Gender specific differences in cognitive changes, frailty and mortality in elderly.

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Abstract

We analyzed how the changes in cognition are related to general health status, in elderly men and women using the longitudinal component of the Canadian Study of Health and Aging (n = 8403). General health status was defined by the Frailty Index combining 40 health related deficits including symptoms, signs, illnesses, and disabilities. Cognitive states were defined as the errors in the modified Mini-Mental State Examination. Both cognitive improvement and declines were modeled using a four-parameter Markov chain with truncated Poisson distribution. The model parameters were dependent on age, education and frailty. We demonstrated that both age and frailty were independently associated with cognitive changes and risks of death while higher education is beneficial to cognition but did not improve survival. Frail women and especially frail men showed significantly higher cognitive decline than non frail women and men. Frail men had also more chances to die comparing to frail women.

Background

The whole organisms is changing with age, both body and mind. Cognitive functions decline with age, and prevalence of cognitive impairments dramatically increases. The same is true for the general health status. The relationships between cognitive and physical health varies, however, across the individuals. What factors influence these variations, at what extent the changes can be modified is a matter of investigations. We have developed an approach of characterizing general health of individuals and populations by a summary measure – the Frailty Index [1,2]. In a series of publications we and other investigators demonstrated that the FI is a strong predictor of adverse effects, including health deterioration and death [3-9]. It was suggested that both general health and cognitive health can contribute independently to the risk of death. To address these issues, we applied a novel approach recently developed to modeling transitions in health and cognition. The approach is based on the parametric representation of the Markov chain with four age, sex, education and frailty specific parameters [10-12]. In this study, we analyzed how general health status, age, and education level influence the changes in cognitive function in men and women.

Methods

The sample

The data come from the Canadian Study of Health and Aging (CSHA), a national, multi-center, prospective cohort study of dementia in persons aged 65 years and older. In 1991, a representative population sample (N =10 263) of people was drawn from provincial records [13]. An initial interview screened for self-rated health, chronic conditions, functional ability, and cognition, the last using the Modified Mini-Mental State (3MS) examination. In these analyses, we examined the change in cognition and risk of mortality at 5-year follow-up (CSHA-2), where the study consisted of the same components as at baseline (CSHA-1).

Measures

A self-administered risk factor questionnaire was completed at baseline and addressed demographic characteristics, occupational and environmental exposures, lifestyle, and medical and family histories. The Frailty Index (FI) was defined as a proportion of the binary variables calculated from 40 self reported conditions (signs, symptoms, illnesses, disabilities) [1-4]. The FI was dichotomized with the cut point of 0.22 approximately corresponding to the other known definition of frailty as a syndrome [7,14]. Of those people who completed the 3MS at CSHA-1 (n=10 057), only participants who both answered the risk-factor questionnaire (n= 8403) and either completed a 3MS examination at CSHA-2 (n= 5376) or died between CSHA-1 and CSHA-2 (n= 2219) were included. In addition, people reported the number of years in formal education, which was dichotomized using the median and entered as covariate a in the models along with sex and age also dichotomized.

Cognitive states

As elaborated elsewhere, cognitive states can be defined according to the number of errors in the Modified Mini-Mental State Examination (3MS) [15-17]. Successive cognitive states - from high cognition/low errors to impaired cognition/high errors - errors were grouped by 3's, where a 3-point difference on the 3MS is clinically detectable [18]. Thus, we consider that the ''0'' state is defined as 0, 1 and 2 errors (corresponding to 3MS scores = 100, 99 and 98). Likewise, the ''1'' state represents 3, 4 and 5 errors and so on until 3MS = 55 represented more than 99% of people in the sample. Death was added as a final absorbing state.

Modified Poisson model

We used the following stochastic model to describe changes in individual cognitive status as a Markov chain [10-12,15-17]. Given any individual's initial cognitive state as '*n*', let P_{nk} be the probability that this individual will have cognitive state '*k*' at the time of the next assessment, and let P_{nd} be the probability of dying before the next assessment. When the number of states is large, (~>10) the transition probabilities between the different numbers of states can be approximated by a modified Poisson distribution [10-12]. Here we use a truncated Poisson distribution to represent the transition probabilities when the number of states, N, is finite and not necessarily small.

$$P_{nk} = \frac{\frac{\rho_n^k}{k!}}{\sum_{j=1}^{N} \frac{\rho_n^j}{j!}} (1 - P_{nd}) \qquad (1)$$

The last term 1-P_{nd} is the probability of survival between two assessments. In other words, for each *n*, the transition probabilities satisfy a modified (by accounting for the survival probability) and truncated Poisson distribution in which the parameter ρ depends on the current state *n* as follows:

$$\rho_n = a_1 + b_1 n \qquad (2)$$

The Poisson parameter can increase with n differently with age, sex, education and exercise and the other conditions. The probability of death can be parameterized as following:

$$P_{nd} = \exp(a_2 + b_2 n) \quad (3)$$

The interpretation of the parameters (a_j and b_j, j=1,2) is following: a_1 is ρ_0 (it is the mean number of k given the *zero* state at baseline, i.e. n=0) and a_2 is the logarithm of the probability of survival at the zero state. The zero-state parameters a_1 and a_2 are estimates of the (ambient) probabilities respectively of death and of accumulating of cognitive errors. The b_1 and b_2 are the state increments when n>0. Similar to the Poisson parameter, the probability of death can increase with n differently by age, sex and other covariates. To incorporate the covariates, here we consider that each of the four parameters can be represented as a linear function of m covariates z_i (i =1,…m)

$$a_j = \alpha_j + \sum_{i=1}^{m} \gamma_i^j z_i \quad (4a)$$

$$b_j = \beta_j + \sum_{i=1}^{m} \delta_i^j z_i \quad (4b)$$

where j=1,2 for transitions between the cognitive states and from cognitive states to death, respectively. In this notation, the regression coefficients *gamma* modifies the estimates of a_j and the *delta* coefficients modify the estimates of b_j. Finally, the full model is represented by equations (1)-(4). The parameters of the model were estimated using the nonlinear least squares optimization procedure *nlinfit* in Matlab 7.5. The procedure is based on the Gauss-Newton algorithm with Levenberg-Marquardt modifications. The confidence intervals for the parameter estimates were calculated using *nlparci* procedure in Matlab 7.5. Goodness of fit of the model was evaluated using the coefficient of correlation, R between the observed and fitted data, and by the mean square error, *MSE*.

Result

The probabilities of five-year improvements, worsening and dying as a function of baseline cognition and four covariates (sex, age, education and frailty) were estimated according to equations (1)-(4)) for six versions of the model. The first four (Model 1 – Model 4) are univariate models and Models 5&6 are multivariate containing 3 covariates and calculated separately in men and women. The parameter estimates for univariate models are presented in Table 1 (in Model 1, women are coded as "0" and men as "1"). Note that all models give close estimates of the parameters responsible for cognitive transitions. At the next step, we calculated multivariate models for women and men separately (Table 2). According to our estimates, both age and frailty were independently associated with cognitive changes and risks of death while higher education is beneficial to cognition but did not improve survival (Table 2). In Figures 1 & 2 one can see substantial differences in the probabilities of transition between cognitive states by frailty: frail men transit to worse cognition more significantly than women (the shift of the black curves to the right comparing to the red curves) and also show significant difference in mortality (Figure 2, Panel B).

Discussion

In this study, using a novel stochastic model, we evaluated the impact of age, sex, education and frailty on cognitive changes simultaneously with the likelihood of death. Instead of analyzing cognitive changes and probability of death separately in each statistical model, we suggest a general parametric approach which allows estimation of the probabilities of changes in cognition at any degree as a function of the current state and simultaneous estimation of the probability of death. Our model allows analysis of the influence of the risk factors on the cognitive transitions and death by separating these effects. We were able to find that frailty is an important risk factor for cognitive decline and mortality and to identify important sex-related differences in the patterns of the changes (Figures 1 & 2).

Our data must be interpreted with caution. The cognitive changes were assessed by the 3MS, which is not a comprehensive measure of all cognitive functions. In addition, about 10% of people were lost to follow up. The demographic characteristics those people might be different from those remained in the study. These limitations, however, should not undermine the applicability of our model, although they might slightly modify the estimates. The high performance of our model (very high values of *R* and low values of *MSE*) was demonstrated in different settings and not only in cognition but also in general health status [10-12]. This suggests that our approach is both general and precise and may be applicable to a variety of biodemographic studies, a possibility which is motivating additional inquiries of our group.

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Table 1. Parameter estimates of the truncated Poisson model and their 95% confidence intervals in four univariate models (Model 1-4).

Covariate	Para-meter	Model 1 Adjusted for gender	Model 2 Adjusted for age	Model 3 Adjusted for education	Model 4 Adjusted for Frailty Index
	α_1	0.83 (0.67, 0.99)*	0.82 (0.67, 0.98)*	0.86 (0.69, 1.02)*	0.85 (0.69, 1.004)*
	β_1	1.07 (0.99, 1.14)*	0.93 (0.86, 1.01)*	0.97 (0.89, 1.05)*	1.06 (0.99, 1.13)*
	α_2	-1.93 (-2.07, -1.8)*	-2.32 (-2.54, -2.1)*	-1.84 (-1.96, -1.71)*	-2.08 (-2.24, -1.92)*
	β_2	0.12 (0.11, 0.13)*	0.13 (0.11, 0.15)*	0.13 (0.12, 0.14)*	0.12 (0.11, 0.14)*
Gender	γ_1^1	0.12 (-0.11, 0.36)			
	δ_1^1	-0.003 (-0.12, 0.11)*			
	γ_1^2	0.31 (0.13, 0.49)*			
	δ_1^2	-0.02 (-0.04, -0.01)*			
Age	γ_2^1		0.38 (0.07, 0.69)*		
	δ_2^1		0.31 (0.16, 0.45)*		
	γ_2^2		0.87 (0.63, 1.13)*		
	δ_2^2		-0.04 (-0.06, -0.02)*		
Education	γ_3^1			0.47 (0.20, 0.75)*	
	δ_3^1			0.07 (-0.04, 0.19)	
	γ_3^2			0.02 (-0.16, 0.21)	
	δ_3^2			-0.02 (-0.03, -0.001) *	
Frailty Index	γ_4^1				0.45 (0.14, 0.75)
	δ_4^1				0.02 (-0.11, 0.15)*
	γ_4^2				0.84 (0.65, 1.03)*
	δ_4^2				-0.05 (-0.07, -0.03)*
R		0.95	0.93	0.95	0.95
MSE		0.0014	0.0018	0.0014	0.0015

*Statistically significant difference between covariate groups ($p<0.05$)

The goodness of fit (*R*, mean square error) of the modified Poisson distribution is displayed

Table 2. Parameter estimates of the truncated Poisson model and their 95% confidence intervals for two multivariable models calculated separately in women and men (Models 5,6).

Covariate	Parameter	Model 5 (Women): adjusted for age, education and Frailty Index	Model 6(Men): adjusted for age, education and Frailty Index
	α_1	0.81 (0.55, 1.08)*	1.11 (0.69, 1.53)*
	β_1	0.76 (0.62, 0.89)*	0.71 (0.50, 0.92)*
	α_2	-2.6 (-3.14, -2.06)*	-2.41 (-2.83, -1.99)*
	β_2	0.15 (0.06, 0.23)*	0.19 (0.12, 0.26)*
Age	γ_1^1	0.20 (-0.15, 0.56)	-0.02 (-0.55, -0.52) *
	δ_1^1	0.48 (0.28, 0.69)*	0.67 (0.29, 1.06)*
	γ_1^2	0.76 (0.33, 1.19)*	0.99 (0.69, 1.29)*
	δ_1^2	-0.05 (-0.12, -0.02)*	-0.11 (-0.16, -0.06)*
Education	γ_2^1	0.56 (0.21, 0.92)*	-0.07 (-0.42, 0.52)
	δ_2^1	0.04 (-0.13, 0.21)	0.31 (0.02, 0.60) *
	γ_2^2	-0.51 (-1.02, 0.01)	-0.08 (-0.39, 0.23)
	δ_2^2	-0.03 (-0.04, 0.12)	-0.03 (-0.08, 0.03)
Frailty Indexes	γ_3^1	0.44 (0.07, 0.80) *	0.03 (-0.52, 0.58)
	δ_3^1	0.02 (-0.16, 0.20)	0.32 (-0.03, 0.67)
	γ_3^2	0.66 (0.23, 1.09)*	1.06 (0.74, 1.39)*
	δ_3^2	-0.002 (-0.07,0.07)	-0.07 (-0.13, -0.01) *
R		0.72	0.75
MSE		0.0070	0.0099

*Statistically significant difference between covariate groups ($p<0.05$)
The goodness of fit (*R*, mean square error) of the truncated Poisson distribution is displayed

Figure 1. The probability of transitions from *n* error-state to *k* error-state is shown at all panels, each cell represents consecutive cognitive baseline state, *n* (defined by 3MS errors). The Y axis shows the probability of transition to the new cognitive state, *k* (on the X axis). In panels A and B, transition probabilities are shown for women and men respectively. In both panels red dots (observational frequencies) and red lines (model fit) correspond to non-frail (FI<0.22) people of younger age, while black color indicates frail women (FI>0.22).

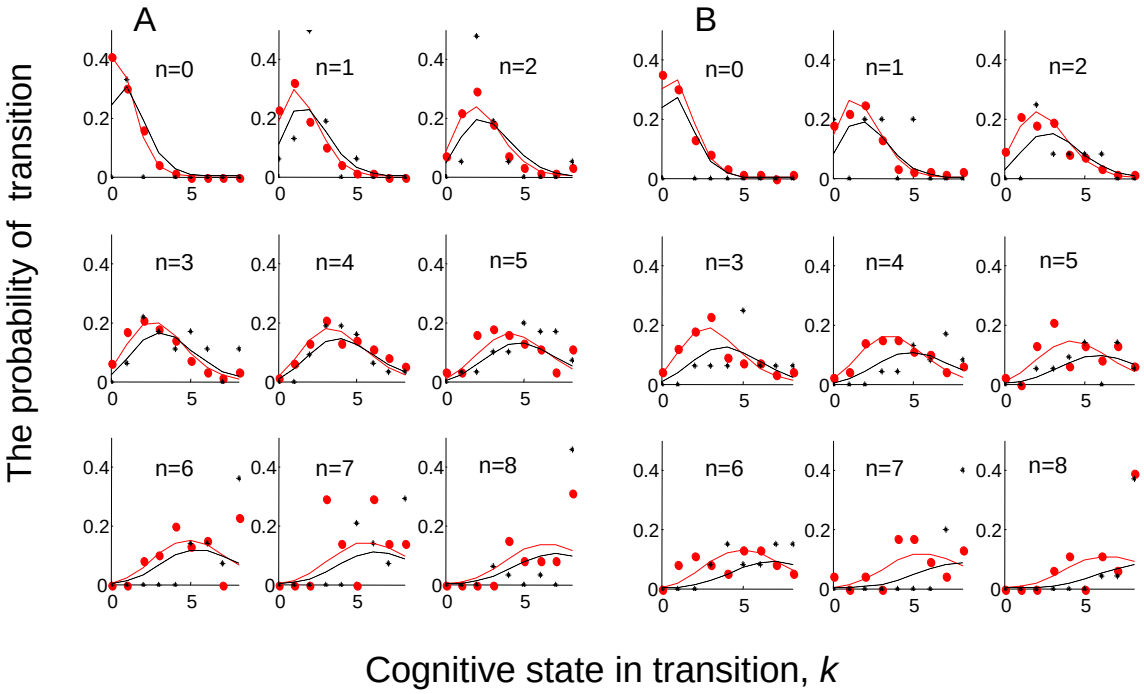

Figure 2. The probability of death as a function of baseline cognitive state, *n* (shown on each X axis). The Y axes show the probabilities of death. Only first 9 states (including the zero state are shown). In panels A and B, the probabilities of death are shown for women and men respectively. In both panels, the red dots (observational frequencies) and red lines (model fit) correspond to non frail women while black color indicates those who were frail.