Patterns of Aging-Related Changes on the Way to 100: An Approach to Studying Aging, Mortality and Longevity From Longitudinal Data

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Abstract

Objective. To investigate dynamic properties of age trajectories of physiological indices and their effects on mortality risk and longevity using longitudinal data on more than 5,000 individuals collected in biannual examinations of the Framingham Heart Study (FHS) original age group during about 50 subsequent years of follow up.

Methods. First, we performed empirical analyses of the FHS longitudinal data. We evaluated average age trajectories of indices describing physiological states for different groups of individuals and established their connections with mortality risk. These indices include body mass index, diastolic blood pressure, pulse pressure, pulse rate, level of blood glucose, hematocrit and serum cholesterol. To be able to investigate dynamic mechanisms responsible for changes in the aging human organisms using available longitudinal data, we further developed a stochastic process model of human mortality and aging (Yashin and Manton 1997), by including in it the notions of "physiological norms," "allostatic adaptation and allostatic load," "stress resistance" and other characteristics, associated with the internal process of aging and effects of external disturbances. In this model, the persistent deviation of physiological indices from their normal values contributes to an increase in morbidity and mortality risks. We used the stochastic process model in the statistical analyses of longitudinal FHS data.

Results. We found that different indices have different average age patterns and different dynamic properties. We also found that age trajectories of long-lived individuals differ from those of the shorter-lived members of the age group for both sexes. Using methods of statistical modeling, we evaluated "normal" age trajectories of physiological indices and the dynamic effects of allostatic adaptation. The model allows for evaluating average patterns of aging-related decline in stress resistance. This effect is captured by the narrowing of the U-shaped mortality risk (considered a function of physiological state) with age. We showed that individual indices and their rates of change with age, as well as other measures of individual variability, manifested during the life course, are important contributors to mortality risks. The biological mechanisms, which might contribute to the age patterns corresponding to exceptional health and/or longevity are discussed.

Key Words: Mortality, Life Span, Longitudinal Data, Statistical Modeling, Healthy Aging, Survival Improvement

Introduction

To provide a good fit to mortality data, the parametric functions approximating age patterns of mortality rates are often used in demographic and actuarial applications. Usually these functions are selected without making connection to factors and mechanisms that contribute to changes in the mortality rate during the life course. As a result, parameters of such models are difficult to interpret from biological or medical points of view. The growing desire to understand why and how biological processes developing in aging humans contribute to age-related increases in the mortality rate stimulates collection of data about aging-related changes in the body and evaluation of their links with survival outcomes aiming to develop mortality models whose parameters could be better interpreted biologically. Ideally, individual data capturing biological and physiological changes developing in the bodies during the entire life course as well as data describing influential factors and processes affecting individuals during this period would be most appropriate to perform this task, taking into account that conditions, experienced by people early in life, are likely to affect their morbidity and mortality risks at late ages. However, such data are practically unavailable, and most available data are incomplete. Some of the best available data collected in the Framingham Heart Study (see the description below) deal with physiological/biological changes and health/survival outcomes, which took place at the interval of aging, i.e., after 30 to 40 years of age in selected age groups of individuals.

The age pattern of the human mortality rate between ages 30 and 85 is well approximated by the Gompertz curve, $\mu(x) = ae^{bx}$, or by the Gompertz-Makeham curve, $\mu(x) = c + ae^{bx}$. After age 85, the exponential growth of the mortality rate decelerates and tends to level off at ages around 110 (Vaupel 2010; Vaupel et al. 1998). Such a description of age trajectory of mortality rates (with different parameter values) is appropriate for populations in different countries and in different time periods. In population studies of aging and mortality with laboratory animals, the differences in the values of the Gompertz parameter, *b*, in the experimental and control groups, are often interpreted as differences in the rates of aging. According to this interpretation, an increase in *b*, resulting from an exposure to certain external conditions, indicates that these conditions increase the individual aging rate in the exposed population. Note that although such one-parameter measure of aging is simple and convenient, it should be used with care. In Yashin et al. (2002), we showed that the

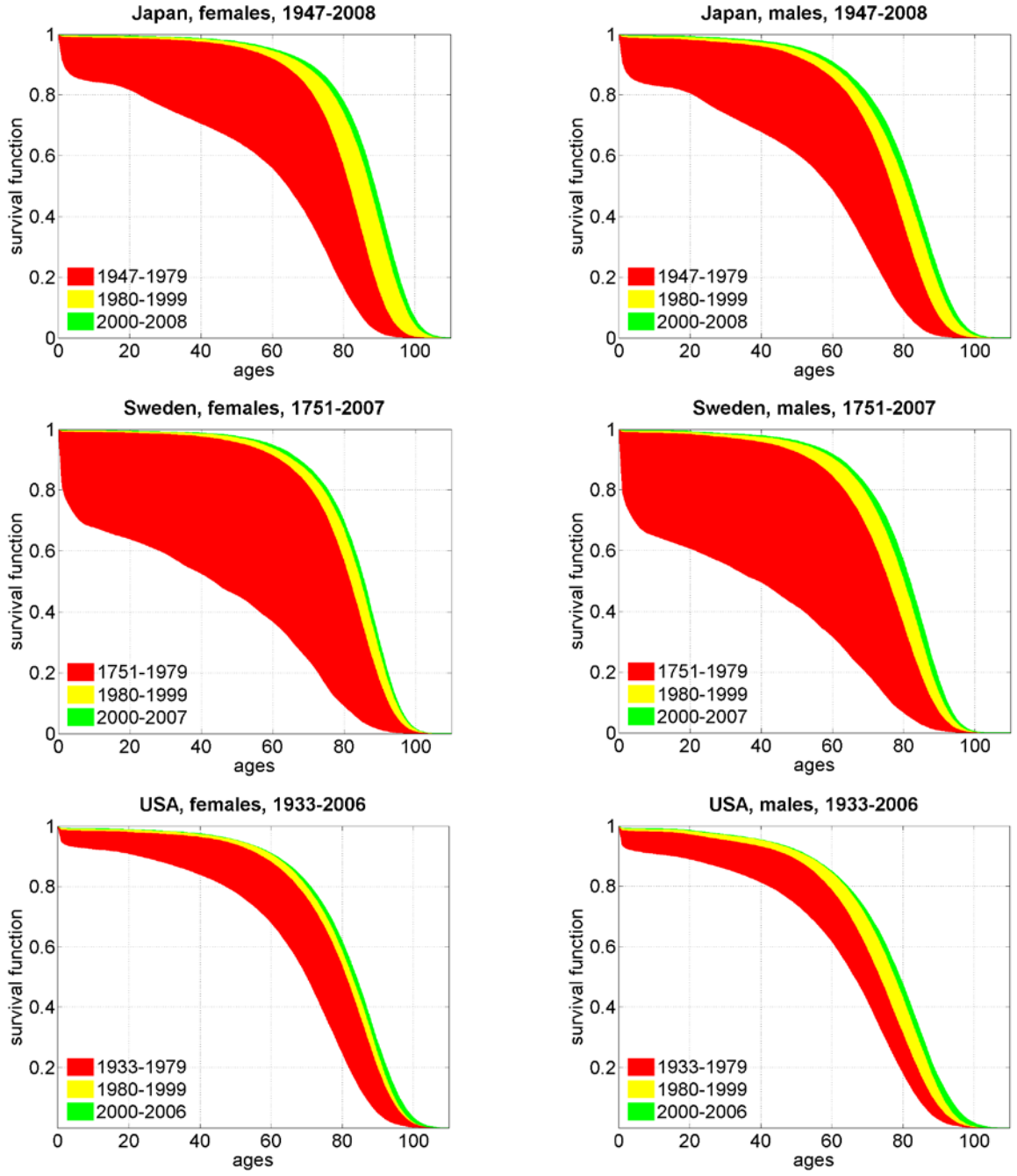
slope of mortality rate can be modulated by many other factors not related to aging. These include changes in distribution of hidden heterogeneity (Vaupel and Yashin 1985), advances in health care (e.g., saving lives) (Vaupel and Yashin 1987; Yashin et al. 2000), and changes in average magnitude of external stresses (Strehler and Mildvan 1960; Yashin et al. 2001; Yashin et al. 2002).

During the past few decades, the studies of aging and factors affecting life span were substantially intensified. Many new factors and important biomarkers of aging were found, their connection to morbidity and mortality risks were evaluated, and many new longitudinal datasets were collected and became available for researchers. Despite this remarkable progress in acquiring new knowledge about aging and longevity, the integrative quantitative analyses linking this information with survival outcomes has not been performed. Therefore, the development of mortality models, whose parameters characterize properties of aging-related changes developing in the human body, as well as effects of other factors and conditions, remains a challenging and important issue.

The interest in better understanding factors and mechanisms affecting human mortality was recently heated by substantial progress in improvements to human survival observed in developed countries during the past century. The improvements can be described in the parameter changes of the Gompertz-Makeham model: Parameter *c*, the background mortality component, and parameter *a* both declined almost monotonically with years. Parameter *b* almost monotonically increased until about 1979 but had many smaller changes later on, whereas parameter *a* showed a clear tendency to continue the decline. This progress in mortality reduction can be illustrated by changes in respective survival curves. Figure 1 shows the age patterns of survival improvement in Japan, Sweden and the United States for males and females.

Figure 1

Period Survival Functions for Females and Males in Japan, Sweden and the United States



Source: the Human Mortality Database, www.mortality.org.

One can see from this figure there are two main patterns of such an improvement. The first one is associated with the "rectangulariazation" of the survival curve, which took place up to about 1979 in all three countries. It is characterized by an increase in survival among young and adult individuals, an increase in the mean life span, a reduction in the variance of life span distribution, and small or no changes in the maximum life span (Edwards and Tuljapurkar 2005; Wilmoth and Horiuchi 1999). The second pattern took place in the most recent decades. It is characterized by a substantial improvement in survival of the elderly, continuing decline in the mortality rate among young and adult individuals, and by slowing down the decline in the variance of life span distribution. These changes are manifested in an almost parallel shift of the entire survival curve to the right in Figure 1. This suggests that surviving to 100 for individuals from today's generation became easier (the most dramatic changes are seen for Japanese females). Note, however, that despite numerous speculations about possible causes of observed mortality decline, there is no model in which connection between influential factors and respective mortality risks is quantitatively described.

Despite the fact that the variance in life span distribution decreased substantially during the last century, the variability in human life span remains high (Lynch and Brown 2001; Murray et al. 2006; Peltzman 2009). This suggests the presence of hidden influential factors (of genetic and nongenetic origin) distributed among individuals in the population. Evaluating such factors and their dynamic effects on mortality risks could be helpful in predicting individual life spans (Cutler et al. 2006). The fact that an additive genetic component explains about 2 percent of variability in life span (Herskind et al. 1996; McGue et al. 1993) indicates that nongenetic factors make substantial contribution to life span. Since an organism is exposed to external factors during the entire life course, and aging itself is an important risk factor, studying factors and mechanisms involved in regulation of aging-related changes developing in the human body will shed light on causes of variability in longevity.

The fact that the age-pattern-of-mortality rate results from interaction between the process of individual aging and external disturbances was understood by Strehler and Mildvan (1960), who developed a respective mortality model (the Strehler-Mildvan, or SM model). The SM model represents mortality rate as a function of two processes: (1) aging-related decline in vitality, a

hypothetical index capturing individual aging, and (2) a random multivariate point process of external disturbances (stresses) characterized by a constant intensity function and an average magnitude of stresses. The death occurs when the magnitude of stress exceeds the value of vitality. Because the vitality declines with age and disturbances are described by a stationary stochastic process, the mortality rates increase with age.

The model explained the negative correlation between the Gompertz parameters, *a* and *b*, observed in comparative analyses of mortality rates in different time periods or in different countries. It also showed the rectangularization pattern of survival improvement may result from the decline in the average magnitude of external disturbances that were experienced by human populations until the end of 1980s. This model shows that the Gompertz growth parameter *b* is directly proportional to the rate of individual aging and is inversely proportional to the average magnitude of external stresses (Yashin et al. 2001a; Yashin et al. 2002a). This means that the reduction in the average magnitude of stresses results in an increase of parameter *b*. It turns out that under such transformation, the values of the Gompertz parameter *a* decline (this parameter also declines when the frequency of stresses declines), so the new total mortality rates in populations subjected to such changes will be lower than before with the higher rate of increase with age. Thus, according to the SM model, a person who plans to maximize chances of living to 100 or more without changing the individual aging related decline in vitality should maximally decrease the magnitude and the frequency of external stresses.

The latter recommendation, however, should be used with care because of the following reasons. First, as one can see from Figure 1, the rectangularization pattern did not take place in the past few decades. There is currently no mathematical model that would provide us with a satisfactory explanation of the recent trend in survival improvement demonstrating “the parallel shift of the entire survival curve to the right” (Yashin et al., 2001a). Second, this conclusion contradicts the experimentally verified concept of longevity hormesis (Le Bourg and Rattan 2008; Le Bourg and Rattan 2006; Michalski et al. 2001; Michalski and Yashin 2002; Wu et al. 2009; Yashin 2009; Yashin et al. 2001), which suggests mild stresses in life may result in a longevity increase. The existence of a hormesis effect indicates that the mortality risk, considered as a function of risk factors, has an “optimal” point where it reaches its minimal possible value. It is

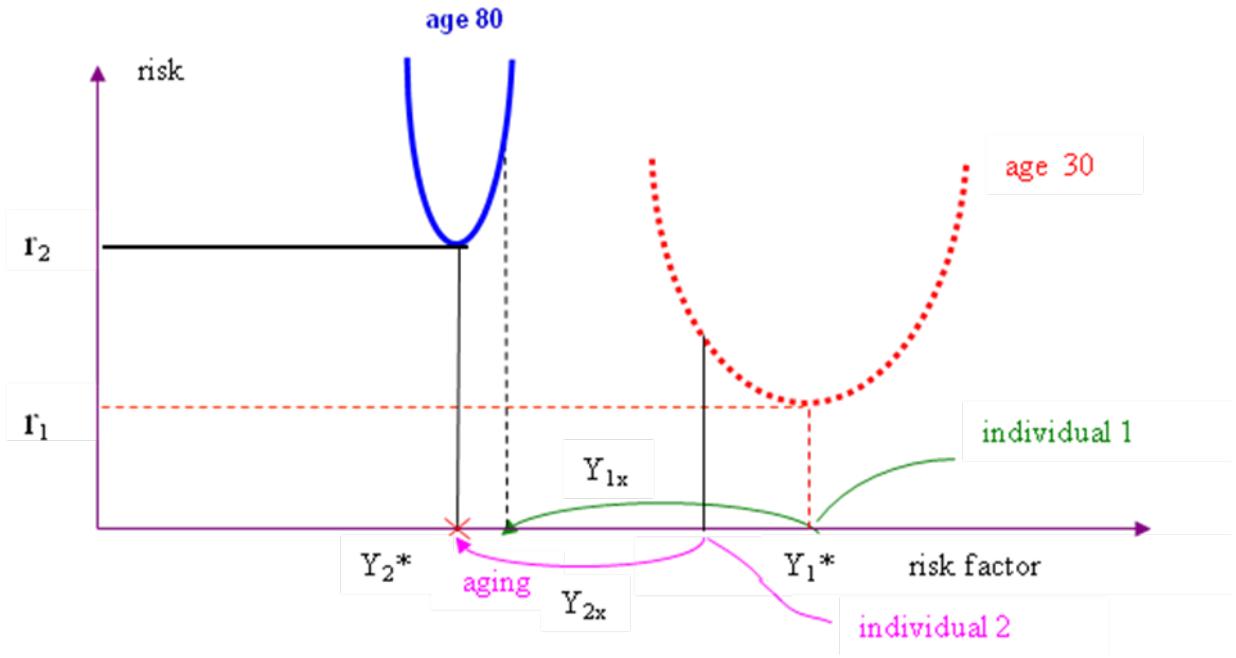
interesting that the U-shaped mortality risk functions were independently detected and intensively investigated in epidemiological studies (Allison et al. 1997; Boutitie et al. 2002; Kulminski et al. 2008; Kuzuya et al. 2008; Mazza et al. 2007; Okumiya et al. 1999; Protogerou et al. 2007; Troiano et al. 1996; van Uffelen et al. 2010) without references to the hormesis effect. This observation suggests that the concept of longevity hormesis is likely to have a solid biological background and should be taken into account in any studies dealing with factors affecting morbidity and mortality risks (Yashin 2009).

Note that the age patterns of mortality rates or survival curves do not provide one with an appropriate background for developing a strategy for increasing chances of living to 100. The recommendation followed from the SM model is too general; it does not specify types of external disturbances, or other risk factors, and does not take a possibility that mortality risk function may be U- or J-shaped into account. More appropriate for developing a proper survival strategy would be considering conditional mortality risks given a set of measurable risk factors, which could be properly modified when needed. For example, smokers could give up smoking to increase longevity, heavy drinkers could reduce the dose, hypertonic people could take proper drugs and maybe change lifestyle, obese individuals must change the diet and increase the level of physical exercises, etc. What should individuals who do not smoke, do not drink heavily, etc., do to increase their chances of living to 100? How can one find additional variables affecting survival chances? Which values of these variables could be used as target values to improve survival? To address these questions, one should have the list of factors suspected for influencing mortality risk; have regular measurements of these factors and survival outcomes during an individual's life course; develop an appropriate way of taking knowledge about aging, accumulated in the field, into account, and linking risk factors with morbidity/mortality risks; describe age dynamics of observed covariates experiencing aging-related changes; and calculate "optimal" trajectories of risk factors and use them as target trajectories, i.e., keep the values of individual's risk factors close to the target trajectories.

Several dynamic features of aging organisms deserve special attention. The first one deals with the fact that the point in the "risk factor space" where risk function reaches its minimum (the "optimal" point) does not remain constant, but changes with increasing age. Figure 2 illustrates this

situation by representing a hypothetical U-shaped mortality risk as a function of two dynamic covariates. Although the causes and regularities of changes in the "optimal" risk values require additional studies, respective age trajectories can be evaluated from longitudinal data when the sample size of these data is large enough.

Figure 2



A hypothetical U-shaped mortality risk as a function of two dynamic covariates: values of risk factors (Y_{1x} for individual 1, and Y_{2x} for individual 2), optimal risk values (r_1 for age 30 and r_2 for age 80) as well as the optimal value of risk factors (Y_1^* for individual 1, and Y_2^* for individual 2) may change with age. The hypothetical quadratic hazard function is shown by the dotted line at age 30 and by a solid line at age 80. Individual 1 has the minimal possible value of risk at age 30 and a nonoptimal risk at age 80. Individual 2 has a nonoptimal value of risk at age 30.

The second property deals with the aging-related changes in the shape of the risk function. For some risk factors, the U-shaped risk function may become narrower with increasing age. This property indicates that the same deviation from the "optimal" point for a given age will be associated with a higher increment in mortality risk at the older ages than at the younger ages, and it characterizes the aging-related decline in resistance to stresses. Since effects of external stresses on

longevity are mediated by physiological response, one can expect manifestation of such decline in stress resistance in the mortality risk considered as a function of physiological variables. It became clear recently (Arbeev et al. 2009; Yashin et al. 2007; Yashin et al. 2008; Yashin et al. 2010; Yashin et al. 2009) that such changes in mortality risks can be evaluated from the data collected in longitudinal studies of aging, health and longevity. The rates of narrowing of such mortality risks are important population characteristics showing how survival chances depend on stresses affecting individuals' physiological state at different periods of their life. At the same time, some factors harmful at the earlier adult ages may become less harmful at the older ages. This could happen because compensatory adaptation and remodeling accompanying the aging process could produce substantial changes in relationships between an organism and the external world.

Thus, to maximize chances of living to 100, one has to know the values of risk factors and age trajectories of physiological indices, which minimize mortality risk at any given age. It would also be important to better understand the properties of aging-related changes in individual physiological indices. The longitudinal data collected in the Framingham Heart Study (FHS) is a useful source of information for investigating these properties.

Data and Method

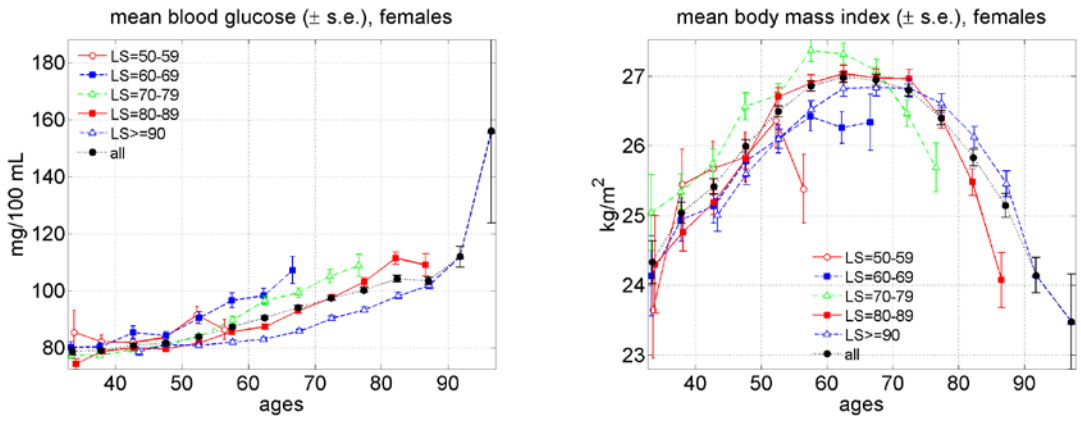
The Framingham Heart Study (FHS) was launched in 1948, with 5,209 respondents (55 percent females) ages 28 to 62 residing in Framingham, Mass., who had not yet developed overt symptoms of cardiovascular disease (Dawber et al. 1951). The study continues to the present with biennial examinations that include detailed medical history, physical exams and laboratory tests (data from exams 1 to 25 were used in this study).

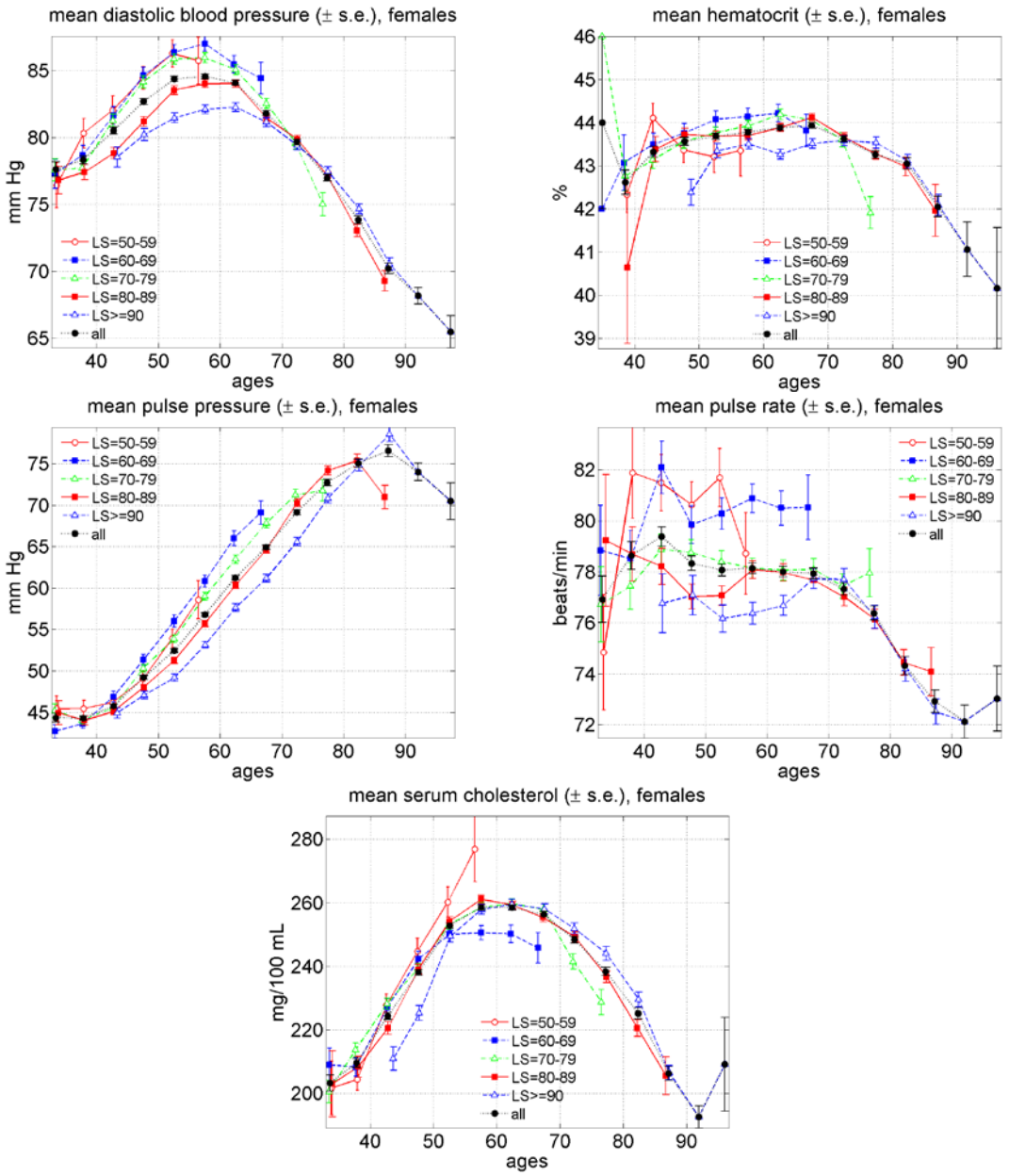
Phenotypic traits collected in the FHS cohorts older than 60 and relevant to our analyses include: life span, ages at onset of diseases (with the emphasis on cardiovascular diseases [CVD], cancer and diabetes mellitus), and indices characterizing physiological state. The occurrence of CVD and cancer and death has been followed through continuous surveillance of hospital admissions, death registries, clinical exams and other sources, so that all the respective events are included in the study. We used data on onset of CVD, cancer (calculated from the

follow-up data) and diabetes (defined as the age at the first exam when an individual has a value of blood glucose exceeding 140 mg/dl and/or takes insulin and/or an oral hypoglycemic agent) to define the age at onset of "unhealthy life" as the minimum of ages at onset of these three diseases. If an individual did not contract any of these diseases during the observation period, then the individual was considered censored at the age of the last follow-up or death. Individuals who had any of the diseases before the first FHS exam were excluded from the analyses of "unhealthy life." Data on physiological indices include: blood glucose (BG) (exams 1 to 4, 6, 8 to 10, 13 to 23); body mass index (BMI) (exams 1 to 25); diastolic blood pressure (DBP) (exams 1 to 25); hematocrit (HC) (exams 4 to 21); pulse pressure (PP) (exams 1 to 25); pulse rate (PR) (exams 1, 4 to 25); and serum cholesterol (SCH) (exams 1 to 11, 13 to 15, 20, 22 to 25).

Average age trajectories of physiological indices and their difference among long- and short-lived individuals. The individual age trajectories of physiological indices are likely to be the product of compensatory adaptation and remodeling developed in people's biological and physiological systems in response to deterioration produced by primary aging (senescence) process, or by external disturbances. The values of such indices affect morbidity and mortality risks and therefore are predictive factors for longevity and healthy life span. Despite the fact that age trajectories of a given index may differ substantially among individuals in the age group, their average age patterns follow remarkable regularities. Figures 3 and 4 (black dots) show two types of average age trajectories.

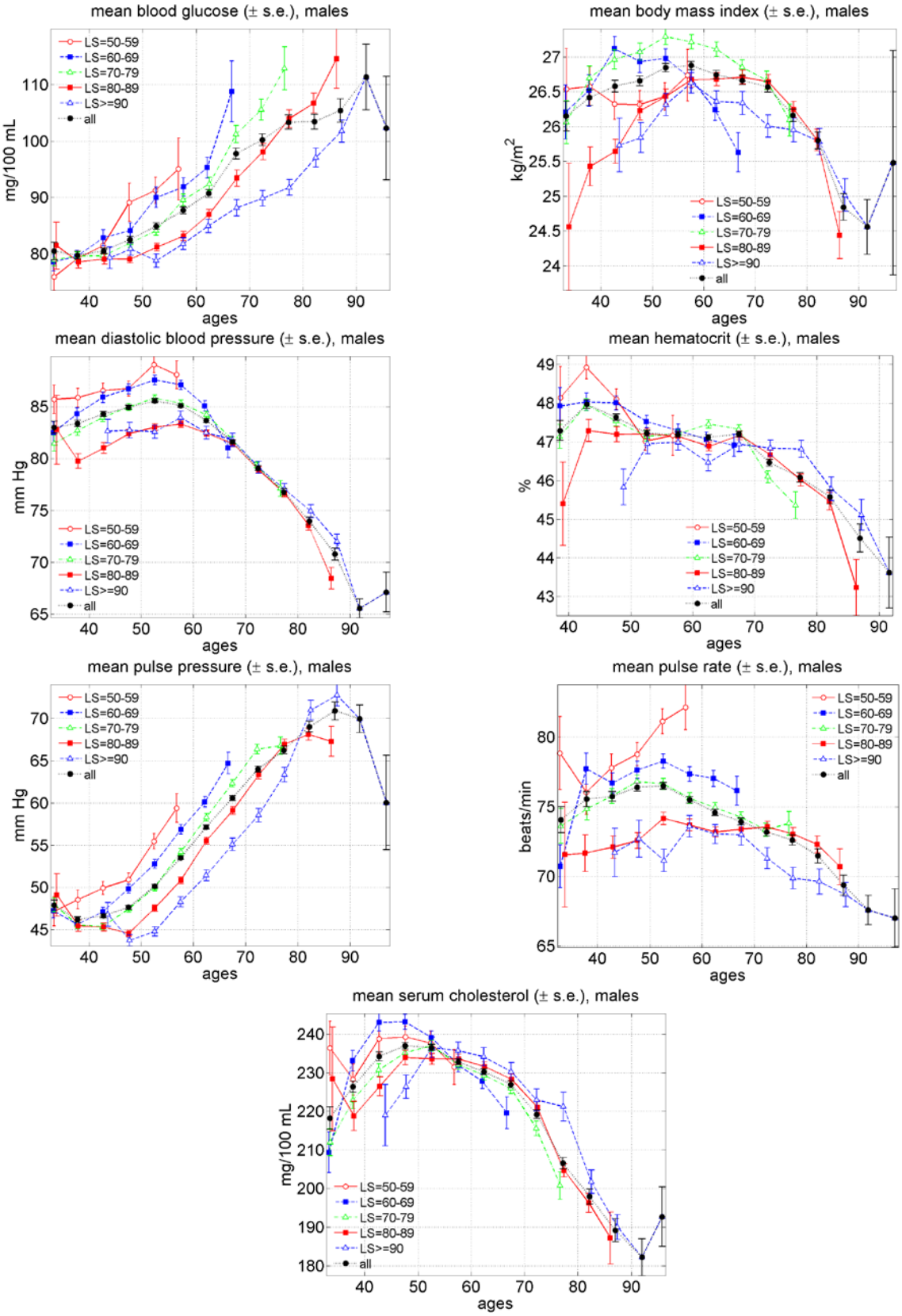
Figure 3





Average age trajectories of physiological indices ± standard error (±s.e.) for long-lived (life span [LS] exceeding 90 years ["LS>=90"]) and short lived (LS=50-59, 60-69, 70-79 and 80-89) females in the Framingham Heart Study (original cohort, pooled data from exams 1 to 25); "all" denotes average trajectories for the entire sample.

Figure 4


mean blood glucose (± s.e.), males
mg/100 mL
ages
mean body mass index (± s.e.), males
kg/m2
ages
mean diastolic blood pressure (± s.e.), males
mm Hg
ages
mean hematocrit (± s.e.), males
%
ages
mean pulse pressure (± s.e.), males
mm Hg
ages
mean pulse rate (± s.e.), males
beats/min
ages
mean serum cholesterol (± s.e.), males
mg/100 mL
ages
LS=50-59
LS=60-69
LS=70-79
LS=80-89
LS>=90
all

Average age trajectories of physiological indices ± standard error (±s.e.) for long-lived (life span [LS] exceeding 90 years ["LS>=90"]) and short lived (LS=50-59, 60-69, 70-79 and 80-89) males in the Framingham Heart Study (original cohort, pooled data from exams 1 to 25); "all" denotes average trajectories for the entire sample.

A distinctive feature of the first type of curves is their almost monotonic changes with increasing age. These include the level of blood glucose and pulse pressure. The average trajectories of the second type are clearly nonmonotonic; they tend to increase and then decline. This group includes body mass index, which increases up to age about 70; diastolic blood pressure, which increases until age 55 to 60; serum cholesterol, which increases until age 50 in males and until age 70 in females; pulse rate, which increases until age 55 in males and until age 45 in females; and hematocrit, which declines after age 70 in both sexes. One can see that these general patterns are similar in males and females.

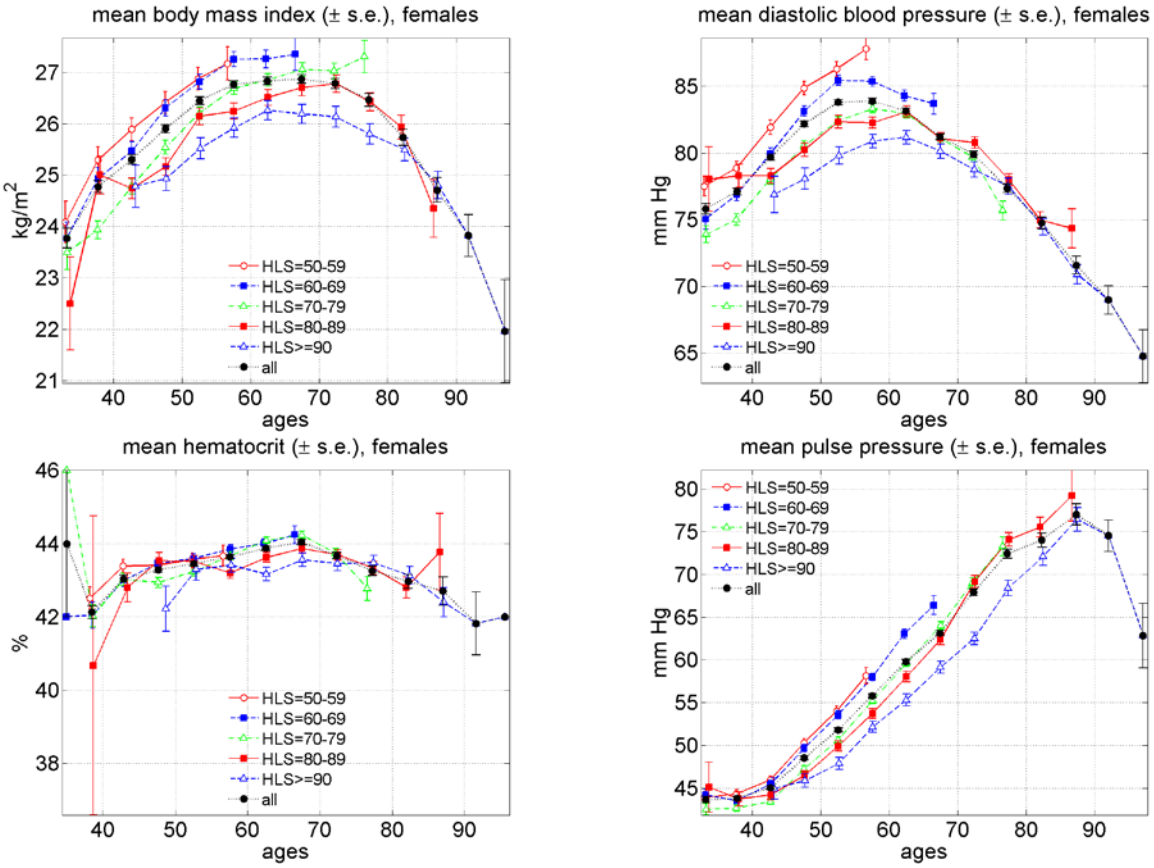
It is important to note that average age trajectories shown in figures 3 and 4 do not represent average biological changes developing in an aging human organism. This is because compositional changes, taking place because of mortality selection, affect the averaging procedure and modify the population mean. Individuals, whose physiological indices substantially deviate from their "optimal" values, experience higher-than-average mortality risks. These individuals tend to die out first and drop out of the averaging procedure. To eliminate effects of compositional changes in such trajectories, we stratified the population cohort into subcohorts by the age at death. The age trajectories of physiological indices for groups of individuals who died at different age intervals are shown in figures 3 and 4.

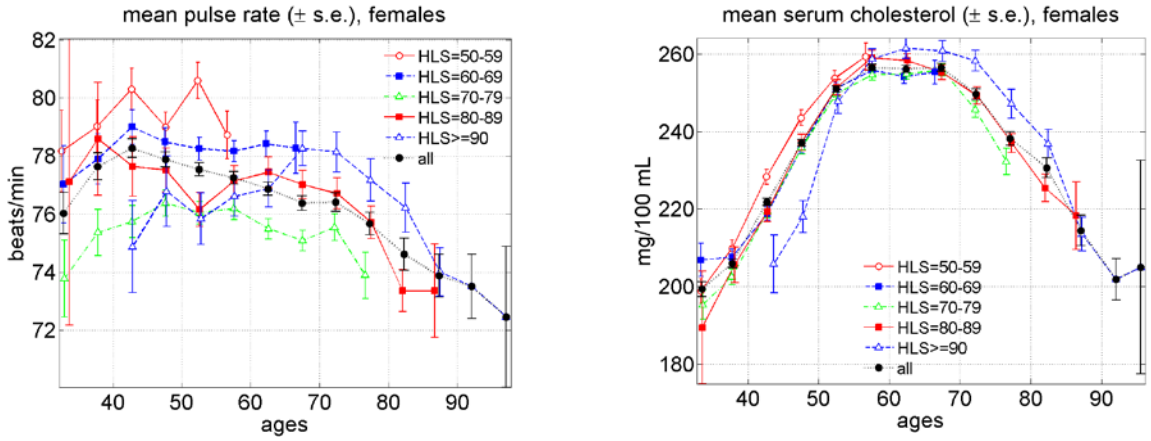
One can see from these figures that individuals who died at different ages had different average age trajectories of physiological indices. Note also that average age trajectories of physiological indices calculated for individuals whose life span exceeded 90 years (long-lived individuals) do not include compositional changes before age 90, and, hence, represent average biological changes developing in an aging organism. One can also see some interesting regularities in age trajectories of those who died prematurely. For example, the age trajectories of blood glucose and pulse pressure for the short-lived individuals of both sexes tend to be higher

than those for the longer-lived people. The situation with other indices looks more complicated and will be discussed later.

Average age trajectories of physiological indices for individuals with different ages at onset of unhealthy life. Variables, describing physiological state, affect morbidity risk. Average age patterns of physiological indices in the groups of individuals stratified by the age at onset of unhealthy life (defined here as onset of CVD, cancer or diabetes, whichever is the earliest) are shown in Figure 5 for females and Figure 6 for males (note that BG is not shown here as its values define the onset of diabetes).

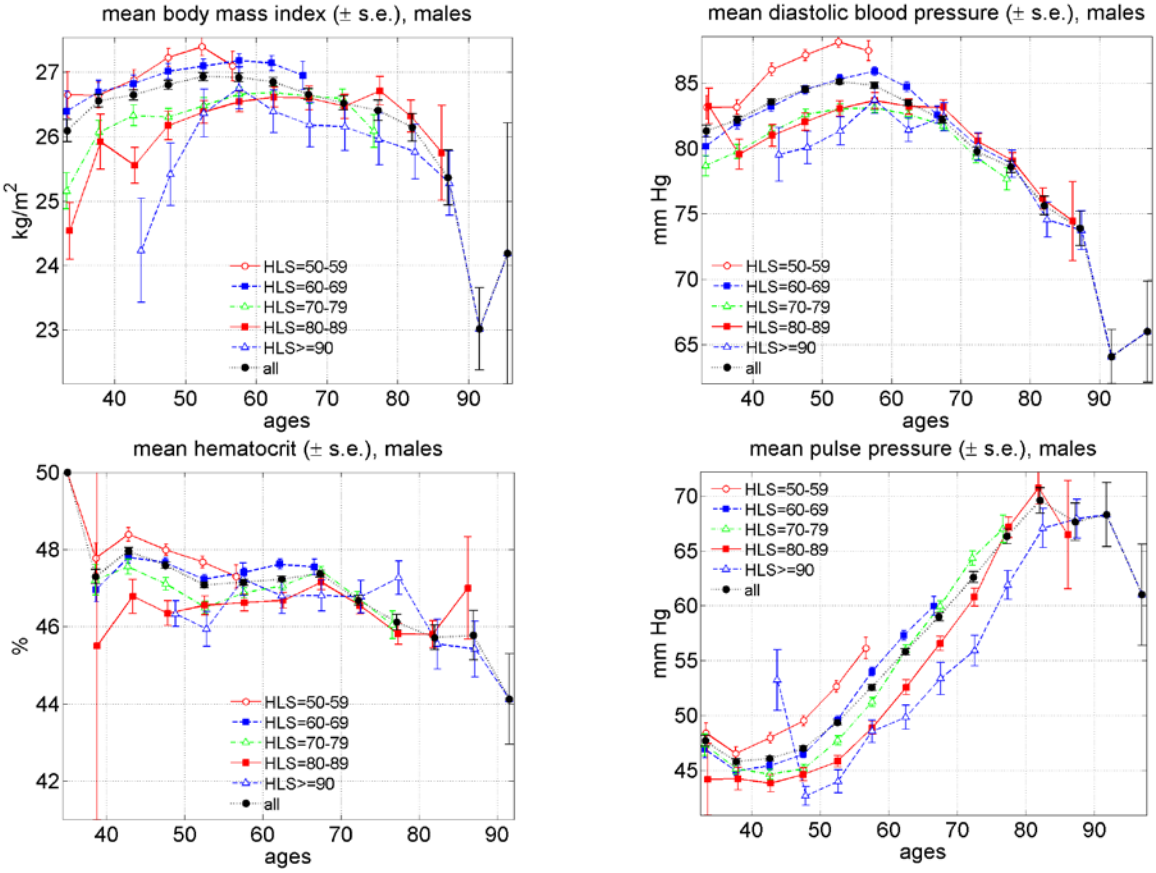
Figure 5

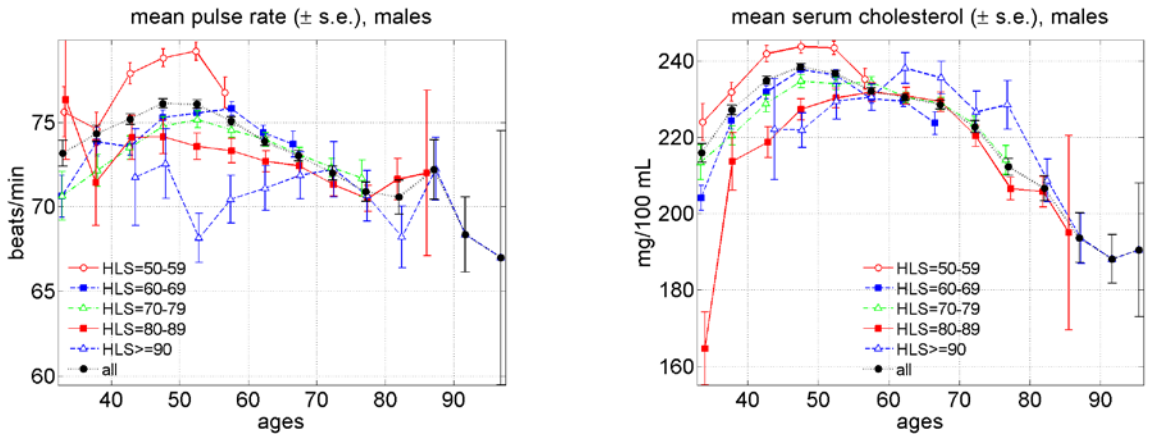




Average age trajectories of physiological indices ± standard error (±s.e.) for females in the Framingham Heart Study (original cohort, pooled data from exams 1 to 25) with different ages at onset of "unhealthy" life (HLS); "all" denotes average trajectories for the entire sample.

Figure 6



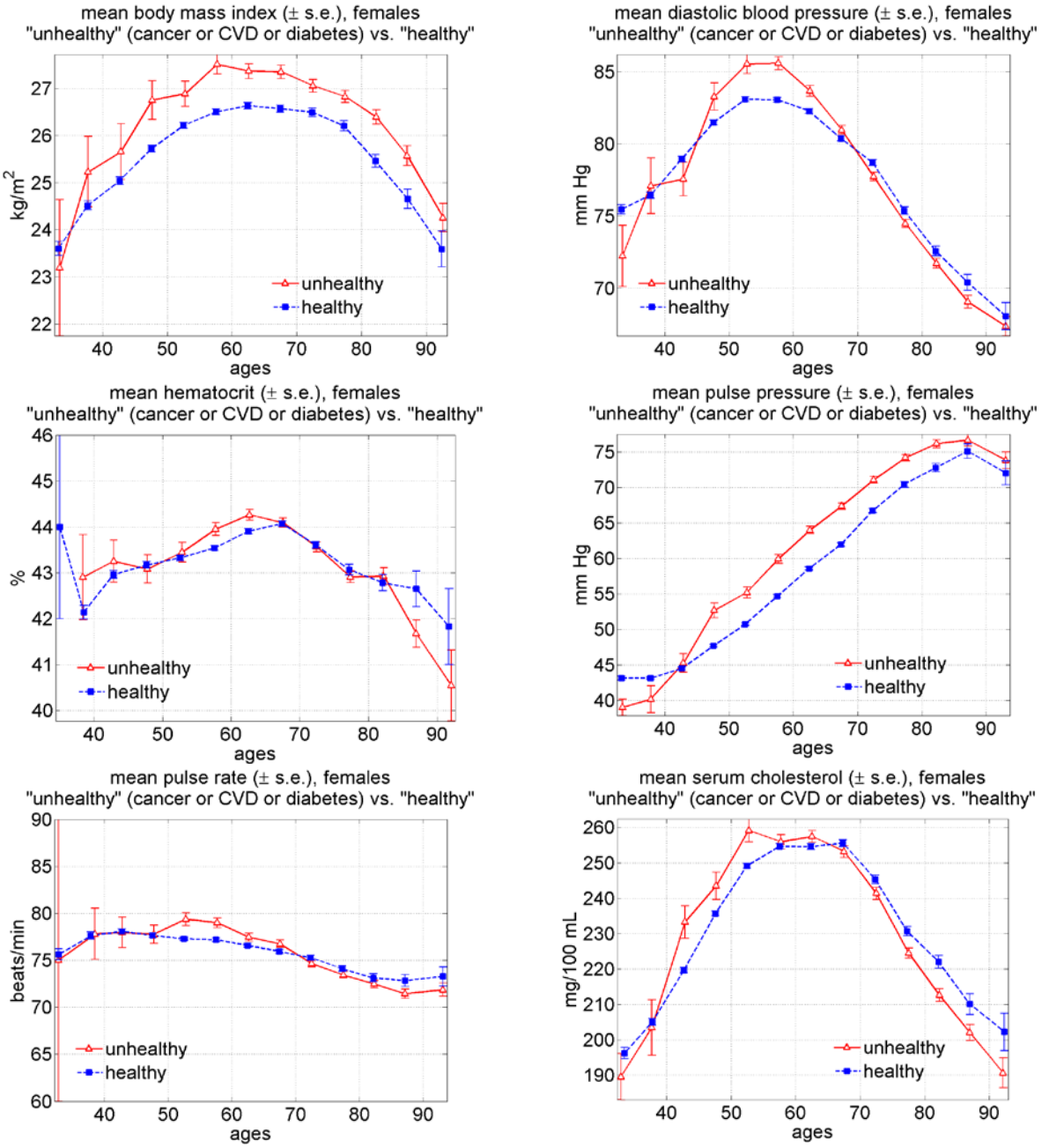


Average age trajectories of physiological indices ± standard error (±s.e.) for males in the Framingham Heart Study (original cohort, pooled data from exams 1 to 25) with different ages at onset of "unhealthy" life (HLS); "all" denotes average trajectories for the entire sample.

One can see from these figures that groups of individuals having different durations of healthy life have different average trajectories of physiological indices. Note that although the age trajectories stratified by the values of life spans differ from those stratified by the values of healthy life spans, their properties look similar. For example, the average age trajectories of pulse pressure for individuals with short healthy life spans tend to be higher than those for individuals having longer healthy life spans. The situation with other indices looks more complicated and will be discussed later.

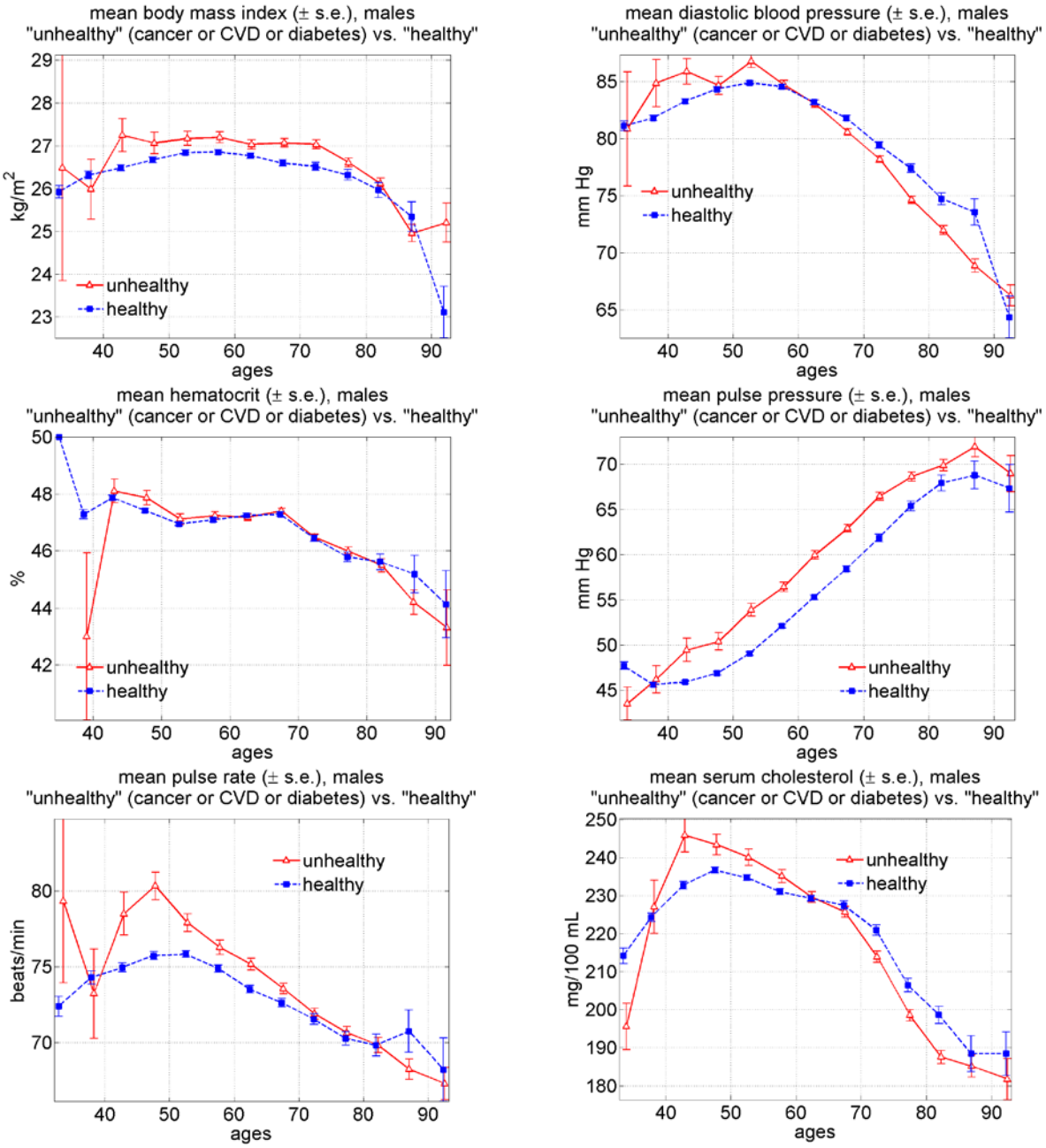
The presence of disease affects dynamic properties of physiological indices. To better understand whether the presence of chronic disease affects the age dynamics of a physiological state, we distinguished between individuals having at least one of three major chronic diseases (cancer, CVD or diabetes) and individuals free of such diseases. Figures 7 and 8 show the difference in average age trajectories of respective indices for healthy and unhealthy individuals.

Figure 7



Average age trajectories of physiological indices ± standard error (±s.e.) for "unhealthy" (those having cancer, cardiovascular disease or diabetes) and "healthy" (those without these three diseases) females in the Framingham Heart Study (original cohort, pooled data from exams 1 to 25).

Figure 8



Average age trajectories of physiological indices ± standard error (±s.e.) for "unhealthy" (those having cancer, cardiovascular disease or diabetes) and "healthy" (those without these three diseases) males in the Framingham Heart Study (original cohort, pooled data from exams 1 to 25).

One can see from these figures that after age 40, the pulse pressure for a healthy individual is lower than that for unhealthy individuals and it remains lower for the rest of their lives. The BMI for healthy individuals is lower than that for unhealthy ones and remains lower for the rest of their lives. Between ages 40 and 60, the average age pattern of serum cholesterol for healthy individuals is lower than that of unhealthy ones. However, after this age, the values of this index for healthy individuals become higher than those of unhealthy ones. Similarly, the level of diastolic blood pressure among healthy individuals is lower than that among unhealthy ones until age 67, and, after this age, the situation reverses. This difference indicates the importance of taking health status into account when investigating age trajectories of physiological indices and their effects on mortality risks. Thus, an individual's physiological state dynamically affects morbidity and mortality risks, and health status affects physiological dynamics and mortality risk. Note that these changes are developing in the presence of other factors affecting physiological dynamics as well as morbidity and mortality risks. These factors often include birth year of the population groups, gender, education, income, occupation, and smoking and drinking habits. An important feature of most longitudinal studies is the limited information about external disturbances affecting individuals in their day-to-day life.

"Dynamic" risk factors. We investigated the dynamic properties of individual age trajectories of the seven physiological indices mentioned above to select factors (referred to as "dynamic" risk factors) capable of affecting mortality risk and the risk of the onset of "unhealthy life" (BG was excluded from the list of indices for analyses of the onset of "unhealthy life" because in the FHS data the onset of diabetes is specifically defined from the values of BG).

First, we evaluated the effect of the rates of change in physiological indices at ages 40 to 60 on mortality risk and the risk of the onset of "unhealthy life" at ages 60 and older. For this purpose, we approximated the individual trajectories of those physiological indices that have nearly linear dynamics (both for females and males) at ages 40 to 60 (BG, BMI, HC and PP) by a linear function of the form $y(x) = a_{40-60} + b_{40-60}(x - 40)$, where x is age and y is the value of a physiological index at age x. Individuals having less than five observations of a respective index at ages 40 to 60 were excluded from the analyses. As a result, we have estimates of three risk factors for each individual and each index: an initial value of an index at age 40 (i.e., a_{40-60},

referred to as **"Intercept$_{40\text{-}60}$"** in the text below), the rate of change in the physiological index at ages 40 to 60 (b_{40-60}, **"Slope$_{40\text{-}60}$"**), and the mean of absolute values of residuals, i.e., deviations of observed values of an index from those approximated by a linear function at ages 40 to 60 (**"Variability$_{40\text{-}60}$"**).

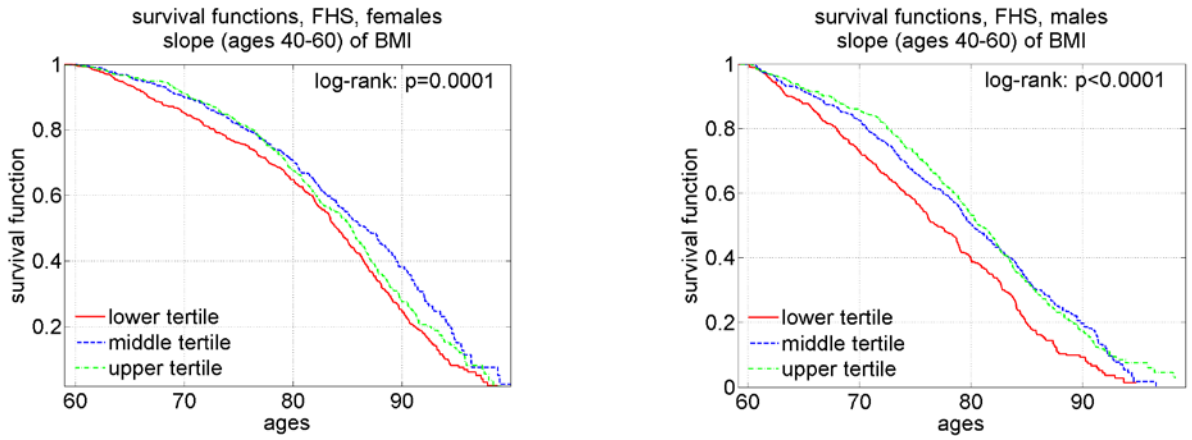
Second, we evaluated the effect of dynamic characteristics of physiological indices with nonmonotonic age trajectories on mortality risk and the risk of the onset of "unhealthy life." For this purpose, we approximated the age trajectories of such indices (BMI, DBP, HC, PR and SCH) by two linear functions. The first one approximates the increase in the trajectory at the initial interval [x_L, $x_{\max}$]: $y(x) = a_L + b_L(x - x_L)$, where x is age and y is the value of a physiological index at age x. The second one approximates the subsequent decline in the trajectory at the interval [$x_{\max}$, x_R] after reaching the maximum value $y_{\max} = a_L + b_L(x_{\max} - x_L)$ at age $x_{\max}$: $y(x) = a_R + b_R(x - x_{\max})$. The intervals [$x_L$, x_R] for the fit were defined empirically for each index and sex as follows: [35, 55] for PR (females); [40, 60] for PR (males) and SCH (males); [45, 65] for BMI (males) and DBP (females and males); [50, 70] for SCH (females); and [55, 75] for BMI (females) and HC (females and males). Note that the following restrictions on parameters were used in the estimation procedures: $b_L > 0$, $b_R < 0$ and $a_R = a_L + b_L(x_{\max} - x_L)$, to ensure the appropriate shape of the fit. Individuals having less than six observations of respective index at ages [$x_L - 5$, $x_R + 5$] and those having estimates of b_L, b_R at the boundary of allowable values (i.e., nearly zero) were excluded from the analyses. As a result, we have estimates of six risk factors for each individual and each index: an initial value of an index at age x_L (i.e., a_L, referred to as **"Intercept$_{2L}$"** in the text below); the rate of increase in the physiological index at ages [x_L, $x_{\max}$] (b_L, **"Left Slope"**); age at reaching the maximal value of the index ($x_{\max}$, **"Age Max"**); the maximal value of the index approximated by two linear functions ($y_{\max}$, **"Max Index"**); the rate of decline in the index at ages [$x_{\max}$, x_R] (b_R, **"Right Slope"**); and the mean of absolute values of residuals, i.e., deviations of observed values of an index from those approximated by two linear functions at ages [x_L, x_R] (**"Variability$_{2L}$"**).

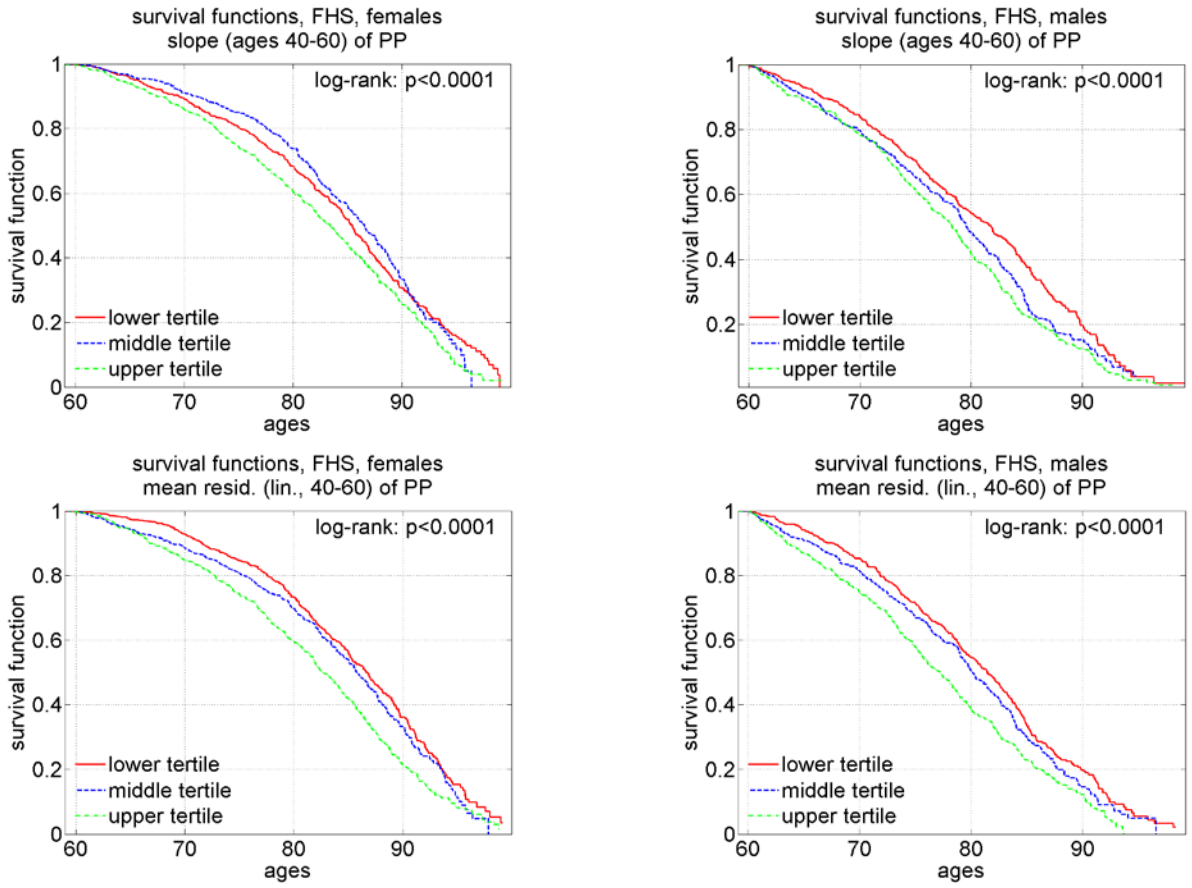
We evaluated the empirical (Kaplan-Meier) estimates of survival functions (and probabilities of staying free of the diseases defining the onset of "unhealthy life") for individuals

with different values of the dynamic risk factors based on the indices with nonmonotonic trajectories (separately for females and males). To do so, we divided the entire sex-specific samples into strata representing individuals with the values of the index in the tertiles of the empirical distribution of respective index. Individuals with ages at death (onset of "unhealthy life")/censoring below x_R were excluded from the analyses as described above. Then we evaluated the Kaplan-Meier estimates for respective strata and tested the null hypotheses about the equality of the curves in the strata using the log-rank test.

The analyses showed the evaluated dynamic characteristics for monotonic indices do influence mortality risk (see some examples in Figure 9). The survival curves for individuals with initial values of an index at age 40 from different tertiles were significantly different for BG in males (p=0.04), BMI in females (p=0.001) and males (p=0.004), HC in females (p=0.0003) and males (p=0.0004), and PP in females (p=0.007). For the slope (rate of change of an index) at ages 40 to 60, the significant differences were observed for BG in females (p=0.005) and males (p=0.01), BMI in females (p=0.0001) and males (p<0.0001), and PP in females (p<0.0001) and males (p<0.0001). The variability (deviations of an index from the linear line at ages 40 to 60) produced significant differences for BMI in males (p=0.03), and PP in females (p<0.0001) and males (p<0.0001). For the majority of cases, the effects were monotonic, with the upper tertiles (i.e., larger initial values at age 40, faster increase at ages 40 to 60 and greater variability at ages 40 to 60) having the worst survival chances. However, in some cases, the U-shape of the effect was observed with the middle tertile having the best survival chances.

Figure 9



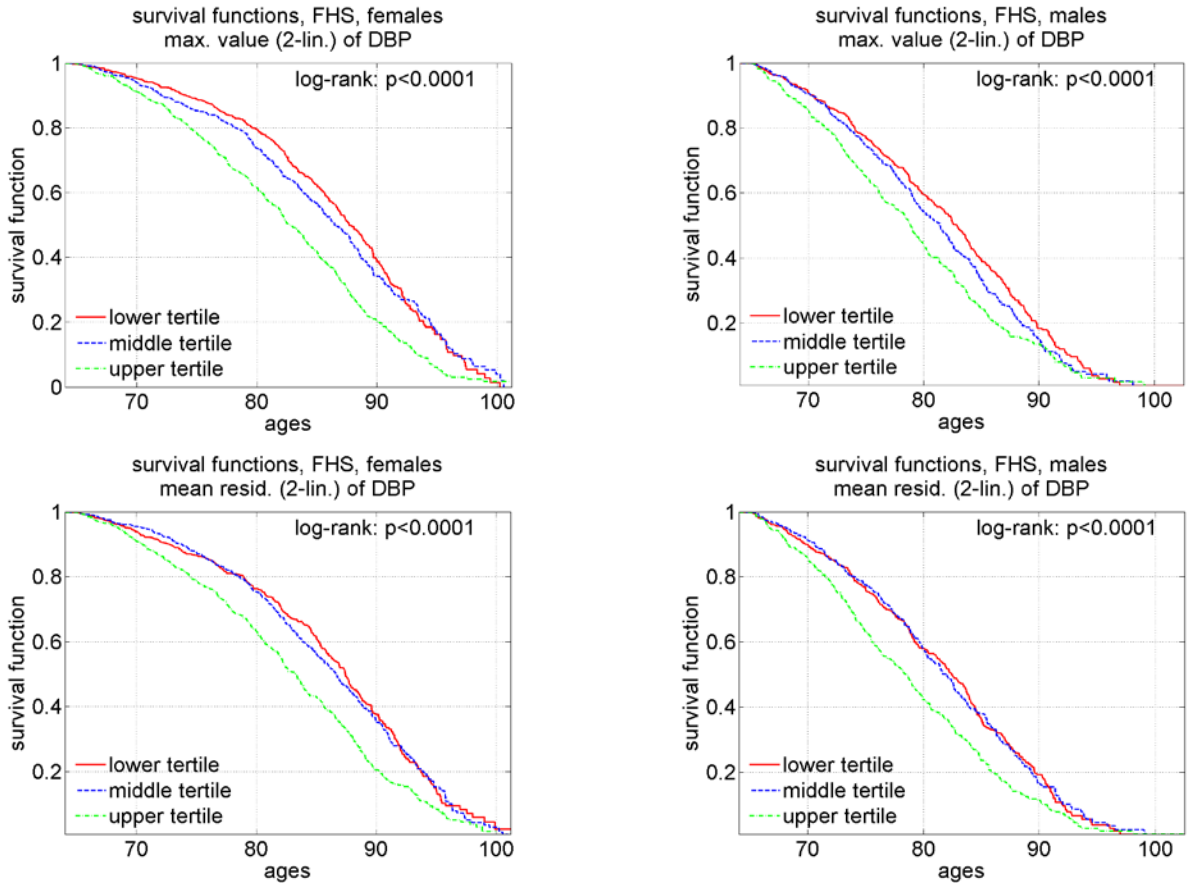


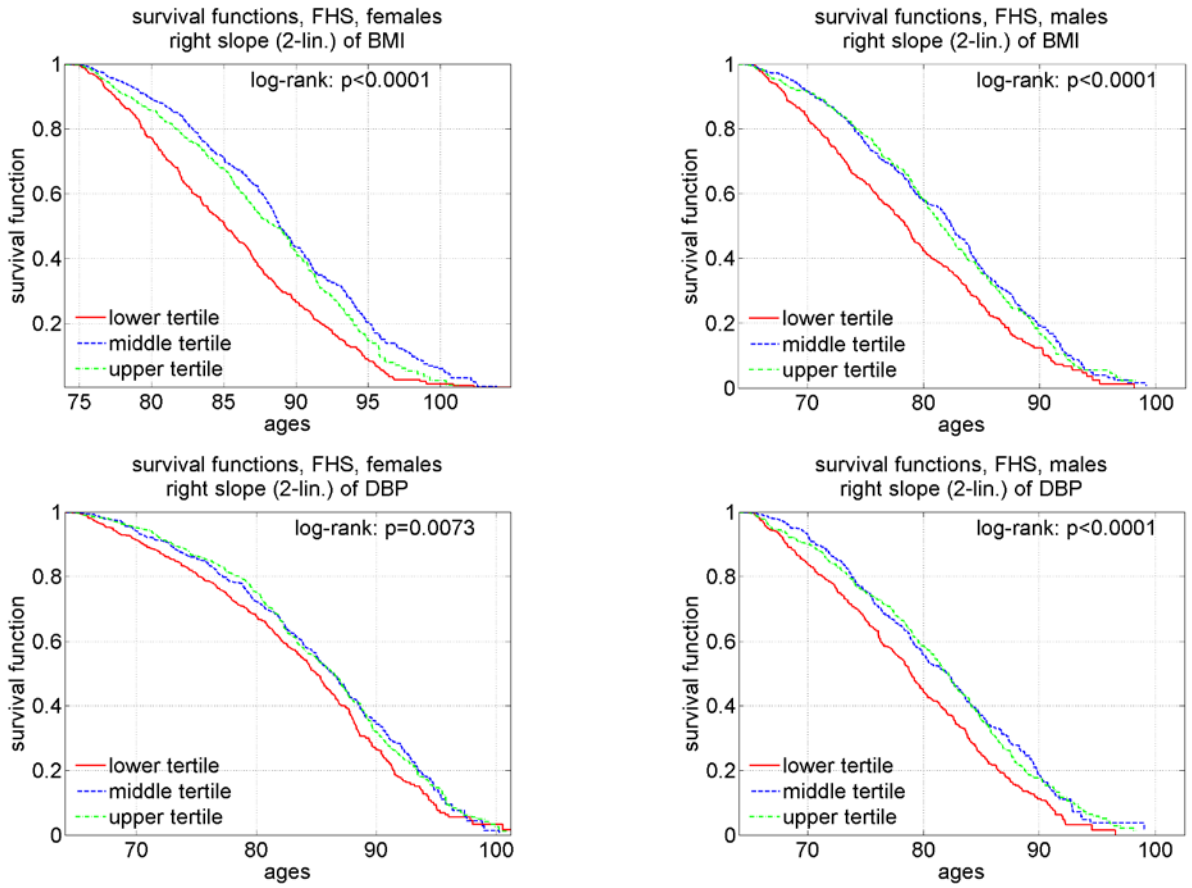
Effect of dynamic characteristics of physiological indices at ages 40 to 60 on survival in females and males from the original cohort of the Framingham Heart Study.

All of nonmonotonic characteristics, except the age at maximum, also influenced mortality risks (see some examples in Figure 10). The maximal value reached significantly affected survival for DBP in females ($p<0.0001$) and males ($p<0.0001$), PR in females ($p=0.0002$) and males (0.0008), and SCH in females ($p=0.009$) and males ($p=0.04$). The variability (deviation from the fitted line) was associated with significant differences in survival for BMI in females ($p=0.0009$) and males ($p=0.001$), DBP in females ($p<0.0001$) and males ($p<0.0001$), PR in males ($p=0.03$), and SCH in females ($p=0.002$) and males ($p=0.003$). An initial value of an index at the beginning of respective age intervals significantly affected survival for BMI in females ($p=0.02$) and males ($p=0.02$), DBP in females ($p<0.0001$) and males ($p=0.0008$), HC in females ($p=0.04$) and males ($p=0.02$), and SCH in males ($p=0.049$). The left slope (the rate of increase before reaching the maximum) significantly influenced survival

chances for BMI in females (p=0.002), DBP in females (p=0.0003), HC in males (p=0.008), and PR in females (p=0.001). The right slope (the rate of decline after reaching maximum), however, had more pronounced effect on survival compared to the left slope (p<0.0001 for BMI in females and males and DBP and SCH in males, p=0.004 for HC in males, and p=0.007 for DBP in females). For the majority of cases, the effects were monotonic, with the upper tertiles (i.e., larger initial values, faster increase before reaching the maximum, and greater variability and the maximal value reached) having the worst survival chances. In case of the right slope, the upper tertile (i.e., those having the slowest rate of decline after reaching maximum) had the best survival chances. However, in some cases the U-shape of the effect was observed with the middle tertile having the best survival chances.

Figure 10





Effect of nonmonotonic dynamic characteristics of physiological indices on survival in females and males from the original cohort of the Framingham Heart Study.

The need for a dynamic model of human aging and longevity. Despite the fact that longitudinal studies of aging, health and longevity tend to collect as much information as possible about aging-related changes developing in the human body, many variables, properties and regularities of aging-related changes are difficult or impossible to measure directly in such studies. At the same time, laboratory and clinical studies provide researchers with new findings and additional knowledge about aging. To develop a systemic integrative view on the role of aging and other factors in mortality and longevity, this information has to be taken into account in the analyses of data. To realize this idea, we extended the stochastic process model of human mortality and aging (Woodbury and Manton 1977; Yashin 1980; Yashin and Manton 1997) by allowing this model to manifest properties of human aging, which were detected in a number of earlier studies and have not been explored in statistical modeling of mortality and longevity before. In particular, we explicitly described a mechanism of adaptive regulation in the processes

of compensatory adaptation and remodeling of the physiological state in response to aging-related changes. This mechanism includes the negative feedback loop with a dynamic set point, f_1(t) (see equation [1] below), resulting from the process of allostasis, i.e., the process responsible for adjusting an organism's interior in response to persistent external conditions. The introduction of such a summary of "physiological" measure of external influence—function $f_1(t)$—whose properties can be evaluated from the data, is especially important in analyzing longitudinal data where most of persistent external disturbances are not measured, and only indirect methods of evaluating consequences of such an exposure can be performed. The results of such allostatic adaptation modify set-points in adaptive mechanisms regulating age trajectories of physiological indices. Deviation of these set-points from the "optimal" ones corresponding to minimal values of mortality risks contributes to an increase in morbidity and mortality risks. Note that the effects of allostatic adaptation may substantially limit longevity when the value of deviation from "optimal" physiological state (allostatic load) is large.

Maintaining a physiological state around an allostatically modified set-point is performed using a homeostatic mechanism with the negative feedback coefficient—function $a(t)$—(see equation [1] below). Since the decline in adaptive capacity of physiological and biological systems with age is an important characteristic of aging (Hall et al. 2000; Rankin and Kushner 2009; Troncale 1996), the absolute value of this coefficient should decline with age. Respective hypothesis can be tested using available data. One more indicator of aging is the decline in resistance to stresses with age (Hall et al. 2000; Robb et al. 2009; Ukraintseva and Yashin 2003; Yashin et al. 2006; Yashin et al. 2007). Longitudinal data do not provide researchers with variables, which could be used to measure stress resistance at different ages. However, this important characteristic could be measured indirectly by evaluating how the U-shaped risk function becomes narrower with age.

The presence of a stochastic component is an important feature of aging-related changes (Finch and Kirkwood 2000). Therefore, mathematical description of such changes has to involve a stochastic process. In our description of individual physiological trajectories (equation [1] below), we use the Wiener process W_t as the main source of dynamic stochasticity. The contribution of this component in physiological dynamics may change with age, which is

reflected by coefficient $b(t)$, which can be estimated from the data.

General model. Formally, the model describes age dynamics of physiological indices, Y_t, over age t using the stochastic differential equation:

$$dY_t = a(t)\left(Y_t - f_1(t)\right)dt + b(t)\,dW_t,\quad Y_0. \tag{1}$$

Here W_t is the Wiener process (independent of the initial normally distributed value Y_0) describing stochastic external challenges affecting the index. The function $f_1(t)$ characterizes the allostatically modified set-point for homeostatic regulation (McEwen and Wingfield 2003) mentioned above, i.e., the physiological state that organisms are forced to maintain by the process of homeostatic adaptation. It represents average effects of interplay among factors controlled by the ontogenetic program, senescence and long-acting environmental stresses exceeding the limits of the homeostatic regulation in human organisms. The negative function $a(t)$ characterizes adaptive capacity of an organism, i.e., the strength of the adaptive response for any deviation of the physiological index from the state $f_1(t)$ that an organism tends to follow. The negative feedback coefficient in (1) forces the trajectories of Y_t to return to $f_1(t)$ in case of disturbances caused by different factors (see also discussion about the feedback coefficient in [1] in Yashin et al. 2007).

The conditional mortality risk is represented by the quadratic function of physiological indices:

$$\mu\left(t, Y_t\right) = \mu_0(t) + \left(Y_t - f(t)\right)^{*} Q(t)\left(Y_t - f(t)\right). \tag{2}$$

This function captures J- or U-shapes of mortality risk considered as a function of physiological indices. Here $\mu_0(t)$ is the baseline hazard characterizing the minimal risk that would remain if the index Y_t followed the "optimal trajectory" represented by the function $f(t)$. We will associate such trajectory with physiological "norm." The nonnegative function $Q(t)$ is a multiplicative factor in the quadratic term in the hazard (referred to as the "quadratic hazard term" throughout the text). The narrowing of the U-shape of the risk function with age, i.e., an

increase in the diagonal elements of $Q(t)$ with age t, characterizes the decline in stress resistance. Generally, $f(t)$ may differ from $f_1(t)$ since the process of allostatic adaptation does not necessarily results in the optimal physiological state. Moreover, this process is considered to be responsible for deviation of the physiological state from its norm. Thus, the difference between $f_1(t)$ and $f(t)$ provides the measure of the allostatic load. This difference can be evaluated from longitudinal data. The parametric representation for unconditional mortality rate results from averaging equation (2):

$$\bar{\mu}(t) = \mu_0(t) + \left(m(t) - f(t)\right)^* Q(t)\left(m(t) - f(t)\right) + Tr\left(Q(t)\gamma(t)\right), \tag{3}$$

where the asterisk denotes transposition, $m(t) = E\left(Y_t \middle| T > t\right)$, and $\gamma(t) = E\left(\left(Y_t - m(t)\right)^* \left(Y_t - m(t)\right) \middle| T > t\right)$ are solutions of the following ordinary nonlinear differential equations:

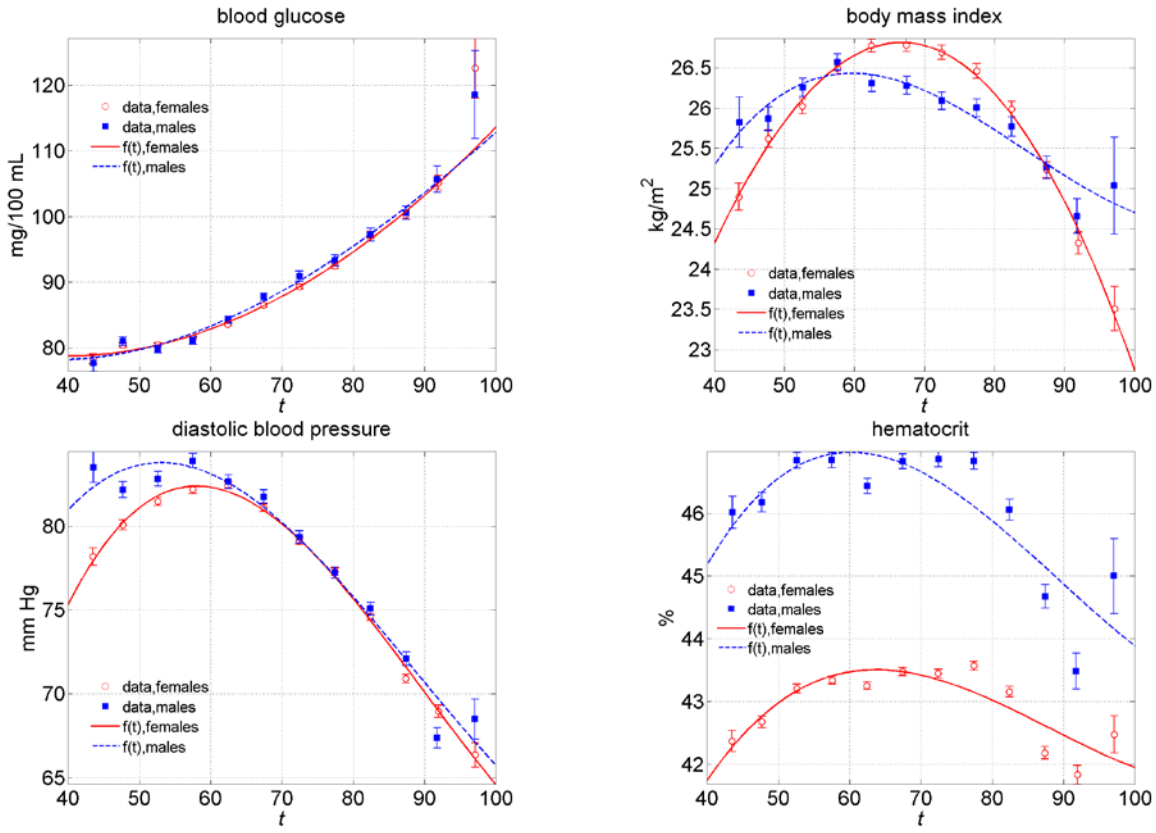
$$\begin{aligned} \frac{dm(t)}{dt} &= a(t)\left(m(t) - f_1(t)\right) - 2\gamma(t)Q(t)\left(m(t) - f(t)\right), \qquad m(t_0) = m_0 \\ \frac{d\gamma(t)}{d} &= a(t)\underset{t}{\gamma}(t) + \gamma(t)a^*(t) + B(t) - 2\gamma(t)Q(t)\gamma(t) \qquad , \gamma(t_0) = \gamma_0 \end{aligned} \tag{4}$$

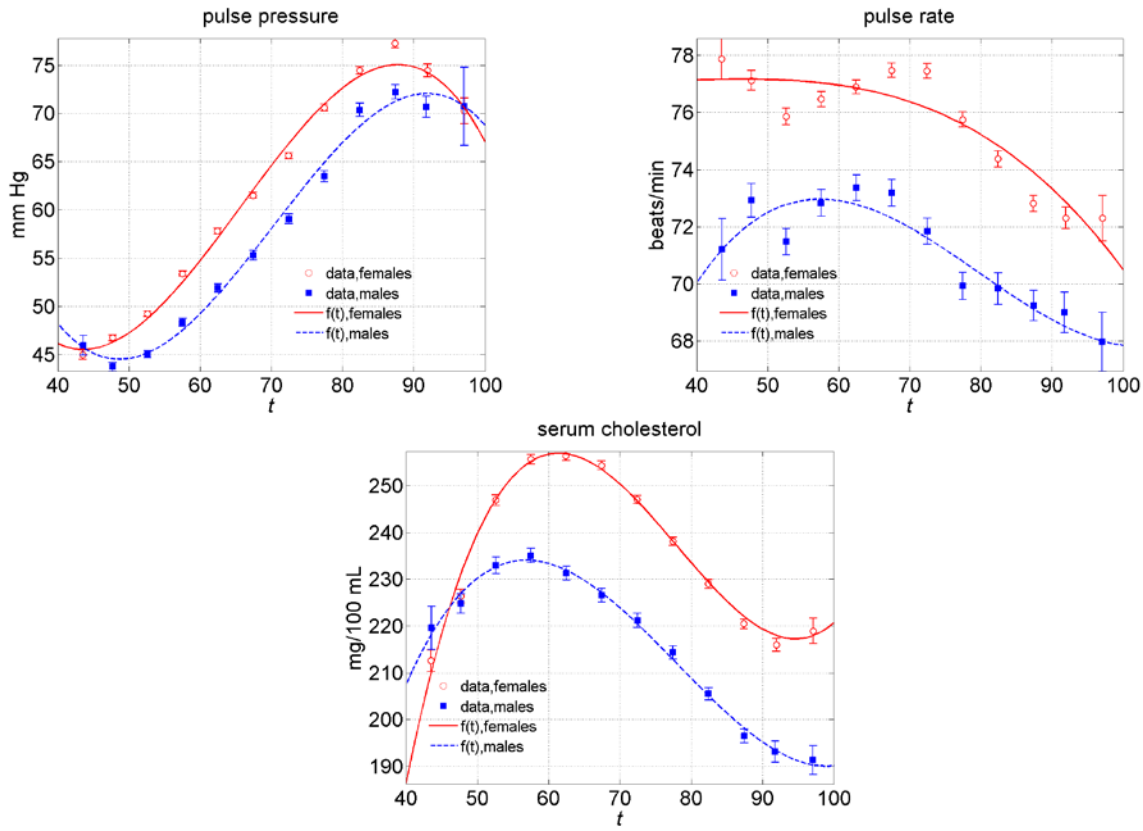
One can see that these equations depend on the same parameters as equations (1) and (2). This means that the mortality rate is now represented in terms of parameters characterizing age dynamics of physiological indices and their effects on mortality risk.

Application of the model to the FHS data. We applied a discrete-time version of model (1)-(2) (with values of physiological indices evaluated at one-year age intervals using respective observations in the adjacent FHS exams) with a constant diffusion $b(t) = \sigma_1$, the linear function for the adaptive capacity, i.e., the negative feedback coefficient $a(t)$; $a(t) = a_Y + b_Y t$; and the logistic (gamma-Gompertz) function for the baseline hazard: $\mu_0(t) = \mu_0^0(t) \Big/ (1 + \sigma_2^2 \int_0^t \mu_0^0(u)d\ )$, where $\mu_0^0(t) = a_{\mu_0} e^{b_{\mu_0} t}$. Initial values Y_0 are assumed normally distributed, $N(f_1(t_0), \sigma_0)$.

To evaluate the "optimal" trajectories $f(t)$, we calculated the average age trajectories of physiological indices for long-lived individuals (those 90 or older), separately for females and males, and fitted these trajectories by the polynomial splines (using the Curve Fitting Toolbox in MATLAB). The fitted curves were used as the estimates of the "optimal" trajectories $f(t)$ (assuming that the long-lived individuals are those who, on the average, managed to keep the age trajectories of the indices close to the optimal ones minimizing the risk of death at respective ages). Note that the observations of indices in long-lived individuals are available only starting at ages 40 and above. Therefore, we restricted applications of our model to observations of indices at ages 40 and above. Figure 11 shows the average trajectories for long-lived individuals and respective fitted trajectories used as $f(t)$.

Figure 11





Application of the dynamic model of human aging and longevity to data on mortality and longitudinal observations of physiological indices in females and males from the original cohort of the Framingham Heart Study: average age trajectories of physiological indices in long-lived individuals (life span of 90 or greater) and their fits representing the optimal trajectories $f(t)$; t denotes age.

Note that we used such surrogate definition of the physiological norm because: (1) the direct evaluation of the age trajectories of physiological indices that minimizes each model of conditional mortality risk from available data results in large standard errors; (2) the long-lived individuals have the lowest mortality risk, and therefore their average age trajectories are closest to the optimal ones for each gender; (3) these age trajectories are located within 95 percent confidence intervals evaluated for directly estimated “normal curves”; and (4) the normal trajectories, estimated using each of two approaches discussed above, describe optimal age trajectories of physiological indices that are the same for each member of the population cohort under study. Although such general consideration allows for detecting important dynamic properties of the conditional mortality risks (e.g., their gender differences, monotonic and

nonmonotonic patterns of their age-related changes), the evaluation of personalized "optimal" trajectories would be a natural next step in further development of this approach.

In our further calculations, we used seven one-dimensional models of aging and mortality linking age trajectories of each of the seven physiological indices described above with respective conditional mortality risks. Taking into account that deviation of physiological index from its "normal" curve may depend on its value and the sign, we use a nonsymmetric form of the quadratic hazard assuming different "penalties" (in terms of an additional mortality risk) for deviations of the index to the left, $Q_L(t)$, and to the right, $Q_R(t)$, from the "norm," $f(t)$: $Q_L(t) = a_{Q_L} + b_{Q_L} t$, if $Y_t \leq f(t)$; $Q_R(t) = a_{Q_R} + b_{Q_R} t$, if $Y_t > f(t)$. We represented the function $f_1(t)$ as $f_1(t) = f(t) + \Delta f(t)$, where $\Delta f(t) = a_f + b_f t$.

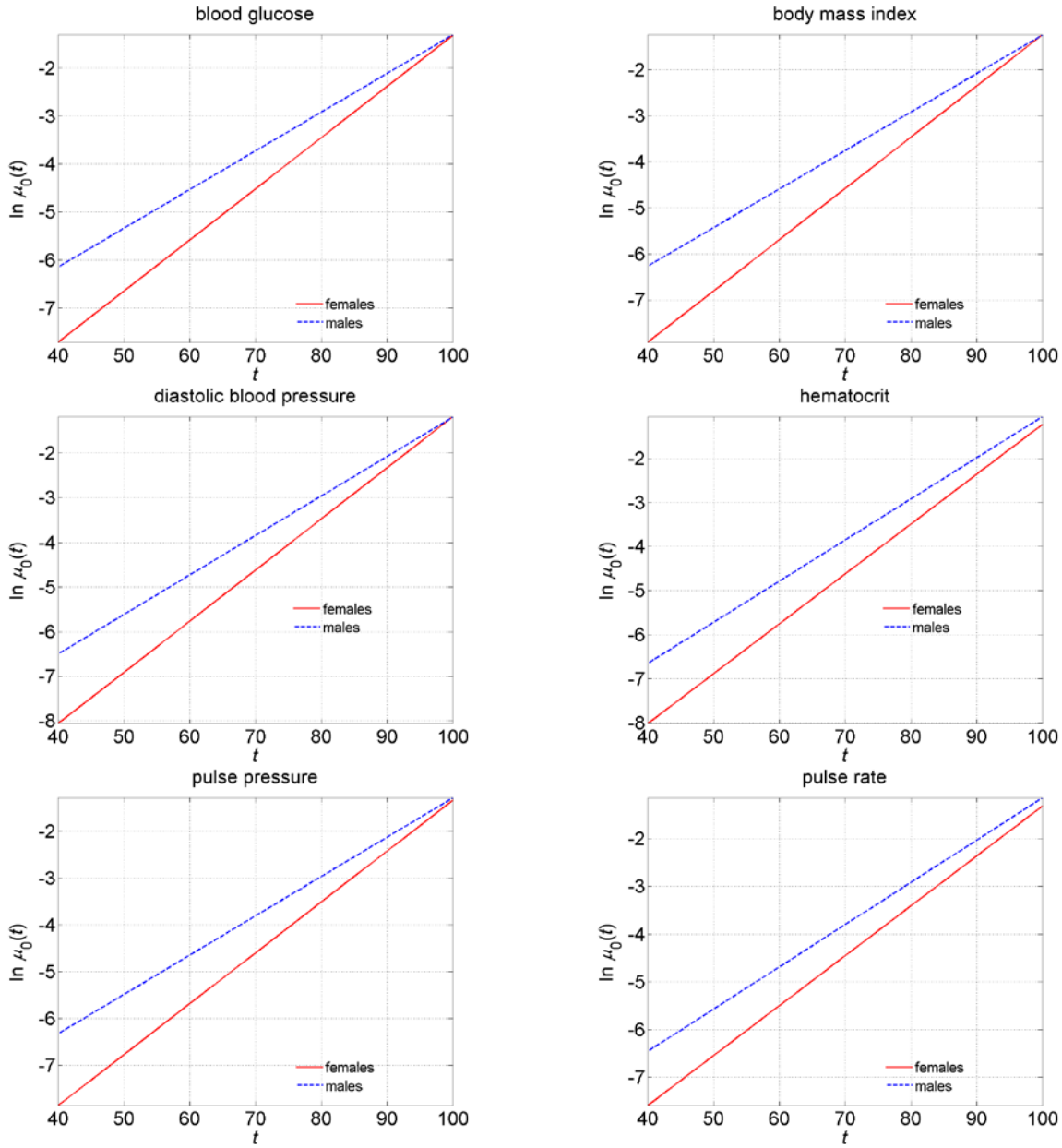
Statistical analysis. Details of the likelihood maximization procedure are given in Yashin et al. (2007). The likelihood maximization was performed using the constrained optimization procedure of MATLAB's Optimization Toolbox (MathWorks Inc. 2008). The constrained maximization algorithm was used to impose necessary restrictions on parameters of: (1) functions $f_1(t)$, to ensure "physiologically reasonable" values of indices at each age; (2) the feedback coefficient $a(t)$, to ensure its negative value at each age so that the trajectories of Y_t tend to $f_1(t)$; (3) the baseline hazard $\mu_0(t)$, to ensure nonnegative values for each age; (4) σ_0, σ_1 and σ_2, to ensure nonnegative values; and (5) the quadratic hazard terms $Q_L(t)$ and $Q_R(t)$, to ensure that the values are nonnegative for each age.

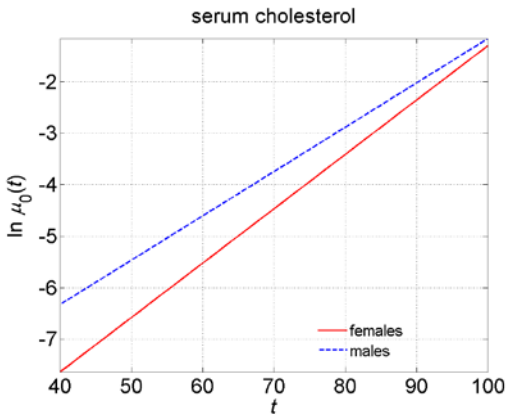
Results and Discussion

Estimates of the logarithm of the baseline hazard rate, $\ln \mu_0(t)$; the quadratic hazard terms, $Q_L(t)$ and $Q_R(t)$; the age-specific adaptive capacity, $a(t)$; and the dynamic set-point function, $f_1(t)$, for the dynamic model of human aging and longevity applied to data on mortality and longitudinal observations of seven physiological indices in females and males from the original cohort of the Framingham Heart Study are shown in figures 12 to 16.

The estimates of the baseline mortality rates $\ln \mu_0(t)$ for seven physiological indices are shown in Figure 12 for males and females. These functions describe age trajectories of "optimal" mortality rates for each of seven models of mortality risks considered as functions of respective physiological indices. Functions $\mu_0(t)$ characterize minimal values of the mortality rate for each of the seven risk models that could be reached by keeping respective physiological trajectories equal to their physiological norms.

Figure 12

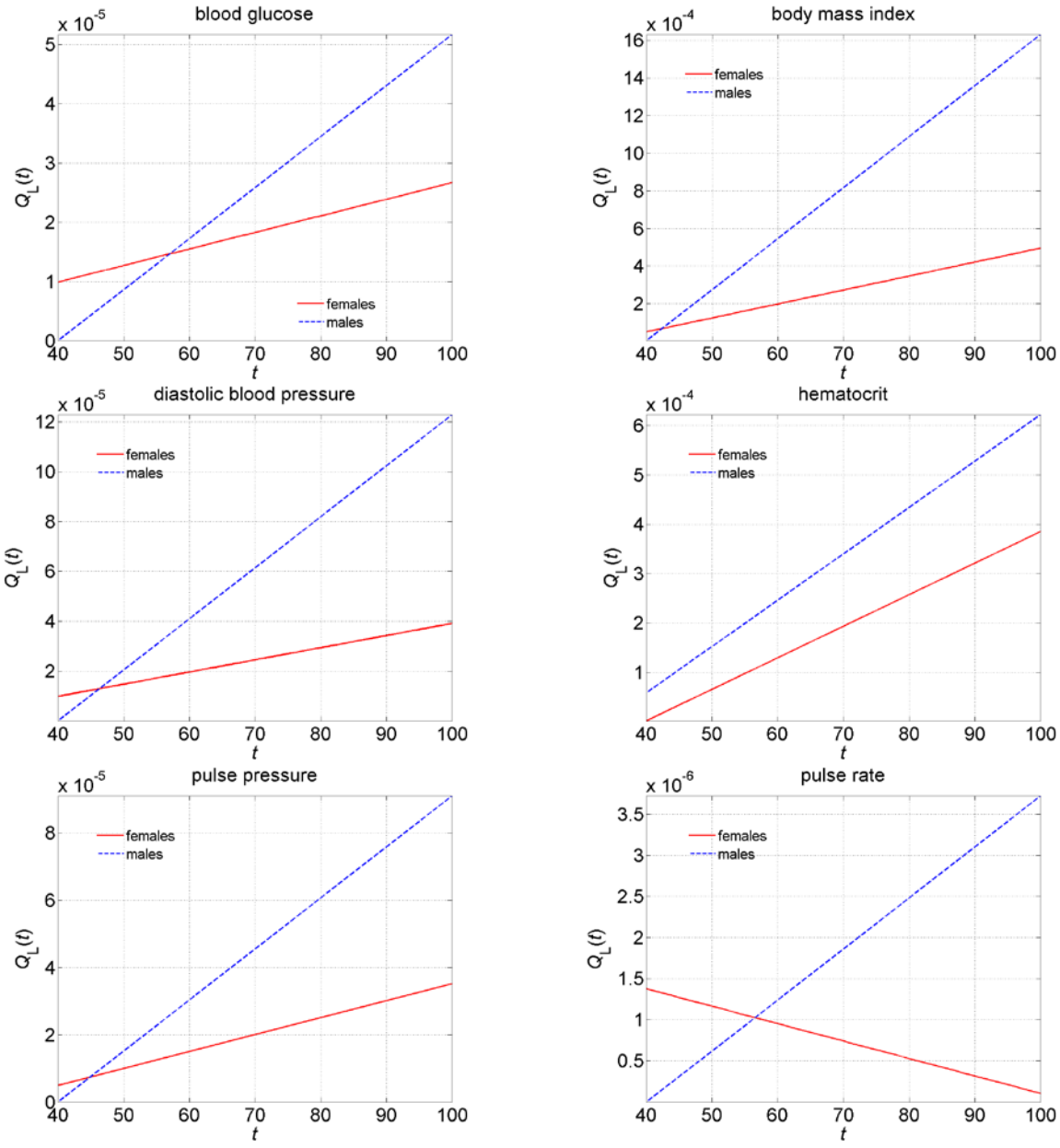


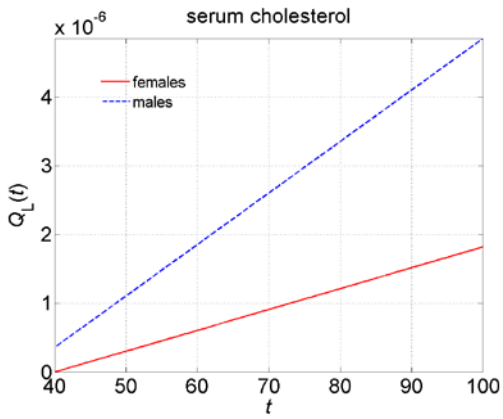


Application of the dynamic model of human aging and longevity to data on mortality and longitudinal observations of physiological indices in females and males from the original cohortof the Framingham Heart Study: estimates of the logarithm of the baseline hazard rate, $\ln \mu_0(t)$; t denotes age.

The estimates of the coefficients $Q_L(t)$ for seven physiological indices are shown in Figure 13 for males and females. These coefficients describe aging-related changes in seven nonsymmetric U-shaped mortality risks each considered as quadratic functions of one of the seven physiological indices described above. The coefficients $Q_L(t)$ show how the deviations of each of the seven physiological indices to the left of the "norm" at a given age effect mortality risk. One can see from this figure that almost all coefficients (except that for pulse rate for females) are increasing functions of age. An increase in these functions corresponds to the narrowing of the left part of the U-shaped mortality risk curve, which is interpreted as a decline in resistance to stresses resulting in deviation of the respective index to the left from its "norm" at a given age. The decline in the index may indicate that the respective risk factor becomes less harmful with age.

Figure 13

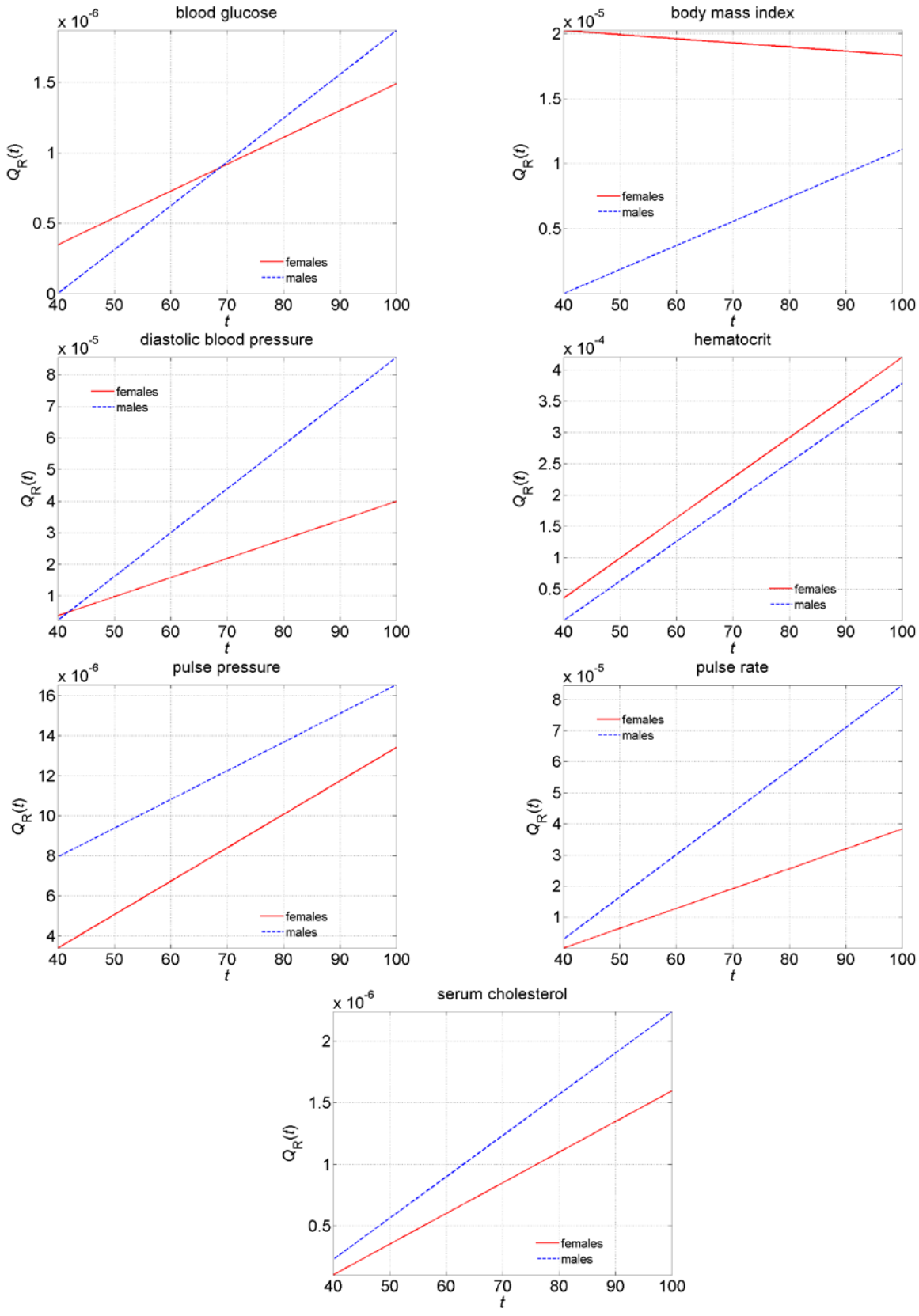

blood glucose
x 10^-5
females
males
body mass index
x 10^-4
females
males
diastolic blood pressure
x 10^-5
females
males
hematocrit
x 10^-4
females
males
pulse pressure
x 10^-5
females
males
pulse rate
x 10^-6
females
males
Q_L(t)
t



Application of the dynamic model of human aging and longevity to data on mortality and longitudinal observations of physiological indices in females and males from the original cohort of the Framingham Heart Study: estimates of the quadratic hazard terms penalizing deviations of trajectories of physiological indices to the left of the "norm," $Q_L(t)$; t denotes age.

The estimates of the coefficients $Q_R(t)$, for seven physiological indices are shown in Figure 14 for males and females. These coefficients describe properties of seven nonsymmetric U-shaped mortality risks each considered as quadratic functions of one of the seven physiological indices described above. The coefficients $Q_R(t)$ show how the deviations of each of the seven physiological indices to the right of the "norm" at a given age affect mortality risk. One can see from this figure that almost all coefficients (except for BMI for females) are increasing functions of age. An increase in these functions corresponds to the narrowing of the right part of the U-shaped mortality risk curve, which is interpreted as a decline in resistance to stresses resulting in deviation of respective index from its "norm" at a given age. The decline in the index may indicate that the respective risk factor becomes less harmful with age.

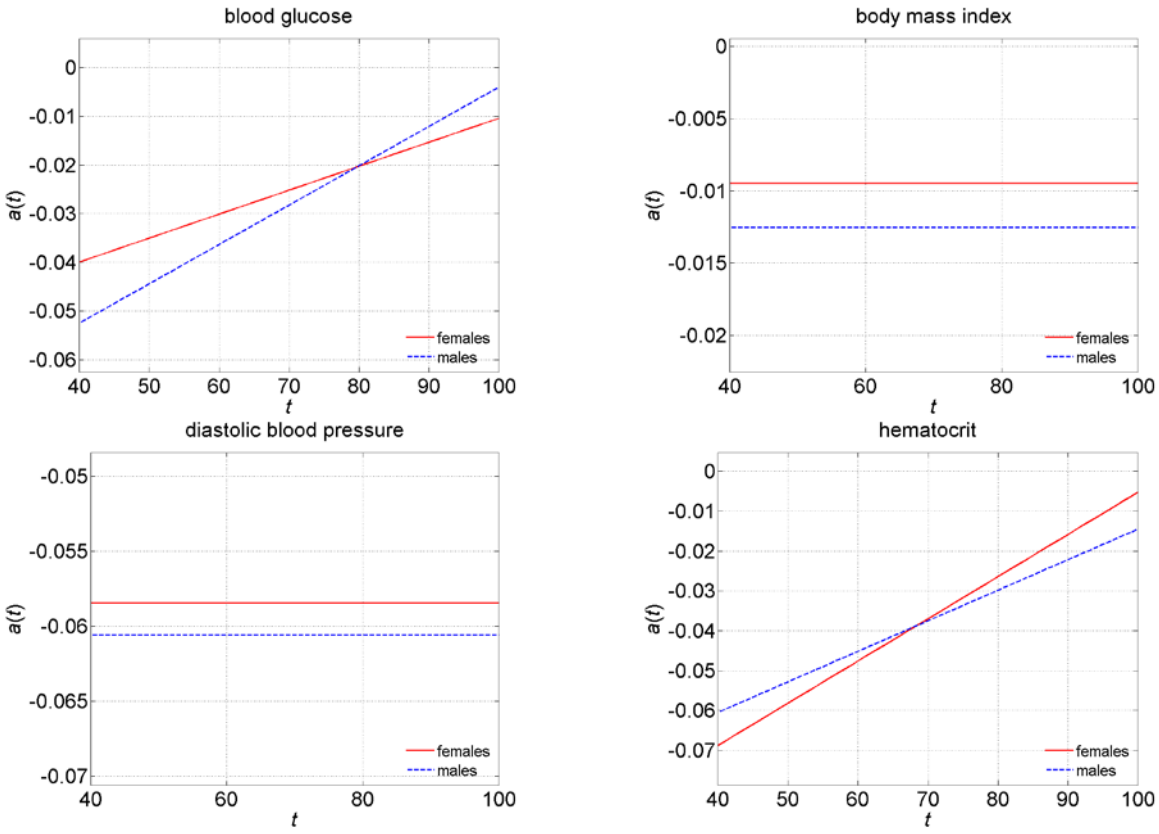
Figure 14

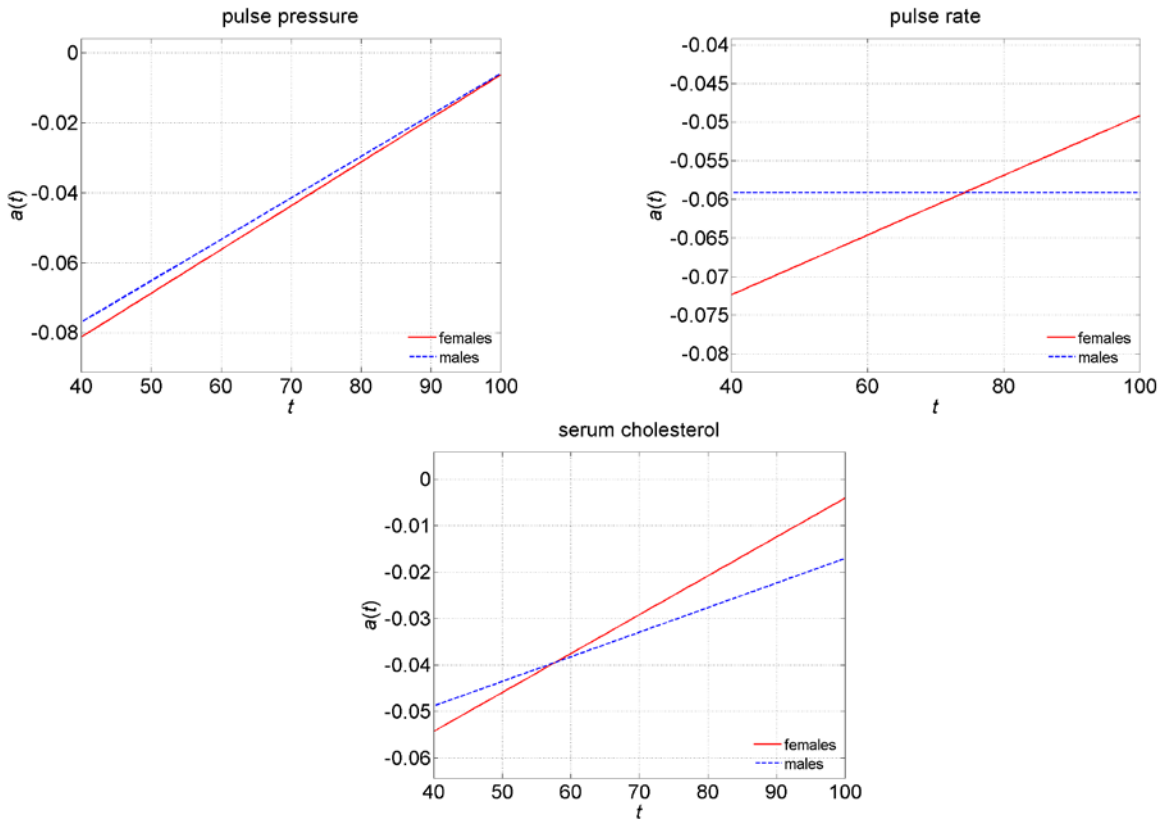

blood glucose
x 10^-6
body mass index
x 10^-5
diastolic blood pressure
x 10^-5
hematocrit
x 10^-4
pulse pressure
x 10^-6
pulse rate
x 10^-5
serum cholesterol
x 10^-6
females
males
$Q_R(t)$
t

Application of the dynamic model of human aging and longevity to data on mortality and longitudinal observations of physiological indices in females and males from the original cohort of the Framingham Heart Study: estimates of the quadratic hazard terms penalizing deviations of trajectories of physiological indices to the right of the "norm," $Q_R(t)$; t denotes age.

The estimates of age-patterns of adaptive capacity, i.e., the negative feedback coefficient, $a(t)$, are shown in Figure 15. One can see from this figure that all coefficients are estimated negative, which confirm their role as negative feedback coefficients in regulation of the physiological state. Note that the estimates of these coefficients either decline or stay constant during the life course. The decline in absolute values of these coefficients with age shown for a number of indices confirms that adaptive capacity associated with these indices experiences aging-related decline.

Figure 15

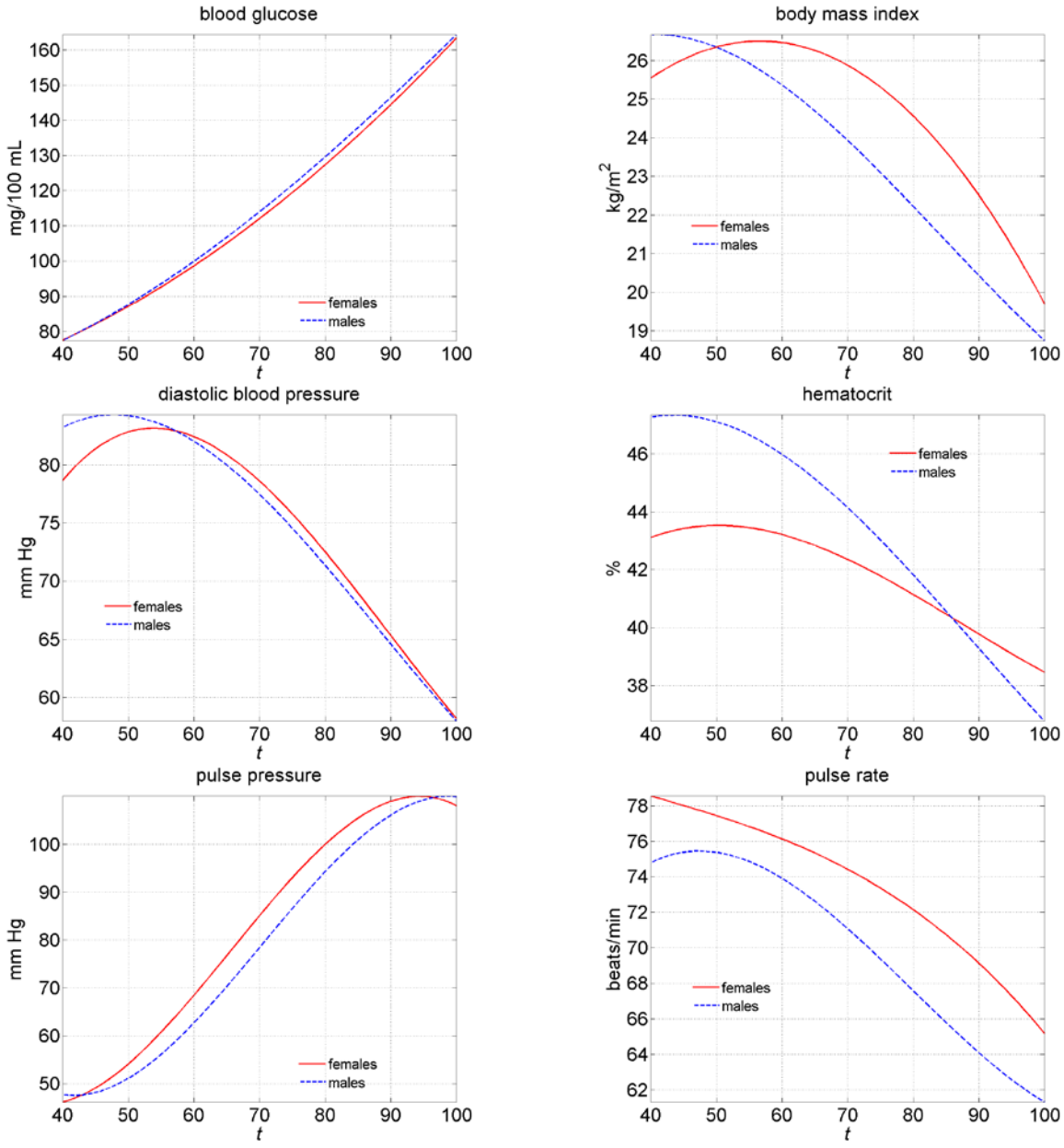


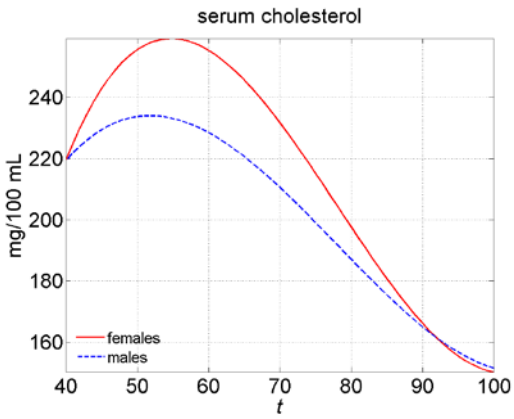


Application of the dynamic model of human aging and longevity to data on mortality and longitudinal observations of physiological indices in females and males from the original cohort of the Framingham Heart Study: estimates of age-specific adaptive capacity, i.e., the negative feedback coefficient $a(t)$; t denotes age.

The estimates of the dynamic set-point function, $f_1(t)$, for seven physiological indices are shown in Figure 16. One can see from this figure that all these characteristics are age dependent. The shapes of these curves reflect adaptive response of the body to persistent disturbances. The nonmonotonic feature of age patterns for some of these indices indicates that the regulatory mechanism of allostatic adaptation for these components of the physiological state may experience substantial changes during the life course. The very opportunity to estimate such drift in the set-points for homeostatic regulation is an important property of the approach.

Figure 16


blood glucose
mg/100 mL
t
females
males
body mass index
kg/m2
t
females
males
diastolic blood pressure
mm Hg
t
females
males
hematocrit
%
t
females
males
pulse pressure
mm Hg
t
females
males
pulse rate
beats/min
t
females
males



Application of the dynamic model of human aging and longevity to data on mortality and longitudinal observations of physiological indices in females and males from the original cohort of the Framingham Heart Study: estimates of the dynamic set-point function, $f_1(t)$; t denotes age.

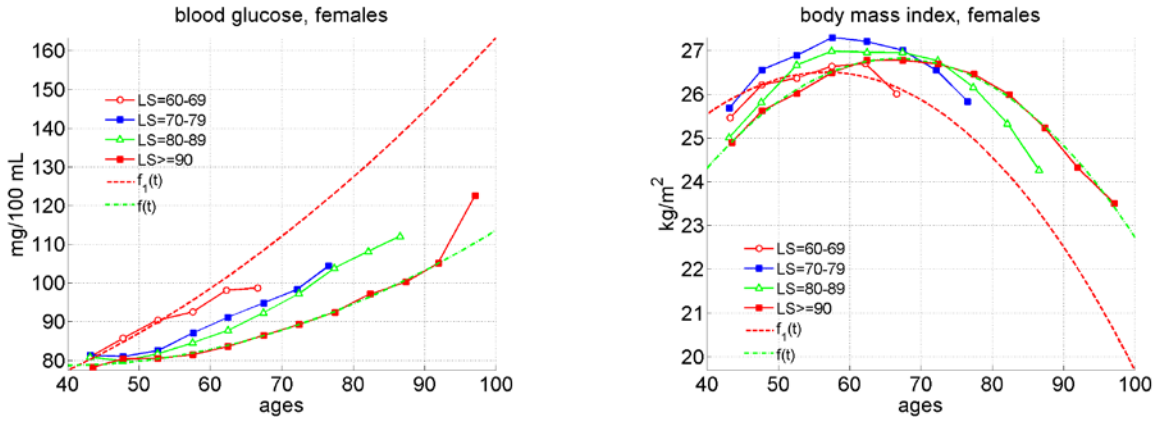
The results show that for all indices and for both sexes, the estimates of parameter σ_2 are nearly zero so that the baseline hazards are effectively represented by the Gompertz curve. Figure 12 shows the estimates of the logarithm of the baseline hazard for females and males follow the same pattern for all indices; it is always lower but increases faster with age in females compared to males. For the majority of indices, as figures 13 and 14 reveal, the quadratic hazard terms penalizing for deviations of trajectories of the indices to the left and to the right of the optimal values also follow the same pattern: They increase with age, and the rate of increase and the values (at least at old ages) for males are larger than those for females. These observations mean that the (nonsymmetric) U-shape narrows with age, the width of the U-shape (at least at the old ages) is narrower in males than in females, and the narrowing of the U-shape with age is faster in males than in females; however, these observations are not universal, as in case of $Q_L(t)$ for pulse rate in females, and $Q_R(t)$ for body mass index and hematocrit. Nevertheless, in most cases, the results indicate that at old ages males generally pay a higher "price" for deviations from the optimal values compared to females. This suggests that males have generally lower resistance to stresses even if they experience the same level of stress as females, and the rate of decline in stress resistance (i.e., the rate of narrowing the U-shape with age) is faster in males than in females. All of this contributes to higher mortality rates in males.

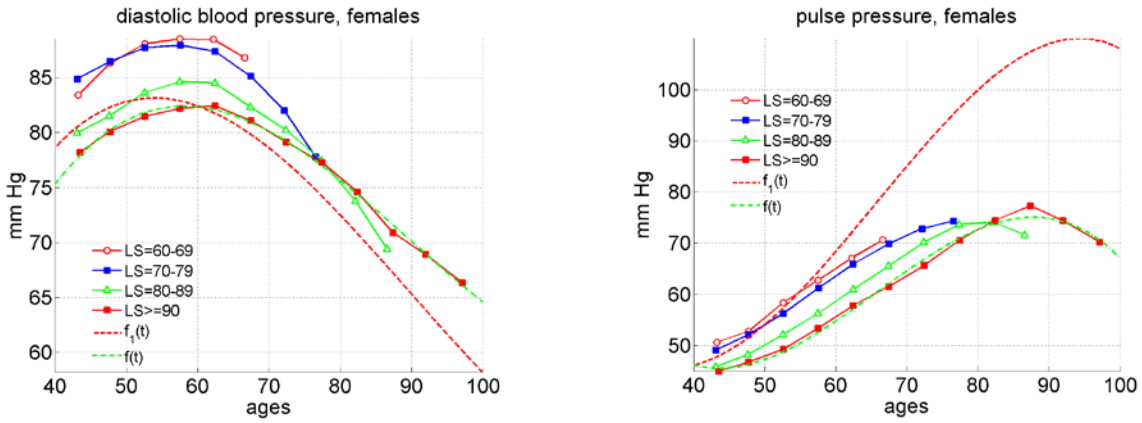
Figure 15 illustrates that the absolute value of the feedback coefficient $a(t)$ tends to decline with age in both females and males for all indices except body mass index and diastolic blood pressure for both sexes and pulse rate for males. This represents a decline in the adaptive capacity of an organism with age, because smaller absolute values of $a(t)$ mean that more time is needed for the trajectories of Y_t to return to $f_1(t)$ in case of disturbances at older ages than at younger ages. However, there is no universal pattern of the decline in the adaptive capacity in females and males as for different indices the rate of decline in $a(t)$ and its initial values show different patterns.

For all indices and both sexes, the estimates of $f_1(t)$ (Figure 16) differ from the optimal trajectories $f(t)$, that is, the estimates of $\Delta f(t)$ are nonzero, and the gap between the optimal trajectory and $f_1(t)$ widens at old ages. Such deviations of set-points $f_1(t)$ from the optimal trajectory minimizing mortality risks at respective ages substantially increase mortality risk and limit longevity when the value of such deviations is large.

Figure 17 illustrates the effects of allostatic load and optimal trajectories in individuals who died at different ages. It shows average age trajectories of four physiological indices (BG, BMI, DBP and PP) for female members of the original FHS cohort who died at different age intervals (60 to 69, 70 to 79, 80 to 89), and those with a lifespan of 90 or greater (this last group also includes individuals censored at ages 90 and above).

Figure 17





Application of the dynamic model of human aging and longevity to data on mortality and longitudinal observations of physiological indices in the original age group of the Framingham Heart Study: estimates of the dynamic set-point function, $f_1(t)$, and optimal trajectories $f(t)$ and average age trajectories of physiological indices for females with different life spans (LS); t denotes age.

The dashed line is the estimate of the effect of allostatic adaptation, $f_1(t)$, and the dash-dotted line is an estimate of "optimal" age trajectory of the respective index, $f(t)$. Other lines on these figures correspond to average age trajectories of respective physiological indices for females having life spans within given limits. One can see from this figure that almost all age trajectories of pulse pressure and blood glucose end up and are located between the optimal curve, $f(t)$, and the curve describing the effect of allostatic adaptation, $f_1(t)$. Since the effects of allostatic adaptation deviate physiological trajectories from their "optimal" curves, one can expect that individuals whose trajectories are closer to $f_1(t)$ have higher mortality risk and therefore will have shorter life spans, compared to individuals whose trajectories are located closer to the optimal ones. The age dynamics of PP and BG illustrates the situation where allostatic adaptation forces physiological indices to deviate in the same direction from the optimal curve during the entire life course. The graphs for diastolic blood pressure and body mass index show that more complicated relationships between allostatic adaptation and physiological dynamics are possible. One can see from these graphs that the curves describing effects of allostatic adaptation, $f_1(t)$, are higher than the "optimal" ones at the age interval before ages 50 to 60. Then they intersect the "optimal" curve and remain lower than this curve after these ages. It looks as if persistent external disturbances acting before ages 55 force DBP to increase and make it higher than the "optimal" DBP curve. After age 55, allostatic regulation for this trait (i.e., body's response on persistent disturbances) works in the opposite direction: It

tends to decrease diastolic blood pressure, keeping it lower than the “optimal” curve. The detected phenomenon may manifest the presence of fundamental changes in mechanisms of physiological regulation around 50 to 60 years of age (Ukraintseva and Yashin 2001). Menopause and related changes in hormonal balance may be the most important contributors. Another reason may be related to changes in external conditions, which may be associated with retirement, changes in lifestyle, environmental conditions, etc. The dynamics of BMI follows similar regularities and may be associated with the same causes. The idea that some fundamental changes in mechanisms regulating aging-related physiological dynamics are developing around ages 50 to 60 in females is also supported by Figure 7, which shows how average age trajectories of physiological state differ in “healthy” and “unhealthy” individuals.

Conclusion

Studying factors and mechanisms responsible for exceptional survival requires systemic integrative approaches capable of quantitatively summarizing available knowledge, new findings and current theoretical concepts to analyze longitudinal data. One such approach can be realized by constructing dynamic mathematical and computer models of aging-related changes and mortality, and using them in the statistical analyses of longitudinal data. The results of our analyses show that such an approach is feasible: The models' parameters can be identified from the data, and models' characteristics can be properly interpreted.

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