Chapter 8

Intrinsic and extrinsic mortality reunited

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Abstract

Intrinsic and extrinsic mortality are often separated in order to understand and measure aging. Here we show that the age patterns of allegedly intrinsic and extrinsic mortality are similar. We argue that aging and death can be better explained by the interaction of intrinsic and extrinsic risk factors than by classifying mortality itself as being either intrinsic or extrinsic. Therefore, scientific methods, clinical reasoning, and public health policies should not be founded on the partitioning of intrinsic and extrinsic mortality, but account for the tight interaction between intrinsic and extrinsic risk factors.

Introduction

To understand and measure how ageing leads to an increase in the rate of mortality, many clinicians and scholars separate intrinsic and extrinsic mortality. They envision intrinsic mortality 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 ageing. 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 ageing[1-3]. This assumption is often made implicitly. However, while the separation of intrinsic and extrinsic mortality has far-reaching consequences for biomedical research, clinical practice, and public health, we challenge that this separation has a scientific basis.

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[4]. Rather, the effects of genes are moderated by the environment and vice versa[5]. Disease and death are not either genetic or environmental, but of mixed genetic and environmental origin[6]. Yet, little attention is given to gene-environment interaction in the context of ageing[4]. Biomedical disciplines are in need of a likewise fundamental understanding of the interaction between intrinsic and extrinsic causes of ageing.

Different classifications of intrinsic and extrinsic mortality have been proposed[1-3], but the separation of intrinsic and extrinsic mortality itself has never been submitted to formal testing. As an empirical test, we compare the age patterns of typical examples of allegedly intrinsic and extrinsic mortality over age. If a distinction can be made, the risk of intrinsic mortality due to ageing is expected to increase over age, while the risk of extrinsic mortality due to environmental hazards is expected to be largely constant over age.

Intrinsic and extrinsic mortality display similar age patterns

We derived age- and cause-specific mortality rates from the European Detailed Mortality Database of the World Health Organization for 31 European countries and Israel in 2009 or 2010. As our focus is on the ageing process, we excluded ages below 10 years, at which congenital, birth-related, and developmental disorders are dominant. According to usual classifications[1-3] we included as typical examples of intrinsic mortality death due to ischaemic heart disease (ICD-10 codes I20-I25), diabetes mellitus (E10-E14), and cancer (C00-C97) and included as typical examples of extrinsic mortality death due to infectious diseases (A00-B99), 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).

Figure 1 shows the age patterns of mortality rates for allegedly intrinsic and extrinsic mortality. Rates of intrinsic mortality increase over age to a maximum at the highest age (left panels). Rates of extrinsic mortality increase over age in a similar manner (right panels).

Because disease is a major risk factor of death, we compare the age patterns of incidence rates for the same typical examples of allegedly intrinsic and extrinsic disorders. For this, we derived age- and cause-specific hospital discharge rates from the European Hospital Morbidity Database of the World Health Organization for 26 European countries and Israel in 2008, 2009, or 2010.

Figure 2 shows the age patterns of incidence rates of allegedly intrinsic and extrinsic disorders. Incidence rates of intrinsic disorders increase over age to a maximum at the near-highest age (left panels). Incidence rates of extrinsic disorders increase similarly over age to a maximum at the highest age (right panels).

Gene-environment interaction in the causation of ageing

The human body is exposed to various stressors that originate within and outside the body. During life, the repetitive exposure to these stressors leads to accumulation of permanent damage, which leads to dysfunction, disease, and ultimately death[6,7]. The various damages that have been acquired at younger ages increase the body's vulnerability to be subsequently damaged by stressors from its genome or environment. As ageing amounts to the increasing risk of disease and death, ageing is a consequence of the accumulation of damages from genetic as well as environmental sources[7,8]. For example, ageing is partly attributed to mutations of the DNA, which are induced by spontaneous chemical reactions, replication errors, metabolic waste products, radiation, and viruses. These mutations impair the DNA's repair function, decrease its resistance to further mutations caused by intrinsic and extrinsic stressors, and increase the risk of disease and death[9]. Ageing depends on the interaction between a genetic susceptibility to damage and the damage caused by genetic and environmental stressors, leading to an increase in susceptibility to further damage from both genetic and environmental stressors. This is reflected by our finding of similar increases over age for different types of mortality and morbidity.

Epidemiological and biological data support that ageing is a result of the interaction between intrinsic and extrinsic stressors. Ischaemic heart disease, diabetes mellitus, and cancer are typically regarded as determined by intrinsic ageing, 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[10]. These environmental hazards affect the structure and functioning of the genome and are required for the development of disease[8,9]. Even the accelerated bodily deterioration caused by well-defined genetic substrates as in Huntington's disease is influenced by the environment[11]. As a consequence, environmental interventions can prevent or postpone ischaemic heart disease, diabetes mellitus, and cancer[12-14].

Infectious diseases, accidents, and natural disasters require environmental risk factors, but cannot be uncoupled from the body's vulnerability that increases over age. Ageing of the immune system increases the risk of infectious diseases[15]. 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[8,16]. Commensal and infectious microorganisms

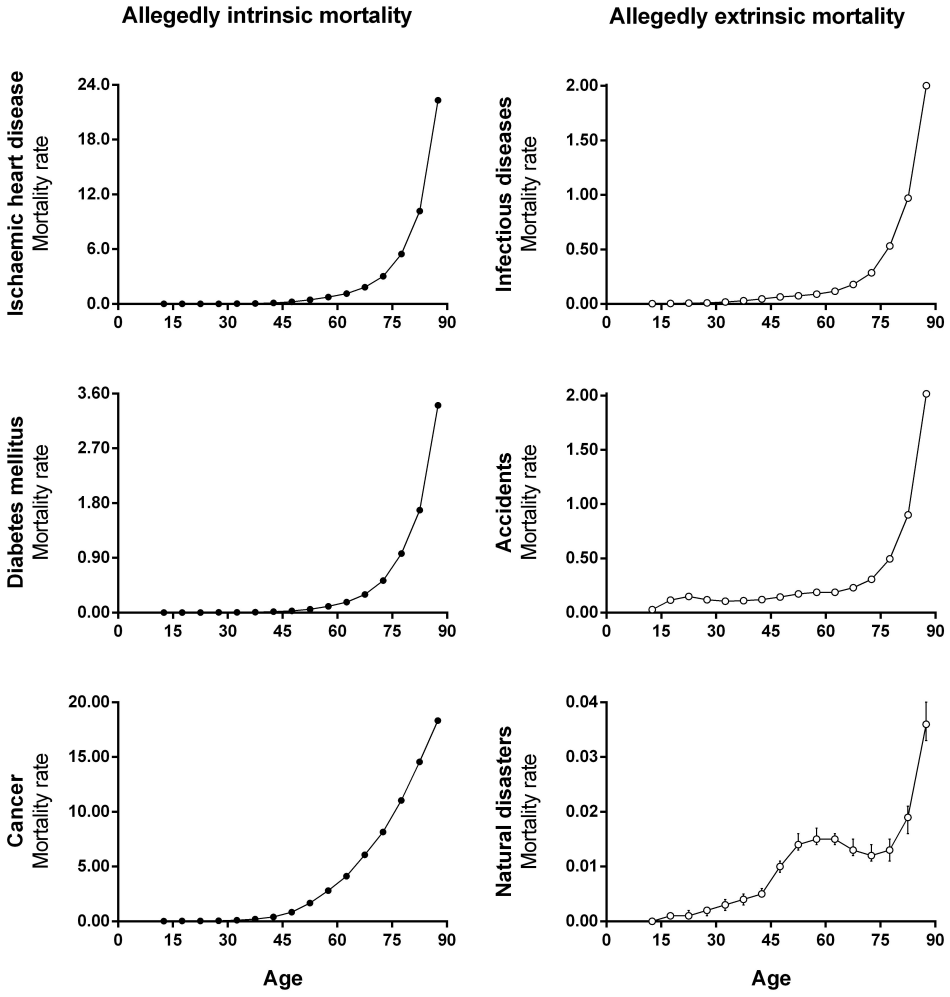

Figure 8.1: **Age patterns of mortality rates for typical examples of allegedly intrinsic mortality due to ageing and extrinsic mortality due to the environment.** Mortality rates are given as number of deaths per 1000 person-years; ages are given as years.

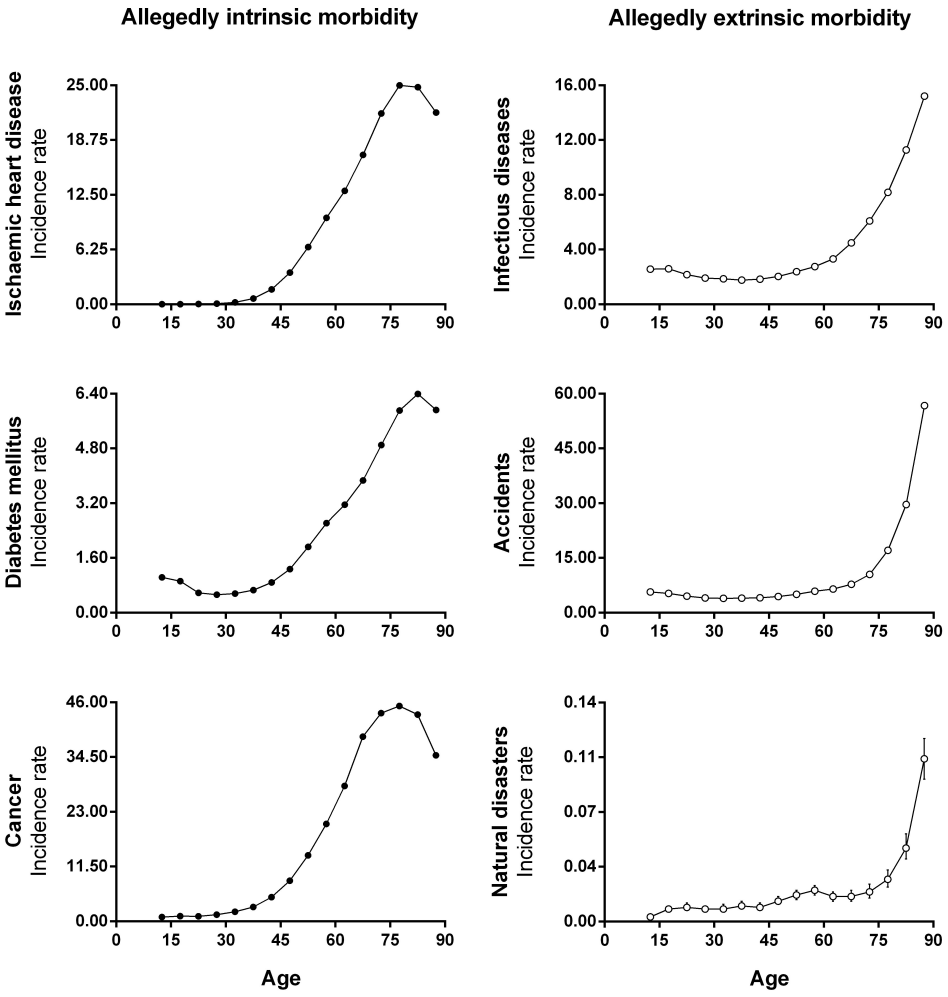

Figure 8.2: **Age patterns of incidence rates for typical examples of allegedly intrinsic disorders due to ageing and extrinsic disorders due to the environment.** Incidence rates are given as number of hospital discharges per 1000 person-years; ages are given as years.

can induce or prevent diseases attributed to ageing, including autoimmune disease, cardiovascular disease, neuropsychiatric disease, and cancer[16]. Even the risk of being affected by seemingly fully stochastic hazards is age-dependent. Sensory, cognitive, and executive dysfunctions, disability, and multimorbidity that accumulate over age predispose to burns, chokes, falls, traffic accidents, and other environmental hazards[17-19].

Relevance to biomedical research, clinical practice, and public health

In biomedical research, intrinsic and extrinsic mortality are separated when measuring the ageing process. Mathematical models are used in such a manner that distinct parameters account for intrinsic and extrinsic mortality[20]. The intrinsic parameter describes an increase in mortality over age that adds to an age-independent risk of dying described by the extrinsic parameter. These models are applied to interpret the effects of experimental interventions as affecting either the rate of ageing or the age-independent risk of dying[21]. Previously, such a biological interpretation of the mathematical parameters has been criticised[22]. The present study reinforces this critique, demonstrating that such a mathematical separation of intrinsic and extrinsic mortality is biologically unfounded. As the measurement of the rate of ageing is essential for research on ageing, alternative approaches are needed to measure this rate correctly by taking into account both allegedly intrinsic and extrinsic mortality as components of ageing[22].

In clinical reasoning, disease and death are classified as intrinsic or extrinsic in an attempt to better understand the ageing process. Disorders such as cardiovascular disease, diabetes mellitus, and cancer are considered as intrinsically progressing with increasing age, while disorders such as infectious diseases, accidents, and natural disasters are considered as environmental. The underlying pathogenic processes are sorted similarly. In dermatology, for example, the deteriorating synthesis of interstitial proteins is attributed to intrinsic ageing, while sun-induced damage is thought to constitute extrinsic environmental damage[23]. However, the damage in the skin that is accrued with increasing age is due to both the deteriorating protein synthesis and sunshine.

When intrinsic mortality due to ageing and extrinsic mortality due to the environment are separated, ageing is accepted as an inevitable side effect of increasing age while environmental hazards are taken as bad luck. In contrast, when genetic and environmental are acknowledged to interact tightly in the causation of ageing, disease, and death, new perspectives arise with both a bad and a good outlook. The bad news is: all mortality is related to ageing. The risk of allegedly extrinsic mortality increases over age similarly as compared with allegedly intrinsic mortality, because they are equally attributable to degeneration of the human body's structures and functions. Consequently, older people are most vulnerable to be struck by environmental hazards. Prevention of mortality due to infectious diseases, accidents, and natural disasters should particularly aim at protecting the frail elderly. Alike, the aged skin should be protected as it is easily bruised or sunburnt.

The good news is: all mortality is related to the environment. The risk of allegedly intrinsic mortality increases over age, but is just as well dependent on environmental hazards. A proper understanding of the tight interaction between the intrinsic and extrinsic components recognises that ageing is not inevitable, but malleable through the environment. Especially lifestyle interventions seem effective, such as limiting sun exposure to delay ageing of the skin. Knowledge on this interaction leads the way to identify other environmental risk factors that cause ageing and can be targeted to prevent ageing[24]. To reach this goal, intrinsic and extrinsic mortality should not be separated in mathematical models when measuring ageing, in clinical reasoning when explaining ageing, and in public health when allocating prevention and intervention.

Key messages

1. Mortality is often partitioned into intrinsic mortality due to ageing and extrinsic mortality due to environmental hazards.
2. This classification of intrinsic and extrinsic mortality is ill-defined and misleading.
3. Empirical data show that the risks of intrinsic and extrinsic mortality increase similarly over age.
4. Genetic and environmental stressors interact to cause ageing and death.
5. The separation of intrinsic and extrinsic mortality should not be incorporated in mathematical models when measuring ageing, should not be applied in clinical reasoning when explaining ageing, and should not be used in public health when allocating prevention and intervention.

Contributors and sources

The authors have extensively investigated and written on the causative mechanisms underlying ageing and on the measurement of ageing by age patterns of mortality. JJEK and MJW study these themes as PhD students. JJEK conceived this study. JJEK, MJW, DvB, and RGJW designed this study. JJEK collected and analysed the data. JJEK, MJW, and DvB drafted the manuscript. All authors contributed to the interpretation of the data and to the intellectual content and revision of the manuscript. All authors approved the final manuscript. RGJW is the guarantor. Data were derived from the European Detailed Mortality Database and the European Hospital Morbidity Database, both provided by the World Health Organization's Regional Office for Europe through:
http://data.euro.who.int/en/data-and-evidence/databases.

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