Journal of Gerontology: MEDICAL SCIENCES
2004, Vol. 59A, No. 6, 627–632

The Estimation of Relative Fitness and Frailty in Community-Dwelling Older Adults Using Self-Report Data

Arnold B. Mitnitski,[1,2] Xiaowei Song,[3] and Kenneth Rockwood[1,3]

[1]Department of Medicine, [2]Faculty of Computer Science, and
[3]Division of Geriatric Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.

Background. While on average health declines with age, it also becomes more variable with age. As a consequence of this marked variability, it becomes more important as people age to have a means of summarizing health status, but how precisely to do so remains controversial. We developed one measure of health status, personal biological age, from a frailty index. The index itself is a count of deficits derived, in the first instance, from a clinical database. In our earlier investigations, personal biological age demonstrated a strong relationship with 6-year survival. Here we extend this approach to self-reported data.

Methods. This is a secondary analysis of community-dwelling people aged 65 years and older ($n = 9008$) in the Canadian Study of Health and Aging. The frailty index was calculated from 40 self-reported variables, representing symptoms, attitudes, illnesses, and function. Personal biological age was estimated for each individual as the age corresponding to the mean chronological age for the index value. Individual frailty (and the related construct of fitness) was calculated as the difference between chronological and personal biological age.

Results. The frailty index showed, on average, an exponential increase with age at an average rate of 3% per year. Although women, on average, demonstrate more frailty than men of the same chronological age, their survival chances are greater. The frailty index strongly correlated (Pearson $r = .992$ for women and .955 for men) with survival.

Conclusions. A frailty index, based on self-report data, can be used as a tool for capturing heterogeneity in the health status of older adults.

FRAILTY appears to be a robust construct for understanding the heterogeneity in health status of older adults, but its operational definition remains controversial (1–5). As reviewed elsewhere (6,7), more precise estimates are being achieved through mathematical modeling of frailty and related constructs, such as allostatic load (8,9) and physiological complexity (10,11). In this article, we extend some observations about a method of estimating fitness and frailty that can capture heterogeneity of health in an older population, while reducing the dimensionality of multivariate modeling of adverse health outcomes.

Our group has defined frailty (and the related construct of fitness) based on two variables: chronological age and a frailty index. The index is an unweighted count of the number of symptoms, signs, functional impairments, or abnormal laboratory values (jointly referred to as *deficits*), as a proportion of all potential deficits considered for a given person. For example, in considering 20 deficits from the clinical sample of the Canadian Study of Health and Aging (CSHA) (12) dichotomized as present or absent, we found that the number of deficits ranged from 0 to 14. Thus the value of the frailty index ranged from 0 to 0.7 (13). We plotted the index value against chronological age, which was well fitted by an exponential curve ($r = .89$).

From this relationship between chronological age (CA) and the index, we ''worked backwards'' to calculate an individual's personal biological age (PBA) (Figure 1). Consider ''A'' and ''B,'' two individuals of the same CA of 77 years. Individual A has a frailty index value that corresponds to the average value of a person with a CA of 86. Individual B has a frailty index value that corresponds to a person with a CA of 66. We proposed that although for both individuals CA = 77, the PBA of A = 86, and the PBA of B = 66, so that A has 9 years (86 − 77 years) of relative frailty and B has 11 years (77 − 66 years) of relative fitness.

We compared the relative abilities of CA and PBA to predict death. On their own, both were negatively correlated mortality, but PBA was correlated more highly than CA ($r = -.09$, $p = .001$ for CA versus $r = -.24$, $p = .000001$ for PBA) and explained more of the variance in death than did CA (13). Given that death is a relevant and nonarbitrary outcome, the ability of the model to predict death with only two dimensions is good evidence of the merit of this approach.

We subsequently have extended these analyses (14). First, we reflected on the intriguing observation that it appeared to be the *proportion* of deficits that made up the frailty index that was important in its relationship to death, and not their *nature*. Thus, we randomly sampled from those deficits recorded in the CSHA clinical database that had little missing data and that were age associated. We found that the slope of the index/age line was stable (as a logarithmic relationship) across randomly selected variables, even though the intercept term varied. Later, we cross-validated the frailty index in another Canadian sample, the much larger ($n = 81,859$) National Population Health Survey (15). That survey exclusively used self-report data; here, too, the

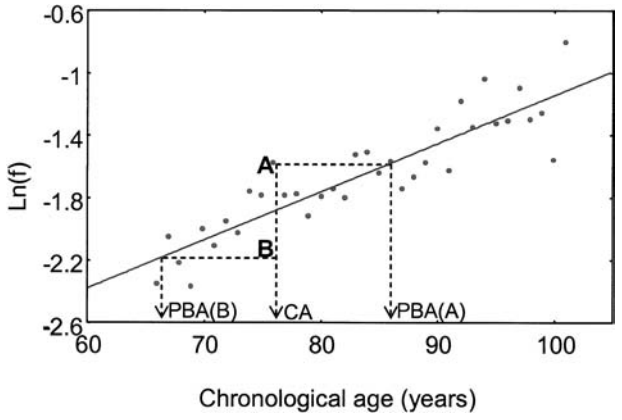

Figure 1. The definition of personal biological age using the frailty index as a function of chronological age. Points correspond to the observational data, with the frailty index averaged in the individuals at the same age. The solid line represents least square regression with the parameters of slope (0.03) and intercept (–4.23) (13). Points A and B represent two persons at the same chronological age. Their biological age is found by comparing their frailty indices with the reference represented by the regression line.

previously observed relationship held. In each of the studies, however, we have exclusively used binary data in calculation of the impairment index. In the present study, we have extended our approach to use nonbinary data, and also to again use only self-report data.

The use of self-report data is of some interest. Self-report assessments of health have long been related to adverse health outcomes, such as death and institutionalization, even in the presence of more objective measures (16,17). Self-report data also show some potential for integrating information about demographic and health-related characteristics (18,19). Self-report data are readily collectable in surveys, without the special instrumentation required by a clinically based operational definition of frailty (20) or of allostatic load (9).

Methods

Population Database

The CSHA is a cohort study assembled in a first phase (12) during which participants were recruited from both the community and institutions on the basis of age-stratified (65 to 74, 75 to 84, and ≥85 years) random samples in 36 urban and surrounding rural areas in all 10 Canadian provinces. Here we report data from the 9008 participants in the community sample. The items that make up the frailty index (the exposures) all come from the CSHA-1 data; outcomes (survival, death, institutionalization) come from CSHA-2 and the interval leading to it. All participants were aged ≥65 years as of October 1, 1990. In 1996, follow-up data collection (CSHA-2) was undertaken (21). Community participants presumed to be free from dementia at CSHA-1 were invited to be rescreened and evaluated as above. Those who had a clinical examination in CSHA-1 were also invited to the CSHA-2 clinical assessment. Informants of participants who had died were contacted to assess the cognition, function, and health care use in the descendents' last year of life.

Table 1. List of Deficits, Their Scale Levels, and Population Means

Deficit Code	Deficits	Levels	Mean
1	Eyesight	5	0.3006
2	Hearing	5	0.2831
3	Help to eat	3	0.0039
4	Help to dress and undress	3	0.0114
5	Ability to take care of appearance	3	0.0093
6	Help to walk	3	0.0303
7	Help to get in and out of bed	3	0.0070
8	Help to take a bath or shower	3	0.0684
9	Help to go to the bathroom	3	0.0085
10	Help to use the telephone	3	0.0309
11	Help to get to place out of walking distance	3	0.0736
12	Help in shopping	3	0.1148
13	Help to prepare own meals	3	0.0656
14	Help to do housework	3	0.1871
15	Ability to take medicine	3	0.0224
16	Ability to handle own money	3	0.0424
17	Self-rating of health	5	0.2353
18	Troubles prevent normal activities	3	0.3491
19	Living alone	2	0.3605
20	Having a cough	2	0.1251
21	Feeling tired	2	0.1756
22	Nose stuffed up or sneezing	2	0.1661
23	High blood pressure	2	0.3388
24	Heart and circulation problems	2	0.3014
25	Stroke or effects of stroke	2	0.0480
26	Arthritis or rheumatism	2	0.5651
27	Parkinson's disease	2	0.0133
28	Eye trouble	2	0.3041
29	Ear trouble	2	0.2876
30	Dental problems	2	0.1975
31	Chest problems	2	0.1722
32	Trouble with stomach	2	0.2560
33	Kidney trouble	2	0.1212
34	Losing control of bladder	2	0.1503
35	Losing control of bowels	2	0.0467
36	Diabetes	2	0.0969
37	Trouble with feet or ankles	2	0.3261
38	Trouble with nerves	2	0.1895
39	Skin problems	2	0.1767
40	Fractures	2	0.0590

Variables

Forty self-report variables were available from the screening survey of community-dwelling participants to characterize health conditions (Table 1). These self-reported items included symptoms, health attitudes, illnesses, and impaired function. These included both standard questions on health and health attitudes, as described in detail elsewhere (22), and items from a checklist, which was proceeded by either the prompt, ''In the past 30 days, have you had any of the following complaints?'' (for the items *tiredness* and *upper respiratory symptoms*) or the prompt ''in the past year'' for the chronic disease items. (I)ADL [(instrumental) activities of daily living] items were scored to reflect ''your situation today.'' All variables were categorical; 22 were binary (e.g., illnesses) while the others represented ordinal scales. Variables were mapped into the interval [0, 1], such that a greater value corresponded to

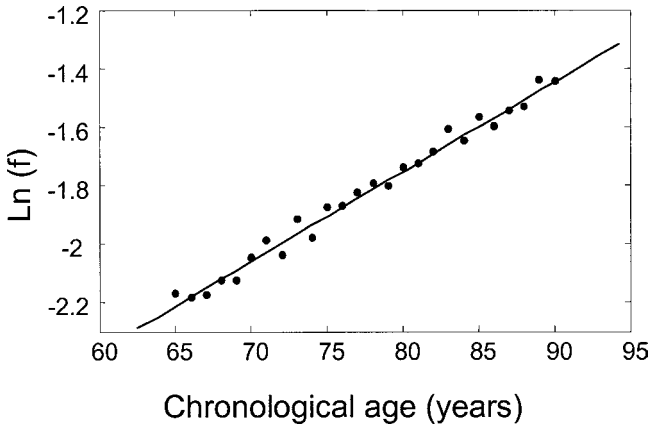

Figure 2. The frailty index calculated using the self-report data as a function of chronological age ($r = .99$). The solid line represents least square regression with the parameters of the slope (0.029) and intercept (–4.05), and the points correspond to the observational data.

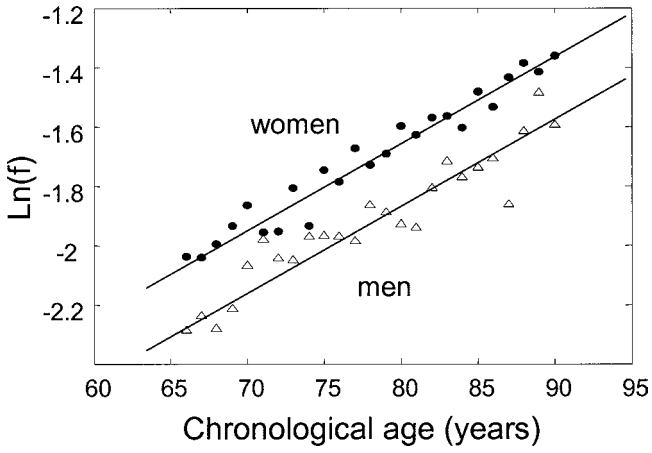

Figure 3. The frailty index as a function of chronological age in men and women. Circles (for women) and triangles (for men) represent observational data, and the solid lines are a least square regressions with the parameters of the slope (0.029) in men and women and the intercept (–3.98 in women and –4.00 in men).

a higher risk. For example, the 3-scale variable ''help to prepare meals'' was coded as 0 (No), 1 (Yes), and 0.5 (Yes, with some help). Analogically, 5-scale variables were coded adding the intermediate values 0.25 and 0.75. After such transformation, all deficits had values from 0 to 1. Of the 9008 cases, 8547 (5089 women, 3458 men) contained complete information for all 40 variables. For those who died (1865), time to death from the assessment was recorded.

Analysis

Each individual in a data file can be represented by an m-dimensional (m-D) vector (where m is number of variables). A frailty index was introduced as an average of the deficits within the individual. Age trajectories of the average frailty index were analyzed for all the population and separately in men and women, using regression techniques. Statistical distributions of the frailty index across the individuals were compared with the theoretical models (goodness of fit) using the chi-squared test. Proportions of survivors were calculated for each age and for each value of the frailty index. In addition, the Cox regression model with chronological and biological age was used in order to compare the relative significance of the covariates. Significance level was set to $p = .05$.

Results

Figure 2 shows the age trajectory for the fitness frailty index. The value of the index increases exponentially with age ($r = .99$). The regression line corresponded to the following equation:

$$\ln(f) = -4.05 + 0.029t \quad [1]$$

where $\ln(f)$ is the natural logarithm of the frailty index averaged across individuals at the same age, t. The regression line representing the population can be used as a frame of reference in assessing individual frailty (13). Using inverse regression, PBA (personal biological age) was estimated according to the equation:

$$\mathrm{PBA} = 138 + 33.2\ln(f) \quad [2]$$

Relative fitness and frailty can be found as a difference between PBA and CA. In Figure 3, the value of the frailty index is shown separately for men and women. At all ages, women, on average, accumulate more deficits than men. The parameters of the slope are (0.029/year).

Figure 4 shows a representative distribution of (here 77 years old individuals) by the frailty index. As can be seen, the distribution of the data is best fit by a gamma density function:

$$p(f) = \lambda^k f^{k-1} e^{-\lambda f}/\Gamma(k) \quad [3]$$

with the parameters of scale ($1/\lambda$) and shape (k), related to the mean $\mu = 0.164$ and standard deviation $\sigma = 0.098$, $\lambda = \mu/\sigma^2$ and $k = (\mu/\sigma)^2$, and $\Gamma(k)$ is the gamma function. The parameters of shape and scale we found were 17.01 and

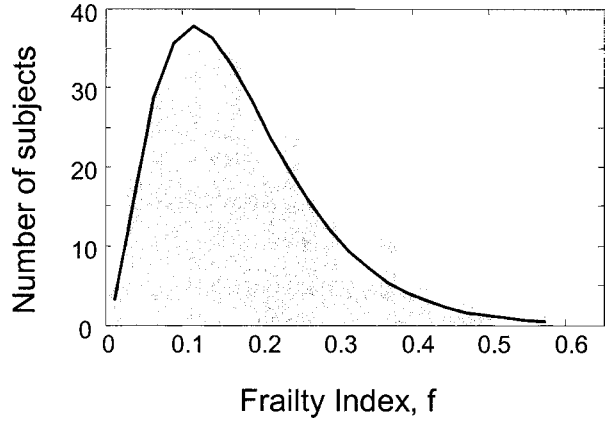

Figure 4. The statistical distribution of the frailty index for the sample of the population at the age of 77 years. The histogram represents the observational data and the solid line is a gamma density function with the parameters of scale (17.01) and shape (2.8).

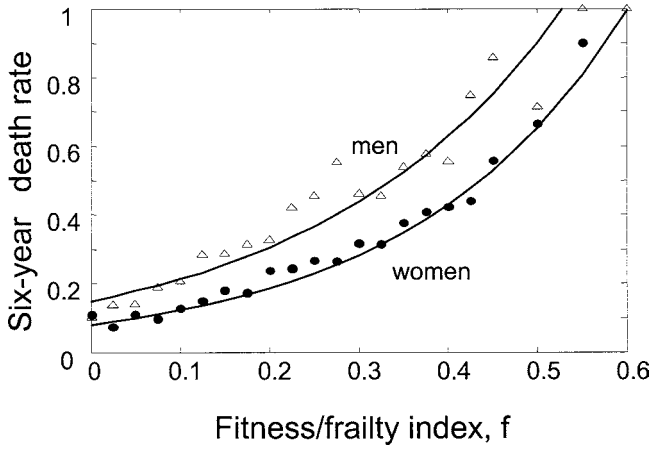

Figure 5. The proportion of those who died within 6-year follow-up as a function of the frailty index. Triangle (men) and circles (women) represent observational data and solid lines are the exponent functions Ae^{Cf}, with the parameters $A = 0.148$ for men and 0.087 for women and $C = 3.612$ for men and 4.116 for women.

2.80, respectively. The chi-squared goodness of fit was 7.22, $p < .05$). The correlation coefficient between the observed and theoretical (gamma) distributions was $r = .989$. The distribution of the frailty index was also analyzed by gender and for each of the other ages, and was again well represented by a gamma density function, although the parameters were different. Means changed with age (Figures 2 and 3).

Figure 5 shows the relationship between the frailty index and the fraction of those who died within 6 years. There is a significant increase in the death rate when the frailty index increases both in men (triangles) and women (circles). These relationships are well represented by exponential curves $A\exp(Cf)$, with the parameters $A = 0.148$, $C = 3.612$ for men ($r = .955$), and $A = 0.087$, $C = 4.116$ for women ($r = .992$).

The relationships between the frailty index and the 6-year death rate indicates the ability of the index to predict overall mortality, but can also be used to predict survival time. We found that BA showed statistically significant relations with time to death ($p = .017$) while CA did not ($p = .259$). The value of the beta coefficient from a Cox regression model with covariates of chronological age (CA) and biological age (BA) was 0.0037 (standard deviation 0.0033) for CA, and 0.0033 (standard deviation 0.0013) for BA. This would correspond to a hazard ratio of 1.003 for each increment in BA (95% confidence interval 1.002 to 1.005).

Discussion

This article generally replicates our previous findings that fitness and frailty can be estimated as differences in PBA and CA using a simple impairment index, which we have called the frailty index. Importantly, we offer predictive (criterion) validation of this approach, in demonstrating the association between the PBA value and mortality. (Necessarily, given their calculation, the same holds for relative fitness and frailty.) In contrast to our earlier work with the CSHA clinical database, these results are based exclusively on self-report data. In addition, we have demonstrated that

Table 2. Parameters of Age Trajectories of Frailty Index Estimated From Different Data

Data Source	No. of Variables	No. of Cases	Slope (*SD*)	Intercept
CSHA (clinical)	20	2,914	0.030 (0.002)	−4.23 (0.14)
CSHA (clinical)	92	2,914	0.033 (0.002)	−4.62 (0.13)
CSHA (self-report)	40	8,547	0.029 (.0007)	−4.05 (0.07)
CSHA (male)	40	3,458	0.029 (.0009)	−4.00 (0.07)
CSHA (female)	40	5,089	0.029 (.0008)	−3.98 (0.07)
NPHS (male)	38	31,410	0.043 (0.001)	−5.77 (0.06)
NPHS (female)	38	33,179	0.031 (0.001)	−4.63 (0.06)

Note: SD = standard deviation; CSHA = Canadian Study of Health and Aging; NPHS = National Population Health Survey.

nonbinary variables can be readily incorporated into the definition of a frailty index. The trajectories of the frailty index showed an exponential increase with age, as was also found in clinical (13,14) and survey data (23). We also demonstrated that, on average, women accumulate more deficits than men of the same age, although their risk of mortality is lower (23). The statistical distribution of the frailty index was well represented by a gamma density function, as was found with the clinical dataset (14). This distribution held for all ages, and in men and women, although the parameter changed with age.

Our data need to be interpreted with caution, however. For example, we have only a single baseline measure of relative fitness/frailty, which we know to be a dynamic and not a static construct (24). Thus, for example, while we again demonstrated that biological age better correlated with survival time using Cox regression than did CA, the greatest difference between BA and CA was observed for those who died within 1 year (BA − CA = 4.9 years, $p < .000001$). This difference between BA and CA significantly diminished after 1 year (BA − CA = 2.6 years, $p < .00001$).

In addition, the precision of the estimation of PBA seems to vary based on the source of the information used. For example, the parameters of the age trajectories of frailty differ somewhat when estimated using different data sources. In Table 2, these parameters are presented from three analyses: CSHA (clinical assessment, 20 variable, 90 variable with random simulations), CSHA (self-report data), and NPHS survey. Note that the last dataset represents a broad range of ages and that the model had an additional parameter (an age-independent term) (23). The parameters of the equation for PBA (2) are, however, different from those obtained earlier for clinical assessment data of 127 and 26 (13) for the intercept and slope, respectively. Though it does not undermine the advantages of PBA as a relative measure of fitness/frailty in a population, the comparison of the PBA across different populations should be done with caution. The parameters of the inverse regression (2) for PBA are close to the inverse values of the parameters of the equation for fitness/frailty trajectory (1). This makes them sensitive to the errors in the estimates of the parameters (1). Despite the proximity of the parameters of the direct regressions (Table 2), the equations for PBA [e.g., Eq. (2)] are generally more sensitive to statistical errors. This question requires additional data analyses, using parametric

and nonparametric techniques. Nevertheless, other estimates are not too far apart. Of particular note, the proximity of the estimates of the rate of accumulation of deficits to 3% per year might be of significant theoretical and practical interest if supported by the studies in other populations. Still, while not all numbers are exactly replicable, our approach does at least offer the possibility of estimating such parameters in contrast to many of the other definitions of frailty now being proposed (25–28).

In contrast to other approaches (25–28), however, ours is less likely to yield a specific biological marker of frailty. Whereas other investigations have emphasized relationships between frailty and, for example, proinflammatory and antiinflammatory markers, coagulation status, and anemia (29,30), here our approach emphasizes the integration (or failure of integration) of many components in a complex system. While the two approaches are not necessarily incompatible (indeed, one can imagine introducing a specific biological marker as a covariate in a reduced multivariate model), they are operationally distinct. Still, from a clinical standpoint, their complementarity is evident. For example, a single marker approach to frailty might be seen as analogous to a single acute illness, viewed against a background of impaired physiological reserve. Just as some of the other approaches offer more precise estimates of the impact of single factors (25–27,29,30), our frailty index offers the possibility of more precisely estimated physiological reserve.

We were interested to again observe that the statistical distribution of the frailty index is well represented by a gamma density function (14). A gamma distribution index is typical for systems with redundant components that can be used in case of the failure of a given subsystem. As such, it is compatible with the general failure model of aging (31,32). The age trajectories of the mean frailty index are well represented by exponential curves, which are compatible with the so-called avalanche-like accumulation of defects (32). The general failure model posits a ''state of nonspecific vulnerability'' (32), which can also be thought of as *critical state*, analogous to instability in complex systems. In such a state, anything can cause failure, which is sometimes also represented as a loss of complexity (11,33).

Another way to address biological redundancy is to consider relationships between variables. As we also found earlier, the variables studied here are not statistically independent, something that often undermines the application of statistical methods, which are based on the presumption of independence (34). Indeed, the independence of variables in the samples that we have studied is rather an exception than a rule, unless impaired populations are considered, for example, Parkinson's and vascular dementia (13,35).

The proximity of the present results to earlier estimates using binary variables (13,14,23) implies that dichotomization of the variables does not affect the major properties of the frailty index such as kinetics of frailty index and its association with mortality at the population level. This might suggests that there is no need to artificially dichotomize multilevel variables. The frailty index, even with multilevel variables, is still based on the assumption of equality of deficits. It would be of interest to parse the variables that might have greater influence at the adverse outcomes. For example, one might use discriminant functions as linear combinations of deficits with different weights (36). Another approach is to apply an artificial neural network to link the adverse outcome (e.g., 1-year mortality) with the input variables (deficits). The demonstration of sufficient biological redundancy, however, suggests that modeling frailty might be practical in any dataset that collected a sufficient number of age-related variables.

Acknowledgments

The data reported in this article were collected as part of the Canadian Study of Health and Aging. The core study was funded by the Seniors' Independence Research Program, through the National Health Research and Development Program of Health Canada [project no. 6606-3954-MC(S)]. The study was coordinated through the University of Ottawa and the Division of Aging and Seniors, Health Canada. Additional analytical support came from a grant to Dr. Mitnitski from the Intramural Research Grant fund of the Faculty of Medicine, Dalhousie University. Dr. Rockwood is supported by an Investigator Award from the Canadian Institutes for Health Research and by the Dalhousie Medical Research Foundation as the Katheryn Allen Weldon Professor of Alzheimer Research.

Address correspondence to Kenneth Rockwood, Division of Geriatric Medicine, Dalhousie University, Suite 1421, 5955 Veterans' Memorial Lane Rd., Halifax, NS, B3H 2E1, Canada. E-mail: kenneth.rockwood@dal.ca

References

1. Rockwood K, Hogan DB, MacKnight C. Conceptualization and measurement of frailty in elderly people. *Drugs Aging*. 2000;17:295–302.
2. Gillick M. Pinning down frailty. *J Gerontol Med Sci*. 2001;56A:M134–M135.
3. Bortz WM II. A conceptual framework of frailty: a review. *J Gerontol Med Sci*. 2002;57A:M283–M288.
4. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults. *J Gerontol Med Sci*. 2001;56A:M146–M156.
5. Morley JE, Perry HM III, Miller DK. Something about frailty. *J Gerontol Med Sci*. 2002;57A:M698–M704.
6. Rockwood K, Mitnitski A, MacKnight C. Some mathematical models of frailty and their clinical implications. *Rev Clin Gerontol*. 2002;12:109–117.
7. Mitnitski AB, Mogilner AJ, Graham JE, Rockwood K. Techniques for knowledge discovery in existing biomedical databases: estimation of individual aging effects in cognition in relation to dementia. *J Clin Epidemiol*. 2003;56:116–123.
8. Seeman TE, Singer BH, Rowe JW, et al. Price of adaptation: allostatic load and its health consequences. *Arch Intern Med*. 1997;157:2259–2268.
9. Seeman TE, McEven BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *PNAS*. 2001;98:4770–4775.
10. Lipsitz LA. Dynamics of stability: the physiologic basis of functional health and frailty. *J Gerontol Biol Sci*. 2002;57A:B115–B125.
11. Yates FE. Complexity of a human being: changes with age. *Neurobiol Aging*. 2002;23:17–19.
12. Canadian Study of Health and Aging Working Group. Canadian Study of Health and Aging: study methods and prevalence of dementia. *Can Med Assoc J*. 1994;150:899–913.
13. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. *BMC Geriatr*. 2002:2:1.
14. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Sci World*. 2001;1:323–336.
15. Swain L, Catlin G, Beaudet MP. The National Population Health Survey: its longitudinal nature. *Health Rep*. 1999;10:69–82.

16. Nybo H, Gaist D, Jeune B, McGue, Vaupel JW, Christensen K. Functional status and self-rated health in 2,262 nonagenarians: the Danish 1905 Cohort Survey. *J Am Geriatr Soc*. 2001;49:601–609.
17. Gutman GM, Stark A, Donald A, Beattie BL. Contribution of self-reported health ratings to predicting frailty, institutionalization, and death over a 5-year period. *Int Psychogeriatr*. 2001;13(Supp 1):223–231.
18. Finch CE, Vaupel JW. Collecting biological indicators in household surveys. In: Finch C, Vaupel J, Kinsella K, eds. *Cells and Surveys—Should Biological Measures Be Included in Social Science Research?* Washington, DC: National Academic Press; 2001:1–8. URL: http://www.nap.edu/books/0309071992/html/
19. Crimmings EM, Seeman T. Integrating biology into demographic research on health and aging (with a focus on the MacArthur Study of Successful Aging). In: Finch C, Vaupel J, Kinsella K, eds. *Cells and Surveys—Should Biological Measures Be Included in Social Science Research?* Washington, DC: National Academic Press; 2001:9–41. URL: http://www.nap.edu/books/0309071992/html/
20. Rockwood K, MacKnight C, Stadnyk K, et al. A brief clinical instrument to classify frailty in elderly people. *Lancet*. 1999;353:205–206.
21. Graham JE, Rockwood K, Beattie BL, et al. Standardization of the diagnosis of dementia in the Canadian Study of Health and Aging. *Neuroepidemiol*. 1996;15:246–256.
22. Gutman GM, Stark A, Donald A, Beattie BL. Contribution of self-reported health rating to predicting frailty, institutionalization, and death over a 5-year period. *Int Psychogeriatr*. 2001;13(Supp 1):223–231.
23. Mitnitski AB, Mogilner AJ, MacKnight C, Rockwood K. The accumulation of deficits with age and possible invariants of aging. *Sci World*. 2002;2:1816–1822.
24. Rockwood K, Fax RA, Stolee P, et al. Frailty in elderly people: an evolving concept. *Can Med Assoc J*. 1994;150:489–495.
25. Ferrucci L, Cavazzini C, Corsi A, et al. Biomarkers of frailty in older persons. *J Endocrinol Invest*. 2002;25:10–15.
26. Reuben DB, Mui S, Damesyn M, et al. The prognostic value of sensory impairment in older persons. *J Am Geriatr Soc*. 1999;47:930–935.
27. Reuben DB, Cheh AI, Harris TB, et al. Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. *J Am Geriatr Soc*. 2002;50:638–644.
28. Rozzini R, Frisoni GB, Ferrucci L, et al. Geriatric Index of Comorbidity: validation and comparison with other measures of comorbidity. *Age Ageing*. 2002;31:277–285.
29. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med*. 2002;162:2333–2341.
30. Leng S, Chaves P, Koenig K, Walston J. Serum interleukin-6 and hemoglobin as physiological correlates in the geriatric syndrome of frailty: a pilot study. *J Am Geriatr Soc*. 2002;50:1268–1271.
31. Gavrilov LA, Gavrilova NS. *The Biology of Life Span. A Quantitative Approach*. New York: Harwood Academic Publishers; 1991:232–285.
32. Gavrilov LA, Gavrilova NS. The reliability theory of aging and longevity. *J Theoret Biol*. 2001;213:527–545.
33. Lipsitz LA, Goldberger AL. Loss of ''complexity'' and aging: potential applications of fractals and chaos theory to senescence. *JAMA*. 1992;267:1906–1809.
34. Kachigan SK. *Multivariate Statistical Analysis: A Conceptual Introduction*. 2nd Ed. New York: Radius Press; 1991.
35. Graham JE, Mitnitski AB, Mogilner AI, Gauvreau D, Rockwood K. Symptoms and signs in dementia: synergy and antagonism. *Dementia*. 1996;7:331–335.
36. McLachlan GJ. *Discriminant Analysis and Statistical Pattern Recognition*. New York: Wiley; 1992

Received February 18, 2003
Accepted March 14, 2003