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SUMMARY

As humans grow older, the structures and functions of their bodies deteriorate. This process is referred to as senescence. In human populations, senescence leads to an increase in the risks of dysfunction, disease, and death with chronological age. In this thesis, we measure senescence in human populations from the increase in these risks.

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. Classically, it is measured as the increase in mortality rate with age on a logarithmic scale. In Chapter 3 we test this measurement by applying it to patients with end-stage renal disease on dialysis treatment, who are clinically known to suffer from accelerated senescence, and we compare them with patients with a functioning kidney transplant and the general population from which these patients originate. We demonstrate that the classical method to measure a population's senescence rate is inaccurate, since it attributes lower senescence rates to the patients on dialysis than the patients with a functioning transplant and the general population. We demonstrate that a novel method, which measures a population's senescence rate through the increase in mortality rate on an absolute scale, is valid, since it attributes the highest senescence rates to the patients on dialysis. We explain how senescence rates can be calculated according to the novel method using the derivative function of the Gompertz model. In Chapter 4 we demonstrate how the same method can be applied non-parametrically without modelling mortality rates. This overcomes the disadvantages of the Gompertz model and other models of the age pattern of a mortality rate. Since it is of quintessential importance for gerontological research to accurately determine and compare senescence rates of populations, senescence rates should not be measured as the increase in mortality rate on a logarithmic, but rather on an absolute scale. As we show, both methods can yield radically different results and interpretations.

The classical method to measure a population's senescence rate through the increase in mortality rate on a logarithmic scale is based on the assumption that mortality is caused by two independent mechanisms: intrinsic mortality would result from the body's senescence unrelated to the environment, while extrinsic mortality would result from environmental hazards unrelated to the body's senescence. In Chapter 5 we explain that the novel method to measure a population's senescence rate through the increase in mortality rate on an absolute scale is inconsistent with this assumption. Moreover, we show that allegedly intrinsic and extrinsic mortality have an exponentially increasing age pattern in common. Theories of senescence as well as epidemiological and biological data indicate that stressors from within the body and from its environment cause senescence and death in interaction. Together, we conclude that the roles of the body and its environment in the causation of senescence cannot be separated. Reversely, the senescence process depends on the characteristics of both the body and its environment.

In Part II of this thesis we investigate how senescence can be measured through the increase in morbidity with age in a traditional rural African population without a western lifestyle and thus be compared with the senescence process in western populations. In Chapter 7 we describe that this population is enriched with genetic variants associated with a proinflammatory immune response, probably due to the high burden of infectious diseases. It has been proposed that inflammation plays an essential role in the causation of senescence and senescence-related diseases. In this population, these genetic variants are associated with a high handgrip strength, which is regarded to indicate a low biological age.

In Chapter 8 we investigate whether handgrip strength predicts mortality in the traditional African population as it does in western populations. Although handgrip strength depends on body mass index, it declines with age and predicts mortality independently of socioeconomic, nutritional, and cardiovascular status. Handgrip strength functions as a measure of biological age and senescence in this non-western as in western populations.

In Chapters 9 and 10 we document that cardiovascular disease — including coronary arterial disease, peripheral arterial disease, and atrial fibrillation — and diabetes mellitus are rare up to the highest ages, whereas these diseases dominate the senescence process in western populations. Meanwhile, risk factors of cardiovascular disease and diabetes mellitus — including obesity, dyslipidæmia, and hypertension — are absent or uncommon. Inflammation alone appears to be insufficient for these diseases to occur. Because the risk factors are closely related to a western lifestyle, diseases such as cardiovascular disease and diabetes mellitus are likely to develop during senescence as a consequence of a western lifestyle.

In Chapter 11 we study the associations of heart rate and heart rate variability at rest with handgrip strength and mortality in the traditional African population. While heart rate is dependent on cardiovascular risk factors and is associated with neither, heart rate variability declines with age and is associated with handgrip strength and mortality independently of these risk factors and similarly to western populations. Heart rate variability, but not heart rate, reflects biological age and senescence across different environments with different lifestyles.

The way of senescence in this non-western population is partly similar and partly very different as compared with western populations. At the same time, the rate of senescence, as measured as the increases in mortality rate with age, is similar in both types of populations. This exemplifies that senescence depends on the interaction between bodily and environmental factors and 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 together with western standards of public health.