Biodemography of exceptional survival:
Lessons from longitudinal data

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Abstract

Maintaining proper level of physiological variables is often recommended for having long and healthy life span. To accomplish this goal quantitative definition of the proper or "normal" physiological state is needed. Although for many physiological indices the notions of "normal" values exist and are widely used in research and medical practices their methodological basis is vague. The need for further elaboration of this notion becomes evident in the context of dealing with aging related changes in human body. The values of physiological indices in human individuals tend to change with age, and these changes are associated with a number of health, and survival problems. Three main components are most likely contributors to such changes: we refer to them as to basal (i.e., representing senescence per se), ontogenetic (e.g., menopause), and exposure related. The process of senescence and ontogenetic changes take place even in the ideal environmental and living conditions. They induce processes of compensatory adaptation and remodeling, which may produce aging related changes in physiological state. As a result the notion of a "proper" level of physiological variables may differ for the young adults and for the old and oldest old individuals. This difference adds more problems for the norm definition, indicating that this notion may differ for individuals of different ages. Thus, not only the concept of normal physiological state has to be developed, but also the question on whether the norm itself evolves when individuals get older has to be addressed.

The deviations of physiological variables from their normal values induced by exposure related component is associated with the process of allostatic adaptation to persistent disturbances of different types, often associated with stressful environmental and living conditions. The price for such adaptation is an increased mortality risks compared to that for the normal level of these indices. Although both types of aging related changes are intensively discussed in the literature, it remains unclear, how to evaluate the normal level of physiological state by analyzing longitudinal data, and how to distinguish it from the effects of allostatic adaptation. Evaluating these components is important for creating appropriate background for developing preventive and treatment strategies aiming to increase healthy life span and longevity.

In this paper we develop an approach which allows for evaluating respective components from longitudinal data collected in the Framingham Heart Study. We show that physiological norm defined as values of physiological state associated with the lowest mortality risk for a given age, as well as effects of allostatic adaptation can be evaluated from longitudinal data. We found that the normal values are age dependent. The effects of new data on evaluating physiological norms as well as effects of allostatic adaptation are discussed. The developed approach can be used for analyzing data on any biomarker of aging, health, and longevity. We investigated aging related changes in blood glucose (BG) level in details. We found that average levels of BG increase with age for both sexes. This dynamics, however, represents effects of both biological aging related changes and population compositional changes occurring due to mortality selection. To separate biological changes in the level of BG from compositional effects we evaluated average BG trajectories for individuals participating in the FHS, who demonstrated exceptional survival (LL-individuals) and compared them with respective age trajectories calculated for several groups of short-lived (SL) individuals. We found that the average level of BG in the all groups including group of exceptional survivors increases with age. However, the

group of individuals with exceptional survival (LL individuals) had lower levels of average age trajectories of BG than any group of individuals with shorter life spans for both sexes. The increase of BG in the LL individuals takes place within the range of BG between 70mg/dl and 110mg/dl. We also found that among SL-individuals of both sexes the shorter is life span the higher the rate of average BG increase. Then we hypothesized that fast increase in average BG is associated with the presence of individuals with T2DM. To test this hypothesis we excluded individuals having this disease from the groups. We found that the rates of BG increase in the reduced groups became substantially closer to each other. The average level of BG for exceptional survivors without T2DM continued to increase with age in both sexes. This increase took place within BG range 75mg/dl and 98mg/dl. These analyses allowed us to expect that the estimate of BG norm obtained using different approaches can be approximated by increasing function of age changing within similar range.

Then we applied extended stochastic process model of human mortality and aging to the analysis of FHS data on aging related changes in BG concentration. The methods of statistical modeling allowed for evaluating a number of other important dynamic characteristics of the BG process in addition to age dependent physiological norm. These include effects of allostatic adaptation, aging related decline in resistance to stresses, and baseline hazards. These analyses have been performed for both sexes. In addition to these analyses we also used extended Cox-type proportional hazard model to describe and evaluate age dependence of physiological norm from the same data. The results of all three types of analyses (empirical, quadratic hazard, and extended Cox-type hazard) suggest that physiological norm for the BG concentration defined as the values of BG minimizing all-cause mortality risk increases with age, and these changes can be approximated by a linear function.

How useful the estimated BG norm is and how can it be further developed? The estimated norm characterizes minimum value of a risk function, which is averaged with respect to other physiological variables and risk factors conditional on BG. When observed level of BG is close to the norm and no other risk factors are observed, no actions affecting one's BG level are needed. This is because individual's mortality risk is close to its minimum value, and there is no information about other components of physiological state, which could affect mortality risk. Note that some individuals from the group with normal BG level may have abnormal levels of other physiological indices (e.g. blood pressure, pulse rate, etc.). The mortality risk for such individuals may substantially exceed minimal value of BG-dependent risk function. Some other individuals with normal BG may have close to normal values of other indices (e.g. blood pressure). The mortality risk for them will be lower than minimal value of BG-dependent risk function. The average risk conditional on BG level is minimal for those who are in the normal BG state.

In contrast: substantial deviation of the BG level from its normal value is an indicator of possible pathological development. Observed deviation is a signal that individual's health requires careful investigation, which will involve measurements of other physiological indices. After such investigation actions aiming to normalize one's BG level are needed. Note that the one-dimensional model of physiological state, described in this paper, cannot be used for proper recommendations on how the level of BG should be normalized: alternative pathways capable of returning BG to its normal values may end up with different values of other physiological variables, and respectively, with different mortality risks. To compare these mortality risks their multidimensional description using a vector of physiological variables is needed. The multidimensional consideration will require revision of the notion of physiological norm, which will become multidimensional vector function. This function minimizes mortality risk conditional on selected physiological variables. This is because physiological indices are interconnected and the normalization of one index, say BG level, will require multidimensional adjustment, in which the knowledge of dynamic connection among various physiological indices, other risk factors, and their effects on mortality risk play crucial role. Note that although existing medical practice tends to use systemic approaches to treatment, the existing notions

of physiological norms are developed without taking into account the multidimensionality of physiological state.

What would be wrong if the BG level, evaluated for the young adults, is considered as physiological norm for the old and oldest old individuals? Keeping young standards for the elderly individuals may dramatically increase mortality risk for such individuals, because the minimal value of such risk is reached at different BG level, which could be used as standard values for the elderly. Human ability to control dynamic behavior of physiological indices and other indicators of aging is limited, so most aging related changes are developing despite human efforts to stop, or postpone them. The fact that the aging individuals in the optimal physiological state have increasing mortality risk may indicate existence of a large number of unobserved variables, which deviation from norms increases with age. Human inability to measure and to fully control for basal and ontogenetic aging related changes, as well as for changes of unobserved indices induced by exposure to persistent disturbances, makes formulating the practical notion of a physiological norm dependent on existing levels of knowledge about aging in humans and the level of technological development in health care. This inability is also responsible for age dependence of a number of normal values of physiological indices basically ignored in the debates but usually taken into account in current medical practice. There is no doubt that an increase in knowledge about aging and diseases will affect the notion of physiological norm, making it more individualized. This will also contribute to the reduction in optimal mortality risk.