One Rate of Aging for All Individuals? Statistical Evidence from Cause-of-Death Data
(Extended Abstract)

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Abstract

Vaupel's hypothesis [1] suggests that the rate of aging, defined as the relative derivative of the baseline risk of dying, might be a biological constant for every species. We test this hypothesis on human mortality data by estimating the rates of aging by cause of death.

Does every human being age at the same rate? Vaupel's hypothesis that *"except for individuals with accelerated aging disorders, all other humans have a similar and perhaps, essentially the same, rate of increase in mortality with age"* [1] questions whether the *rate of aging* is a biological constant invariant across individuals and over time. What does the *rate of aging* mean? First, when we study *aging*, we apply a survival model that captures mortality patterns at *adult* ages. Second, in accordance with [1], we define the *rate of aging* as the *relative derivative* of the *baseline* hazard of death in this survival model. Vaupel's hypothesis addresses the *individual rate* of aging (iRoA) as opposed to the rate of aging for the entire *population* (pRoA). The latter equals the relative derivative of the *population's* hazard of death. The pRoA, addressed by demographers as the *life-table aging rate* (LAR) [2, 3], is a different characteristic that varies age-wise according to population's composition [4, 3, 5].

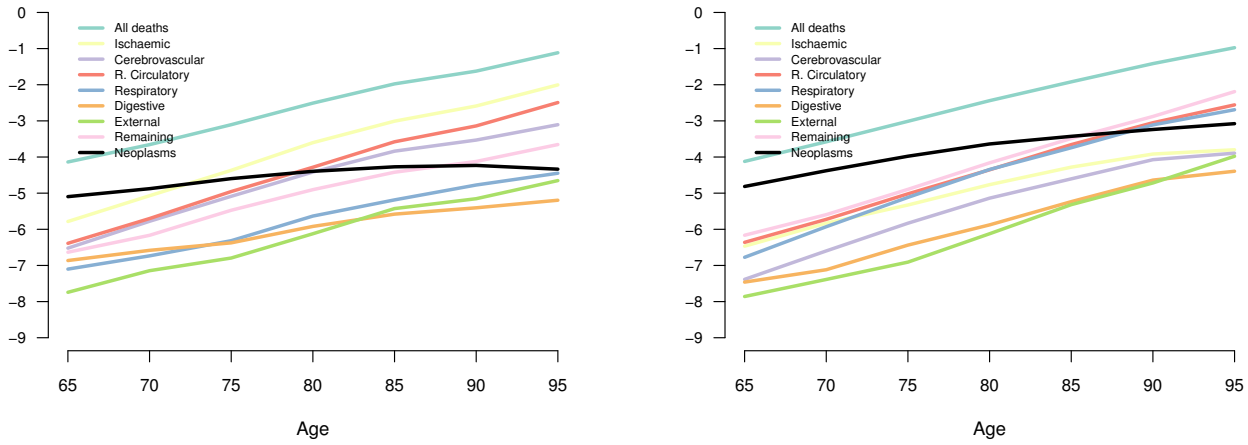
Demographers view populations as a heterogeneous mixture of individuals that share the same baseline hazard of death, to which they are susceptible in a different (random) way. By assumption [6, 7], the baseline hazard $\mu(x)$ at age x ($x = 0$ refers to some adult age) follows a Gompertz curve $\mu(x) = ae^{bx}$, where a is the level of mortality at the starting age, and b is the relative derivative of $\mu(x)$, i.e. the iRoA. That is why we will call Vaupel's hypothesis [1] the b-hypothesis.

Individual susceptibility can be reflected in different individual a's (relative risk models), in different b's (accelerated life models), or in both. However, recent evidence for the existence of a human mortality plateau [8] speaks in favor of relative risks only, as accelerated-life models lead to a vanishing hazard of death [9, 10]. Let a random variable Z, called *frailty* [7], capture individual susceptibility. Then, in relative risk models the hazard of death $\mu(x \mid z)$ for individuals with frailty z is given by $\mu(x \mid z) = z\,\mu(x)$. An additional standard [7] and theoretically justified [10, 11] assumption about frailty Z, being gamma-distributed with a unit mean and γ variance, leads to the widely used *gamma-Gompertz* (ΓG) *frailty model*.

One way to check the b-hypothesis is to compare the iRoA for individuals belonging to different subpopulations. Cause-of-death (COD) data offer such stratification and, if properly aggregated, provide large sample sizes that facilitate meaningful statistical analysis. Can we speak of one and the same rate of aging across all different causes, or is each cause associated with its own iRoA? We use *death counts*, grouped by major COD (according to the ICD 10 revision) from the World Health Organization (WHO) Mortality Database, and *exposures* from the Human Mortality Database (HMD). We study data, arranged by 5-year age groups, the last one covering ages 95+, in the 1999-2009 period for the current life-expectancy leader Japan and three types of countries: 1) with a high life expectancy in the 1950s that witnessed a deceleration thereafter (Sweden and the Netherlands), 2) with a lower life expectancy in the 1950s followed by a steady increase afterwards that lead to overtaking countries from the previous group (Spain), and 3) with a low life expectancy in the 1950s and a low rate of increase afterwards (Hungary). Following the WHO recommendation [12] to avoid uncertainty that comes from changes and updates in the classification system, we took advantage of data for *underlying cause of death*, i.e., the disease or injury which initiated the sequence

of events that lead to death. We looked at major COD groups: (1) neoplasms, (2) ischaemic heart diseases, (3) cerebrovascular diseases, (4) remaining diseases of the circulatory system, (5) diseases of the respiratory system, (6) diseases of the digestive system, (7) external causes of death, and (8) remaining causes of death. In all selected countries the ill-defined COD constituted less than 3.5% of all deaths after age 65 over the study period, which is a sign of good data quality [13].

Figure 1: Age-specific log-death rates for Hungarian females (left) and Dutch males (right) in 2009



We estimate the iRoA b for each chosen country (Japan, Sweden, Netherlands, Spain, and Hungary), for each single year in the 1999-2009 period, and for each gender separately by fitting a ΓG model, starting from age 65. Our time-axes choice reflects the fact that (1) after age 65 background mortality, captured usually by a Makeham term [14], becomes negligible, (2) 1999 was the first year when all five countries used ICD 10 and 2009 was the last year with available COD data for all selected countries. Figure 1 presents observed age-specific death rates by COD on a log-scale for Hungarian females and Dutch males. While patterns across different COD look all linear, the slopes of certain COD (especially neoplasms) are smaller than the slopes for all other COD, including the one by all COD.

Table 1: Estimated iRoA b for Spanish females and Swedish males with the associated standard errors by cause of death for the year of 2009

	Spanish Females		Swedish Males	
Cause of Death	iRoA	Std Error	iRoA	Std Error
Neoplasms	0.080	0.00137	0.096	0.00284
External	0.113	0.00441	0.114	0.00686
Digestive	0.143	0.00293	0.100	0.00793
All Causes	0.144	0.00066	0.119	0.00140
Ischaemic	0.163	0.00233	0.121	0.00310
R. Causes	0.173	0.00138	0.135	0.00340
Cerebrovascular	0.182	0.00227	0.167	0.00528
R. Circulatory	0.182	0.00173	0.162	0.00408
Respiratory	0.184	0.00231	0.153	0.00564

Figure 2 presents the estimated yearly iRoA b for Spanish females and Swedish males. While the b for females seems to be higher across all COD, the rates of aging by COD seem to form three groups (see also Table 1): 1) cerebrovascular diseases, remaining diseases of the circulatory system, respiratory system diseases, and remaining causes of death share a rate of aging around 0.18 for females and 0.16 for males; 2) ischaemic heart diseases and digestive system diseases seem to have an iRoA close to b by all COD (between 0.13 and 0.16 for females and between 0.10 and 0.12 for males); 3) neoplasms (around 0.08 for females and 0.09 for males) and external COD (between 0.08 and 0.11 for females and around 0.105 for males) seem to

have a much lower b.

Figure 2: Individual rate of aging by cause of death for Spanish females (left) and Swedish males (right)

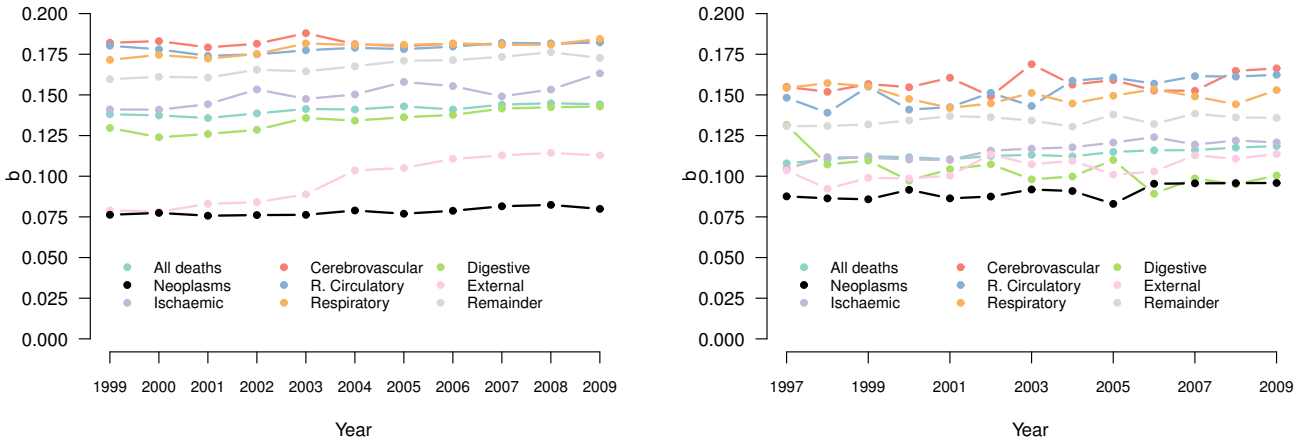


Table 2 shows the estimated iRoA b for Spanish females and Swedish males with the associated standard errors. We observed similar patterns when fitting the ΓG model to all other countries. The lower b for neoplasms might result from the fact that (1) cancer is often a consequence of earlier behavioral patterns (e.g., smoking increases lung cancer changes), (2) cancer mortality depends on the stage, at which the disease gets diagnosed, which affects age-specific cancer mortality rates, (3) different types of cancer witness different mortality patterns – by grouping all of them together, we are getting an "average" cancer iRoA. As a result the patterns of cancer-related mortality differ from the ones of the COD in the first two groups (see [15] for a thorough discussion). External COD reflect usually accident-related mortality, to which it might be less intuitive to attribute a measure like the rate of aging.

Table 2: Estimated iRoA b for Spanish females and Swedish males with the associated standard errors

	Spanish Females		Swedish Males	
Year	iRoA	Std Error	iRoA	Std Error
1999	0.138	0.00067	0.112	0.00156
2000	0.137	0.00068	0.111	0.00156
2001	0.136	0.00068	0.110	0.00153
2002	0.139	0.00067	0.112	0.00151
2003	0.141	0.00065	0.113	0.00153
2004	0.141	0.00067	0.112	0.00152
2005	0.143	0.00066	0.115	0.00148
2006	0.141	0.00068	0.116	0.00148
2007	0.144	0.00067	0.116	0.00144
2008	0.145	0.00066	0.118	0.00143
2009	0.144	0.00066	0.119	0.00140

The estimated COD-specific b's across males and females in Japan, Sweden, Netherlands, Spain, and Hungary show that the iRoA is probably not exactly the same for human subpopulations, stratified by COD. Nevertheless COD-specific iRoA's seem to stay constant over calender time in each of the studied countries. Factors that could have influenced iRoA estimates $\hat{b}$ include: (1) data format (data by 5-year age groups, which provide less detail than data by single age), (2) data credibility (death certificates do not always reflect the actual COD, especially at the oldest ages), (3) possible existence of competing risks (the ΓG model that we fit to each separate COD does not account for competing risks), (4) existence of "triggers" for specific COD (e.g., smoking for lung cancer) that result in premature deaths for a fraction of the population at risk (e.g., smokers) and affect the estimate for the associated iRoA. As a result, we might

not have enough evidence against the b-hypothesis unless we study the iRoA within each COD by stratifying the associated subpopulation once again according to associated risk factors (e.g., smokers vs nonsmokers for cancer or alcohol consumption for diseases of the digestive system). Grouping death counts according to a different COD choice might also lead to iRoA's in favor of a common b. We decided to work with the major COD to provide for each country large enough sample sizes in each age group by every COD.

The estimation of iRoA, defined as the relative derivative of the baseline hazard, across different human subpopulations, stratified according to different factors, can shed more light onto the b-hypothesis. Zarulli [16] studied the effect of mortality shocks (Ukrainian famine, imprisonment of Australians on Java during WWII) on the respective iRoA. Estimated b's speak in favor of the b-hypothesis in the Australian prisoners-of-war case, but not in the case of the Ukrainian famine.

Evidence of the iRoA's across COD can serve as a starting point towards testing the b-hypothesis. Statistical analysis of mortality data for different human subpopulations, e.g. comparing individuals with smoking habits against non-smokers, obese against non-obese, etc., will provide further evidence for or against the b-hypothesis. Evolutionary biology could provide further insight: is it optimal for a species, from an evolutionary perspective, to have all of its members sharing the same b?

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