Published in final edited form as:
J Gerontol A Biol Sci Med Sci. 2008 October ; 63(10): 1053–1059.

Cumulative Deficits and Physiological Indices as Predictors of Mortality and Long Life

Alexander M. Kulminski, PhD, **Svetlana V. Ukraintseva, PhD**, **Irina V. Culminskaya, PhD**, **Konstantin G. Arbeev, PhD**, **Kenneth C. Land, PhD**, **Lucy Akushevich**, and **Anatoli I. Yashin, PhD**

Center for Population Health and Aging Duke University Population Research Institute and Duke University, Department of Sociology Trent Hall, Room 002, Box 90408, Durham, NC, 27708, USA.

Abstract

We evaluated the predictive potential for long-term (24-year) survival and longevity (85+ years) of an index of cumulative deficits (DI) and six physiological indices (pulse pressure, diastolic blood pressure, pulse rate, serum cholesterol, blood glucose, and hematocrit) measured in mid-to-late-life (44-88 years) for participants of the 9th and 14th Framingham Heart Study exams. For all ages combined, the DI, pulse pressure, and blood glucose are the strongest determinants of both long-term survival and longevity, contributing cumulatively to their explanation. Diastolic blood pressure and hematocrit are less significant determinants of both these outcomes. The pulse rate is more relevant to survival, while serum cholesterol is more relevant to longevity. Only the DI is a significant predictor of longevity and mortality for each 5-year age group ranging from 45 to 85 years. The DI appears to be a more important determinant of long-term risks of death and longevity than the physiological indices.

Keywords

Mortality; longevity; physiological risk factors; Framingham Heart Study

1. Introduction

A long life span in humans is the result of a complicated interplay among various deterministic and stochastic processes developing in the human organism. These processes include senescence, ontogeny, genetic, epigenetic, environmental, behavioral, social, economic, life style and other factors affecting an individual functioning [1-5]. The problem, however, is that neither the number nor a complete list of the most important factors contributing to survival and longevity are known. Moreover, aging-related changes in variables, describing physiological states or other life history traits, are often small, and their effects on health and survival outcomes are often non-significant. The sets of factors contributing to long life, evaluated in different studies, often differ substantially. This situation calls for the development of new methods of data analyses, which would allow for (i) utilizing information on variables with small effects, and (ii) capturing systemic integrative aspects of aging and longevity despite difference in the sets of variables measured in different studies.

A number of prior studies of health and longevity largely focused on the effects of specific biologically-motivated risk factors (e.g., physiological) that might affect health and mortality

Corresponding Author: Alexander Kulminski Center for Population Health and Aging, Duke University Trent Hall, Room 002, Box 90408, Durham, NC, 27708, USA Phone: 919-684-4962; Fax: (919) 684-3861 E-mail: E-mail: Alexander.Kulminski@duke.edu.

risks. These include separate studies of the role of serum cholesterol, blood pressure, blood glucose, body mass index, etc. in different aspects of health and survival (e.g., [6-12]). The impact of blood pressure on survival and longevity is one of the best documented [13] and was largely studied in connection with heart disease and premature death [see, e.g., 14]. The human organism is a complex system in which all processes are, generally, dependent. Accordingly, an improved understanding of the determinants of longevity, which is among major governmental priorities [15], can be achieved by integrating diverse health characteristics [12,16].

The need for such integrative approaches in studying survival, health, and longevity is increasingly recognized [12,16,17]. For instance, the additive effect of such major risk factors for heart disease as blood pressure, serum cholesterol, glucose intolerance, smoking, body mass index, physical activity, antihypertensive treatment, and left ventricular hypertrophy was studied using the Framingham Heart Study (FHS) data [11]. Willcox et al. [12] studied the effect of midlife biological, lifestyle, and socio-demographic risk factors on longevity using the Honolulu Heart Studies. They reported on the association of grip strength, overweight, hyperglycemia, hypertension, smoking, and excessive alcohol consumption in males with these outcomes. Nevertheless, studies of the joint effects of diverse health characteristics on longevity are rare. This is partly explained by the low predictive power of traditional health risk factors for longevity outcomes.

A promising strategy for integrative approach is to construct composite measures to predict the survival and longevity outcomes (e.g., the Framingham Risk Score [18], the Survival Risk Score [12]). Because the effect of many aging-associated changes in the human organism can be small, inconsistent or non-significant, further insights into understanding long life can be gained by combining composite characteristics of aging and health with individual physiological indices [16].

Recently, a new cumulative measure of health/well-being and aging status, called a *frailty index* [19-21] or an *index of cumulative deficits* (DI) [22,23], has been proposed. The DI is designed to gather different manifestations of health deterioration with aging (regardless of their individual significance) into a single measure which might be more informative about survival and longevity compared to individual manifestations. Prior studies show that, indeed, the DI can be an efficient predictor of death, hospitalization, disease and disability [23-31]. It can also be a useful alternative to chronological age for characterizing the overall burden of senescence in individuals [23-31], thus representing a measure of aging-related processes in humans [23,29-31]. An important advantage of the DI is that it can be constructed using the set of deficits available in any specific study. This is because statistical properties of the DI (e.g., age patterns) and its effect on other outcomes (e.g., mortality) are weakly sensitive to the selection of specific set of deficits. This remarkable property of the DI is confirmed in several studies using different sets of deficits [21,25,26,29].

Historically, studies of properties of the DI were largely limited to elderly individuals. Current priorities of aging research are the identification of the most important factors contributing to a long and healthy life throughout the entire life course. Consequently, a focus on a wide spectrum of potential determinants of long and healthy life as well as on early-life conditions is of importance [15]. Does the DI retain its predictive power for younger (e.g., middle-aged) individuals? How effectively can the DI predict survival and longevity outcomes? Can the DI compete with traditional (e.g., physiological) health risk factors? Answers to these questions can greatly contribute to understanding aging-associated processes because the underlying tool, the DI, has the potential to bring into the analysis additional health dimensions typically ignored due to their small, inconsistent or non-significant effects on the survival and longevity outcomes.

In this study, we address these questions by focusing on the DI and a set of six physiological indices that are among major health risk factors consistently assessed and documented in the FHS [18,32], namely, pulse pressure, diastolic blood pressure, pulse rate, serum cholesterol, blood glucose, and hematocrit. We examine how these characteristics, measured in mid-to-late-life, contribute to long-term survival (i.e., survival of individuals who live for a long time after the last measurement but not necessary into the oldest ages) and longevity of individuals who participated in the FHS.

2. Methods

The FHS data

Beginning in 1948, 5,209 respondents (46% male) aged 28–62 years residing in Framingham, Massachusetts were enrolled in the FHS. Selection criteria and study design have been previously described [33]. The study participants have been followed for the occurrence of certain diseases (e.g., heart disease, cancer, diabetes mellitus) and death for more than 50 years and have been biennially evaluated with a physical examination, laboratory tests, detailed medical history, and extensive cardiovascular history.

Index of cumulative deficits (DI)

In traditional analyses, events or conditions with small or non-significant contributions to risks of adverse health outcomes are usually ignored. When the number of such “small-effect” conditions is large enough, however, their cumulative effect on chances of occurring adverse health outcomes may become significant and, thus, an integrative or cumulative measure might become a reliable predictor of health and vital status as well as the level of aging-associated decline [21-24,28,29,31]. The aggregation of a number of various health traits (including small-effect traits) into a single measure is capable of providing detectable effect on health/mortality outcomes, is an underlying paradigm of the DI. The DI is conceptualized as the proportion of failed (e.g., definitive deficits) or abnormal (e.g., doubtful deficits) health traits occurred by age x—that is a summary measure of the average level of an organism's deterioration at age x. Thus, an empirical estimate of this proportion in a given individual, i.e., the $DI(x)$, can be calculated by selecting a sub-set of M units out of a full set of N such units. Specifically, summing the number of failed or abnormal units from selected set by age x, $m(x)$, an empirical estimate of the DI can be evaluated as $DI(x)=m(x)/M$. For instance, if an individual has been administered 30 questions and responded positively (there is a deficit) to five and negatively (no deficit) to 21 of them, then the DI for the given person will be 5/26. Thus, based on a large and diverse array of deficits, the DI will be quasi-continuous quantity ranging theoretically between 0 (no deficits or perfect health) and 1 (pure health) or, equivalently, between 0 and 100%.

Analyses

The rationale behind the DI mandates assessing the presence of a wide range of heath-related conditions, e.g., signs, symptoms, abnormal lab tests, functional limitations, disabilities, diseases (called deficits). Consequently, the present analyses focused on two representative exams of the FHS performed in 1964 (9^{th} exam) and 1974 (14^{th} exam) in which the same 39 deficits (Table 1) with comparable diagnostic procedures across time were selected. Seventeen deficits were either dichotomous (yes, or no) or dichotomized for the sake of consistency between exams. The remaining 22 deficits were rescaled to the unit interval to reflect the degree of abnormality, e.g., the urinary sugar level was recoded as negative (0 or no deficit), doubtful (0.5) and positive (1 or yes deficit). To ensure that coding of non-dichotomous variables did not affect the estimates, we also performed analyses focusing only on the dichotomized variables. The results were not significantly affected by the coding uncertainty.

To characterize longevity, a cut-point of 85 years was adopted throughout this study in agreement with prior FHS studies [11] and overall survival of individuals in this cohort (there are about 25% survivors by age 85 years and only about 10% by age 90 years in this sample). There were 3833 individuals aged between 44 and 78 years who participated in the 9th FHS and 2871 individuals aged between 55 and 88 years who participated in the 14th FHS.

The Cox proportional hazard regression model was used to evaluate the effects of the six physiological indices and the DI—all as measured in the baseline exams (Table 2, explanatory variables)—on the hazard of death considering deaths that occurred within the maximum follow-up period for the 14th exam, i.e., 24 years (the last known vital status assessment was at the 25th exam performed in 1998). A test of the proportionality of the hazard shows that this assumption is reasonable for the time horizons considered both for the DI and the physiological variables. The effects of the baseline values of these explanatory variables on longevity then were estimated using logistic regressions in which the dependent variable was long-livers vs. others. Analyses were initially performed for each exam to ensure that the estimates were not affected by the possible differences in birth cohorts. Since the results were comparable across these exams the participants of these exams were combined into one sample to increase the precision of the estimates. All regression models were either sex-specific or adjusted for sex, age, body mass index, and smoking (Table 2).

To select the best-predictive model, all analyses were performed using the covariate-substitution technique and likelihood ratio tests. All explanatory variables (Table 2) in the regression models were used as continuous indices with 10% increments for the DI, 5% for hematocrit, 10 mm Hg for pulse pressure and diastolic blood pressure, 10 beats/min for pulse rate, and 10 mg/100 ml for cholesterol and blood glucose selected for the purpose of presentation. The choice of increments for covariates does not affect significance of the results. The analyses were performed for all ages combined and for 5-year age groups. To assess whether the nature of the deficits used in the DI affects the estimates, the same analyses were performed with some deficits excluded (see the “Results” section for details).

3. Results

Table 3 (first two rows labeled “All ages”) shows that for all ages combined, the hazard of death within the 24 years of follow-up was predicted with high significance by the DI and four physiological indices (pulse pressure, diastolic blood pressure, pulse rate, and blood glucose). The hazard ratios (HRs) evaluated in the “univariate” analysis (i.e., each of the physiological indices or the DI included in the model individually; Table 3, first row) resemble those in the “multivariate” analysis (all six physiological indices and the DI included simultaneously; Table 3, second row). The hazard ratios for males resemble those for females. Multivariate analysis shows also additional weakly significant contribution of hematocrit (HR=0.95; 95% Confidence Interval [CI]=0.90-0.99), which is attributable to males (HR=0.90; CI=0.84-0.97). Exclusion of deaths that occurred within the first 10 years of follow-up after each exam (Table 3, third row) did not change the results for the pulse pressure, diastolic blood pressure, and blood glucose. Significance of the hazard ratio attributable to the pulse rate, however, essentially decreases consistently with no role of this factor for longevity (see below).

Despite different proportions of deaths and distinct lengths of time between observation and death in different age groups, age stratification (Table 3) reveals that the hazard ratios remain highly significant (either on $p<0.001$ or $p<0.0001$ levels) for the DI for each 5-year age group. In contrast, significance of the hazard estimates for the physiological indices decreases in majority of the age groups making some estimates insignificant (Table 3, blanks). The most significant predictors of long-term risks of death among physiological indices are the pulse pressure and blood glucose. The diastolic blood pressure- and pulse rate-attributable hazards

are either insignificant or have small predictive power in all age groups. In all multivariate analyses the cholesterol is not predictive of long-term survival.

Table 4 shows that for the 50-84 year age group (see ‖footnote to Table 4) longevity is associated with the DI, pulse pressure, diastolic blood pressure, cholesterol, and blood glucose both in univariate and multivariate analyses, although the association with cholesterol is weak in both these analyses being attributable to females. The diastolic blood pressure is highly significant in univariate analysis but its significance decreases when other indices are included. Again, its effect is attributable to females. Each increment in the DI, pulse pressure, diastolic blood pressure, and blood glucose decreases the likelihood of surviving to ages 85+ years. Cholesterol level seems to be directly associated with longevity (i.e., long lived individuals have higher cholesterol levels) in these FHS exams.

In the age-stratified analyses, the DI remains a highly significant predictor of longevity ($p<0.0001$) for each age group except 50-54 years (which might be attributable to small number of long-livers). This high level of statistical significance holds despite different percentages of long-livers across age groups and, most importantly, despite difference in the age when health status was assessed. Physiological indices are less predictive of longevity than the DI since they are retained in the models only for some age groups. The pulse rate does not consistently predict longevity in the multivariate analyses.

To assess whether these results are sensitive to the specifics of the deficits selected for inclusion in the DI, we performed Cox regression analyses of the predictive power of mortality of all the 39 deficits for participants of the 9th FHS exam, considering each deficit as an individual covariate. These analyses showed that only 9 of 39 deficits (see Table 1) are significantly associated individually with the probability of death occurring within the 24-year follow-up. These 9 deficits were excluded from the original DI resulting in the 30-defict index (DI_{30def}). Table 4 shows that the odds ratios for the DI_{30def} resemble those for the DI_{39def} for all ages combined and for each 5-year age group. Of note is that age groups of 50-59 years are composed of only participants of the 9th FHS (see ‖footnote to Table 4). Randomly excluding selected deficits produced similar results.

4. Discussion and Conclusions

In this study, we applied an approach of cumulative deficits to add new health dimensions to the study of determinants of survival and longevity. These new dimensions are associated with health traits which often exhibit small, inconsistent, or insignificant effect on these outcomes and, therefore, are typically ignored in traditional analyses. Aggregation of such small-effect traits into a single measure, the DI, can be more informative compared to the use of individual traits. We considered how informative the DI could be in predicting long-term survival and longevity and whether it could compete with traditional factors such as physiological indicators. All these health indicators were measured in mid–to–late life in participants of the 9th (1964) and 14th (1974) representative exams of the FHS.

The primary determinants of long-term survival for all ages combined in this sample are the DI, pulse pressure, diastolic blood pressure, and blood glucose (Table 3). The effects of these indices on long-term risks of death are highly significant for each sex and for males and females combined. Each index contributes to mortality both individually and in an additive superposition with other indices. This fact indicates an additive (cumulative) role of the DI and physiological indices in explaining mortality chances, i.e., the DI and physiological indices characterize non-intersecting health dimensions contributing to mortality through different pathways. Note that this finding is in agreement with additive effects of major physiological risks evidenced in prior studies (e.g., [18,34]). The role of pulse rate is less significant than

that of the other primary determinants. The role of diastolic blood pressure and pulse rate diminishes when considering delayed mortality, i.e., death occurred at least after 10 years of life (Table 3, third row). This, in fact, is in agreement with non- (pulse rate) and low- (diastolic blood pressure) significant effects of these factors on longevity (see below).

The strongest mid-life (ages 45-49 years) predictors of long-term survival are the *DI, pulse pressure, and blood glucose* (note that the association with the latter two factors is in agreement with prior FHS studies [35]). Although for older ages the other two physiological indices (diastolic blood pressure and pulse rate) can significantly contribute to explanation of the long-term risks of death, only pulse pressure and blood glucose remain significant for majority of age groups. Unlike physiological indices, the DI contributes to explanation of the risks of death in all age groups and these contributions are highly significant for all of them (at the level of $p<0.001$ or $p<0.0001$). This makes the DI a more important predictor of long-term survival than the physiological indices. The weak sensitivity of the estimates for the DI to the proportion of deceased individuals in each age group and the time between measured health status and death are consistent with the proposed role of the DI as a characteristic of aging-associated processes in an organism and as an alternative to chronological age [20,21,23,29-31]. In contrast, the sensitivity of the physiological indices to these factors supports the role of these indices as predictors of death due to specific age-associated health conditions.

Highly significant ($p<0.0001$) determinants of long life in multivariate analyses for all ages combined are the *DI, pulse pressure, and blood glucose* (Table 4, second row). Blood glucose is less significant predictor of longevity for males than for females. Serum cholesterol and diastolic blood pressure play less significant role in explaining association with longevity than other three indices. Their effect is attributed to females. The effect of the diastolic blood pressure might be mediated by other physiological indices and the DI since its predictive power essentially decreases in multivariate analyses. Thus, the role of the diastolic blood pressure might be less critical in comprehensive analyses especially for later ages (see next paragraph) compared to the case when other risk factors are not assessed. Since significance and odds ratios of the DI, pulse pressure, serum cholesterol, and blood glucose are the same both in univariate and multivariate analyses, they are strong additive contributors to explaining chances to live long life. Similarly to the case of mortality, this means that the DI and physiological indices reflect complementary pathways leading to longevity. Pulse rate appears to be not relevant to longevity while hematocrit might provide highly significant contribution for a certain age.

Significant mid-life (ages 50-54 years) contributors to longevity are the *DI, diastolic blood pressure, and blood glucose*. These factors are also among the most significant physiological predictors of longevity since they are retained in more 5-year age groups than serum cholesterol and diastolic blood pressure. Again, only the DI is consistently significantly associated with longevity for all age groups. This suggests that while physiological factors are important for predicting long life, the DI is a superior predictor. The weak sensitivity of the DI to chronological age makes this index a promising indicator of chances for individuals to live long lives.

A major shortcoming of the approach of cumulative deficits is that it requires the collection of information on a large and diverse array of deficits. This disadvantage of the DI is sometimes criticized with respect to the difficulty of its operationalization. However, the widespread use of information technologies in health services in recent years has resulted in the routine collection of a wealth of health-related information. Information technologies are among the major potential domains of improvement of medical care and savings in medical expenditures due to considerable wastes in the respective services [36]. Because it appears that DI is weakly sensitive to the nature of deficits (i.e., the proportion of deficits from a selected set appears to

be of importance but not which deficits exactly are accumulated in individuals [26]), the use of the DI provides a way of employing these information technologies and the data they generate for improving mortality and longevity forecasts with practically no additional costs. In addition, this remarkable property makes the DI practical because it can be constructed using those health traits which are available in a particular study but not necessarily those reproducing any particular set.

In sum, mid-to-late-life *DI*, *pulse pressure*, *and blood glucose* are the strongest determinants of both long-term survival and longevity in the male and female participants of the 9th and 14th FHS exams contributing to their explanation cumulatively. Diastolic blood pressure and hematocrit might be determinants of both these outcomes. The pulse rate is more relevant to long-term survival, while serum cholesterol is more relevant to longevity. The DI is a more important determinant of long-term risks of death and longevity than the physiological indices.

5. Acknowledgements

The research reported in this paper was supported by the National Institute on Aging grants 1R01 AG028259, 1R01-AG-027019 and 5P01-AG-008761. The Framingham Heart Study (FHS) is conducted and supported by the NHLBI in collaboration with the FHS Investigators. This Manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the FHS or the NHLBI.

REFERENCES

1. Vaupel JW, Carey JR, Christensen K, Johnson TE, Yashin AI, Holm NV, et al. Biodemographic trajectories of longevity. Science 1998;280:855–860. [PubMed: 9599158]
2. Perls T, Terry D. Genetics of exceptional longevity. Exp Gerontol 2003;38:725–730. [PubMed: 12855277]
3. Ukraintseva SV, Yashin AI. How individual age-associated changes may influence human morbidity and mortality patterns. Mech Ageing Dev 2001;122:1447–1460. [PubMed: 11470132]
4. Yashin AI, Ukraintseva SV, De Benedictis G, Anisimov VN, Butov AA, Arbeev K, et al. Have the oldest old adults ever been frail in the past? A hypothesis that explains modern trends in survival. J Gerontol A Biol Sci Med Sci 2001;56:B432–442. [PubMed: 11584028]
5. Varcasia O, Garasto S, Rizza T, Andersen-Ranberg K, Jeune B, Bathum L, et al. Replication studies in longevity: puzzling findings in Danish centenarians at the 3′ APOB-VNTR locus. Annals of Human Genetics 2001;65:371–376. [PubMed: 11592926]
6. Dawber, TR. The Framingham study : the epidemiology of atherosclerotic disease. Harvard University Press; Cambridge, Mass.: 1980.
7. Franco OH, Peeters A, Bonneux L, de Laet C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women: life course analysis. Hypertension 2005;46:280–286. [PubMed: 15983235]
8. Franklin SS, Pio JR, Wong ND, Larson MG, Leip EP, Vasan RS, et al. Predictors of new-onset diastolic and systolic hypertension: the Framingham Heart Study. Circulation 2005;111:1121–1127. [PubMed: 15723980]
9. Kannel WB, Vasan RS, Levy D. Is the relation of systolic blood pressure to risk of cardiovascular disease continuous and graded, or are there critical values? Hypertension 2003;42:453–456. [PubMed: 12975387]
10. Port SC, Boyle NG, Hsueh WA, Quinones MJ, Jennrich RI, Goodarzi MO. The predictive role of blood glucose for mortality in subjects with cardiovascular disease. Am J Epidemiol 2006;163:342–351. [PubMed: 16373527]
11. Terry DF, Pencina MJ, Vasan RS, Murabito JM, Wolf PA, Hayes MK, et al. Cardiovascular risk factors predictive for survival and morbidity-free survival in the oldest-old Framingham Heart Study participants. J Am Geriatr Soc 2005;53:1944–1950. [PubMed: 16274376]
12. Willcox BJ, He Q, Chen R, Yano K, Masaki KH, Grove JS, et al. Midlife risk factors and healthy survival in men. JAMA 2006;296:2343–2350. [PubMed: 17105797]

13. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. JAMA 1996;275:1571–1576. [PubMed: 8622248]
14. Pekkanen J, Tervahauta M, Nissinen A, Karvonen MJ. Does the predictive value of baseline coronary risk factors change over a 30-year follow-up? Cardiology 1993;82:181–190. [PubMed: 8324779]
15. Hadley EC, Rossi WK. Exceptional survival in human populations: National Institute on Aging perspectives and programs. Mech Ageing Dev 2005;126:231–234. [PubMed: 15621201]
16. Yashin AI, Arbeev KG, Akushevich I, Kulminski A, Akushevich L, Ukraintseva SV. Model of hidden heterogeneity in longitudinal data. Theor Popul Biol 2008;73:1–10. [PubMed: 17977568]
17. Wei JT, Dunn RL, Sandler HM, McLaughlin PW, Montie JE, Litwin MS, et al. Comprehensive comparison of health-related quality of life after contemporary therapies for localized prostate cancer. J Clin Oncol 2002;20:557–566. [PubMed: 11786586]
18. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–1847. [PubMed: 9603539]
19. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007;62:722–727. [PubMed: 17634318]
20. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001;1:323–336. [PubMed: 12806071]
21. Goggins WB, Woo J, Sham A, Ho SC. Frailty index as a measure of biological age in a Chinese population. J Gerontol A Biol Sci Med Sci 2005;60:1046–1051. [PubMed: 16127111]
22. Kulminski AM, Ukraintseva SV, Akushevich IV, Arbeev KG, Yashin AI. Cumulative index of health deficiencies as a characteristic of long life. J Am Geriatr Soc 2007;55:935–940. [PubMed: 17537097]
23. Yashin AI, Arbeev KG, Kulminski A, Akushevich I, Akushevich L, Ukraintseva SV. Cumulative index of elderly disorders and its dynamic contribution to mortality and longevity. Rejuvenation Res 2007;10:75–86. [PubMed: 17378754]
24. Mitnitski A, Graham J, Mogilner A, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr 2002;2:1. [PubMed: 11897015]
25. Mitnitski A, Song X, Skoog I, Broe GA, Cox JL, Grunfeld E, et al. Relative fitness and frailty of elderly men and women in developed countries and their relationship with mortality. J Am Geriatr Soc 2005;53:2184–2189. [PubMed: 16398907]
26. Rockwood K, Mitnitski A, Song X, Steen B, Skoog I. Long-term risks of death and institutionalization of elderly people in relation to deficit accumulation at age 70. J Am Geriatr Soc 2006;54:975–979. [PubMed: 16776795]
27. Woo J, Goggins W, Sham A, Ho SC. Public health significance of the frailty index. Disabil Rehabil 2006;28:515–521. [PubMed: 16513584]
28. Kulminski A, Ukraintseva SV, Akushevich I, Arbeev KG, Land K, Yashin AI. Accelerated accumulation of health deficits as a characteristic of aging. Exp Gerontol 2007;42:963–970. [PubMed: 17601693]
29. Kulminski A, Yashin A, Arbeev K, Akushevich I, Ukraintseva S, Land K, et al. Cumulative index of health disorders as an indicator of aging-associated processes in the elderly: Results from analyses of the National Long Term Care Survey. Mech Ageing Dev 2007;128:250–258. [PubMed: 17223183]
30. Kulminski A, Yashin A, Ukraintseva S, Akushevich I, Arbeev K, Land K, et al. Accumulation of health disorders as a systemic measure of aging: Findings from the NLTCS data. Mech Ageing Dev 2006;127:840–848. [PubMed: 16978683]
31. Yashin AI, Arbeev KG, Kulminski A, Akushevich I, Akushevich L, Ukraintseva SV. Health decline, aging and mortality: how are they related? Biogerontology 2007;8:291–302. [PubMed: 17242962]
32. Gagnon DR, Zhang TJ, Brand FN, Kannel WB. Hematocrit and the risk of cardiovascular disease--the Framingham study: a 34-year follow-up. Am Heart J 1994;127:674–682. [PubMed: 8122618]
33. Dawber TR, Kannel WB, Lyell LP. An approach to longitudinal studies in a community: the Framingham Study. Ann N Y Acad Sci 1963;107:539–556. [PubMed: 14025561]
34. Grundy SM, Pasternak R, Greenland P, Smith S Jr. Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 1999;100:1481–1492. [PubMed: 10500053]

35. Menotti A, Lanti M, Kafatos A, Nissinen A, Dontas A, Nedeljkovic S, et al. The role of a baseline casual blood pressure measurement and of blood pressure changes in middle age in prediction of cardiovascular and all-cause mortality occurring late in life: a cross-cultural comparison among the European cohorts of the Seven Countries Study. J Hypertens 2004;22:1683–1690. [PubMed: 15311095]

36. Cutler DM. The potential for cost savings in Medicare's future. Health Aff (Millwood) 2005;24(Suppl 2):W5R77–80.

Table 1

A set of the 39 deficits used in the analyses

N	Deficit	N	Deficit
1	*urinary sugar* *	*21*	*increased antero-posterior diameter*
2	urinary albumin	22	abnormal breath sounds
3	chronic cough	23	rales
4	trouble with wheezing	24	abnormal heart sounds
5	*dyspnea or exertion*	25	distended neck veins
6	increase in dyspnea	26	abnormal breast
7	orthopnea	27	localized breast mass
8	paroxysmal nocturnal dyspnea	*28*	*axillary breast nodes*
9	ankle edema	*29*	*liver enlarged*
10	chest discomfort	30	left ankle edema
11	*frequent coldness in one hand/foot*	31	right ankle edema
12	discomfort in lower limbs while walking	32	peripheral pulses: dorsal pedis
13	arcus senilis	*33*	*peripheral pulses: posterior tibial*
14	xanthelasma	34	peripheral pulses: femoral
15	xanthomata	35	peripheral pulses: radial
16	thyroid exam: scar	36	venous insufficiency or varicose veins
17	thyroid exam: single nodule	37	premature beats on ECG
18	thyroid exam: multiple nodules	*38*	*clinically diagnosed functional class*
19	thyroid exam: diffuse enlargement	*39*	*pulmonary disease*
20	other manifestation of thyroid disease		

* Italicized and underlined deficits are significantly associated individually with the probability of death occurring within the 24-year follow-up for participants of the 9th FHS exam (see discussion in the “Results” section).

Table 2

Baseline characteristics of individuals in the combined sample of participants in the 9th and 14th FHS exams

Covariates	Males&Females N=6704		Males N=2828		Females N=3876	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age, years	63.1 (9.1)	44-88	62.5 (8.8)	44-86	63.5 (9.2)	44-88
Cigarettes/day	6.6 (11.7)	0-90	9.2 (14.1)	0-90	4.9 (9.4)	0-50
BMI, kg/m^2	26.6 (4.2)	15.5-54.2	26.8 (3.6)	15.5-54.2	26.4 (4.6)	16.5-53.2
Explanatory variables:						
DI, %	5.1 (5.7)	0-54.3	5.1 (5.9)	0-42.2	5.1 (5.6)	0-54.3
PP, mm Hg	57.7 (16.2)	18-157	55.9 (14.9)	24-139	59.1 (16.9)	18-157
DBP, mm Hg	81 (10.7)	37-140	81.9 (10.8)	37-131	80.3 (10.6)	40-140
PR, beats/min	76.8 (12.9)	30-150	75.3 (13.3)	41-150	77.8 (12.5)	30-130
SCH, mg/100 ml	237 (44.3)	96-625	225 (41.0)	96-413	245 (44.7)	96-625
BG, mg/100 ml	90.7 (30.2)	37-460	91.7 (32.9)	37-460	89.9 (28.1)	44-392
HC, %	44.6 (4.0)	21-62	46.5 (3.7)	30-62	43.2 (3.6)	21-62

SD=standard deviation; BMI=body mass index; DI=deficit index; PP=pulse pressure (the difference between systolic and diastolic blood pressures); DBP=diastolic blood pressure; PR=pulse rate; SCH=serum cholesterol; BG=blood glucose; HC=hematocrit.

J Gerontol A Biol Sci Med Sci. Author manuscript; available in PMC 2009 October 1.

Table 3

Cox regression model estimates of relative risks of death for the 24-year follow-up period for the combined sample of the participants of the 9th and 14th FHS exams

Age, years	Sample	N_{TL} N_{Died}	DI, 95% CI	PP, 95% CI	DBP 95% CI	PR, 95% CI	BG, 95% CI
All ages#	M&F		1.67* 1.58-1.76	1.15* 1.13-1.18	1.14* 1.10-1.17	1.10* 1.07-1.12	1.06* 1.05-1.07
All ages	M&F	5882 3571	1.62* 1.53-1.71	1.11* 1.08-1.13	1.09* 1.05-1.13	1.05† 1.02-1.07	1.05* 1.04-1.06
	Males	2370 1641	1.75* 1.61-1.91	1.09* 1.05-1.13	1.09† 1.04-1.15	1.05§ 1.01-1.09	1.04* 1.03-1.05
	Females	3512 1930	1.52* 1.41-1.64	1.12* 1.09-1.16	1.09† 1.04-1.14	1.04§ 1.01-1.08	1.06* 1.05-1.08
All ages§	M&F	4551 2240	1.49* 1.38-1.62	1.12* 1.08-1.15	1.08† 1.03-1.13	1.04§ 1.00-1.07	1.06* 1.04-1.07
45-49	M&F	433 93	2.53† 1.55-4.13	1.26§ 1.05-1.51			1.07§ 1.01-1.14
50-54	M&F	714 241	1.60† 1.26-2.03	1.15§ 1.03-1.28	1.17§ 1.03-1.32		1.07* 1.05-1.13
55-59	M&F	1064 447	1.85* 1.54-2.22	1.14† 1.06-1.23	1.20* 1.10-1.31		1.05† 1.02-1.08
60-64	M&F	1232 707	1.68* 1.47-1.91	1.08‡ 1.02-1.13	1.09§ 1.01-1.18		1.06* 1.03-1.08
65-69	M&F	1036 778	1.59* 1.42-1.79	1.15* 1.10-1.21	1.07§ 1.00-1.15		1.05* 1.03-1.07
70-74	M&F	763 677	1.62* 1.43-1.82	1.16* 1.11-1.22		1.07§ 1.01-1.14	1.04* 1.02-1.07
75-79	M&F	420 409	1.64* 1.41-1.91				1.05‡ 1.02-1.09
80-84	M&F	186 185	1.54† 1.23-1.93	1.12‡ 1.03-1.22		1.13§ 1.02-1.26	

All models are adjusted for sex, age, smoking, and body mass index.

N_{TL}=the number of subjects in the analysis; N_{Died}=the number of died individuals.

DI=deficit index (%); PP=pulse pressure (the difference between systolic and diastolic blood pressures; mm Hg); DBP=diastolic blood pressure (mm Hg); PR=pulse rate (beats/min); SCH=serum cholesterol (mg/100 ml); BG=blood glucose (mg/100 ml); HC=hematocrit (%).

"All ages" group with N_{TL}=5882 includes also 33 subjects aged 85+ years and 1 subject aged <45 years.

[#] denotes "univariate" analysis when adjusted models included only one of the explanatory variables (see Table 2). The number of subjects is not shown since these numbers are different for each model due to difference in the missing values (these numbers are, however, larger than those in the case of multivariate model). All other models are "multivariate" with all the explanatory variables included.

[§] the analysis is performed for 24 years of follow-up with death occurred within first 10 years excluded

$p<0.05$.

[*] $p<0.0001$

[†] $p<0.001$

[‡] $p<0.01$

Table 4

Logistic regression associations (odds ratios) between a set of physiological indices and the DI and long-lived individuals (survived to ages 85+ years) for the combined sample of the participants of the 9th and 14th FHS exams

Age, years	Sample	N_{TL} N_{LL}	DI_{39def}, 95% CI	PP, 95% CI	DBP 95% CI	SCH, 95% CI	BG, 95% CI	HC, 95% CI	DI_{30def}, 95% CI
50-84 //,#	M&F		0.44* 0.39-0.49	0.79* 0.76-0.83	0.87* 0.82-0.92	1.02§ 1.00-1.03	0.91* 0.87-0.93		0.52* 0.46-0.58
50-84 //	M&F	4950 2066	0.48* 0.42-0.54	0.83* 0.79-0.87	0.93§ 0.87-0.99	1.02§ 1.00-1.03	0.92* 0.90-0.95		0.55* 0.49-0.62
	Males		0.40* 0.32-0.50	0.80* 0.74-0.86			0.93‡ 0.90-0.97		0.46* 0.36-0.57
	Females		0.52* 0.45-0.61	0.85* 0.80-0.89	0.90§ 0.83-0.98	1.02§ 1.00-1.04	0.92* 0.89-0.95		0.59* 0.52-0.69
50-54	M&F	714 138	0.48§ 0.27-0.86		0.69† 0.55-0.86		0.85§ 0.75-0.97		0.53§ 0.31-0.90
55-59	M&F	599 253	0.40* 0.26-0.62	0.71* 0.61-0.83					0.52† 0.35-0.76
60-64	M&F	1232 369	0.39* 0.28-0.55				0.89† 0.83-0.95	0.72† 0.59-0.83	0.48* 0.35-0.65
65-69	M&F	1036 497	0.46* 0.35-0.59	0.76* 0.69-0.84			0.94§ 0.90-0.99		0.55* 0.43-0.70
70-74	M&F	763 391	0.48* 0.37-0.63	0.79* 0.71-0.87			0.92‡ 0.87-0.97		0.55* 0.42-0.71
75-79**	M&F	420 256	0.47* 0.34-0.65					1.39§ 1.06-1.82	0.56† 0.40-0.78

Models are adjusted for sex, age, smoking, and body mass index.

N_{TL}=the number of subjects in the analysis; N_{LL}=the number of long-lived (85+ years) individuals.

DI=deficit index (%); PP=pulse pressure (the difference between systolic and diastolic blood pressures; mm Hg); DBP=diastolic blood pressure (mm Hg); PR=pulse rate (beats/min); SCH=serum cholesterol (mg/100 ml); BG=blood glucose (mg/100 ml); HC=hematocrit (%).

# denotes "univariate" analysis when adjusted models included only one of the explanatory variables (see Table 2). The number of subjects is not shown since these numbers are different for each model due to difference in the missing values (these numbers are, however, larger than those in the case of multivariate model). All other models are "multivariate" with all the explanatory variables included.

// Individuals from the <50 age category for exam 9 (N=579) and the <60 age category for exam 14 (N=465) were excluded because they could not have achieved age 85 years before the end of follow-up at exam 25.

* p<0.0001

† p<0.001

$\neq_{p<0.01}$

$\S_{p<0.05}$.

** The 80+ age category (N=186) was excluded due to small number of controls (N=24), i.e., individuals who did not survive until age 85. This group is retained in the 50-84 sample.