# INTRINSIC AND EXTRINSIC MORTALITY REUNITED

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Intrinsic and extrinsic mortality are often separated in order to understand and measure senescence. Intrinsic mortality is assumed to be a result of senescence and to increase with age, whereas extrinsic mortality is assumed to be a result of environmental hazards and be constant with age. However, allegedly intrinsic and extrinsic mortality have an exponentially increasing age pattern in common. Theories of senescence assert that a combination of intrinsic and extrinsic stressors underlies the increasing risk of death. Epidemiological and biological data support that the control of intrinsic as well as extrinsic stressors can alleviate the senescence process. We argue that senescence and death can be better explained by the interaction of intrinsic and extrinsic stressors than by classifying mortality itself as being either intrinsic or extrinsic. Recognition of the tight interaction between intrinsic and extrinsic stressors in the causation of senescence leads to the recognition that senescence is not intractable, but malleable through the environment.

To understand and measure how senescence leads to an increase in the rate of mortality, many clinicians and scholars separate intrinsic and extrinsic mortality. Intrinsic mortality is envisioned as the result of processes of physical and functional degradation originating within the human body. As these processes arise with increasing age, intrinsic mortality would represent senescence. Extrinsic mortality is seen as the result of hazards from the environment. As the human body is exposed to these hazards uniformly across ages, extrinsic mortality would not represent senescence and would be constant during life.1-3 While intrinsic and extrinsic mortality are often separated implicitly, their separation influences biomedical research, clinical practice, and public health.

Different classifications of intrinsic and extrinsic mortality have been proposed, without any having received general acceptance. Meanwhile, the assumption that causes of death originate in either the intrinsic senescence process or the extrinsic environment has never been formally tested. Here, we compare the age patterns of typical examples of allegedly intrinsic and extrinsic mortality, discuss theories of the intrinsic and extrinsic causes of senescence, and summarise epidemiological and biological data on intrinsic and extrinsic causes of senescence. We argue that the partitioning between intrinsic and extrinsic mortality is not meaningful.

# Intrinsic and extrinsic mortality have exponentially increasing age patterns

Figure 5.1 shows the traditional and alternative investigations of the age patterns of allegedly intrinsic and extrinsic mortality. As a traditional investigation, the numbers of intrinsic and extrinsic deaths as proportions of the total number of deaths are plotted against age (Figure 5.1A). The proportions give the impression that intrinsic mortality concentrates at higher ages, while extrinsic mortality concentrates at lower ages. However, since they do not reflect any differences in the total number of deaths, the proportions of either intrinsic or extrinsic deaths cannot be compared directly between ages. By contrast, when the absolute numbers of intrinsic and extrinsic deaths are plotted against age, the numbers of either intrinsic or extrinsic deaths can be compared between ages and both intrinsic and extrinsic mortality concentrate at the highest ages (Figure 5.1B). As another traditional investigation, rates of intrinsic and extrinsic mortality are plotted against age on a logarithmic scale



**Figure 5.1 • Traditional and alternative investigations of the age patterns of allegedly intrinsic mortality due to senescence and extrinsic mortality due to the environment.** Intrinsic mortality includes death due to ischæmic heart disease (ICD-10 codes I20–I25), diabetes mellitus (E10–E14), and cancer (C00–C97). Extrinsic mortality includes death due to infectious diseases (A00–B99) and due to so-called external causes (V01–Y98), among which accidents and natural disasters. Data have been derived from the European Detailed Mortality Database of the World Health Organization for 31 European countries and Israel in 2009 or 2010.<sup>43</sup> In panels B and D, allegedly intrinsic mortality is plotted on the left axis and allegedly extrinsic mortality on the right axis.

(Figure 5.1C). The logarithmic rates give the impression that intrinsic mortality increases continuously, while extrinsic mortality is almost constant with age. However, on a logarithmic scale, multiplicative changes are revealed while absolute changes are concealed. We have previously illustrated that interpretations of multiplicative changes in mortality rates with age do not necessarily apply to the absolute changes in the same mortality rates (Chapter 2 of this thesis).4 Plotting allegedly intrinsic and extrinsic mortality on an absolute scale reveals an exponential increase with age for both (Figure 5.1D). Whereas the traditional investigations seem to support a distinction between the age patterns of intrinsic and extrinsic mortality, the alternative investigations reveal that both intrinsic and extrinsic mortality have exponentially increasing age patterns.

In Figure 5.2, the age patterns of mortality rates are shown on an absolute scale for typical examples of allegedly intrinsic and extrinsic causes of death.1,2 Minor differences between the age patterns can be observed. Mortality rates due to cancer start increasing at earlier ages. Mortality rates due to accidents are slightly elevated throughout adulthood. Mortality rates due to natural disasters are elevated from the age of 50 to 60 years and decrease slightly from the age of 60 to 75 years. However, the rates of intrinsic and extrinsic mortality share the common feature of an exponential increase with the highest values at the highest ages.

The age patterns of incidence rates for the same typical examples of allegedly intrinsic and extrinsic disorders can also be compared. Although minor differences can be observed, the incidence rates of intrinsic and extrinsic disorders share the common feature of an exponential increase to a maximum at the highest ages, as shown in Figure 5.3.

# Intrinsic and extrinsic stressors interact in the causation of senescence

The human body is exposed to intrinsic stressors originating within and extrinsic stressors originating outside the body. During life, the repetitive exposure to these stressors leads to an accumulation of permanent damage, which leads to dysfunction, disease, and ultimately death.5 The various damages that have been acquired up to a certain age increase the body's vulnerability to be damaged by intrinsic and extrinsic stressors at subsequent ages. As senescence amounts to the increasing risks of disease and death, senescence is a consequence of the accumulation of damages from intrinsic as well as extrinsic sources.5,6 For example, senescence is partly attributed to damage to the DNA, which is induced by intrinsic stressors such as spontaneous chemical reactions, replication errors, and metabolic waste products, but also by extrinsic stressors such as radiation and viruses. Damage impairs the DNA's repair function, decreases its resistance to further damage caused by intrinsic and extrinsic stressors, and increases the risks of disease and death.7



**Figure 5.2 · Age patterns of mortality rates for typical examples of allegedly intrinsic mortality due to senescence and extrinsic mortality due to the environment.** As typical examples of intrinsic mortality, death due to ischæmic heart disease (ICD-10 codes I20–I25), diabetes mellitus (E10–E14), and cancer (C00–C97) have been included. As typical examples of extrinsic mortality, death due to infectious diseases (A00–B99), accidents such as transport accidents, falls, drowning, and exposure to mechanical forces (V01–X29), and natural disasters such as excessive heat or cold, lightning, earthquakes, storms, and floods (X30–X39) have been included. Data have been derived from the European Detailed Mortality Database of the World Health Organization for 31 European countries and Israel in 2009 or 2010.<sup>43</sup> Mortality rates are given as numbers of deaths per 1000 person-years (py) with 95% confidence intervals.



**Figure 5.3 • Age patterns of incidence rates for typical examples of allegedly intrinsic disorders due to senescence and extrinsic disorders due to the environment.** As typical examples of intrinsic disorders, ischæmic heart disease (ICD-10 codes I20–I25), diabetes mellitus (E10–E14), and cancer (C00–C97) have been included. As typical examples of extrinsic disorders, infectious diseases (A00–B99) and disorders due to accidents such as transport accidents, falls, drowning, and exposure to mechanical forces (V01–X29) and due to natural disasters such as excessive heat or cold, lightning, earthquakes, storms, and floods (X30–X39) have been included. Data have been derived from the European Hospital Morbidity Database of the World Health Organization for 26 European countries and Israel in 2008, 2009, or 2010.<sup>44</sup> Incidence rates are given as numbers of hospital discharges per 1000 person-years (py) with 95% confidence intervals.

Other processes than damage accumulation are identified as the cause of senescence by alternative theories. Notably, senescence is attributed to a continuation and hyperfunction of processes that facilitate development early in life.8 These developmental processes originate within the body and may be regarded as intrinsic stressors, but are inextricably linked with the body's environment. The developmental processes are, as early as their intrauterine onset, modulated by environmental conditions such as nutrition.9,10 Later in life, the overgrowth of developmental processes only causes senescence in combination with stressors from the environment. For example, cellular senescence is explained by excessive cell growth induced by developmental growth factors, which depend on environmental signals such as nutrient levels. The cell growth only leads to cellular senescence when the cell cycle has been arrested by intrinsic stressors such as oxidative stress and oncogenes or by extrinsic stressors such as chemical toxins and radiation.8

Traditional biological theories explain the evolution of senescence by separating intrinsic and extrinsic mortality. They propose that extrinsic mortality due to the environment constrains survival up to high ages, as a result of which selective pressure declines with increasing age. The decline in selective pressure facilitates the occurrence of senescence, which appears as intrinsic mortality.<sup>11,12</sup> However, empirical studies have failed to consistently confirm a relationship between the level of extrinsic mortality and the process of senescence.<sup>3,12</sup> It has been theoretically demonstrated that the level of extrinsic mortality cannot explain the evolution of senescence, unless extrinsic stressors are acknowledged to interact with and to be modulated by the body's vulnerability that declines with age.<sup>13,14</sup>

It is a fundamental theorem in biology that every phenomenon is explained by the interaction of genes and environments. From this point of view, it is a misconception to equate genes with causal factors within the body and the environment with those outside it.<sup>10</sup> Rather, the effects of genes are modulated by the environment and vice versa.15 Disease and death are not either genetic or environmental, but of mixed genetic and environmental origin.<sup>16</sup> Yet, little attention is given to gene-environment interaction in the context of senescence.10 The intrinsic and extrinsic stressors to which the human body is exposed can be regarded as genetic and environmental stressors that interact to exert detrimental effects. These effects again interact with the body's genetic susceptibility and increase its vulnerability to further detrimental effects, ending in senescence and death. Since senescence and death are the outcomes of both genes and the environment, they cannot be partitioned as either intrinsic or extrinsic. This is reflected by the exponential increasing age patterns that allegedly intrinsic and extrinsic mortality have in common.

# Intrinsic and extrinsic stressors interact in epidemiological and biological studies on senescence

Epidemiological and biological data support that senescence is a result of the interaction between intrinsic and extrinsic stressors. Cardiovascular disease, diabetes mellitus, and cancer are typically regarded as determined by intrinsic senescence, but are meanwhile largely attributable to hazards that originate in the environment, including tobacco and alcohol use, sunlight, pollution, an excessive dietary composition, and a minimal necessity of physical activity.17 These environmental hazards affect the structure and functioning of the genome and are required for the development of disease.6,7 Even the accelerated bodily deterioration caused by well-defined genetic substrates as in Huntington's and Duchenne's diseases is influenced by the environment.<sup>18,19</sup> As a consequence, environmental interventions can prevent or postpone cardiovascular disease, diabetes mellitus, and cancer.20-22

Infectious diseases, accidents, and natural disasters require environmental risk factors, but cannot be uncoupled from the body's vulnerability that increases with age. Senescence of the immune system increases the risk of infectious diseases.<sup>23</sup> The immune system is influenced by microorganisms and other environmental factors, like smoking, sunlight, and dietary components and meanwhile plays an essential role in the pathogenesis of cardiovascular disease and cancer.<sup>6,24</sup> Commensal and infectious microorganisms can induce or prevent diseases attributed to senescence, including autoimmune disease, cardiovascular disease, neuropsychiatric disease, and cancer.<sup>24</sup> Even the risk of being affected by seemingly fully stochastic hazards is age-dependent. Sensory, cognitive, and executive dysfunctions, disability, and multimorbidity that accumulate with age predispose to burns, chokes, falls, traffic accidents, and other environmental hazards.<sup>25-27</sup>

That the senescence process depends on both intrinsic and extrinsic stressors becomes apparent when populations across different environments are compared. For example, both western populations and populations exposed to endemic infections, malnutrition, and physical labour share similar declines in muscle strength and heart rate variability with age (Chapters 8 and 11 of this thesis).28,29 This indicates that the senescence process contains components that are independent of the environment. On the other hand, while senescence in western populations is accompanied by a predominance of allegedly intrinsic disorders like cardiovascular disease and diabetes mellitus, these disorders are uncommon up to the highest ages in the populations exposed to endemic infections, malnutrition, and physical labour (Chapters 9 and 10 of this thesis).<sup>30,31</sup> This indicates that the senescence process is shaped by the environment.

# Relevance to biomedical research, clinical practice, and public health

Senescence is commonly defined to encompass deleterious, progressive, and intrinsic age-related changes that culminate in death. The intrinsic nature of senescence is understood as being independent of modifiable environmental factors.<sup>32</sup> This traditional definition is rooted in a separation of intrinsic mortality due to senescence and extrinsic mortality due to the environment, neglects the tight interaction between intrinsic and extrinsic stressors as causes of senescence, but influences biomedical research, clinical practice, and public health.

Firstly in biomedical research, intrinsic and extrinsic mortality are separated when measuring the senescence process. Mathematical models are used in such a manner that distinct parameters account for intrinsic and extrinsic mortality.3,33 For example, one parameter of the Gompertz model describes the minimal risk of dying during adolescence and is used as a measure of extrinsic mortality. Another parameter describes the increase in mortality rate over subsequent ages, which is linear when plotted on a logarithmic scale, as shown in Figure 5.1C. The single parameter that determines this linear increase is used as a measure of intrinsic mortality. Models like the Gompertz model are applied to interpret the effects of experimental interventions as affecting either the intrinsic rate of senescence or the extrinsic age-independent risk of dying. A change in the minimal risk of dying is interpreted as a change in the environmental risk of dving. while a change in the linear increase of the logarithmic mortality rate is interpreted as a change in the rate of senescence.34,35 We have previously criticised such a biological interpretation of the mathematical parameters.4 We have argued that the rate of senescence should be measured by the increase in mortality rate with age on an absolute scale, as shown in Figure 5.1D (Chapter 3 of this thesis).<sup>36</sup> The absolute increase in mortality rate is determined by both parameters of the Gompertz model. This illustrates that allegedly intrinsic and extrinsic mortality should not be partitioned to correctly measure the rate of senescence, which is essential for research on senescence.

Others have argued similarly that studies on the relationship between environmental hazards and senescence are handicapped as models and experiments do not take into account the interaction between the environmental hazards and the body's increasing vulnerability with age. This interaction is essential to understand how the environment has facilitated the evolution of senescence and how environmental factors continue to shape the senescence process.<sup>12,14</sup> The comparison of populations across different environments is essential for unravelling the intrinsic and extrinsic components of the senescence process. Here, we focus on the senescence process in western human populations. Our argumentation can be further investigated by comparing human populations living across different environments and by rearing animal models in different environments. Such research on the interaction between the environment and senescence will be valuable and may yield results that are different from those of traditional investigations.<sup>12,36</sup>

Secondly in clinical reasoning, disease and death are classified as intrinsic or extrinsic in an attempt to better understand and target the senescence process. Disorders such as cardiovascular disease, diabetes mellitus, and cancer are considered as degenerative disorders that progress intrinsically with increasing age. Curative and preventive endeavours focus on the senescence process, but the role of environmental factors in their causation is underestimated.37,38 Conversely, disorders such as infectious diseases, accidents, and natural disasters are considered as environmental, but the effect of age on the risks of these disorders is underestimated. Alternatively, senescence and death are not explained by a single cause, but by intrinsic and extrinsic stressors that congregate with age and each constitute partial causes.<sup>16</sup> Strategies to combat senescence and death need to take into account their different intrinsic and extrinsic causes to be successful, as has been recently pled for infectious diseases.39

Underlying pathogenic processes are sorted similarly. In dermatology, for example, the deteriorating synthesis of interstitial proteins is attributed to intrinsic senescence, while sun-induced damage is thought to constitute extrinsic environmental damage.<sup>40</sup> However, also molecular and cellular phenomena of senescence and environmental damage are extensively interconnected.<sup>6</sup> The damage in the skin that is accrued with increasing age is due to both the deteriorating protein synthesis and sunshine.

Thirdly in public health, the distinction between intrinsic and extrinsic mortality is misleading when designing preventive strategies against senescence and environmental hazards. Above, we have described that disorders attributed to senescence can be prevented by environmental interventions and that the old are most vulnerable to be struck by environmental hazards. Consequently, prevention of mortality due to cardiovascular disease, diabetes mellitus, and cancer should not only be sought in a delay of the senescence process, but may be more readily attained by confining the exposure to their environmental risk factors. Prevention of mortality due to infectious diseases, accidents, and natural disasters should particularly aim at protecting the frail elderly. Hygienic precautions and vaccination against contagions are essential, participation in traffic requires safety measures that compensate for disabilities, and the old skin should be protected as it is easily bruised or sunburnt. Especially lifestyle interventions seem effective, such as limiting sun exposure to delay senescence of the skin.

### Conclusion

When intrinsic mortality due to senescence and extrinsic mortality due to the environment are separated, senescence is accepted as an intractable side effect of increasing age while environmental hazards are taken as bad luck. In contrast, when intrinsic and extrinsic stressors are acknowledged to interact tightly in the causation of senescence, disease, and death, new perspectives arise with both a bad and a good outlook. The bad news is: all mortality is related to senescence. The risk of allegedly extrinsic mortality increases exponentially with age just like allegedly intrinsic mortality, because they are both attributable to degeneration of the human body's structures and functions. The good news is: all mortality is related to the environment. The risk of allegedly intrinsic mortality increases with age, but is just as well dependent on environmental hazards. A proper understanding of the tight interaction between intrinsic and extrinsic stressors recognises that senescence is not intractable, but malleable through the environment. Knowledge on this interaction leads the way to identify environmental stressors that cause senescence and can be targeted to prevent senescence.<sup>41,42</sup> To reach this goal, intrinsic and extrinsic mortality should be reunited in mathematical models when measuring senescence, in clinical reasoning when explaining senescence, and in public health when allocating prevention and intervention.

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