Age dynamics of physiological indices as determinant of healthy life: Evidence from longitudinal data

Konstantin G. Arbeev*, Svetlana V. Ukraintseva, Igor Akushevich, Alexander M. Kulminski, Liubov S. Arbeeva, Lucy Akushevich, Irina V. Culminskaya, Anatoliy I. Yashin

Center for Population Health and Aging, Duke University, USA

* **Corresponding author:** Dr. Konstantin G. Arbeev, Center for Population Health and Aging, Duke University, Trent Hall, Room 002, Box 90408, Durham, NC, 27708-0408, USA. Tel.: +1-919-668-2707; fax: +1-919-684-3861; e-mail: konstantin.arbeev@duke.edu

Abstract

Longitudinal data provide possibilities to analyze how dynamics of physiological indices impacts morbidity/mortality risks. We analyzed relationship between the risk of onset of "unhealthy life" (defined the onset of cancer, cardiovascular disease or diabetes) and longitudinal observations of six physiological indices: body mass index, diastolic blood pressure, hematocrit, pulse pressure, pulse rate, and serum cholesterol, in the Framingham Heart Study using the stochastic process model of aging. We evaluated that: 1) "optimal" trajectories of the physiological indices (minimizing the risk of onset of "unhealthy life") are age-dependent; 2) these trajectories deviate from those resulting from the processes of allostatic adaptation of an organism; 3) ranges of "tolerable" deviations of indices from the "norm" reduce with age, i.e., U-shapes of the risk narrow with age. The model estimates that individuals might enjoy up to several additional years of healthy life if their indices followed the "optimal" age trajectories. The mechanisms contributing to observed results are discussed.

Key words: stochastic process model, cancer, cardiovascular disease, diabetes, physiological norm, Framingham Heart Study

Introduction

Longitudinal data available to date often contain limited information that can be directly associated with mechanisms of aging-related changes in an organism, such as homeostatic regulation, allostatic load, stress resistance, and so on, which, in turn, can be related to mortality/morbidity risks. However, such mechanisms may be mediated by age-trajectories of various physiological indices in an organism. Longitudinal measurements of physiological indices available for participants of longitudinal studies of health and longevity constitute a valuable source of information that can be used to reveal these mechanisms and associate them with risks of death or onset of chronic diseases (Arbeev et al., 2009; Yashin et al., 2006; Yashin et al., 2009a; Yashin et al., 2009b). Mathematical modeling may provide a useful tool to help reveal regularities in aging-related changes hidden in the age-dynamics of physiological indices. Yashin et al. (2007) suggested the stochastic model that incorporates several major concepts of aging known to date and that links individual trajectories of physiological indices measured in longitudinal data and mortality/morbidity risks. The mortality/morbidity risk is assumed to be a quadratic function of physiological indices capturing J- or U-shapes of the risks observed for many indices in different studies.

In this paper, we apply the model developed by Yashin et al. (2007) to analyze relationship between "healthy lifespan" (defined as free of cancer, cardiovascular and diabetes lifespan) and longitudinal observations of six physiological indices: body mass index, diastolic blood pressure, hematocrit, pulse pressure, pulse rate, and serum cholesterol, measured in participants of the Framingham Heart Study (FHS) data. The approach allows us to evaluate the values (or ranges of values) of physiological indices minimizing the risk of onset of "unhealthy life" (i.e., one of the three diseases mentioned above) and test the hypotheses whether these "norms" are age-dependent. It also addresses the question whether the age-trajectories of physiological indices which organisms are forced to follow by mechanisms of adaptive regulation coincide with the trajectories that minimize the risk of onset of "unhealthy life." The model provides the mechanism to evaluate the "allostatic load" as a measure of difference between the two functions and also estimate the number of additional years of healthy life (i.e., free of the three diseases mentioned above) for an individual if his/her age-trajectories of physiological indices followed the "optimal" ones.

Data and Method

Framingham Heart Study (FHS). The FHS Original Cohort consists of 5,209 respondents (nearly all are Caucasians, 46% male) aged 28-62 years residing in Framingham, Massachusetts, between 1948 and 1951, and who had not yet developed overt symptoms of cardiovascular disease or suffered a heart attack or stroke (Dawber, 1980; Dawber et al., 1951). The study continues to the present with biennial examinations (29 exams to date, data from exams 1-25 were used in this study) that include detailed medical history, physical exams, and laboratory tests. The FHS Original Cohort has been followed for about 60 years for the occurrence of cardiovascular diseases (CVD), cancer, diabetes mellitus, and death through surveillance of hospital admissions, death registries, and other available sources. Examination of participants, including an interview, physical examination, and laboratory tests, has been taken biennially. Phenotypic traits collected in the FHS Original Cohort over 60 years and relevant to our analyses include: life span, ages at onset of diseases (with the emphasis on cardiovascular diseases (CVD), cancer, and diabetes mellitus), as well as indices characterizing physiological state. The occurrence of diseases (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 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 than the individual was considered censored at the age of the last follow-up or death. Individuals who had any of the diseases before (for cancer and CVD) or at (for diabetes) the first FHS exam were excluded from the analyses of "unhealthy life." Data on physiological indices that we used include: body mass index (BMI, exams 1-25), diastolic blood pressure (DBP, exams 1-25), hematocrit (HC, exams 4-21), pulse pressure (PP, exams 1-25), pulse rate (PR, exams 1, 4-25), and serum cholesterol (SCH, exams 1-11, 13-15, 20, 22-25).

Model. The model as suggested by Yashin et al. (2007) represents the dynamics of a physiological index (Y_t, t is age) in the form of the stochastic differential equation:

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

where W_t is a Wiener process (independent of the initial normally distributed value Y_0) describing exogenous challenges affecting the index. The function $f_1(t)$ describes the functional state that organisms subject to allostasis (McEwen and Wingfield, 2003) are forced to follow by the process of adaptive regulation at age t (the "mean allostatic state"). The function $a(t)$ characterizes the rate of adaptive regulation, i.e., the rate of the adaptive response for any deviation of the physiological index from the state $f_1(t)$ which an organism tends to follow.

The hazard rate (i.e., the risk of onset of cancer, CVD or diabetes) is assumed as the quadratic function of Y_t:

$$\mu(t, Y_t) = \mu_0(t) + (Y_t - f(t))^2 Q(t), \quad (2)$$

where $\mu_0(t)$ is the baseline hazard characterizing the risk which would remain if the index Y_t followed the "optimal trajectory" represented by the function $f(t)$. This "optimal" function corresponds to the minimal value of the hazard rate (i.e., incidence of "unhealthy life" in our applications) at respective age and thus represents the notion of (age-specific) physiological "norm" for the respective index in terms of minimizing this hazard at age t. Here $Q(t)$ is a non-negative-definite function representing the quadratic term in the hazard. The narrowing of the U-shape of the risk function with age (i.e., an increase of $Q(t)$ with 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. Thus, the difference between $f_1(t)$ and $f(t)$ provides the measure of the allostatic load.

Application to FHS data. In applications of model (1)-(2) to the FHS data, we used constant $a(t) = a_Y$ and $b(t) = \sigma_1$, linear functions (of age t) for the quadratic term in the hazard ($Q(t)$) and the age-specific physiological "norm" ($f(t)$): $Q(t) = a_Q + b_Q t$ and $f(t) = a_f + b_f t$, the logistic (gamma-Gompertz) function for the baseline hazard: $\mu_0(t) = \mu_0^0(t) \Big/ (1 + \sigma_2^2 \int_0^t \mu_0^0(u)du)$, where $\mu_0^0(t) = a_{\mu_0} e^{b_{\mu_0} t}$, and the quadratic function for the "mean allostatic state": $f_1(t) = a_{f_1} + b_{f_1} t + c_{f_1} t^2 f_1(t)$. Initial value Y_{t_0} was assumed normally distributed, $N(f_1(t_0), \sigma_0)$. The specific choice for the baseline hazard is explained by the observations that the incidence rates of many aging-related diseases (e.g., such as cancer, which is used in the definition of onset of "unhealthy life") decelerate at advanced ages in the literature and the empirical observations of the incidence rates of onset of "unhealthy life" in the Framingham Heart Study data (Fig. 1). Note that this general specification reduces to the exponential (Gompertz) hazard rate if $\sigma_2 = 0$ allowing for testing respective hypotheses on decelerating rates in the applications. The choice of the quadratic function for the "mean allostatic state" comes from the empirical observations of the average trajectories of the physiological indices in the FHS, which generally have a quadratic form (see Fig. 2), although the mean trajectories does not necessary have to follow those of $f_1(t)$ exactly, of course. We also estimated the model with linear $f_1(t)$ and the null hypothesis in favor of the linear model was rejected for all indices and both sexes ($p<0.0001$ in all cases except PR for males ($p=0.004$)) excluding PP for females.

Figs. 1-2 about here

In addition to the "basic" model described above, we estimated the model with a non-symmetric form of $Q(t)$, i.e., assuming different "penalties" (in terms of an additional risk) for

deviations of the index to the left and to the right from the "norm" $f(t)$ ($Q_L(t)$ and $Q_R(t)$). We also tested whether the respective indices have a single "optimal" value minimizing the risk of onset of "unhealthy life" at each age, or there is a range of such values with minimal risk. For this purpose, we estimated the models with optimal "ranges," or

$$\mu(t, Y_t) = \mu_0(t) + (Y_t - f_L(t))^2 I(Y_t < f_L(t)) Q_L(t) + (Y_t - f_R(t))^2 I(Y_t > f_L(t)) Q_R(t),$$

where $I(.)$ is an indicator function (which equals one if the condition in the parentheses holds and zero otherwise), $f_L(t)$ and $f_R(t)$ are two functions defining the left and right boundaries of the "optimal range," which were also taken as linear or quadratic functions.

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: a) functions $f_1(t)$ and $f(t)$ (to ensure "physiologically reasonable" values of indices at each age); b) the feedback coefficient a_Y (the negative value to ensure that the trajectories of Y_t tend to $f_1(t)$); c) the baseline hazard $\mu_0(t)$ (to ensure non-negative values for each age); d) variances σ_0, σ_1, and σ_2 (to ensure non-negative values); and e) the quadratic term in the hazard $Q(t)$ (to ensure that the value is non-negative for each age). Model comparison was performed using the likelihood ratio test for nested models and the Akaike Information Criterion (Akaike, 1974) for non-nested models. Hypotheses on age-dependence of functions $f_1(t)$, $f(t)$ and $Q(t)$, and on coincidence of $f_1(t)$ and $f(t)$, and $Q_L(t)$ and $Q_R(t)$ were tested using the likelihood ratio test.

Results and Discussion

Estimates of the baseline hazard rate ($\mu_0(t)$), the quadratic term in the hazard ($Q(t)$), the "mean allostatic state" ($f_1(t)$), and the age-specific "norm" ($f(t)$) for six physiological indices in the quadratic hazard model applied to data on onset of "unhealthy life" in females and males in the Framingham Heart Study (original cohort) are shown and Figs. 3-8. Estimates of parameters are given in Table 1.

Figs. 3-8 about here

Table 1 about here

The results show that for all indices and for both sexes the estimates of parameter σ_2 are non-zero indicating the decelerating pattern of the baseline hazard with age (see upper left graphs in Figs. 3-8). Thus, our *a priori* expectations about the pattern of the risk of onset of "unhealthy life" corresponding to unspecified factors represented by $\mu_0(t)$ are confirmed. For all indices and both sexes, the trajectories of the quadratic term in the hazard ($Q(t)$) increase with age (see upper right graphs in Figs. 3-8). This means that the width of the U-shape of the risk (as a function of respective physiological index) is getting narrower with age. This, in turn, suggests that the range of the values of respective physiological indices corresponding to a "tolerable" increase in the risk is also getting narrower with age and the "price" for the same magnitude of deviation from the "norm" (in terms of an absolute increase in the risk of onset of "unhealthy life" compared to the baseline level $\mu_0(t)$ at that age) is higher at older ages. For all indices except hematocrit, the trajectory of $Q(t)$ for males lies above that of females meaning the higher "price" for deviations from the norm for males. Combined with higher values of the baseline

hazard for males, this may partly explain the observed higher incidence rate for males (see Fig. 1). We also checked whether the "penalties" for deviations of the index to the left and to the right from the "norm" $f(t)$ are different. In all cases except DBP for males (p=0.037) the respective null hypotheses in favor of the simpler model were not rejected at the 0.05 level.

For all analyzed indices and both sexes, the resulting estimates of the "mean allostatic state" $f_1(t)$ and the "optimal" trajectory $f(t)$ were age-dependent (significant at 0.05 level). Age-dependence of the "optimal" trajectory $f(t)$ indicates that the values of an index that minimize the risk of onset of unhealthy life for young and middle-age adults may differ from those of old and oldest-old individuals. Therefore, the strategies aiming at maintaining the level of a physiological index at oldest ages similar to the level optimal for younger individuals may actually increase the risk of development of cancer, CVD or diabetes. Furthermore, the notion of the "norm" used here minimizes the risk of onset of any of the three diseases from the definition of "unhealthy life" at respective ages, and, hence, is a "compromise" measure from the disease-specific "norms" (which may have different patterns if a physiological index has different impact on the risk of different diseases). However, if the goal is to minimize the risk of onset of any of the three diseases rather than to minimize the risk of one disease at a possible cost of increased risks for other diseases, then such approach may be preferable to analyses of disease-specific data. Also, it may happen that the trajectory that minimizes the risk of onset of "unhealthy life" differs somewhat from that minimizing the risk of death. Thus, similar studies need to be performed to evaluate the "optimal" trajectories in terms of mortality risks and compare them with those evaluated here for the onset of "unhealthy life." Therefore, the concept of physiological "norms" deserves careful additional studies.

For all indices and for both sexes, the null hypotheses on coincidence of $f_1(t)$ and $f(t)$ were rejected at 0.05 level. This means that the processes of compensatory adaptation and remodeling regulating the age dynamics of respective physiological states force the age-trajectories of the indices to follow the curves which do not tend to minimize the risk of onset of "unhealthy life." Persistent deviations from the "norm" characterize the effects of allostatic adaptation and the magnitudes of such deviations for each physiological index can be associated with components of allostatic load leading to increased chances of development of the diseases (if the estimates of the quadratic term in the hazard, $Q(t)$, are not zero, which is the case in our applications). If one takes two individuals, the first one being a "typical person" whose age trajectory of some physiological index drifts along the "mean allostatic state" $f_1(t)$ and the second one who manages to keep his/her age trajectory at the "optimal" level corresponding to $f(t)$, then the first individual will have increased chances of getting the diseases compared to the second one (if all other factors, i.e., those summarized in $\mu_0(t)$, are the same). As the result, the "healthy life expectancy" in two individuals will be different and such a difference can be evaluated from the model. In case of our applications, the difference in healthy life expectancy reaches 6.58 years for PP in females and 3.05 years for PP in males.

We also tested whether the respective indices have a single "optimal" value minimizing the risk of onset of "unhealthy life" at each age, or there is a range of such values with minimal risk. Although in all cases the respective null hypotheses in favor of the simpler model were not rejected at the 0.05, the optimal ranges $f_L(t)$ and $f_R(t)$, rather than the optimal trajectories $f(t)$, were estimated for the majority of indices. In all cases where such ranges were estimated, the ranges narrowed with age indicating that the range of "acceptable" values of indices with minimal risk of onset of "unhealthy life" shrinks as an individual gets older (data not shown).

This can be considered as a manifestation of decline in stress resistance with age in addition to the observation that the respective U-shape of the risk narrows with age as discussed above.

The limitations of the approach considered in this paper deal with the fact that it evaluates average effects of allostatic adaptation and average optimal functions. It would be useful to investigate individual dynamic effects of allostatic adaptation and individual optimal age trajectories of physiological indices. Such extension, however, would involve more data and require development of more sophisticated dynamic models describing numerous aging related changes in their mutual connection and their effects on mortality/morbidity risk. Also, we used a rather simplified assumption that the feedback coefficient $a(t)$ is constant, whereas the adaptive capacity may decline with age.

One more limitation is that the approach uses a one-dimensional description of physiological state. However, different physiological indices may be mutually dependent and evaluating the "norms" and other parameters independently may introduce a bias in estimates. Thus, multidimensional analysis of different indices is important. At the same time, a substantial deviation of some index from its one-dimensional "norm" may serve as an important indicator of a possible pathological development that may lead to overt symptoms of chronic diseases.

Conclusions

In conclusion, the results show that analyzes of longitudinal data using the approach discussed in this paper may substantially increase our knowledge on factors and mechanisms responsible for aging related changes in humans and help reveal the impact of age dynamics of physiological indices on the risk of onset of "unhealthy life."

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Tables:

Table 1: Estimates of parameters of the quadratic hazard model applied to data on onset of "unhealthy life" and age-trajectories of physiological indices in females and males in the Framingham Heart Study (original cohort)

Sex	Index	Parameters												
		$a_{\mu_0} \cdot 10^4$	b_{μ_0}	σ_2	$a_Q \cdot 10^4$	$b_Q \cdot 10^4$	a_Y	σ_0	σ_1	a_{f_1}	b_{f_1}	c_{f_1}	a_f	b_f
females	BMI	0.545	0.106	1.305	-0.9023	0.0322	-0.007	4.44	0.66	9.90	0.580	-0.005	29.82	-0.113
	DBP	0.665	0.100	1.219	-0.2005	0.0072	-0.052	11.53	3.47	55.16	1.054	-0.010	93.00	-0.362
	HC	0.044	0.146	1.632	-2.7158	0.0970	-0.043	3.02	1.02	33.79	0.367	-0.003	43.13	-0.011
	PP	0.446	0.110	1.442	0.0766	0.0004	-0.055	12.54	4.73	6.40	1.069	-0.001	39.73	0.028
	PR	0.515	0.107	1.268	-0.1305	0.0047	-0.058	12.91	4.03	67.54	0.455	-0.005	73.90	-0.078
	SCH	0.373	0.113	1.298	-0.0074	0.0003	-0.033	43.41	10.78	60.71	6.273	-0.052	229.43	-0.164
males	BMI	0.693	0.111	1.051	-1.1606	0.0482	-0.008	3.50	0.54	20.31	0.255	-0.003	26.09	-0.057
	DBP	0.617	0.110	0.994	-0.3166	0.0113	-0.054	11.30	3.46	66.21	0.807	-0.009	74.91	-0.018
	HC	0.088	0.141	1.268	-1.6388	0.0585	-0.042	3.11	1.06	42.56	0.221	-0.003	48.80	-0.113
	PP	0.839	0.108	1.074	-0.2427	0.0087	-0.055	11.63	4.35	37.38	0.004	0.007	22.63	0.393
	PR	0.686	0.110	1.044	-0.1776	0.0063	-0.054	12.96	3.97	67.48	0.337	-0.004	70.94	-0.162
	SCH	0.344	0.122	1.097	-0.0090	0.0003	-0.041	43.37	10.78	208.43	1.206	-0.017	178.36	-0.270

Figures:

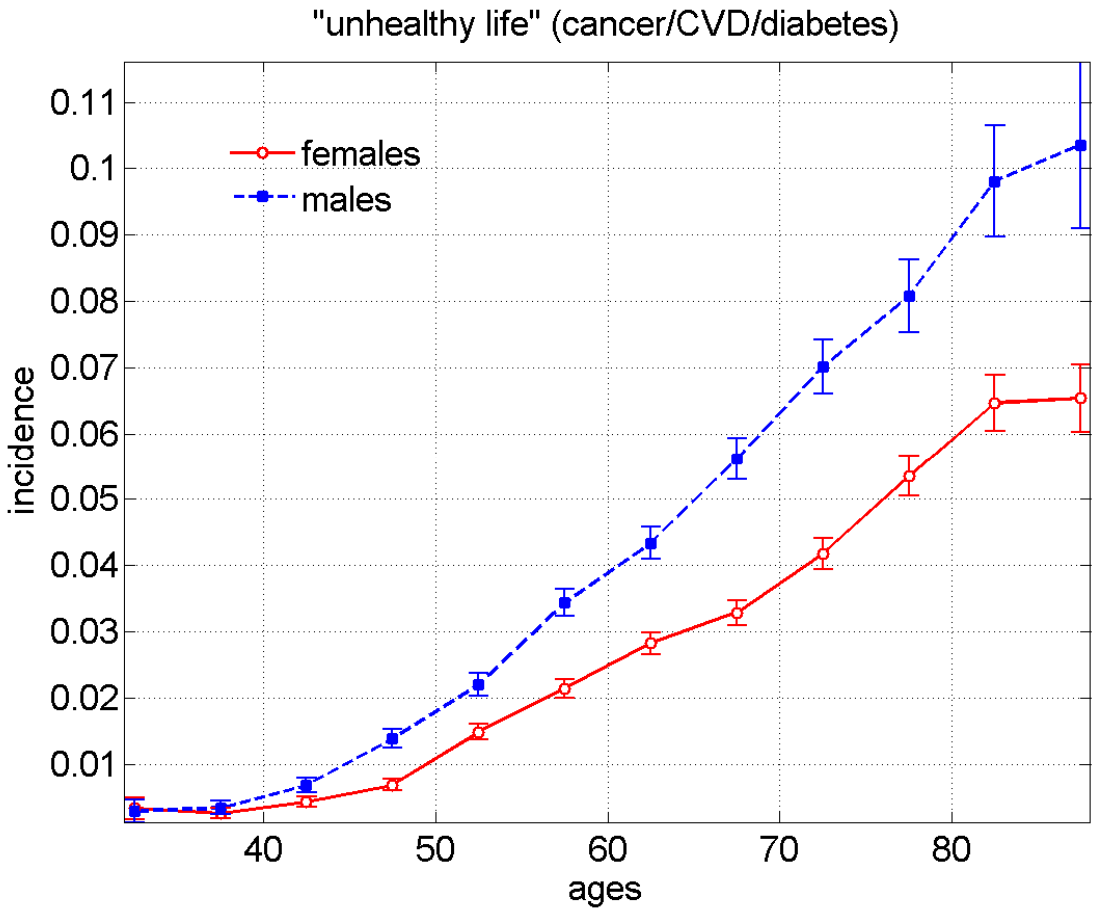

Fig. 1: Incidence rates of onset of "unhealthy life" (i.e., cancer, CVD, or diabetes) in females and males in the Framingham Heart Study (original cohort)

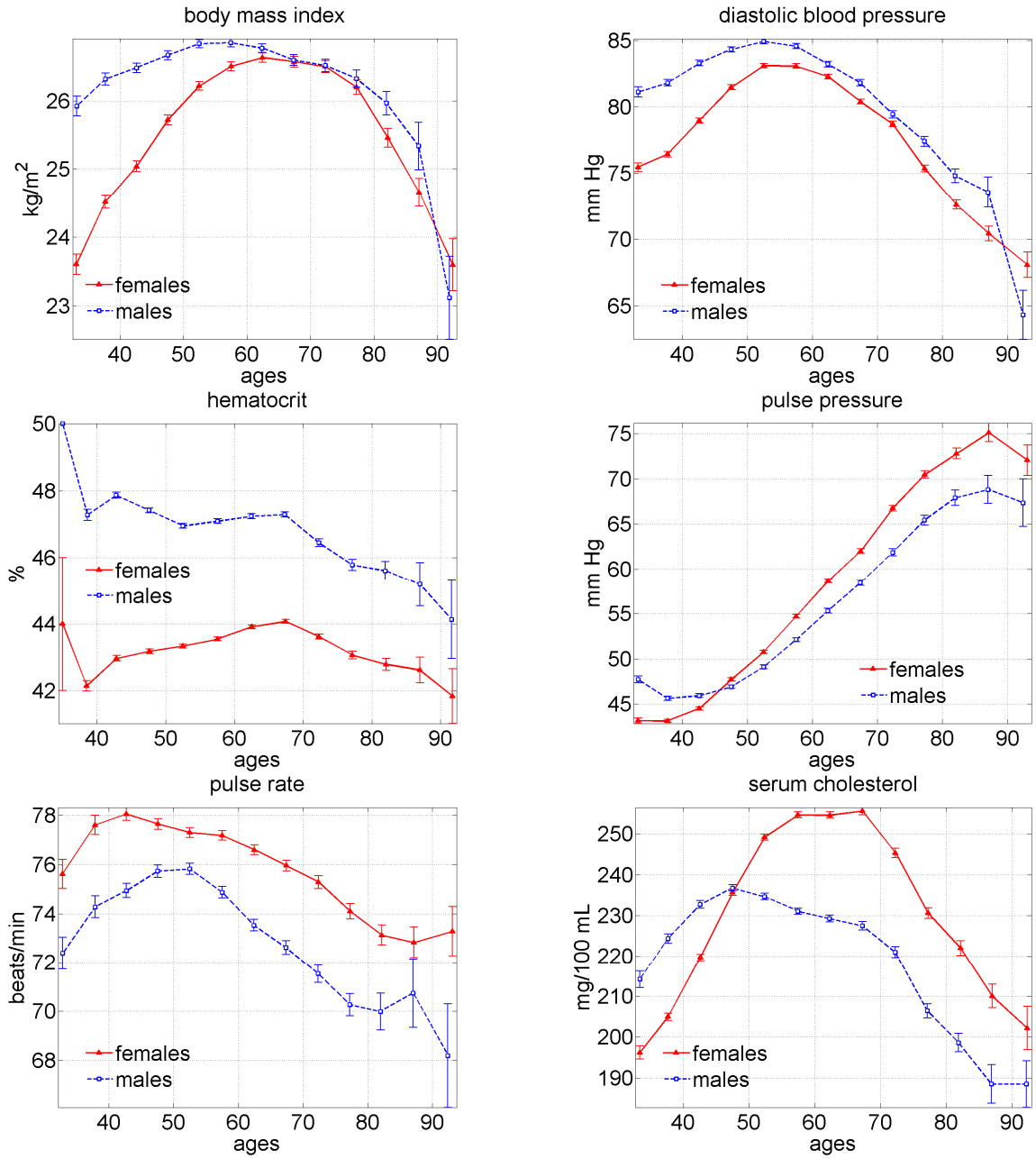

Fig. 2: Average trajectories of six physiological indices in females and males in the Framingham Heart Study (original cohort). **Note:** values of the indices measured after the onset of any of the three diseases defining "unhealthy life" (i.e., cancer, CVD, diabetes) are excluded from the calculations.

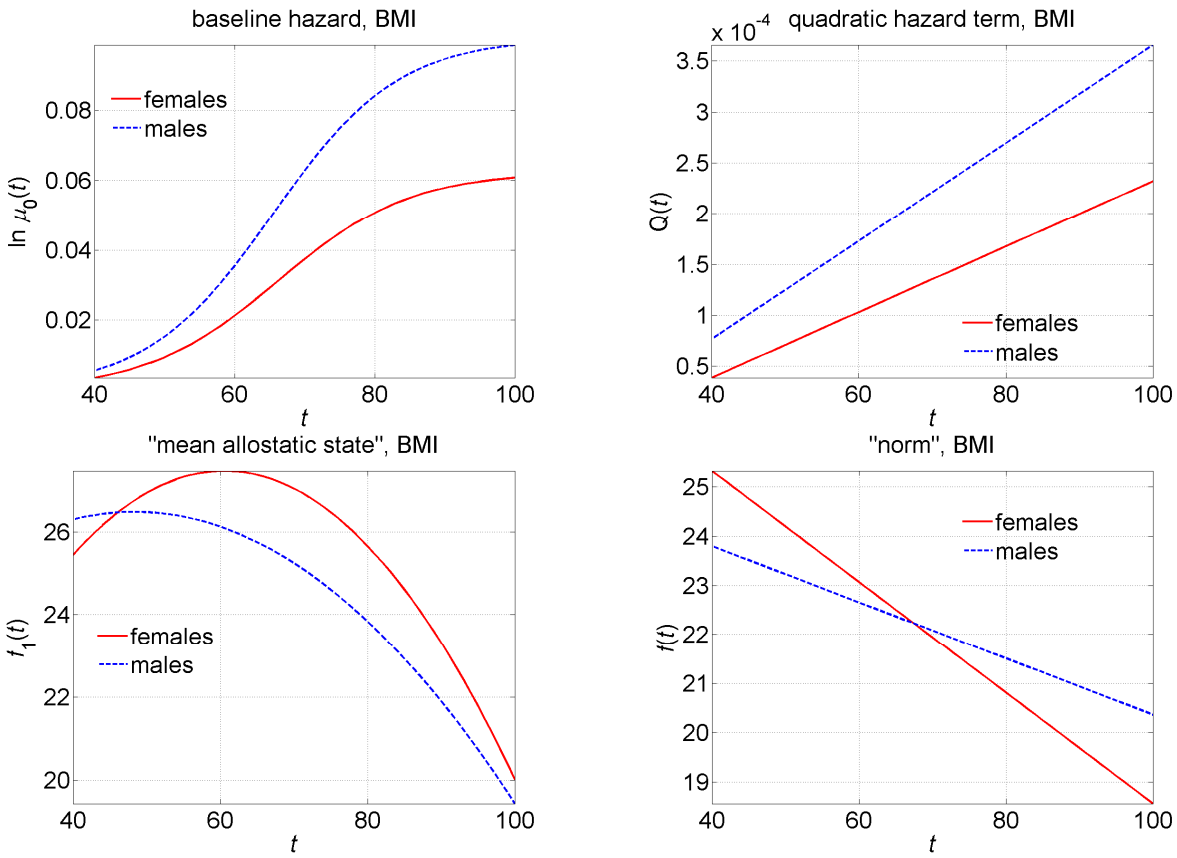

Fig. 3: Estimates of the baseline hazard rate ($\mu_0(t)$), the quadratic term in the hazard ($Q(t)$), the "mean allostatic state," and the age-specific "norm" of body mass index (BMI) in the quadratic hazard model applied to data on onset of "unhealthy life" in females (solid red lines) and males (dashed blue lines) in the Framingham Heart Study (original cohort)

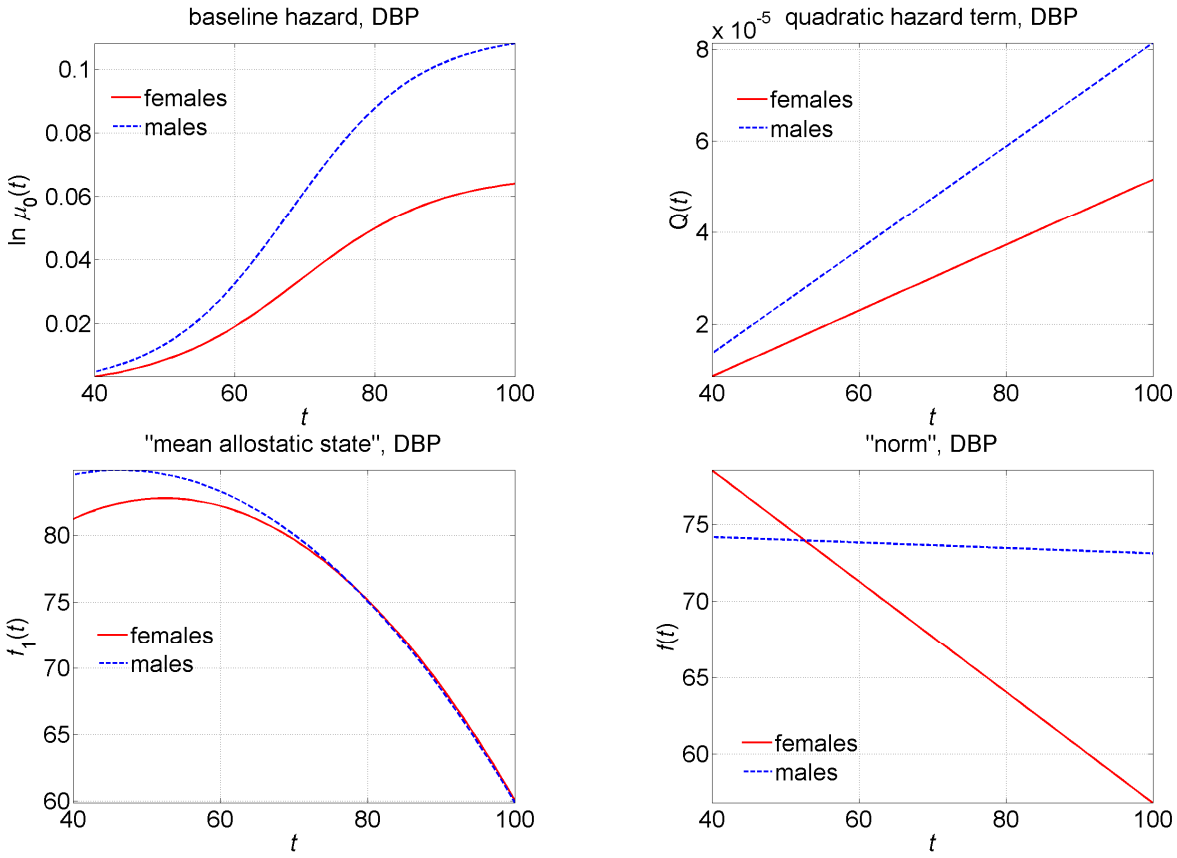

Fig. 4: Estimates of the baseline hazard rate ($\mu_0(t)$), the quadratic term in the hazard ($Q(t)$), the "mean allostatic state," and the age-specific "norm" of diastolic blood pressure (DBP) in the quadratic hazard model applied to data on onset of "unhealthy life" in females (solid red lines) and males (dashed blue lines) in the Framingham Heart Study (original cohort)

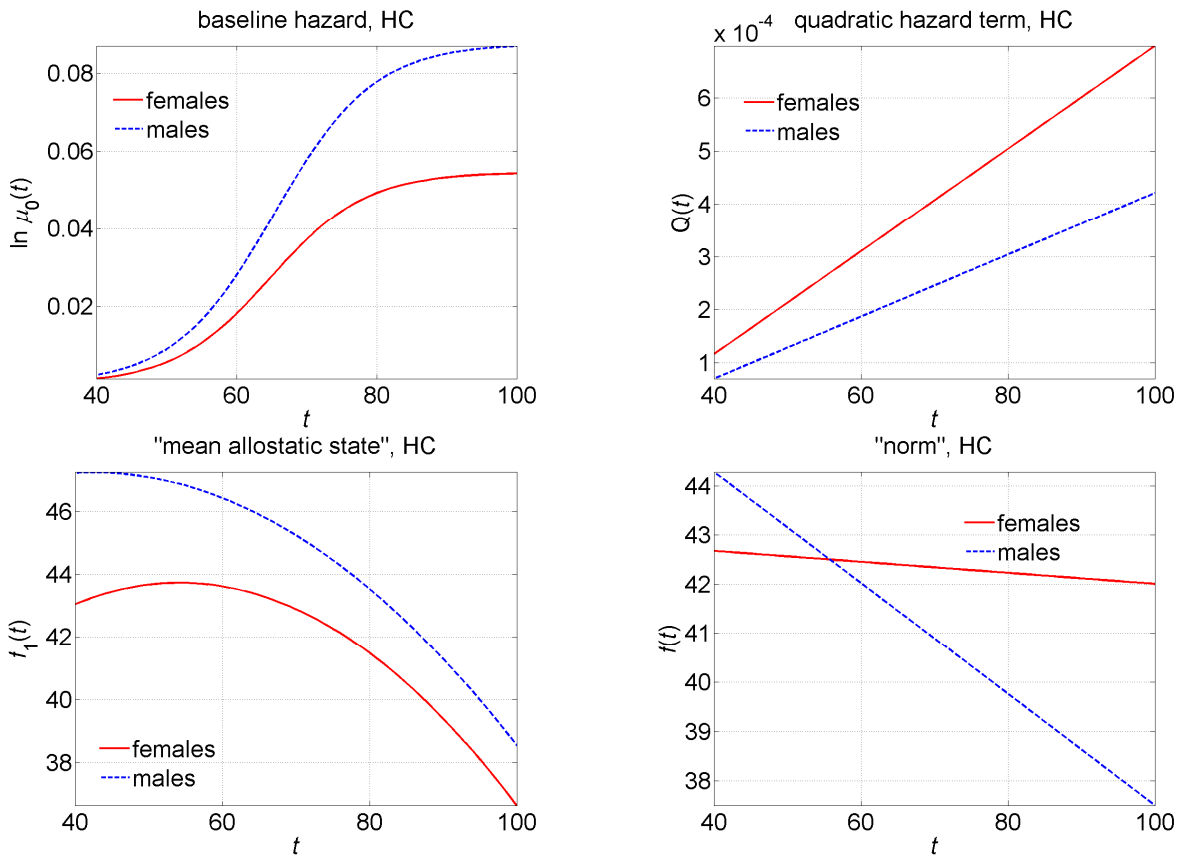

Fig. 5: Estimates of the baseline hazard rate ($\mu_0(t)$), the quadratic term in the hazard ($Q(t)$), the "mean allostatic state," and the age-specific "norm" of hematocrit (HC) in the quadratic hazard model applied to data on onset of "unhealthy life" in females (solid red lines) and males (dashed blue lines) in the Framingham Heart Study (original cohort)

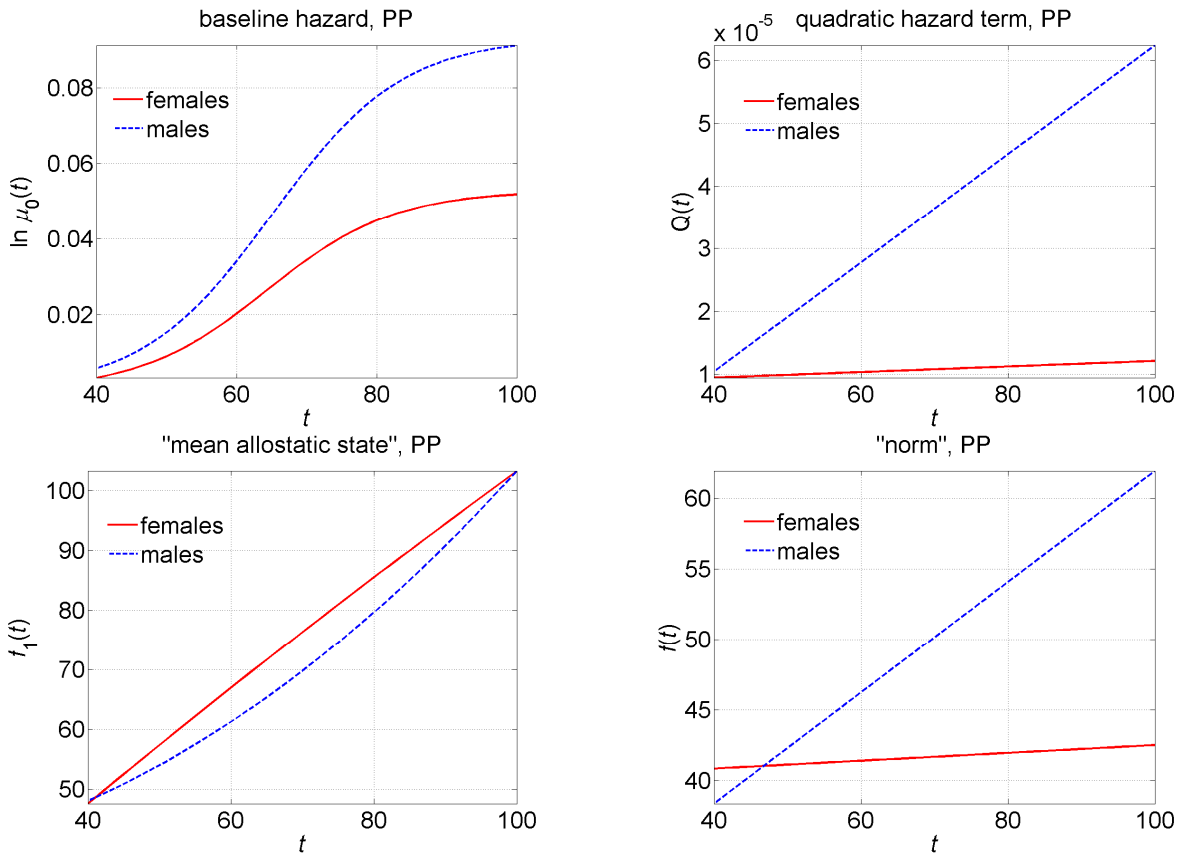

Fig. 6: Estimates of the baseline hazard rate ($\mu_0(t)$), the quadratic term in the hazard ($Q(t)$), the "mean allostatic state," and the age-specific "norm" of pulse pressure (PP) in the quadratic hazard model applied to data on onset of "unhealthy life" in females (solid red lines) and males (dashed blue lines) in the Framingham Heart Study (original cohort)

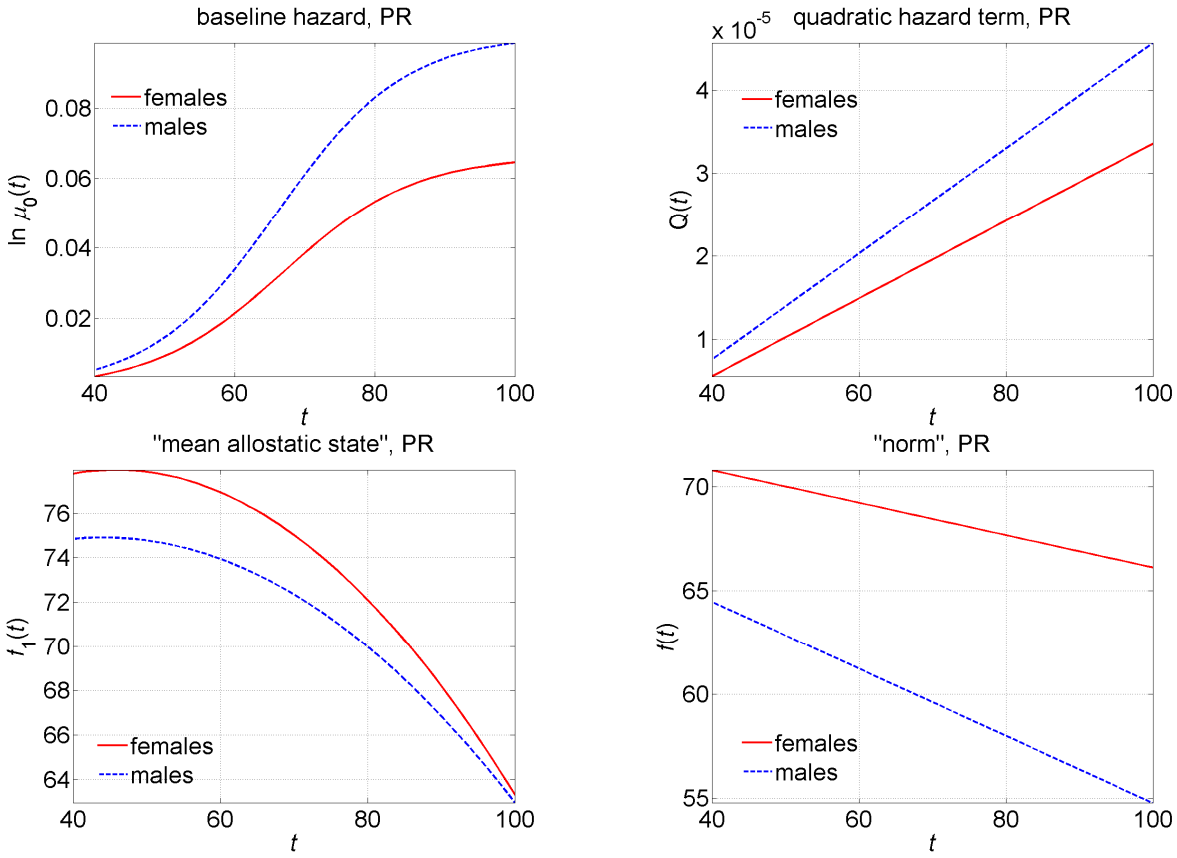

Fig. 7: Estimates of the baseline hazard rate ($\mu_0(t)$), the quadratic term in the hazard ($Q(t)$), the "mean allostatic state," and the age-specific "norm" of pulse rate (PR) in the quadratic hazard model applied to data on onset of "unhealthy life" in females (solid red lines) and males (dashed blue lines) in the Framingham Heart Study (original cohort)

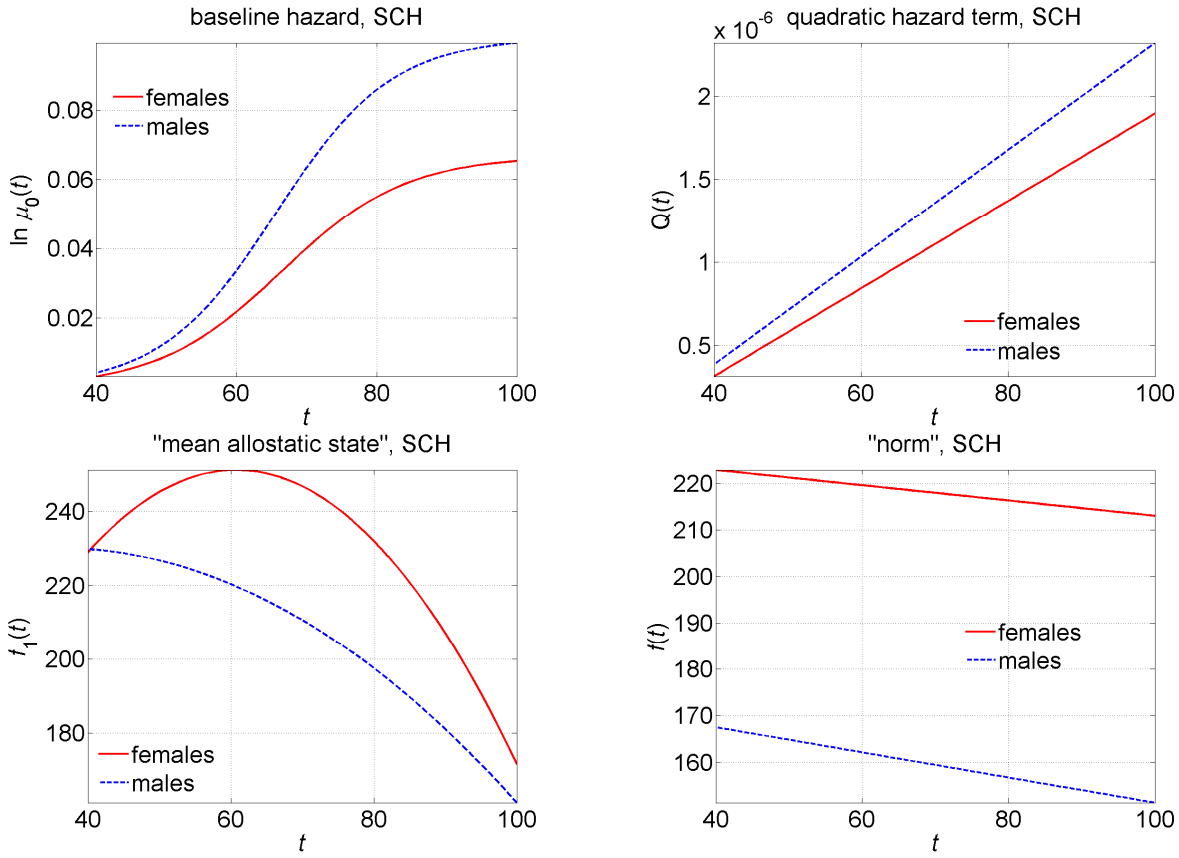

Fig. 8: Estimates of the baseline hazard rate ($\mu_0(t)$), the quadratic term in the hazard ($Q(t)$), the "mean allostatic state," and the age-specific "norm" of serum cholesterol (SCH) in the quadratic hazard model applied to data on onset of "unhealthy life" in females (solid red lines) and males (dashed blue lines) in the Framingham Heart Study (original cohort)