

# The rate of aging: the rate of deficit accumulation does not change over the adult life span

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**Abstract** People age at different rates. We have proposed that rates of aging can be quantified by the rate at which individuals accumulate health deficits. Earlier estimates, using cross-sectional analyses suggested that deficits accumulated exponentially, at an annual rate of 3.5 %. Here, we estimate the rate of deficit accumulation using longitudinal data from the Canadian National Population Health Survey. By analyzing age-specific trajectories of deficit accumulation in people aged 20 years and over ( $n = 13,668$ ) followed biannually for 16 years, we found that the longitudinal average annual rate of deficit accumulation was 4.5 % ( $\pm 0.75$  %). This estimate was notably stable during the adult life span. The corresponding average doubling time in the number of deficits was 15.4 (95 % CI 14.82–16.03) years, roughly 30 % less than we had reported from the cross-sectional analysis. Earlier work also established that the average number of deficits accumulated by individuals ( $N$ ), equals the product of the intensity of environmental stresses ( $\lambda$ ) causing damage to the organism, by the average recovery time ( $W$ ). At the individual level, changes in deficit accumulation can be attributed to both changes in

environmental stresses and changes in recovery time. By contrast, at the population level, changes in the number of deficits are proportional to the changes in recovery time. In consequence, we propose here that the average recovery time,  $W$  doubles approximately every 15.4 years, independently of age. Such changes quantify the increase of vulnerability to stressors as people age that gives rise to increasing risk of frailty, disability and death. That deficit accumulation will, on average, double twice between ages 50 and 80 highlights the importance of health in middle age on late life outcomes.

**Keywords** Deficit accumulation · Longitudinal analysis · Aging · Frailty · Recovery time · NPHS

## Introduction

People age at different rates, but how to quantify rates of aging is an important challenge. We have proposed that the rate of aging in individuals and populations is estimated by the rate of health deficit accumulation. Health deficits in this account of aging are broadly defined, and include biological and clinical characteristics, commonly found in most clinical and epidemiological databases (Mitnitski et al. 2001; Rockwood and Mitnitski 2007) and even in laboratory test records (Howlett et al. 2014). The resulting “frailty index” is based on a simple count of deficits, expressed as the ratio of the deficits present in the individual to the total number of available deficits counted (Mitnitski

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et al. 2001; Woo et al. 2006). When the frailty index (FI) is elevated compared with others of the same age, it suggests an increase in the vulnerability to stresses that defines frailty (Clegg et al. 2013).

In 2013, we further suggested that the origin of deficit accumulation lies in the complex interplay between stochastic damage to the organism, arising from both the internal and the external environment, and its ability to repair/sustain such damage. In so doing, we worked with Little's Law ( $N = \lambda W$ ), restated here so that  $N$  is the average number of deficits,  $\lambda$  is the intensity of environmental stresses, and  $W$  is the average (net) recovery time (Mitnitski et al. 2013, 2015). During the adult lifespan, the number of deficits accumulated in Canadians changes by an order of magnitude, and triples in the last three decades of life, after the age of 65 (Mitnitski et al. 2013; Mitnitski and Rockwood 2015). The quantitative estimates of the changes in the number of deficits were obtained from cross-sectional analysis. These showed that the annual rate of deficit accumulation was about 3 %, an estimate obtained by using the exponential approximation of the age-specific deficit (frailty) trajectories (Mitnitski et al. 2005; Rockwood et al. 2011). These estimates, first reported for people over age of 65 (Mitnitski et al. 2005) varied depending on the data, generally between 2 and 4 % (e.g., Shi et al. 2011, Harttgen et al. 2013). This corresponds to doubling time in the number of deficits between 17 and 34 years. Our most recent estimate for the whole of the adult lifespan gave the value of 3.5 %, towards the upper part of the prior range (Mitnitski et al. 2013). As longitudinal data have become available, we have used such data to model transitions between numbers of deficits up to 16 years (Mitnitski et al. 2012). Of note, the individual trajectories of the number deficits are volatile, showing great stochastic variations (Mitnitski et al. 2012, 2015). At the level of population, however, under the assumption that the damage rate is fairly constant, it appears that fluctuation in the number of deficits can be attributed to the changes in recovery time (Mitnitski et al. 2013). In consequence, although the number of deficits will increase each year, the rate at which the deficits increase would be constant, reflecting a constant degree of lengthening in the recovery time with age.

In this paper, we estimate the rates of changes in the number of deficits in the National Population Health Survey (NPHS) across the adult lifespan, using

longitudinal components of the NPHS. In particular, we wanted to address whether the rate of deficit accumulation changes over the adult lifespan (after about 20 years of age) or remains the same.

## Methods

We used data from the NPHS, a large Statistics Canadian study which began in 1994/95 and was conducted in nine biannual cycles from 1994 to 2008. Self-reported information was gathered at baseline and every 2 years, as was vital status (Singh et al. 1994). Of 13,668 participants aged between 20 and 92 at baseline, 54 % were women. Thirty-nine self-reported variables (referred to as “deficits”, and dichotomized for this purpose) including medical conditions, disabilities and health history were used to calculate each individual's health status, combined in a FI (Mitnitski et al. 2013, Supplementary file). Data were coded so that the presence of a deficit was represented by a “1”, and the absence of the deficit by “0”. For any individual, their FI represents the number of deficits present, divided by 39 (the number of deficits considered). Note that even though the theoretical range of the FI is 0 (no deficits) to 1 (all 39 deficits present), in almost every circumstances—including patients admitted with acute medical problems (Evans et al. 2014; Dent et al. 2014), the limit to the FI is seen at an upper value of  $\sim 0.7$  (Rockwood and Mitnitski 2006; Bennett et al. 2013; Armstrong et al. 2014). Here we report the results using the FI, rather than the deficit count, so as to facilitate comparison with other studies (past and future) which typically will employ varying numbers of deficits.

## Statistical analysis

The age-specific trajectories of the number of deficits were fitted using the exponential function; the parameters were estimated using least squares regression. The statistical significance level was set to  $p = 0.05$ .

## Ethics

The Statistics Canada ethics review process approved the NPHS, and participants provided oral informed consent. Approval for these additional analyses came

from the Research Ethics Committee of the Capital District Health Authority, Halifax, Nova Scotia, Canada.

## Results

In Fig. 1 (Panel a), age-specific cross-sectional average trajectories for the 9 cycles of the NPHS are shown, over 16 years of follow-up, repeated every 2 years. All follow-up trajectories virtually coincide. The solid line represents the average exponential fit, and demonstrates slope parameter  $b_C = 0.035$  (95 % CI 0.033, 0.036) and intercept =  $-4.163$  (95 % CI  $-4.430$  to  $-3.895$ ). In Fig. 1 (Panel b), longitudinal 16 year trajectories (averaged at each age at baseline) are shown overlaid with the average cross-sectional age-specific trajectory (dashed line).

Eight longitudinal average trajectories are exemplified in Fig. 1, Panel a for 22, 31, 41, 52, 62, 72, 80, and 92 baseline ages. Longitudinal 16-year trajectories were fitted at each age by exponential curves. The slope parameter for each baseline age are shown in Fig. 2 (Panel a), and the histogram of the slopes is shown in Fig. 2 (Panel b). The average longitudinal slope  $b_L$  is 0.045 (95 % CI 0.038–0.052) shown by the dashed line, along with the cross-sectional slope = 0.035 (the solid line). There is no evidence of a secular trend in the slope parameter. For example, the mean slope for people younger than 60 years at baseline was 0.043 (95 % CI 0.044–0.050) and the slope parameter for those older than 60 years was

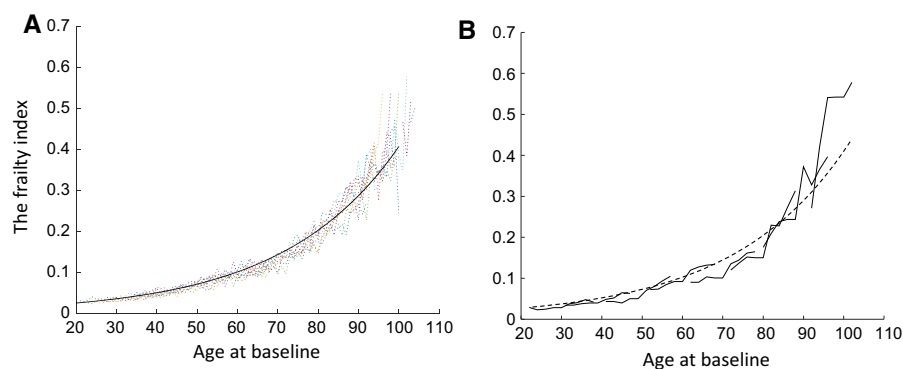
0.047 (95 % CI 0.041–0.045). The histogram of the longitudinal slope is presented in Fig. 2 (Panel b).

The doubling time (the period of time required for a the number of deficits to double is an inverse function of the slope),  $T_d = \ln(2)/b$ . Using the longitudinal estimates, the doubling rate (the time for the number of deficits to increase by a factor of two) is calculated as  $T_d = 15.3$  (95 % CI 14.82–16.03) years, whereas the cross-sectional estimate corresponds to  $T_d = 20$  years (95 % CI 19.07–20.59). Note that the ratio of doubling of the mean FI score to time is constant across the life span, even though the number of deficits accumulated in any year accelerates with age.

## Discussion

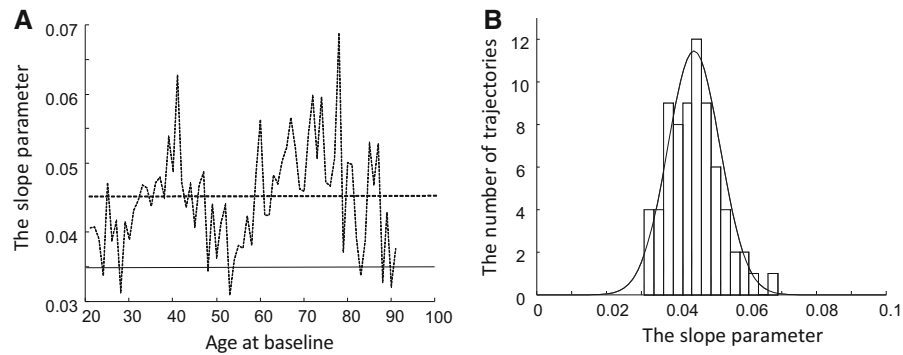
In this paper, we estimated the rate of deficit accumulation in a representative sample of Canadians across the adult life span from age 20 years. Using the baseline and eight biannual follow-up cycles of longitudinal data, we found that the annual rate of changes equals 4.5 % (3.75–5.25). This result, obtained over 16 years of follow-up, was significantly higher than the 3.5 % (3.3–3.7) rate of annual deficit accumulation previously estimated by us from cross-sectional analyses from the same dataset. The new doubling time estimate of 15.4 (14.8–16.0) years, significantly less than the estimate from the cross-sectional data, which was 20 years.

The ability to represent the rate of deficit accumulation by a single parameter (i.e., the annual rate or the



**Fig. 1** The dynamics of deficit accumulation. **a** cross-sectional age-specific trajectories of deficit accumulation for 9 consecutive cycles of the NPHS. **b** longitudinal age-specific trajectories of deficit accumulations for individuals at the same

baseline ages (*solid lines*) shown for selected 8 baseline ages 22, 31, 41, 52, 62, 72, 80, and 92, overlaid with the cross-sectional average trajectory (*dashed line*)



**Fig. 2** The distribution of the longitudinal slope of deficit accumulation at each baseline age. **a** the slope as a function of baseline age. The mean values of the longitudinal slope is shown

by the *dashed line*, the mean value of the cross-sectional slope is shown by the *solid line*. **b** the histogram of the longitudinal slope overlaid with the normal curve

doubling time) is a consequence of the exponential approximation of the kinetics of deficit accumulation. While we and others reported an exponential pattern of increase in deficit accumulation using cross-sectional analyses (Mitnitski et al. 2005, 2013; Rockwood et al. 2011; Shi et al. 2011; Harttgen et al. 2013), other groups have indicated some leveling off, at older ages, of the age-specific rates at which people accumulate deficits (García-González et al. 2009; Kulminski et al. 2007; Gu et al. 2009). Gu et al. (2009) suggested a logistic fit of the FI to account for saturation of its values at advanced ages. It remains to be seen if this decline is an artifact that might be explained by there being just a small number of people at the oldest ages available for study. Even so, the pattern of deficit accumulation is generally convex, showing age-related acceleration (Mitnitski et al. 2005, 2013, 2015; Rockwood et al. 2011; Kulminski et al. 2007; Theou et al. 2014). Such a nonlinear pattern implies that deficits do not accumulate independently of each other (Taneja et al. 2014).

Our results should be interpreted with caution. The deficit accumulation approach to quantifying aging also extends to characteristics at different levels from the subcellular to the organism (Howlett and Rockwood 2013). Likewise, deficits span between self-reported clinical variables to laboratory abnormalities (Howlett et al. 2014) to cellular biomarkers of immunosenescence (Mitnitski et al. in revision). Here, however, we used only self-reported variables, as these were the only such variables available in this dataset. Another important limitation is that in our assessment of deficit accumulation we ignored

mortality. Accounting for mortality is necessary for accurate estimates of longitudinal trajectories of any health characteristics (Yashin et al. 2007, 2012), otherwise the rate of increase of deficit accumulation might be underestimated: people with higher value of frailty die sooner than those with the lower level of deficits. We plan to address this issue in future studies.

We have to acknowledge that our estimates for the rate of deficit accumulation was based on differing numbers of people in each baseline age. As is typical in survey data, people of differing ages are not equally represented in population samples. For example, the number of people in younger group was an order of magnitude higher than the number of people of older ages, monotonically declining after age of 30 year old (from about 350) to less than 30 over age of 80). As the consequence, the variance of the estimates of the rate increases for the older ages but there is no evidence of the secular trend in the rate estimate (Fig. 1a).

Of some interest to studying mortality is that the pattern of deficit accumulation resembles the Gompertz Law of mortality (Milne 2008; Kirkwood 2015). Note too that the mortality rate doubling time (about 8 years) is about two times higher than the doubling rate of deficit accumulation, as might be expected if higher levels of deficit accumulation are relatively lethal.

Our results might shed light on understanding of how increasing vulnerability (or decreasing resilience) of the human organism is related to recovery time from various stresses and insults. At the individual level, the observed changes in deficit accumulation could be attributed to both changes in environmental stresses,  $\lambda$

and changes in recovery time,  $W$ . At the level of population, the environmental component of Little's Law ( $\lambda$ ) is approximately constant for the cohort. Accounting for secular trends by considering people of the same age, changes in the average number of deficits can be attributed to changes in recovery time. Such changes might also reflect change in the severity of deficits, as those which are more severe would take more time to recover than those that are less severe, even at the same age. Our results therefore indicate that the average recovery time doubles approximately every 15 year, independently of age. Experimental data on recovery time are sparse but it is known to increase with age (Yanai et al. 2011, 2015; Akushevich et al. 2013; Gould et al. 2015).

Recovery is an enormously complex process, even for very simple conditions such as skin wound healing, and involves many different processes and systems, across many scales—e.g., cellular, mitochondrial, and molecular (Gurtner et al. 2008; Moskalev et al. 2013; Gould et al. 2015). In many instances, these processes can be modulated by medical interventions, and these likely are responsible for much of the life extension observed in developed countries (GBD 2014). It has been suggested that society faces an urgent need “to combat middle-age decline at the stage before incipient old-age problems develop into full-blown diseases” (Wang 2007). Our approach, by accounting for a range of age-related deficits, and not just comorbidities and functional limitations, allows such changes to be traced systematically, thereby laying the groundwork for its more widespread use in health care and in gerontological research. Indeed, especially with responsive methods to count deficits in animals, (Parks et al. 2012; Whitehead et al. 2014; Feridooni et al. 2015; Kane et al. 2015) which yield FI results comparable to what is seen in humans, this approach allows a tractable means for research on age-related illnesses to quantify the effects of ageing on the whole organism. In so doing, we offer a pragmatic way to get to grips with a compelling critique of much contemporary disease-related research, being its neglect of the fact that “the problems of old age come as a package” (Fontana et al. 2014).

Given that the recovery rate is related to the number of accumulated deficits, it is tempting to pose the question: what causes age-associated changes in recovery time? Does age-related changes in the time of recovery causes accumulation of deficits, or the

opposite is true: the accumulation of deficits causes increase in recovery time? In order to answer these questions, we need a more elaborated systems biological model that considers complex network model of the organism where both the interaction between the network nodes corresponding to the different subsystems of the organism and external interactions with the environment are taken into account (Taneja et al. 2014; Mitnitski et al. 2013, 2014). Detailed investigation of such models is motivating further inquiries by our group.

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