: „The harm done to the [prisoners of war] manifests itself in the increased death rate and can be put down to a process of rapid pathologic ageing. Of course the death rate is not the only indication of this process; there are many more, but the others are, although clearly visible, difficult to take down in figures. The premature greying of the hair, the excessive wrinkling of the skin, the difficulty in walking, the general hypotony of the musculature, the monotony in thought, the difficulty experienced in realising and analysing present problems, the predominance of past memories – all these and many more signs pointed in the same direction. But as mentioned before, the death rate as a symptom has two definite advantages: it is calculable and it is irreversible."[39]

It is generally ignored that logarithmic transformation renders an additive model into a multiplicative model. The increase in the mortality rates on a logarithmic scale, thus the slope of the straight curves



described by γ, reflects the factor by which the mortality rates are multiplied as the age increases by one year (Figure 2.3A). The increase in the mortality rates on an absolute scale reflects the factor that is added to the mortality rate as the age increases by one year (Figure 2.3B). In other words, when a linear age pattern of the mortality rate shifts upwards but remains parallel on a logarithmic scale, the difference in its crude exponential age pattern is unmasked on an absolute scale.[35]

For the mathematical assessment of a biological interaction, the use of additive models rather than multiplicative models is recommended.[40] From a multiplicative point of view, the equal increases in mortality rates with age across different environments suggests an absent interaction between the environment and the senescence process, but such an interaction becomes apparent by comparing their increases from an additive point of view.

Figure 2.3 • Age patterns of mortality rates of prisoners of war and civilians during the Second World War. The age patterns are shown on a logarithmic scale, as is classically done (A), and on an absolute scale (B). The dotted tangent lines indicate the rates at which the mortality rates increase on an absolute scale at the age of 70 years (C).[35] The data of the prisoners of war were derived from their original publication[36] and those of the civilians from the Human Mortality Database.[47] Figure A has also been presented by others.[2,37,38]

Following this line of reasoning, it has been proposed that a population's senescence rate should not be measured as the linear increase in its mortality rate on a logarithmic scale, but could be measured as the exponential increase in its mortality rate on an absolute scale. The latter increase is mathematically described by the derivative function of the exponential age pattern of the mortality rate. In Figure 2.3C, tangent lines at the age of 70 years illustrate the derivative functions and estimate the increases in the mortality rates at that age. According to the derivative function, the mortality rates increase more with age in the prisoners of war as compared with the civilians, indicating that the senescence rate is higher in an adverse environment.[35]

When the linear increases in the mortality rates on a logarithmic scale, described by γ, are interpreted as the senescence rates of both populations, their senescence rates would be not only invariant across different environments, but even unaffected by chronological age (Figure 2.3A). This would imply that the senescence rate of a 20-year-old civilian equals the senescence rate of an 80-year-old prisoner of war.[35] This classical interpretation runs counter to the fact that all molecular-cellular, physiological, and epidemiological markers of senescence rise or fall with age.[41-46] By contrast, when their senescence rates are measured as the increases in their mortality rates on an absolute scale by using the derivative function, the mortality rates increase more at higher ages, thus the senescence rates are higher at higher ages. This alternative conclusion is in line with the age-dependency of the markers of senescence.

Partitioning of intrinsic and extrinsic mortality

The classical interpretation of the Gompertz model's parameter γ as a measure of a population's senescence rate is based on the assumption that mortality is caused by two independent mechanisms. On one hand, intrinsic mortality would result from senescence unrelated to the environment. On the other hand, extrinsic mortality would result from environmental hazards unrelated to senescence. While the Gompertz model's parameter γ is thought to reflect intrinsic mortality, the parameter α is thought to reflect extrinsic mortality.[13,19,35] This classical line of thinking is supported by observations of stable senescence rates across different environments such as described above.

However, when the derivative function of the Gompertz model is used as a measure of a population's senescence rate, the increase in mortality rate with age is not solely described by γ, but dependent on both parameters. In addition, according to the derivative function, senescence rates vary across different environments. This raises the question whether intrinsic and extrinsic mortality are biological or merely mathematical phenomena.

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