12 GENERAL DISCUSSION

In this thesis, we measure senescence in human populations, defined as an increase in the risks of dysfunction, disease, and death with chronological age. In Part I of this thesis we investigate how a population's senescence rate can be measured through the increase in mortality rate with age. In Part II of this thesis we investigate how senescence can be measured through the increase in morbidity with age in a non-western population and thus be compared with the senescence process in western populations.

The rate of senescence

A population's senescence rate is classically measured as the increase in mortality rate with age on a logarithmic scale, which is described by the Gompertz model's parameter γ. This measure has been criticised and, as an alternative, it has been proposed to measure a population's senescence rate as the increase in mortality rate with age on an absolute scale.[1]

Some who have criticised the classical measure of a population's senescence rate have fallen back to measures of senescence that summarise the varying levels of mortality throughout the entire life in a single age-independent constant, such as the mean lifespan.[2] As such measures are not informative about the age pattern of mortality, they cannot improve on the classical measure.[3]

Others have designed new approaches other than measuring the increase in mortality rate on an absolute scale. Notably, it has been put forward that age patterns of mortality rates can be separated into two dimensions: the pace of senescence and the shape of senescence. The pace of senescence captures the time during which mortality occurs and can be described by life expectancy or maximum lifespan. The shape of senescence does not depend on time, but captures the extent to which mortality changes independently of the pace of senescence.[4] Although this approach provides a thoughtful conceptual view on the measurement of senescence[5] and is already applied to characterise senescence processes,[6,7] the assumptions underlying the separation of both dimensions of senescence have never been empirically tested.

We are the first to empirically verify an alternative measure of a population's senescence rate, derived from the increase in its mortality rate with age on an absolute scale (Chapter 3 of this thesis).[8] We have tested this measure by applying it to populations that are known to have different senescence rates. We have confirmed that this alternative measure yields valid senescence rates, whereas the classical measure yields invalid senescence rates. We have demonstrated how senescence rates can be determined according to the alternative measure by using the derivative function of the Gompertz model. This principle can be applied to any model of the age pattern of a mortality rate other than the Gompertz model. Furthermore, to overcome the limitations of such models, we have demonstrated how senescence rates can be determined according to the same principle by using a non-parametric method that does not require any modelling of mortal-

ity rates (Chapter 4 of this thesis).[9] This method can be applied to any age pattern of a mortality rate.

The validity of the increase in mortality rate on a logarithmic scale as a measure of the senescence rate can also be questioned on mathematical grounds. According to the Gompertz model, the increase in mortality rate m with age t equals $m'(t) = \gamma$ and has the unit per year of age.[10] Non-parametrically, this increase equals:

$$\ln(m'(t)) = m'(t) \,/\, \mathrm{m}(t) \qquad (12.1)$$

which likewise has the unit per year of age. By contrast, the senescence rate measured as the increase in mortality rate on an absolute scale — which is according to the Gompertz model:

$$m'(t) = \alpha\, \gamma\, e^{\gamma t} \qquad (12.2)$$

and is non-parametrically described as:

$$m'(t) = dm \,/\, dt \qquad (12.3)$$

— is expressed with the unit deaths per person-year per year of age, thus mortality rate per year of age. The latter unit matches best with the definition of senescence as the increase in mortality rate with age.

The Gompertz model's parameter γ is not by itself a measure of a population's senescence rate, but the senescence rate is described by the model's derivative function that is dependent on both parameter α and γ. Moreover, it is not necessary to model the age pattern of a mortality rate to measure the senescence rate. It follows that the parameters of the Gompertz model — or of any other model of the age pattern of a mortality rate — cannot be interpreted to have specific biological meanings. Such an interpretation assumes that mortality can be partitioned in intrinsic mortality due to senescence and extrinsic mortality independent of senescence. We have substantiated in Chapter 5 of this thesis[11] why this assumption is false. Accordingly, the function of the parameters is limited to their original function, that is to fit and describe the age pattern of a mortality rate merely mathematically.

Figure 12.1 illustrates the mathematical meanings of both parameters of the Gompertz model. Variation in α as well as in γ affects the decrease in survival with age, the distribution of deaths over age, and the increase in mortality rate with age and, thus, affects the senescence rate. Conversely, the differences in these age patterns that are brought about by variation in either parameter cannot be distinguished as either reflecting a difference in the senescence rate or not.

The way of senescence

Because much is unknown about senescence in populations without a western lifestyle, we have studied senescence in a traditional rural African population in one of the least developed regions of Ghana (Chapters 7 through 11 of this thesis). This population contrasts sharply with western populations: its environment is not affluent and sedentary, but typified by poverty, limited nutrition, regular hunger, continuous physical activity, and many endemic infectious diseases.

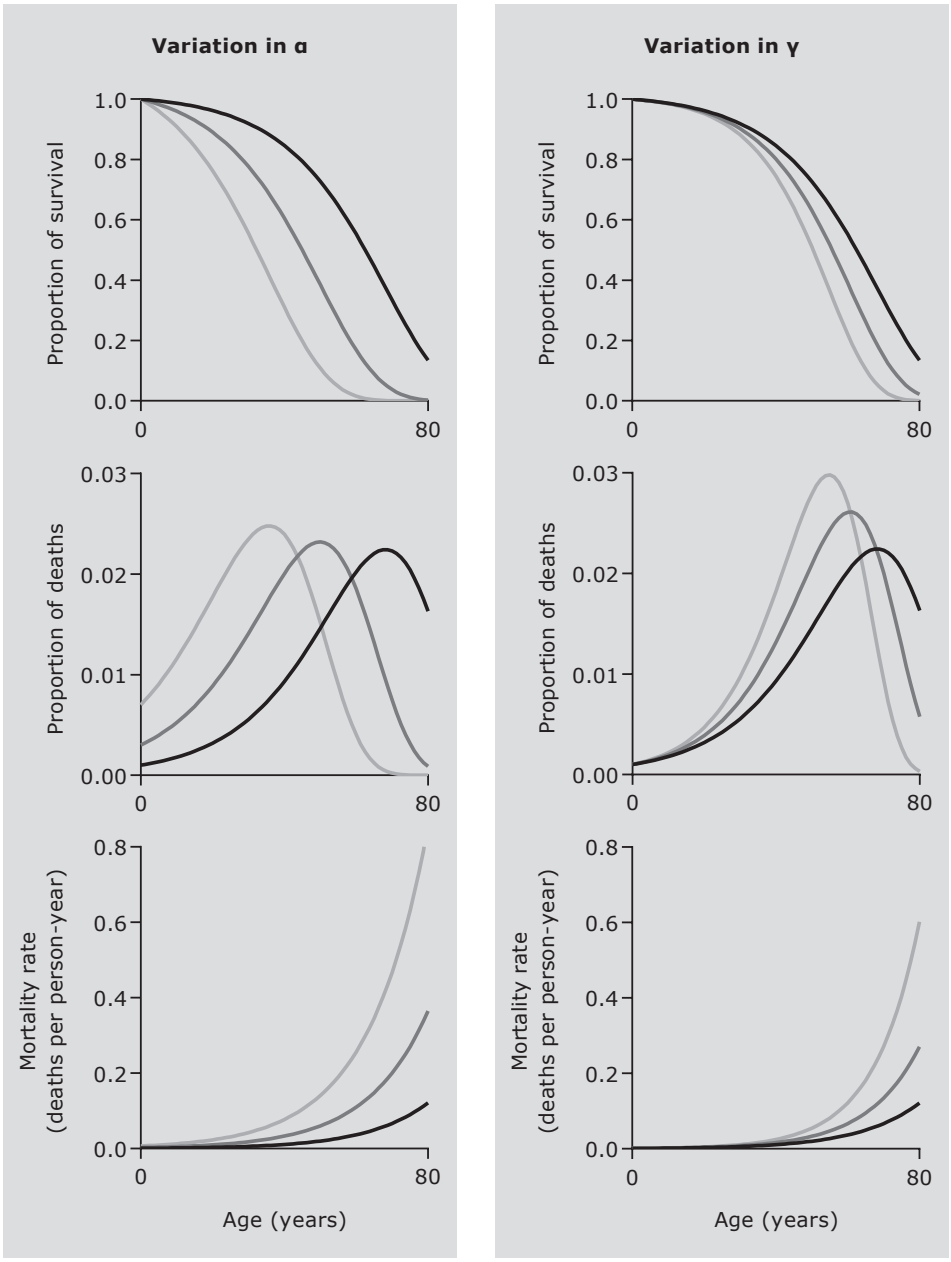

Figure 12.1 • The effects of variation in the Gompertz model's parameters α and γ on the age patterns of a population's survival, deaths, and mortality rate. In the left panels, α is 0.001, 0.003, and 0.007 from black to grey and γ is constantly 0.06. In the right panels, γ is 0.06, 0.07, 0.08 from black to grey and α is constantly 0.001. Others have assessed these effects similarly.[12]

In some respects, the way of senescence is similar in the Ghanaian study population and western populations. We have shown that handgrip strength declines with age and predicts mortality similarly in both types of populations (Chapter 8 of this thesis).[13] Heart rate variability at rest also declines with age and is associated with handgrip strength and mortality similarly in both types of populations (Chapter 11 of this thesis).[14] Handgrip strength and heart rate variability apparently reflect biological age and senescence across different environments and different lifestyles.

In other respects, our studies show that the way of senescence is different in this non-western population as compared with western populations (Chapters 9 and 10 of this thesis).[15,16] Senescence does not manifest as sharp increases with age in the prevalences of cardiovascular disease — including coronary arterial disease, peripheral arterial disease, and atrial fibrillation — and diabetes mellitus. It neither manifests as an increase in heart rate at rest, which is associated with disease and death in western populations. Meanwhile, risk factors of cardiovascular disease, diabetes mellitus, and an increased heart rate — including obesity, dyslipidæmia, and hypertension — are absent or uncommon. Because their risk factors are closely related to a western lifestyle, the development of diseases such as cardiovascular disease and diabetes mellitus and the increase in heart rate during senescence are likely consequences of a western lifestyle.

In western populations, chronic smouldering inflammation arises during senescence and is associated with the diseases that are related to senescence, among which cardiovascular disease and diabetes mellitus. It has been proposed that inflammation plays an essential role in the causation of senescence and senescence-related diseases.[17-22] In the Ghanaian study population, a high burden of infectious diseases and an enrichment of a proinflammatory immune system[23,24] have not resulted in chronic smouldering inflammation, cardiovascular disease, or diabetes mellitus.[15,16,25] Other studies have confirmed that chronic smouldering inflammation in western populations is rather an effect than a cause of cardiovascular disease, diabetes mellitus, and their risk factors, of which most notably obesity.[26-29] In the Ghanaian study population and other similar non-western populations, inflammation is rather acute and attributable to infectious diseases.[25,30-32]

Cardiovascular disease is closely related to senescence in western populations. Its pathogenesis consists of an accumulation of damage in the vascular wall and the heart during ageing due to a disturbance of the blood flow, a deposition of lipids, and a maladaptive inflammatory response.[33,34] These processes are associated with markers of senescence at the molecular and cellular level.[35,36] During life, these processes lead to dysfunction and disease of the vessels and heart[37-39] and are associated with the occurrence of other age-related disorders.[40,41] By contrast, the environment and lifestyle in non-western populations expose their inhabitants to other kinds of bodily damage. Rather than high levels of lipids and chronic smouldering inflam-

mation, damage accumulates during their lives as a consequence of malnutrition and acute inflammation evoked by infectious diseases. The different kinds of damage lead to different kinds of dysfunction and disease. Senescence in non-western populations is not characterised by cardiovascular disease, but by diseases that are unfamiliar from a western point of view.

The rate and way of senescence

Our investigations of the rate of senescence and the way of senescence in human populations converge when we apply our method of measuring a population's senescence rate in order to compare the senescence rates of the Ghanaian study population with those of a western population.

Figure 12.2 shows the age patterns of the causes of death in the general population of the USA and the Ghanaian study population. As is well known for western populations, most deaths during adolescence and young adulthood are due to traumata, while most deaths at higher ages are due to non-infectious diseases such as cardiovascular disease, diabetes mellitus, and cancer (Figure 12.2A). By contrast, in the Ghanaian study population, most deaths are due to infectious diseases at any age, while deaths due to non-infectious diseases account for a minority of deaths (Figure 12.2B). The way of senescence differs between this non-western population and western populations.

Figure 12.3A shows the age patterns of the mortality rates of the general population of the USA and the Ghanaian study popu-

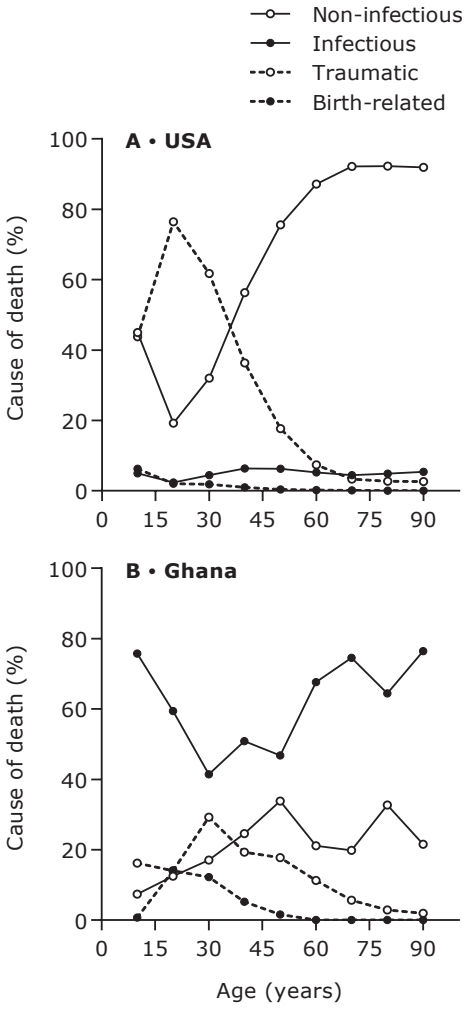

Figure 12.2 • Age patterns of causes of death in the general population of the USA (A) and in the traditional rural Ghanaian study population (B). Data on the general population of the USA are from 1990 through 2010 and were derived from CDC WONDER.[49] Data on the Ghanaian study population are from 2003 through 2011 and were obtained by verbal autopsy.[50,51] Differences in the coding between both sources have been equalised.

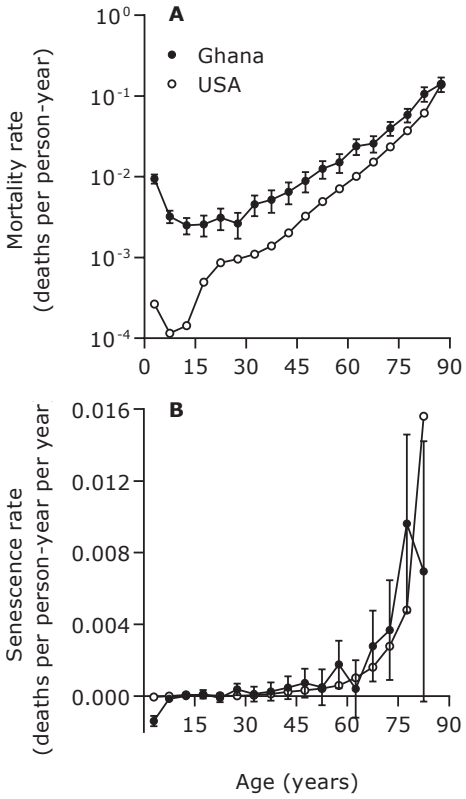

Figure 12.3 • Age patterns of mortality rates (A) and senescence rates (B) in the general population of the USA and in the traditional rural Ghanaian study population. Data on the general population of the USA are from 1990 through 2010 and were derived from CDC WONDER.[49] Data on the Ghanaian study population are from 2003 through 2011 and were registered as described elsewhere.[52,53] The mortality rates and senescence rates are shown with 95% confidence intervals. The senescence rates were calculated from the increase in the mortality rates with age on an absolute scale, as described in Chapter 4 of this thesis.[9]

lation on a logarithmic scale. Conforming to the Gompertz model, these mortality rates increase linearly during adulthood. If these linear increases would be interpreted according to the classical method, the senescence rate of the general American population would be estimated higher than that of the Ghanaian study population. However, if we calculate their senescence rates from the increase in their mortality rates on an absolute scale, another conclusion is drawn. Figure 12.3B shows the senescence rates calculated in this manner. Despite the different ways of senescence, the rates of senescence are similar in both populations.

As discussed in Chapters 1 and 5 of this thesis,[11] senescence is the result of intrinsic and extrinsic stressors that damage the human body in interaction. The comparison of populations with different environments and lifestyles discloses the effects of extrinsic stressors from the environment: the way of senescence differs between the Ghanaian study population and western populations. Meanwhile, our findings of similar declines in handgrip strength and heart rate variability with age and of similar senescence rates in these different environments hint at causes of senescence that are intrinsic to the human body and render it susceptible to damage and deterioration.

It has been hypothesised that the human species exhibits a specific fixed senescence rate.[42] This hypothesis is enfeebled by our observation that senescence rates can vary within a population, as described in Chapters 3 and 4 of this thesis.[8,9] Yet, the

mortality rates of both non-western and western populations and of both individuals with and without end-stage renal disease increase exponentially with age on an absolute scale and thereby conform to the Gompertz model. The same holds for the mortality of animal models and the decay of inanimate objects.[43] Even more, an exponential age pattern is observed in the performance of sportsmen[44] and in markers of cellular senescence.[45-48] The Gompertzian age pattern seems to be universal. Different interactions of intrinsic and extrinsic stressors lead to different senescence processes and different causes of death, but apparently underlie similar exponential increases in mortality rate with age.

Limitations

When measuring a population's senescence rate from the increase in mortality rate, we do not account for the potential effects of population heterogeneity. As explained in Chapter 4 of this thesis,[9] differences in the age patterns of mortality rates between subgroups of a population can produce an age pattern of the mortality rate for the population as a whole that does not reflect the age patterns of the subgroups. To verify that our findings are not distorted by population heterogeneity, our studies can be repeated in homogeneous populations, which is practically possible by studying the mortality of inbred animals housed under standardised conditions. We have tried to approach this goal by stratifying the study population into known subgroups; this has not refuted our conclusions. More sophisticated statistical methods have been developed to investigate the potential effects of population heterogeneity, which merit integration in our future studies.

It is sometimes objected that the measurement of a population's senescence rate from the increase in mortality rate is hampered by the level of the mortality rate. For example, patients with end-stage renal disease who receive dialysis treatment have mortality rates that greatly exceed those of the general population. It is reasoned that high mortality rates cannot increase as much as low mortality rates. However, this line of reasoning is often based on the mortality rates as shown on a logarithmic scale. When the mortality rates are shown on an absolute scale, they increase exponentially in the patients on dialysis as well as in the general population (Figure 3.1). Furthermore, we have not been able to discover any effect of the level of the mortality rate on the increase in the mortality rate by adjusting for follow-up and by longitudinally examining the age patterns of the mortality rates of subgroups of patients with end-stage renal disease.[54] To further assess this objection, it is worthwhile to test our method in cohort studies with lifelong follow-up.

A distinction must be made between the level of a mortality rate and the increase in mortality rate with age. We base the measurement of the senescence rate on the latter only. One may want to correct the increase in mortality rate on an absolute scale for the absolute level of the mortality rate, for example by $m'(t) / m(t)$. However, as mentioned above, $m'(t) / m(t) = [\ln m(t)]'$. Thus, such a correction renders a measure that is

equal to the increase in mortality rate on a logarithmic scale, equally relative, and equally invalid. Moreover, theoretically, if it is accepted that senescence at the population level is defined as an increase in the risks of disease and death with increasing age and that a population does not senesce if its mortality rate is constant with age,[55,56] it follows that senescence is equally absent in populations with mortality rates that are constant with age, but differ from each other. Nonetheless, when comparing populations, for example the Ghanaian study population and the general population of the USA (Figure 12.3), it remains valuable to compare the increases in their mortality rates with age as well as their mortality rates *per se*.

Others have objected that our method of measuring a population's senescence rate is scientifically incomplete, because it does not link the changes in the population's mortality rate with the biological changes in the senescing bodies of the individuals.[57] This is true for any measure of a population's senescence rate. While senescence at the individual level determines senescence at the population level, the measurement of senescence at the population level cannot always be related directly to senescence at the individual level, for example due to population heterogeneity as explained above. These limitations can be largely overcome with data from cohorts with lifelong follow-up, in homogeneous populations such as animal models, or by means of statistical methods that take into account population heterogeneity. Moreover, it is worthwhile to investigate whether and how the methods for measuring senescence rates from the increase in mortality rate, as proposed here, can also be used to measure senescence in individuals, for example from the decrease in handgrip strength with age.

When comparing the senescence process in different populations — for example between patients on dialysis and patients with a functioning transplant or between western and non-western populations — it seems that one compares chalk and cheese. Only the fittest patients on dialysis are eligible for transplantation. Western and non-western populations differ not only in their lifestyles, but also in their health care systems, climates, and genetics. Still, it is our aim to compare these populations precisely because they differ.[58,59] We make use of the facts that patients on dialysis senesce faster than patients with a functioning transplant and that western populations have developed into more affluent and sedentary societies than non-western populations. To be able to discern which of the differences exactly contribute to the differences in the senescence process, it is necessary to make similar comparisons between other populations.

One of the differences that is inherent to the comparison of western and non-western populations is the great inequality in health care facilities. Consequently, studies of the prevalence of disease in non-western populations are at risk of a survival bias: individuals may die from the disease before it can be detected. Have we found little cardiovascular disease and diabetes mellitus because these diseases are highly lethal in the Ghanaian study population?

Causes of death in this population have been determined by means of verbal autopsy.[50,51] Infectious diseases are the main cause of death and deaths due to cardiovascular disease and endocrine disease are uncommon, accounting for 3% of all deaths and 5% of the deaths with a known cause (Figure 12.2B).[50] In other non-western populations, physical autopsy studies have as well shown that cardiovascular disease is uncommon up to high ages.[60-62] These figures support that cardiovascular disease is verily uncommon in non-western populations.

Implications for biomedical research

For gerontological research it is of quintessential importance to determine and compare senescence rates of populations. The classical measure of the senescence rate, derived from the increase in mortality rate on a logarithmic scale, is extensively used to study the process of senescence. It is employed to compare senescence rates between species and environments and to explain the evolutionary underpinnings of senescence.[63-66] It is applied to animal models to assess whether genetic and environmental interventions, such as dietary restriction, affect the rate of senescence or delay the onset of senescence.[67-73] It is used in human populations to compare senescence rates across calendar years,[42,65,66,74,75] birth cohorts,[66,75,76] and ethnicities.[77] We have, however, demonstrated that senescence rates should not be measured as the increase in mortality rate on a logarithmic, but rather on an absolute scale.[1,8,9]

Our studies have shown that the results and interpretations of studies can be radically different when senescence rates are measured as the increase in mortality rate on an absolute instead of a logarithmic scale. A population with a higher senescence rate compared with another population according to the increase in their mortality rates on a logarithmic scale, can have a lower senescence rate according to the increase in their mortality rates on an absolute scale. Two populations with different senescence rates according to the increase in their mortality rates on a logarithmic scale, can have similar senescence rates according to the increase in their mortality rates on an absolute scale. It is necessary to examine whether and to what extent this is true for previous studies and to reevaluate the interpretations of these studies. For example, dietary restriction is thought to decrease the senescence rate in rodents, since it slows the increase in their mortality rates on a logarithmic scale.[73] However, the effect of dietary restriction on the increase in mortality rate on an absolute scale has not been studied, while it may lead to another conclusion.

Although a logarithmic scale serves the visualisation of age patterns of mortality rates, the widely adopted habit to interpret the slope of their straight lines as the senescence rate should be abandoned. In addition, the closely related assumption that intrinsic mortality due to senescence and extrinsic mortality independent of senescence can be separated should be left. Rather, senescence rates should be presented and judged in their relation to age separately from the age patterns of mortality rates.

Implications for western populations

In western populations, senescence is accompanied by sharp increases in the prevalences of non-infectious diseases such as cardiovascular disease and diabetes. These senescence-related diseases are generally regarded as inevitable consequences of a senescence process that is intrinsic to the human body. Indeed, atherosclerosis is already present in young adults,[78-80] has been found in ancient mummies,[81] and cardiovascular disease and diabetes mellitus are not entirely absent in non-western populations.[60-62]

Still, senescence-related diseases can better be considered as lifestyle-related diseases. Our studies support the notion that the senescence process is not intrinsic and intractable, but malleable and much dependent on the environment.[11,15,16] The essential role of the environment in the causation of senescence-related diseases has been confirmed by others and for other diseases that are attributed to senescence.[82] In the absence of a western lifestyle, cardiovascular disease and diabetes mellitus are uncommon even in the eldest.

From an evolutionary perspective, the diseases that arise during senescence in western populations are, at least partly, attributable to a mismatch between, on one hand, the genetic variants that have been selected during a long history in harsh environments and, on the other hand, the modern affluent environment that has been experienced by only very few generations.[83,84] Prolonged selection of thrifty and proinflammatory genetic variants have bestowed humans with qualities, desires, and impulses that predispose to these diseases, but are not so simply suppressed. Prevention and treatment of senescence-related diseases such as cardiovascular disease and diabetes mellitus will be more successful when they are aimed at improvements of the environment rather than the genetic predisposition.[82,85] If food is less readily available and less energy-rich, physical activity is an everyday habit, and infections may once in a while evoke an inflammatory response, our thrifty and proinflammatory natures are well suited and our senescence process is bettered.

Implications for non-western populations

In non-western populations, senescence is not accompanied by sharp increases with age in the prevalences of non-infectious diseases such as cardiovascular disease and diabetes mellitus because of the absence of a western lifestyle. Instead, infectious diseases dominate non-infectious diseases up to the highest ages. Differences in the environment explain why the inhabitants of these populations senesce in a different way compared with western populations. The question how they senesce remains, however, open to further scrutiny.

Meanwhile, western lifestyles are quickly spreading over the world and only few populations have not yet been pervaded. The emergence of western lifestyles goes hand in hand with the emergence of obesity, dyslipidæmia, hypertension, cardiovascular disease, and diabetes mellitus.[86-88]

Whereas western lifestyles have developed over a few generations in western popula-

tions, it is introduced within a generation in non-western populations. This renders non-western populations at an increased risk of suffering from the diseases that are caused by a western lifestyle because of three reasons. Firstly, these populations have experienced the selective pressures exerted by harsh environments until very recently. Thrifty and proinflammatory gene variants that predispose to these diseases are present in these populations.[89] Secondly, these populations have experienced a harsh environment at low age, when genes are epigenetically tuned to the environment. It has been established that exposure to hunger and infectious diseases early in life increases the risk of cardiovascular disease and diabetes mellitus when these conditions have improved later in life, at least partly through epigenetic mechanisms.[90-93] Thirdly, because of the poor environment, ideals of unhealthy foods, corpulence, and physical inactivity are culturally preserved.[94-97] Accordingly, a western lifestyle is eagerly adopted and its consequences are liked.

The prevention of lifestyle-related diseases by environmental interventions is, therefore, especially urgent in non-western populations where a western lifestyle has recently been or is currently introduced. Unfortunately, most public health policies concerning these regions have remained nearsighted and focus on hunger, infectious diseases, and maternal and child mortality. This is meaningfully exemplified by the current endeavours of the United Nations to formulate Sustainable Development Goals. Out of seventeen proposed goals, only one addresses health directly with the intention to „ensure healthy lives and promote well-being for all at all ages". Out of the thirteen statements, in which this goal is subdivided, only one specifically addresses „non-communicable diseases", together with „mental health and well-being".[98]

Conclusions

In this thesis, we show that a population's senescence rate should not be measured, following the classical method, as the increase in mortality rate with age on a logarithmic scale, but rather as its increase on an absolute scale. We present how this novel method can be applied to both modelled and non-modelled mortality rates. The novel method yields conclusions that are radically different from those provided by the classical method. The novel method also acknowledges that senescence results from an interaction between bodily and environmental factors. This interaction becomes apparent when we compare the senescence process in a non-western population with that in western populations. In some respects, the way of senescence is similar, as handgrip strength and heart rate variability at rest decline similarly with age. The rate of senescence is similar too. In other respects, the way of senescence is different, as cardiovascular disease and diabetes mellitus are uncommon up to the highest ages. This indicates that the senescence process can be modulated through the environment and lifestyle. We suggest that the senescence process can be ameliorated when environmental interventions unite the best of both worlds: a non-western lifestyle, which is nutritionally thrifty and physically active, together with western standards of public health.

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