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MEASURING SENESCENCE RATES WITHOUT USING THE GOMPERTZ MODEL

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Background • A population's senescence rate can be inferred from the rate at which its mortality rate increases with age. Such a senescence rate is generally estimated from parameters of a mathematical model fitted to the age pattern of the mortality rate. However, such models have limitations and underlying assumptions. Notably, they do not fit mortality rates at low and high ages.

Methods • We developed a novel method to directly calculate senescence rates from the increase in mortality rate without modelling the mortality rates. We applied the different methods to age-group-specific mortality data from the ERA-EDTA Registry, including patients with end-stage renal disease on dialysis, who are known to suffer from increased senescence rates (n = 302 455), and patients with a functioning kidney transplant (n = 74 490).

Results • From the age of 20 to 70 years, senescence rates were comparable when calculated with or without a model. However, when using non-modelled mortality rates, senescence rates were obtained at low and high ages that remained concealed when using modelled mortality rates. At low ages senescence rates were negative, while senescence rates declined at high ages.

Conclusion • Senescence rates can be calculated directly from non-modelled mortality rates, overcoming the disadvantages of an indirect estimation based on modelled mortality rates.

Across populations and species, mortality rates exhibit different age patterns.[1] Mortality rates can increase, be constant, or decrease with age. Demographers interpret increasing mortality rates at the population level as a manifestation of senescence at the organismal level. Likewise, they interpret constant or decreasing mortality rates as a manifestation of absent senescence.[2-5] Senescence is a result of manifold biological mechanisms that lead to an increasing vulnerability to death. Although biologists have made strong effort at explaining and measuring senescence, the nature of these biological mechanisms remains unclear and a reliable biomarker of senescence is lacking.[6,7] Moreover, it is continuously debated whether senescence and disease are distinct or related phenomena.[4,8]

The rate of mortality can be regarded as a speed function: it expresses the number of deaths per unit of time comparably with the speed of a car that is expressed as the number of driven metres per unit of time. It follows that an increase in mortality rate corresponds with an acceleration of mortality, while a decrease in mortality rate corresponds with a deceleration of mortality, similar to the acceleration or deceleration of the car.[9,10] As senescence is represented by an increase in mortality rate with age, the rate of senescence can be calculated from the acceleration of

mortality and is expressed as the increase in mortality rate per year of age.[9,11] As an advantage to both demographers and biologists, this approach requires neither any assumptions on the age pattern of accelerations and decelerations of mortality nor on the biological mechanisms underlying the process of senescence.

In this study, we describe and test a method to calculate the rate of senescence directly from non-modelled age-specific mortality rates. This method can be used at all ages and is free of biological assumptions. It is purely based on the definition of senescence as the increase in mortality rate with age and calculates the rate of senescence as the acceleration of mortality with age. We apply this method to mortality data of patients with end-stage renal disease who are either on dialysis therapy or have undergone kidney transplantation. Patients on dialysis therapy are biologically and clinically known to suffer from increased senescence rates.[12-16] Mortality rates and senescence rates in patients with a functioning transplant are lower than in those on dialysis[17] and approach those of the general population.[12]

Methods

Study population

Data were provided by the Registry of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA Registry), which records the treatment and survival history of European patients receiving renal replacement therapy, either dialysis or kidney transplantation.[18] Patients were included when renal replacement therapy was started during a period from 1985 through 2011. Follow-up ended on 1 January 2012. Individual patient data were available from 1985 for Austria, the French-speaking region of Belgium, Finland, Greece, Iceland, the Netherlands, Norway, and Scotland, from 1994 for the Flemish-speaking region of Belgium, from 1990 for Denmark, from 2006 for Romania, from 1991 for Sweden, and from 1997 for England, Wales, and Northern Ireland. In addition, individual patient data were available for several regions in France from 2008, for several regions in Italy, including data from 2007 for Abruzzo, Aosta Valley, Basilicata, Emilia-Romagna, Sardinia, Umbria, and Veneto, and from 1997 for Calabria, and for several regions in Spain, including data from 1985 for Andalusia, from 2002 for Aragon, from 1995 for Asturias, from 1992 for Basque Country, from 1985 for Catalonia, from 1994 for Cantabria, from 2003 for Castile-La Mancha, from 2002 for Castile and León, from 2005 for Extremadura, from 2007 for Galicia, and from 1992 for Valencia.

Mortality rates were calculated based on the follow-up data contributed by each individual patient, separated for follow-up during dialysis and follow-up with a functioning transplant. For patients on dialysis, follow-up started six months after initiation of dialysis therapy, to account for early treatment-related mortality, and lasted until death, transplantation, recovery of renal function, loss to follow-up, or censoring on 1 January 2012. For patients with a functioning transplant, follow-up started six months after transplantation, to ac-

count for acute surgery-related mortality, and lasted until death, transfer to dialysis due to transplant failure, loss to follow-up, or censoring at 1 January 2012. For both treatment groups, the age-specific mortality rates were derived by dividing the number of deaths by the years of follow-up per 5-year age group.

Reference population

As a reference, mortality rates were also calculated for the general European population. Numbers of deaths and population sizes were derived from Eurostat for the countries and regions included in this study.[19] For each 5-year age group, the number of deaths was divided by the population size, both summed for the countries and regions and the years during which the countries and regions contributed data. As data were mostly available up to the age of 100, we excluded mortality rates from that age onward.

Analyses

To compare the use of non-modelled mortality rates with the use of modelled mortality rates, the mortality rates were modelled with the Gompertz model and senescence rates were estimated as previously described (Chapter 3 of this thesis).[12] The Gompertz model is mathematically described as $m(t) = \alpha\, e^{\gamma t}$, where $m(t)$ is the mortality rate at age t in years and α and γ are the model's parameters. The minimal mortality rate at $t = 0$ is determined by α, while the subsequent exponential increase in mortality rate with age is determined by γ. On a logarithmic scale, the model conforms to a straight line, which is described by $\ln m(t) = \ln \alpha + \gamma t$. The slope of this line is determined by γ, describes the acceleration of mortality on the logarithmic scale, and estimates the relative senescence rate. The derivative function of the Gompertz model describes the acceleration of mortality on an absolute scale, estimates the absolute senescence rate, and is mathematically described by $m'(t) = \alpha\, \gamma\, e^{\gamma t}$. Considering the applicability of the model, mortality data were included for the ages of 20 to 85 years.[12,20]

The method proposed here calculates the absolute senescence rate directly from non-modelled mortality rates on an absolute scale. The method is based on the mathematical definition of a derivative function.[21] In general, for a given function $y = f(x)$, the derivative function is $f'(x) = dy / dx$, where d denotes an infinitesimal change in y or x. In the case of mortality rate m calculated for age t, the notations y and x are replaced: $m'(t) = dm / dt$. When we take d as small as possible, dt corresponds to the difference in age between two age groups and dm equals the difference in mortality rate between both age groups. Using this method, we calculate the rate at which the mortality rate changes, thus the acceleration of mortality, between two age groups on average. Applied, we calculated the senescence rate of an age group as the mortality rate of the following age group minus the mortality rate of the age group of interest, divided by the difference in age between both age groups, the latter constantly being 5 years because of the use of 5-year age groups.

We excluded mortality rates from the analyses when the number of person-years was less than 200 per 5-year age group. Patients on dialysis aged 100 years and older were excluded, corresponding to less than 0.01% of follow-up and 0.01% of deaths. Patients with a functioning transplant aged 90 years and older were excluded, corresponding to 0.02% of follow-up and 0.05% of deaths. Due to the nature of this method, senescence rates could not be calculated for the highest age group. It was not necessary to exclude mortality data for the lowest age groups.

The calculations of the age-specific mortality rates were performed using SPSS Statistics 20 (IBM, Armonk, NY, USA). The Gompertz model was fitted to the mortality data using Stata/SE 12.1 (StataCorp, College Station, TX, USA), as previously described.[12]

Results

Table 4.1 provides the general characteristics of the study population of patients with end-stage renal disease on dialysis or with a functioning kidney transplant. As patients could successively undergo dialysis treatment and kidney transplantation, some patients contributed follow-up to both treatment groups; this was the case for 59 781 patients (18.8%) and 554 809 years of follow-up (41.5%). The maximum number of different treatment periods per patient was 13.

In Figure 4.1, the different methods to infer senescence rates from mortality rates are compared. For comparison with the method proposed here, we replicated the estimations of senescence rates from mortality data that were modelled by the Gompertz model, as described previously (Chapter 3 of this thesis).[12] Figures 4.1A and 4.1B show the modelled mortality rates against age on a logarithmic scale and the relative senescence rates estimated from the model's parameters. According to this method, senescence rates were constant with age, lowest in patients on dialysis, intermediate in patients with a functioning transplant, and highest in the general population. Figures 4.1C and 4.1D show the modelled mortality rates against age on an absolute scale and the absolute senescence rates estimated from the model's parameters. According to this method, senescence rates increased with age, were highest in patients on dialysis, intermediate in patients with a functioning transplant, and lowest in the general population.

Figure 4.1E shows the crude non-modelled mortality rates against age on an absolute scale. For both patients on dialysis and patients with a functioning transplant, the exponential increase in mortality rates from the age of 20 to at least 70 years provided visual justification for the application of the Gompertz model. However, in both groups, at lower and higher ages mortality rates deviated from the exponential increase and the Gompertz model was not applicable. Before the age of 20 years, mortality rates decreased with age. From the age of 70 to 90 years onward, the exponential increase in mortality rates levelled off. At all ages, mortality rates were highest in patients on dialysis and lowest in the general population.

Table 4.1 • General characteristics of the study population of patients with end-stage renal disease

	All patients	Patients on dialysis	Patients with a functioning kidney transplant
By number of patients			
Total number of patients	317 168	302 455	74 490
Men, %	61.5	61.5	62.7
Age, median (iqr) years			
at first treatment	64.1 (51.0–73.7)	65.0 (52.4–74.1)	48.6 (36.9–58.6)
at death	72.2 (63.5–78.8)	73.1 (64.8–79.3)	63.5 (54.7–70.6)
Follow-up per patient, median (iqr) years	2.7 (1.1–5.6)	2.0 (0.9–3.8)	5.4 (2.3–9.8)
By years of follow-up			
Total years of follow-up, person-years (%)	1 337 832	841 109 (62.9)	496 723 (37.1)
Men, %	60.6	59.8	62.0

As patients could successively undergo dialysis treatment and kidney transplantation, patients can be represented in both the patient group on dialysis and the patient group with a functioning transplant. Iqr: interquartile range.

Figure 4.1F shows the absolute senescence rates as calculated directly from the non-modelled mortality rates by the method proposed here. In contrast with the results obtained when using modelled mortality rates, senescence rates could be calculated for all ages. From the age of 20 to approximately 70 years, the absolute senescence rates were comparable to those determined with the derivative function of the Gompertz model (Figure 4.1D). Using this direct calculation from non-modelled mortality rates, senescence rates were negative below the age of 5 years and increased thereafter in the general population. In patients with a functioning transplant, senescence rates were negative below the age of 20 years, then increased until the age of 75 years, after which they decreased to a similar level as in the general population. In patients on dialysis, senescence rates were negative below the age of 15 years and were more pronounced than in patients with a functioning transplant and the general population. Above this age, their senescence rates increased until the age of 90 years, after which they decreased to a lower level than in the general population.

Discussion

The aim of this study is to describe and empirically test a method for calculating the rate of senescence directly from non-modelled mortality rates. This method strictly follows the definition of senescence as the increase in mortality rate with age.[2-5] In line with this definition, the method calculates the senescence rate as the acceleration of mortality with age, similar to the calculation of a derivative function. We validated our method by applying it to mortality data of patients with end-stage renal disease on dialysis, who are known to suffer from increased senescence rates, and of patients with a functioning kidney transplant, who have senescence rates that approach those of the general population. As an immediate advantage, this method yielded senescence rates for low and high ages that remained unrevealed when using modelled mortality rates.

We compared the outcomes of different methods to determine senescence rates from mortality rates. Classically, mortality rates are modelled by the Gompertz model and subsequently presented on a logarithmic scale, rendering easily comparable straight lines of which the slopes are determined by a single parameter of the Gompertz model (Figure 4.1A). Senescence rates are derived from the increase in these lines and are thus fixed with age (Figure 4.1B).[2,22-24] Due to the logarithmic scale, this method estimates the senescence rate as the relative acceleration of mortality with age. However, it has been theoretically objected that the estimation of the senescence rate from the relative acceleration of mortality with age is false[25-27] and that the senescence rate should be defined instead as the absolute acceleration of mortality with age (Chapter 2 of this thesis).[11] According to this view, we have proposed to model mortality rates on an absolute scale (Figure 4.1C). Earlier, we have demonstrated that senescence rates can be adequately derived from the absolute acceleration of mortality with age, using the derivative function of the Gompertz model (Figure 4.1D; Chapter 3 of this thesis).[12] Contrary to the relative senescence rates, but in line with biological and clinical knowledge, the absolute senescence rates were highest in patients on dialysis and lowest in the general population. The principle of using the derivative function can be applied to any model of the age pattern of a mortality rate.

Modelled mortality data are not always preferably used over crude mortality data. The ability of mathematical models to describe mortality is limited to a specific age range. The Gompertz model does not fit mortality rates at the lowest and highest ages.[20,28] This is explained by the fact that these models necessarily mould mortality data into a prescribed pattern. The Gompertz model assumes mortality rates to increase exponentially with age.[28] The mortality rates at the lowest and highest ages in patients on dialysis and patients with a functioning transplant deviated from an exponential increase with age, which became only apparent when assessing non-modelled mortality rates (Figure 4.1E). Models as the Gompertz model do not account for such deviating age patterns of mortality rates that may be valuable

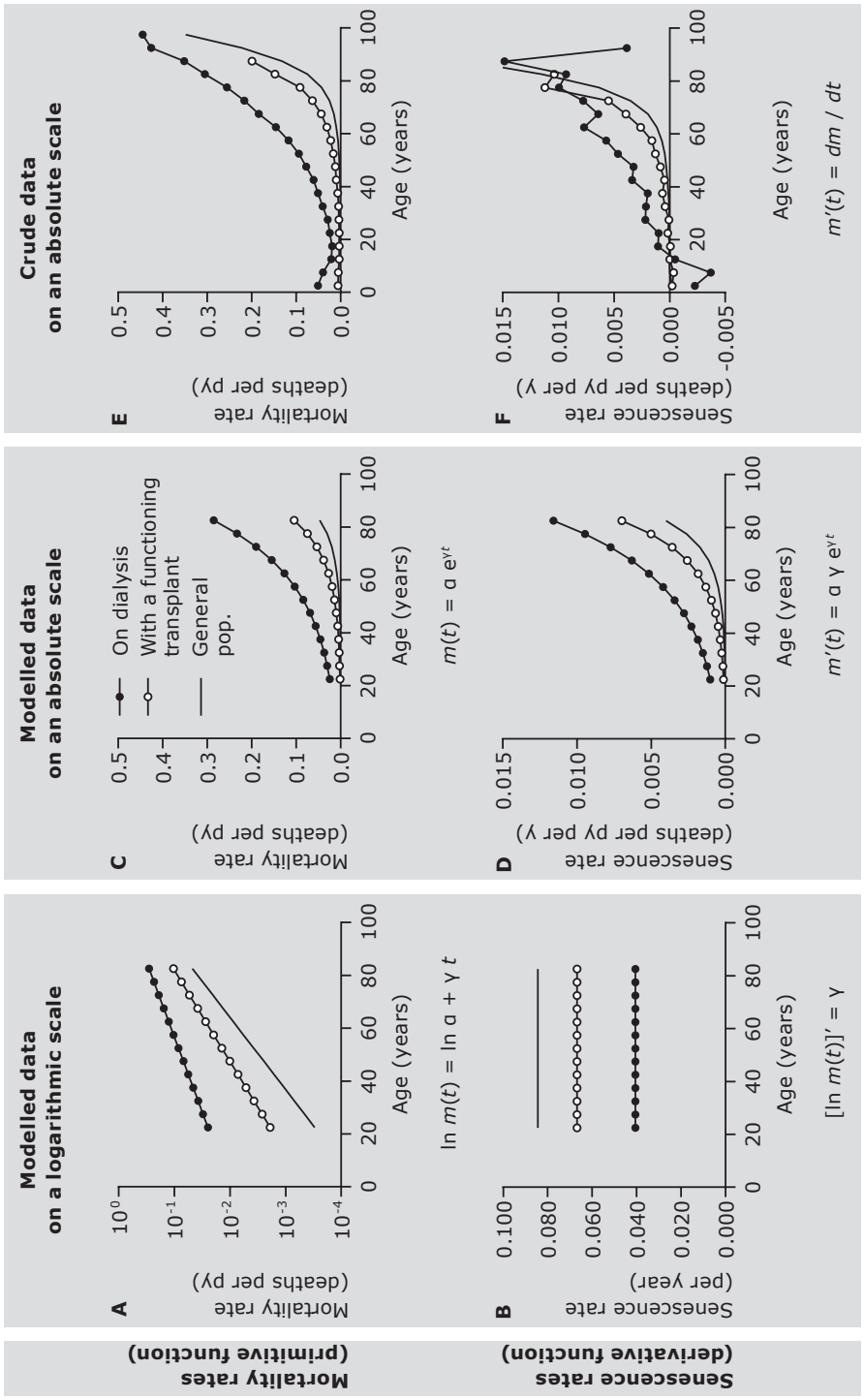

Figure 4.1 • A comparison of different methods to infer senescence rates from mortality rates. This overview shows different methods that use age-specific mortality rates (A, C, E) to calculate senescence rates (B, D, F), including the classical method (A, B), a method as proposed earlier by us (C, D), and a method presented in this article (E, F). The methods were applied to patients with end-stage renal disease on dialysis therapy and with a functioning kidney transplant and to the general population, as explained in the text. Py: person-year. Y: year.

to measure, as will be discussed hereafter. Moreover, these models, which are by themselves of only mathematical nature, are mistakenly interpreted biologically.[28-30] Apart from the Gompertz model, the Weibull model and the logistic model are often used without any of them superiorly fitting age patterns of mortality. The choice of a model is consequently based on biological assumptions explaining the age pattern that is imposed by the model.[28,31] As we have shown previously (Chapter 3 of this thesis),[12] such a biological meaning is generally attributed to the mathematical parameters of the Gompertz model, but has no empirical foundation and is biologically invalid.[11,25-27] An alternative method has been proposed to calculate senescence rates from non-modelled mortality rates, but only on a logarithmic scale, thus rendering relative senescence rates.[32,33]

Here we extend our earlier analyses by applying a method that circumvents the need to first model mortality rates for the calculation of senescence rates on an absolute scale (Figures 4.1E and 4.1F). From the age of 20 to approximately 70 years, the senescence rates calculated by this method were similar to those estimated by the derivative function of the Gompertz model. However, this method additionally offers the possibility to calculate senescence rates for low and high ages that are unaccounted for by the Gompertz model.

At low ages, the method proposed here disclosed negative senescence rates. Senescence rates were more negative in patients on dialysis than in patients with a functioning transplant and in the general population. Negative senescence rates at low ages have not been frequently addressed for humans, as changes in mortality are mainly studied from adolescence onward. For several non-human species it has been recognised that mortality rates decline during life, a finding which has been termed negative senescence.[34] At the beginning of human life, negative senescence is universally observed as a decline in mortality rate caused by processes that are distinct from senescence. It may be the result of a reduction in children's vulnerability during development and growth or of a reduction in a population's vulnerability due to the early death of the frailest children and the selective survival of healthier children.[35,36] In the cases of dialysis therapy[37] and kidney transplantation,[38] development and growth are impaired in children, although the deficits are partly compensated at a later age. The negative senescence rates in both groups more likely arise from a sharp decline in mortality rate due to early death of the frailest patients and the selective survival of healthier patients. Particularly in the lowest patients, mortality rates are high due to the underlying renal disease, congenital disorders that are associated with pædiatric renal disease, and the complications of dialysis therapy or transplantation.[39-41] The more negative senescence rates in children on dialysis as compared with children with a functioning transplant and the general population can be explained as they display higher mortality rates at the lowest ages with a subsequent sharper decline in mortality and improved growth. In addition, their negative senescence rates may be more pronounced due to a stronger effect of se-

lective survival of the less frail patients: as those selected for transplantation are relatively healthier,[40] the survival probabilities of children admitted to dialysis vary more than those of children undergoing kidney transplantation and in the general population. Negative senescence early in life has received little attention of gerontologists, but interacts closely with senescence later in life.[36] It would be interesting to include the age at which negative senescence rates turn into positive rates in studies on senescence. Comparable turning points in the age pattern of senescence rates have been studied, but only at higher ages.[42]

At high ages, the method proposed here uncovered declining senescence rates that are not accounted for by many models. The phenomenon of levelling mortality rates, and thus declining senescence rates, at high ages has been described in different populations.[2,43] Heterogeneity in survival patterns due to individual differences in frailty is thought to bring about levelling mortality rates.[44] In selected homogeneous populations, mortality rates continue to increase exponentially up to the highest ages.[45] The decline in senescence rates in patients on dialysis and patients with a functioning transplant can be explained by the selective survival to the higher ages of the relatively healthier patients and by the selection of relatively healthier patients to undergo these therapies at higher ages. That the senescence rates in patients with a functioning transplant declined at lower ages compared with patients on dialysis suggests that these selective processes are stronger in this group, probably because of the reluctance to perform kidney transplantation in older patients. Senescence rates in the general population did not decrease, probably because heterogeneity effects emerge at higher ages in large populations with low senescence rates.[2,43] The method proposed here can be applied to further study declines in senescence rates in populations at the highest ages.

This study investigated methods that determine senescence rates at the population level. The senescence rate of an individual cannot be inferred directly from the senescence rate of the population to which he belongs.[26] Still, the increased senescence rates in patients on dialysis can be attributed to biological and clinical mechanisms that have been observed and promote senescence in the individual patients.[8,46] In patients with end-stage renal disease as well as in older people in the general population, podocytes lining the epithelium of glomeruli show signs of damage and dysfunction, resulting in glomerulosclerosis and reduced glomerular filtration.[47] Renal dysfunction causes accumulation of mineral and uræmic toxins, oxidative stress, and systemic inflammation, which are normally seen at high ages. These processes promote cellular senescence through DNA damage, mitochondrial dysfunction, and telomere shortening. Widespread cellular injury and dysfunction lead to increased risks and rates of atherosclerosis, cardiac disease, cancer, immune deficiency, cognitive impairment, sarcopenia, and osteoporosis. These disorders, together with dialysis therapy itself, again induce further hæmodynamic and immunological disturbances and loss of renal function. Eventually, these disorders lead to increased

mortality rates.[12-16,47-50] The method proposed here can be applied to compare the senescence rates of different populations, to identify populations with increased or decreased senescence rates, and to evaluate the effects of interventions on the senescence rate.

The method presented here has several advantages. As it does not use modelled mortality rates, it can be applied to any mortality data, at all ages, and independent of species, geographic origin, calendar period, and birth cohort. As it does not mould the mortality rates into a prescribed age pattern, it closely follows the crude mortality data, does not discard any mortality data, and is very sensitive to changes in the senescence rate. Particularly those patterns of mortality that are not predicted by models may be informative about the process of senescence, as illustrated earlier for low and high ages. Finally, as this method is free of assumptions about the age pattern of mortality or the biological determinants underlying these patterns, it can only be interpreted based on its mathematical meaning. It measures the acceleration of mortality with age and thereby, given the definition of senescence as the increase in mortality rate with age, describes the senescence rate.

The use of non-modelled mortality data for the calculation of the senescence rate also has disadvantages. First, substantial amounts of age-specific crude data are required to prevent high variability in the estimates due to measurement error. Although large cohorts were available in this study, the senescence curves that were calculated with the proposed method show more variability than those calculated with the Gompertz model. We excluded age groups with few observations; each of these comprised less than 25 person-years of follow-up. Each age group included in the study comprised more than 200 person-years of follow-up. It is difficult to determine a level above which variability is unacceptably high. We cannot distinguish whether variability has arisen from measurement error or real age-related effects, which are both suppressed by modelling. Much of the variability depends on the width of the age groups for which the mortality rates have been calculated. This width can be adjusted in this method to reduce the effect of data variability. This reduction in variability will probably render the senescence rates more similar to those calculated from modelled mortality data. Furthermore, this method can be extended with techniques to smoothen the senescence curves, but that again introduces modelling based on statistical or biological assumptions. Second, the senescence rate can only be determined for those age groups with available mortality data. Without a model of the age pattern of mortality, extrapolation to other ages is not possible.

In conclusion, this study shows how the absolute rate of senescence can be calculated directly from age-specific non-modelled mortality rates. The methodology is simple, sensitive to changes in mortality with age, free of limitations in its applicability, and does not require any biological interpretation of mathematical models.

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