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Trajectories of changes over twelve years in the health status of Canadians from late middle age

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ABSTRACT

Aging in a given individual can be characterized by the number of deficits (symptoms, signs, laboratory abnormalities, disabilities) that they accumulate. The number of accumulated deficits, more than their nature, well characterizes health status in individuals — the proportion of deficits present in an individual to deficits considered is known as a frailty index. While on average deficits accumulate with age, individual trajectories in the number of deficits is highly dynamic. Transitions in the number of deficits over a fixed time interval can be represented by the Poisson law, with the Poisson mean dependent on the deficit numbers at baseline. Here we present an extension of the model to make possible predictions for any given time period. Using data from the Canadian National Population Health Survey of people aged 55 and over (n = 4330), followed during 7 cycles being the baseline and 6 cycles of follow-up every 2 years, we found that the transition in the number of deficits during any time period can be approximated using a time dependent Poisson distribution with the Poisson mean tending to decelerate over time, according to square-root-of-time kinetics characteristic for stochastic processes (e.g. diffusion, Brownian motion) while the probability of death shows a pattern of time acceleration with a high degree of precision, "explaining" over 98% of variance. The model predicts a variety of changes in health status including the possibility of health improvement indicating the repair/remodeling abilities of the organism. The model is valuable for estimating how changes in health can influence mortality across the life course from late middle age.

1. Introduction

Aging is intrinsically associated with the accumulation of impairments, illnesses, disabilities, and with increasing risks of adverse outcomes such as death and loss of independence. It is well established that aging in a given individual can be characterized by the number of deficits (symptoms, signs, laboratory abnormalities, and disabilities) that they accumulate (Fulop et al., 2010; Goggins et al., 2005; Kulminski et al., 2007; Mitnitski et al., 2001, 2005; Rockwood and Mitnitski, 2007; Yang and Lee, 2010; Yashin et al., 2007a). Aging develops gradually and starts from small changes in health (Kulminski et al., 2007; Merrill et al., 2008; Mitnitski et al., 2001) which accumulate across the adult life course (Rockwood et al., 2011). While many of the variables, when considered in isolation from each other, have only small effects on health, their cumulative effect becomes significant (Kulminski et al., 2007). These cumulative effects can be quantified by combining health related variables in a so-called "frailty index" (FI is also sometimes referred to as a "deficit index"). Such measures have been investigated in both epidemiological surveys and clinical databases (Dupre et al., 2009; Kulminski et al., 2006; Mitnitski et al., 2005; Rockwood and Mitnitski, 2007; Rockwood et al., 2011; Woo et al., 2006; Yang and Lee, 2010). These indices are found to be useful indicators of aging and good predictors of adverse outcomes such as worsening health (Fallah et al., 2011; Mitnitski et al., 2006), institutionalization (Rockwood et al., 2007) and death (Kulminski et al., 2007; Mitnitski et al., 2005; Yashin et al., 2007a). Most importantly, the properties of the FIs depend more on the number of deficits from which the FIs are comprised rather than on their nature (Rockwood et al., 2006, 2007).

The concept of frailty as deficit accumulation has been further developed in a transition model which summarizes changes in the number of deficits. Specifically, we have developed a stochastic multistate model of transitions in health states during fixed periods of time (Fallah et al., 2011; Mitnitski et al., 2006, 2007a, 2007b, 2011). Of note, in contrast to typical regression models which estimate only the average effects, this model allows the simultaneous estimation of the probabilities of changes in individual health states in all directions: improvement, deterioration and death. Here we report the extension of this model to any time interval, so that we can make predictions about changes in health status and mortality when the

Abbreviations: CI, confidence interval; FI, frailty index; MSE, mean square error; NPHS, National Population Health Survey.

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time period is not fixed. We apply the model to a representative Canadian cohort of people from late middle age on, who were followed for up to 12 years. In addition to this methodological development, our goal was to investigate the time kinetics of changes in the parameters of the model, so as to elucidate the laws governing dynamics of health deficits during aging.

2. Materials and methods

2.1. Subjects and setting

We analyzed data from the National Population Health Survey (NPHS), a large Canadian study which began in 1994. The NPHS employs multistage stratification by geographic and socio-economic characteristics and clustering by Census Enumeration Areas and asks questions about physical and mental health status, health care service use, physical activities and the social environment (Singh et al., 1994). The NPHS contains longitudinal information on the health of 17,276 Canadians followed up from 1994 every 2 years and has been the subject of other reports by our group (Mitnitski et al., 2007b; Rockwood et al., 2011). Self-reported information was gathered at baseline and every 2 years, as was vital status. Of 4330 participants aged 55+ at baseline, 2548 were women. Their mean (±SD) age at baseline was 68.4±9.0 years. By 12 years (i.e., 2006–7), 1688 (39.0%) people had died, and 136 (3.1%) were institutionalized. And 486 (11.2%) were lost to follow-up. Overall household response rates varied from 83 to 88%. Vital status data, verified through database was known for >99.5% of people.

2.2. Deficits count (frailty index)

Thirty-one dichotomized variables (referred to as "deficits") including medical conditions, disabilities and health history (Appendix) were used to calculate each individual's health status, combined in a frailty index (FI). Data were coded so that the presence of a deficit was represented by a "1", and the absence of a deficit by "0". For any individual, their frailty index represents the number of deficits present, divided by 31 (the number of deficits considered). Note that the theoretical range of the FI is 0 (no deficits) to 1 (all 31 deficits present). Note too that individuals with a score of 0 are said to belong to the "zero state" and are considered to be the fittest.

2.3. Mathematical model

Our model of changes in health status over a fixed time interval uses a Poisson approximation, where the Poisson mean depends on the deficit count at baseline. (Note that the model requires integers and employs a deficit count; obviously, after re-scaling it is equivalent to the FI.) The precision is very high: the goodness of fit typically extends beyond 90% of "explained" variability, (Fallah et al., 2011; Mitnitski et al., 2006, 2007a). Let $P(n,k)$ be the probability of transitions from n deficits at baseline to k deficits at follow-up:

$$P(n,k) = \frac{\rho(n)^k}{k!}\exp(-\rho(n)) \tag{1}$$

where the Poisson mean ρ is a function of initial state (the number of baseline deficits), n. We have suggested a simple approximation of the Poisson mean ρ as a linear function of initial state (Mitnitski et al., 2006):

$$\rho(n) = a_1 + a_2 n \tag{2}$$

with constants a_1, a_2. When $n=0$ (the zero state) the parameter $a_1 = \rho(0)$ characterizes transitions of those people who had no problems at baseline (in this sense, it represents the "transition of the fittest"). Likewise, a_2 is a state increment: it shows how the Poisson mean varies in relation to the number of deficits at baseline. Note that change in the number of increments depends not just on an individual's health, but also on other factors (e.g., lifestyles, social networks); particularly in the case of people in the zero state at baseline, a_1 reflects the ambient state of health in that environment. For example, we would expect that the value of a_1 would be greater in a less developed country than in a more developed country. Likewise, for people with an allele associated with worse health, we would expect that those with the allele, who nevertheless were in the zero state at baseline, would, at follow-up have a higher number of deficits, on average, compared to those who did not carry the allele.

The probability of death generally shows a sigmoidal pattern and can be modeled using a logistic function:

$$P(n,d) = \frac{\exp(b_1 + b_2 n)}{1 + \exp(b_1 + b_2 n)} \tag{3}$$

where $P(n,d)$ is the probability of death, which depends on the number of deficits at baseline n; and b_1, b_2 are constants. They operate analogously to the constants a_1 and a_2. The zero state parameter, b_1 characterizes the risk of death (i.e., the logarithm of odds of death) of the fittest, $b_1 = \ln(P(0,d)/(1-P(0,d))$. Similarly, b_2 shows how the logarithm of odds of death increases with the baseline number of deficits, n.

We estimated the parameters (a_i ,b_i) for six consecutive biannual intervals, separately from 2 to 12 years, using the nonlinear least squares optimization procedure (Appendix). Parameters with time dependent trends were further modeled using specific functions of time, $a_i(t)$ and $b_i(t)$ with the parameters estimated using the nonlinear least squares. These parameters, and the time independent parameters, were re-estimated for the time dependent transition model using the entire data set (Appendix).

3. Results

3.1. Illustrative example

Fig. 1 illustrates a variety of changes in health status, here represented both by the number of deficits (left axis) and the frailty index (right axis) in twelve randomly selected individuals from the NPHS. Individual trajectories are represented by dots connected by thin lines overlaid with the age-specific deficit count (the average cross-sectional trajectory) shown by the dashed line. Note that even

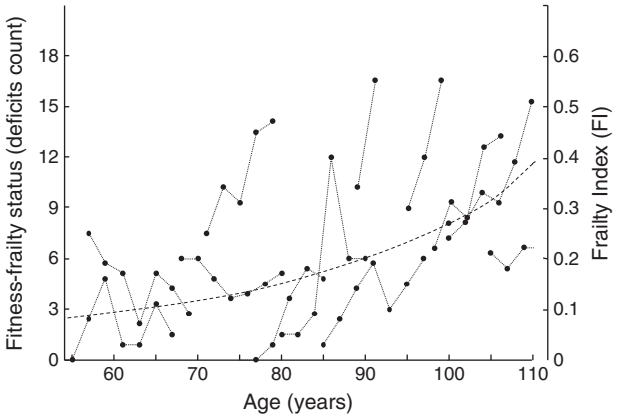

Fig. 1. Examples of individual trajectories of the deficits count in 12 randomly selected participants of the NPHS. Individual trajectories are represented by dots connected by dashed lines. The age-specific deficit count (the average cross-sectional trajectory) is shown by the dashed line. Of note, the values of the individual numbers of deficits were changed to satisfy Statistics Canada privacy requirements, but the patterns have been preserved.