Factors influencing improvement and decline in cognition in elderly Canadians, in relation to mortality

Nader Fallah, Arnold Mitnitski, Laura Middleton, Kenneth Rockwood

Abstract

We investigated five-year changes in cognition (including improvement and decline) in relation to age, sex, education and exercise levels and how these changes affect mortality. The data came from the Canadian Study of Health and Aging (n = 8403, 60.7% women). Cognitive states were defined as errors in the Modified Mini-Mental State Examination (3MS) score. Both improvement and declines were modeled in a unified way using a four-parameter truncated Poisson distribution. In contrast to conventional approaches, our model let us analyze how different risk factors affect cognition to any degree, and simultaneously survival. We found that higher education is beneficial for cognitive function both in men and women but does not improve survival. Exercise was beneficial for everybody but differently by sex: women had a survival advantage compared with men, but men most benefited in cognitive functioning. The exceptionally high fit suggests that these findings are reliable.

Background

The whole world is aging and as a consequence, the chances of reaching old age are getting higher [1]. So are the chances of becoming demented, as cognitive declines and dementia are highly associated with aging. The number of people with dementia is estimated to rise from 8.1 million to 24.3 million by 2040 [2]. Risks factors for cognitive decline and dementia are extensively investigated, but still remain understood. How education and lifestyles can be protective is especially a matter of debate [3-5].

On average, cognition, like many other physiological functions, declines with age. This average decline, however, can mask complex dynamics [4,5]. Changes with age do not occur uniformly – not only do people decline at different rates, but improvements are also possible. We have recently suggested a novel approach to modeling transitions in general health and cognition based on the Markov chain analysis with Poisson distribution which provides the excellent data fit [6-11]. Here we report an important modification of the model by including covariates in the analysis. Specifically, we illustrate how sex, age, education and exercise level might influence such transitions, and how they can be incorporated into a stochastic model of change.

Methods

The sample

As with our most recent report [11], 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 [12]. 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. Two questions, based on the frequency and intensity of exercise, assessed the level of physical activity as validated elsewhere [11]. People were classified as participating in 'high exercise' (≥ 3 times per week, at least as intense as walking) and 'low/no exercise' (all other exercisers and no exercisers). 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) [9,11,13]. 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 [11]. 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 [6-11]. 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 [6-11]. 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 in different ways [6,10,11]. Here we consider the following approximation:

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

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 the current state of cognition and four covariates (sex, age, education and exercise) 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. In Model 1 where sex is a covariate women are coded as "0" and men as "1". The parameter estimates for univariate models are presented in Table 1. Note that all models give close estimates of the parameters responsible for cognitive transitions. In Model 1, sex appeared to be significantly associated with mortality; while in Models 2 to 4, age, education and exercise are also significant for both cognition and mortality adjustments. Based on these results we ran multivariable model for age, education and exercise in each sex (Table 2). In Models 5 and 6, age is strongly associated with the changes in cognition and with the probability of death. The higher education level is beneficial for cognitive function both in men and women but does not affect survival (Table 2). Exercise was beneficial for everybody but in a slightly different way in relation to sex: women had higher survival advantage while men most benefited in cognitive functioning (Table 2). Cognitive

transitions calculated according to equations (1)-(4) are shown in Figure 1, and transitions to death are displayed in Figure 2.

Discussion

In this study, using a novel stochastic model, we evaluated the impact of age, sex, education and exercise levels 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 not only exercise is beneficial to both cognition and survival but identify important sex-related differences in the patterns of the changes.

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. Possible misreporting of physical activity is the other concern. These limitations, however, should not undermine the applicability of our model, although they might slightly modify the estimates. The high performance of our model was demonstrated in different settings and not only in cognition but also in general health status [6-8]. 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.

Acknowledgment

These analyses were supported by the Canadian Institutes for Health Research (CIHR) operating grants, and by the Dalhousie Medical Research Foundation (DMRF).

References

1. Ebrahim S. Ageing, health and society. *Int J of Epidemiol* 2002; 31: 715-718.
2. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005; 366: 2112–2117.
3. Brayne C. The elephant in the room – healthy brains in later life, epidemiology and public health. *Nat Rev/Neuroscience* 2007; **8**:233–239.
4. Rockwood K, Middleton L. Physical activity and the maintenance of cognitive function: Epidemiology. *Alz Dement* 2007; 3(2): S38–S44.
5. Hodges JR. Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain* 2006:**129**(Pt 11): 2811-2822.
6. Mitnitski A, Bao L, Rockwood K. Going from bad to worse: a stochastic model of transitions in deficit accumulation, in relation to mortality. *Mech Ageing Dev* 2006; 127: 490-3.

7. Mitnitski A, Bao L, Skoog I, Rockwood K. A cross-national study of transitions in deficit counts in two birth cohorts: implications for modeling ageing. *Exp Gerontol* 2007; 42: 241-6.
8. Mitnitski A, Song X, Rockwood K. Improvement and decline in health status from late middle age: modeling age-related changes in deficit accumulation. *Exp Gerontol* 2007; 42: 1109-15.
9. Mitnitski A, Rockwood K. Transitions in cognitive test scores over 5 and 10 years in elderly people: evidence for a model of age-related deficit accumulation. *BMC Geriatr* 2008 8:3
10. Mitnitski A, Fallah N, Rockwood K. A parametric approach to modeling health transitions. *Annual Meeting of Population Association of America Proceeding*. April 17-19, New Orleans, 2008 P4:46
11. Middleton LE, Mitnitski A, Fallah N, Kirkland SA, Rockwood K. Changes in cognition and mortality in relation to exercise in late life: a population based study. *PLoS ONE* 2008 Sep 1;3(9):e3124.
12. Canadian study of health and aging: study methods and prevalence of dementia. *CMAJ* 1994; 150: 899-913.
13. Andrew MK, Rockwood K. A five-point change in Modified Mini-Mental State Examination was clinically meaningful in community-dwelling elderly people. *J Clin Epidemiol* 2008;61:827-31.

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

Covariate	Para-meter	Model 1 Adjusted for gender	Model 2 Adjusted for age	Model 3 Adjusted for education	Model 4 Adjusted for exercise
	α_1	0.83 (0.67, 0.99)*	0.82 (0.67, 0.98)*	0.86 (0.69, 1.02)*	0.86 (0.69, 1.04)*
	β_1	1.07 (0.99, 1.14)*	0.93 (0.86, 1.01)*	0.97 (0.89, 1.05)*	0.97 (0.89, 1.05)*
	α_2	-1.93 (-2.07, -1.8)*	-2.32 (-2.54, -2.1)*	-1.84 (-1.96, -1.71)*	-2.27 (-2.47, -2.07)*
	β_2	0.12 (0.11, 0.13)*	0.13 (0.11, 0.15)*	0.13 (0.12, 0.14)*	0.15 (0.13, 0.17)*
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) *	
Exercise	γ_4^1				-0.02 (-0.29, 0.24)
	δ_4^1				0.26 (0.12, 0.39)*
	γ_4^2				0.69 (0.46, 0.93)*
	δ_4^2				-0.05 (-0.07, -0.03)*
R		0.95	0.93	0.95	0.93
MSE		0.0014	0.0018	0.0014	0.0019

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

The goodness of fit (*R*, and mean square error) of the truncates 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 exercise	Model 6 (Men): Adjusted for age, education and exercise
	α_1	0.74 (0.52, 0.97)*	2.01 (1.66, 2.36)*
	β_1	0.71 (0.59, 0.84)*	0.45 (0.29, 0.611)*
	α_2	-3.97 (-4.75, -3.21)*	-2.41 (-2.81, -1.99)*
	β_2	0.39 (0.28, 0.51)*	0.21 (0.14, 0.27)*
Age	γ_1^1	0.37 (0.07, 0.68)*	-0.49 (0.75, -0.24)
	δ_1^1	0.43 (0.25, 0.63)*	0.74 (0.49, 0.98)*
	γ_1^2	1.34 (0.74, 1.93)*	0.91 (0.56, 1.26)*
	δ_1^2	-0.15 (-0.23, -0.06)*	-0.09 (-0.15, -0.04)*
Education	γ_2^1	0.55 (0.25, 0.84)*	-0.61 (-0.89, -0.32)*
	δ_2^1	0.08 (-0.15, 0.16)	0.48 (0.29, 0.68) *
	γ_2^2	0.01 (-0.59, 0.57)	0.03 (-0.29, 0.36)
	δ_2^2	-0.03 (-0.12, 0.05)	-0.05 (-0.11, 0.01)
Exercise	γ_3^1	0.07 (-0.21, 0.36)	-0.92 (-1.23, -0.62) *
	δ_3^1	0.22 (0.05, 0.38)*	0.31 (0.11, 0.51)*
	γ_3^2	1.12 (0.55, 1.68)*	0.36 (0.05, 0.67)*
	δ_3^2	-0.11 (-0.19, -0.03)*	-0.01 (-0.05, 0.05)
R		0.74	0.75
MSE		0.0066	0.0077

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

Figure 1. Transitions from *n* cognitive errors at baseline to k errors. In all panels, each cell represents consecutive cognitive baseline state indicated within each cell. The Y axes show the probability of transition to the new cognitive state, *k* (in the X axis). Only first 9 states (including the zero state are shown).
Panel A is for sex: men (black) and women (red) people
Panel B is for age: older (black) and younger (red) people
Panel C is for the education level: low education (black) and high education (red) people
Panel D is for the exercise level: low exercise (black) and high exercise (red) people

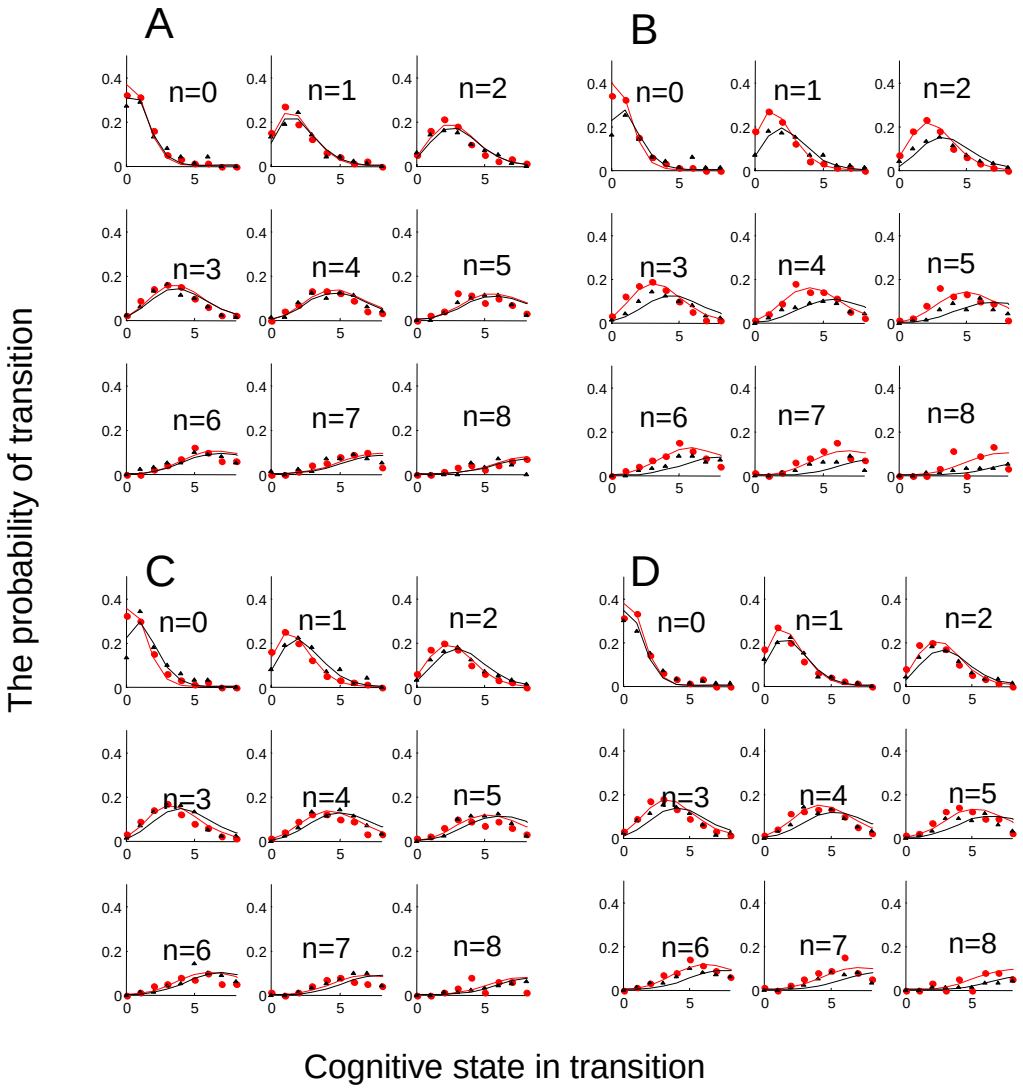

Figure 2. The probability of death as a function of baseline cognitive state, *n* (shown in each X axis). The Y axes show the probabilities of death. Only first 12 states (including the zero state are shown).
Panel A is for sex: men (black) and women (red) people
Panel B is for age: older (black) and younger (red) people
Panel C is for the education level: low education (black) and high education (red) people
Panel D is for the exercise level: low exercise (black) and high exercise (red) people