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How Genes Influence Life Span: The Biodemography of Human Survival

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Abstract

Background: In genome-wide association studies (GWAS) of human life span, none of the genetic variants has reached the level of genome-wide statistical significance. The roles of such variants in life span regulation remain unclear.
Data and Method: A biodemographic analyses was done of genetic regulation of life span using data on low-significance longevity alleles selected in the earlier GWAS of the original Framingham cohort.
Results: Age-specific survival curves considered as functions of the number of longevity alleles exhibit regularities known in demography as "rectangularization" of survival curves. The presence of such pattern confirms observations from experimental studies that regulation of life span involves genes responsible for stress resistance.
Conclusion: Biodemographic analyses could provide important information about the properties of genes affecting phenotypic traits.

Introduction

Genome-wide association studies (GWAS) of complex traits have been developed to perform intensive analyses of genetic influences on such traits. These studies have helped identify hundreds of genetic variants and have provided valuable information about their roles in such traits.[1] Despite this evident progress, GWAS have not entirely met the expectations of many researchers. Most genetic variants identified so far confer relatively small effects on the traits of interest. Many of the detected effects remain below the levels of statistical significance established to correct the analyses for multiple comparisons. These small-effects, low-significance single-nucleotide polymorphism (SNP) alleles conventionally have been excluded from further analyses of their roles in molecular metabolic pathways. The small contribution of selected SNP alleles to the variability of complex traits has generated debates about "missing heritability."[1–5] The use of data from the whole-genome scan combined with an intensive search for rare alleles has been suggested as an alternative to existing GWA approaches. However, genetic data for populations of appropriate sizes with such levels of genetic details are not yet available to researchers.

GWAS of human longevity share all these limitations. The candidate-gene approach used in genetic association studies of longevity has resulted in finding a number of genes whose connection to long life can also be associated with the roles they play in metabolic pathways. The effects of a number of such genes have been replicated in independent studies.[6–9] Surprisingly, however, these genes have not shown significant effects in genome-wide association studies of human longevity.[10,11]

Lunetta et al.[10] performed GWAS using genetic data on 100K SNPs collected for participants of the original and offspring cohorts of the Framingham Heart Study (FHS). The authors concluded that longevity and aging traits are associated with SNPs on the Affymetrix 100K GeneChip. However, none of the associations achieved genome-wide significance.

Newman et al.[11] performed a meta-analysis of GWAS in Caucasians from four prospective cohort studies. The authors found 273 SNP associations with $p<0.0001$, but none reached the prespecified significance level of 5×10^{-8}. Another recent meta-analysis of GWAS from nine studies also found no genome-wide significant SNPs for all-cause mortality and survival free of major disease or death.[12]

Two recent GWA studies confirmed the role of the apolipoprotein E (APOE) gene as the major genetic determinant of survival into old age. Deelen et al.[13] found one SNP located in TOMM40 at chromosome 19q13.32 close to the APOE gene ($p=3.39\times10^{-17}$). Nebel et al.[14] found one SNP near the

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APOC1 gene ($p = 1.8 \times 10^{-10}$), and this association was fully explicable by linkage disequilibrium with the APOE allele e4. No other SNPs reached the genome-wide significance level in these studies.

Yashin et al.[15] found that genetic variants that were individually selected using methods of GWAS may jointly influence life span. The joint effect of polygenic score ("genetic dose") on life span was substantial and highly statistically significant. The relationship was replicated using data on an independent population. The set of selected genetic variants was able to predict a similar relationship in the replicate population. Here we evaluate age patterns of mortality and survival for subgroups of individuals having different numbers of longevity SNP alleles in their genomes. We show that survival functions in the subgroups differ substantially and that the difference in age patterns is similar to that in population-level survival observed in the distinct time points of the last century. We explain these differences and similarities using biodemographical methods and show that these explanations are consistent with recent findings from studies of aging and longevity. Note that the construction of the polygenic score (genetic dose), which counts the number of longevity alleles contained in person's genome, resembles that of the frailty (or cumulative deficits) index,[16–18] which counts accumulation of deficits in individual during his/her life course.

Data and Methods

Data and general approach

To reduce possible effects of missing data on survival functions of individuals having different genetic backgrounds, we used data that passed a high-level of quality control procedure with SNP call rates of 97% and with subsequent imputation of missing genotypes. These procedures resulted in 954 individuals from the original FHS cohort. Note that this number is smaller than that used in Yashin et al.[15] For each of these individuals, we calculated the number of longevity alleles contained in their genomes (out of 39 longevity alleles selected from 550,000 SNPs in Yashin et al.[15]). The detailed description of the FHS and the FHS genome-wide genotyping data can be found on the dbGaP website (phs000007.v3.p2).

Using 39 longevity alleles selected from data on the original FHS cohort, we constructed two polygenic score indices: One index measuring the additive genetic component of life span and another index counting the number of genetic variants contained in each subject's genomes (see details in Supplemental Data at www.liebertpub.com/rej). Each index was used for evaluating the joint influence of subsets of genetic variants on survival. We showed that the two indices explain about the same percentage of life span variance and are able to predict life spans in individuals from the offspring FHS cohort using genetic variants detected from the data on the original FHS cohort. We divided participants of the original FHS cohort into subcohorts of individuals having different numbers of longevity alleles in their genomes. Then we evaluated the joint influence of subsets of genetic variants on the age patterns of mortality and survival in these subcohorts. We separately fitted the Gompertz model to the mortality data at available age ranges in the subcohorts, constructed the corresponding survival functions, and compared them. We used the Strehler–Mildvan mortality model[19] to guide our analysis of how the Gompertz parameters are affected by the genetic factors and "life saving" mortality model[20] to get insights about functional roles of detected genes in aging, health and life span.

Results

Regularities of genetic influence on survival

Figure 1A illustrates the pattern of survival improvement observed in developed countries during the 20th century (sex-specific patterns are shown in Fig. S5 in Supplemental Data). Demographers have characterized such population survival curve improvements as "rectangularization," or "compression of mortality," by which is meant a shift toward very low mortality levels through childhood and younger adult ages followed by steep decreases in survivorship at the older ages.

Using survival data on the participants of the FHS cohort carrying different numbers of 39 "longevity alleles" (*i.e.*, alleles, having positive effects on survival) selected in Yashin et al.[15] from the original FHS cohort, we evaluated mortality rates and survival curve patterns for the three groups of individuals having different numbers of such alleles in their genomes. We divided the entire sample of 954 individuals

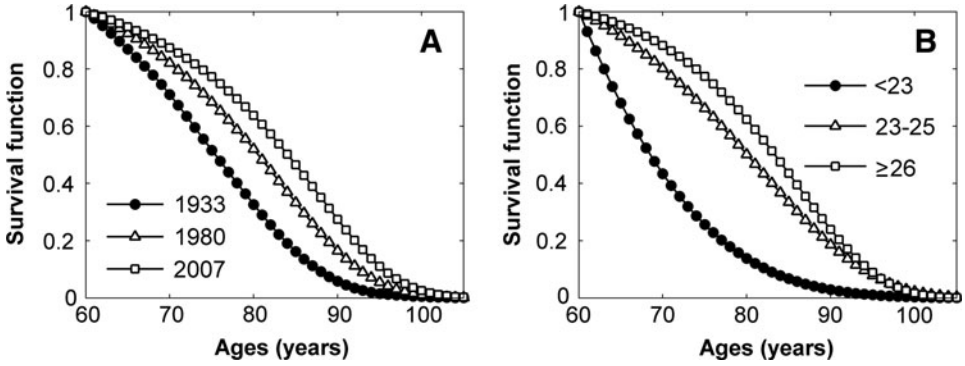

FIG. 1. Different factors produce similar patterns of changes in survival. **(A)** Survival curves (conditional at age 60) in the U.S. total population (both sexes) in years 1933–2007 (data source: Human Mortality Database). **(B)** Patterns of changes in survival of carriers of different numbers of longevity alleles detected in our genome-wide association study (GWAS) of the original Framingham Heart Study (FHS) cohort corresponding to Gompertz approximations of corresponding mortality curves.

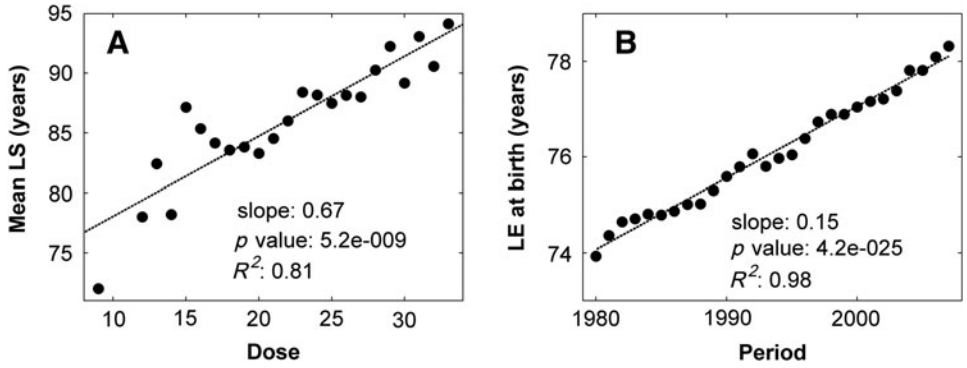

FIG. 2. Different factors produce similar changes in mean life span. **(A)** The "genetic dose—phenotypic response" relationship between the numbers of selected "low-effect longevity" alleles (39 total) contained in individuals' genome and mean life span (LS) of individuals carrying a given number of longevity single-nucleotide polymorphisms (SNPs) in their genomes (analyses of 500K SNP data, original Framingham Heart Study [FHS] cohort). (Black dots) Observed data; (dashed line) fitted linear regression. Longevity alleles were selected using a linear regression procedure, which involved comparison of characteristics of life span distributions among carriers and noncarriers of each of 500K genetic variants. **(B)** Life expectancy (LE) at birth in the U.S. total population (both sexes), 1980–2007 (data source: Human Mortality Database). (Dots) Observed data; (dashed line) fitted linear regression.

into these three groups so that the number of individuals in each group is approximately the same (344, 306, and 304, respectively). The number of longevity alleles carried by each individual in the first group was less than 23. The second group consisted of individuals each having 23–25 longevity alleles in their genomes. The third group contained individuals with 26 or more longevity alleles. Figure 1B shows that survival function for individuals from the second and third groups look more "rectangular" than that in the first group resembling difference in survival patterns observed in distinct time periods (see Fig. 1A).

Another striking similarity is between an almost linear increase of average life span as a function of the number of longevity alleles[15] and an almost linear increase in the life expectancy at birth over time.[21] Figure 2 shows an increase in average life span for groups of individuals whose number of longevity alleles varies from 0 to 39 (Fig. 2A) and the historical data on life expectancy at birth in the United States in 1980–2007 (Fig. 2B; sex-specific patterns are shown in Fig. S6 in Supplemental Data).

What mechanisms might be responsible for such similarities in survival and life expectancy changes caused by two evidently different causes? To address this question the use of two biodemographic models could be helpful. The first one[19] represents human mortality rates as a result of interplay between the process of external disturbances or stresses and an age-dependent decline in "vitality"—an index characterizing an individual's ability to withstand stresses of life. The second model[20,22] shows that observed trends in mortality decline can be explained by a process of "saving lives" resulting from improvement in economic and living conditions, as well as advances in health care and medical treatment.

The Strehler–Mildvan model of aging and mortality

More than 50 years ago, *Science* published the seminal Strehler and Mildvan[19] paper, in which the exponential increase with age, x, in the Gompertz mortality rate, $\mu(x) = R_0 \exp(\alpha x)$, was represented as a result of interplay between external disturbances (stresses of/challenges to life) and the decline in the "vitality" variable describing individuals' resistance to stresses. The model explained a striking regularity detected in comparisons of the Gompertz mortality rates across different populations: The parameters R_0 and α of this curve were not changing independently from one population to the next, as one might expect, but showed a strong negative correlation, later called the Strehler–Mildvan (SM) correlation. This model has been applied to explaining differences in mortality rates among different populations[19,23,24] and to differences in mortality rates in the same country at different time periods, or in subsequent subcohorts,[24–26] as well as in cause-specific mortality rates.[27]

Figure 3 shows the logarithms of the Gompertz mortality rates evaluated for groups of individuals in the original FHS

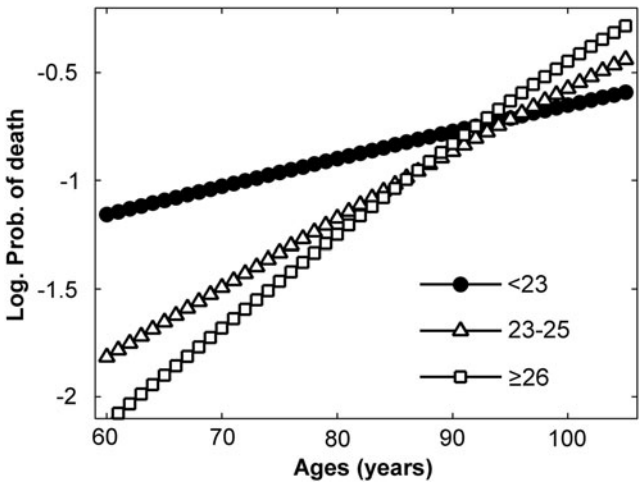

FIG. 3. Mortality rates for populations with different genetic background show Strehler–Mildvan (SM) correlation. The logarithms of estimated mortality rates approximated by the Gompertz curves in groups of Framingham Heart Study (FHS) original cohort members having different numbers of low-effect longevity alleles in their genomes.

cohort having different numbers of longevity alleles in their genomes.

The pattern of changes across the trajectories is typical of that for rectangularization of survival curves. The evaluation of the dependence of life span on the number of "longevity" alleles individual possess may shed more light on genetic nature of this trait.

How the SM model explains observed patterns in survival improvements over time

The SM model represents the age-specific Gompertz mortality function $\mu(x) = R_0 \exp(\alpha x)$ (which typically gives a good fit to population patterns of human mortality rates between ages 30 and 85 years) in terms of two sets of parameters: One describes the age-dependent decline in vitality and the second characterizes external stresses. In the framework of the SM model, the observed rectangularization pattern of survival improvement over time (first time period in Fig. 1A) can be explained by a decline in the average magnitude of external stresses. The parallel shift of the entire survival curve to the right over time (second time period in Fig. 1A) can be explained by the decline in the frequency of external disturbances (see Supplemental Data for details). These are parameters in the model characterizing the properties of external disturbances. Note that external factors could also affect other two parameters describing initial vitality and its rate of decline with age. Although the possibility of such influence was discussed by Strehler and Mildvan,[19] it was not represented explicitly in terms of parameters of external disturbances. Thus, in the framework of SM model, observed trends can be explained by changes in parameters of external disturbances.

How the SM model explains differences in survival for groups of individuals with different genetic backgrounds

The explanations given above are not valid for the patterns shown in Fig. 1B. This is because, instead of considering of how changes in external conditions over time influence human survival, we consider how such survival is affected by differences in genetic parameters of individuals taken from the same population cohort (original FHS cohort) and is exposed to the same external conditions. Therefore, different age patterns of survival (mortality rates) for these subcohorts are likely to be associated with differences in the parameters of the vitality function, which are likely to depend on the genetic backgrounds of the individuals comprising the respective subcohorts. The representation of the parameters of the Gompertz mortality curve (see Supplemental Data) together with the distinct patterns of survival functions shown in Fig. 1B indicate that the rectangularization pattern of changes in survival, in this case, can be observed if the initial value of vitality increases with an increase in the number of longevity alleles contained in individual genomes. In populations with such genetic backgrounds, the relative rate of decline in vitality remains unchanged, so the absolute rate of decline increases (see Supplemental Data).

This connection between genetic changes and modifications of the hypothetical vitality curve, estimated from real data, indicates that changes in the genetic background of individuals may affect dynamic parameters of aging-related changes in physiological indices measured in longitudinal data. The use of the SM model shows what types of effects on the dynamic parameters of the age trajectories of physiological indices can be expected (*e.g.*, improvement in survival may take place with and without changes in the rate of aging-related changes in relevant biomarkers) when the genetic backgrounds of the study participants change. A better understanding of the roles of such genetic factors in biomarkers of aging may also shed light on the role of gene–environment interactions in survival changes over time (Fig. 1A). New environmental conditions may activate new genes, which may modulate parameters of the vitality curve.

The presence of the SM correlation in the Gompertz parameters is associated with the "rectangularization" pattern of survival improvement.[28] The corresponding decline in mortality rates can be represented by counterclockwise rotation of the logarithms of the mortality curves around some point, so that the logarithm of the parameter a declined and the parameter b increased. The use of the SM model allows for interesting interpretation of the roles of the longevity alleles in mechanisms responsible for changes in the shape of mortality rate. The effect of counterclockwise rotation takes place if the number of such alleles determines the initial value of the vitality function (see Fig. S2). This may indicate that each such allele contributes to an increase in robustness and in resistance to stresses.

Additional insights about possible biological mechanisms responsible for such patterns of changes can be gained by comparing these curves with those resulting from the "saving lives" model,[20,29] where the rectangularization pattern of survival changes corresponds to an increase in the number of times "individuals' lives have been saved." "Saving lives" can be achieved not only by direct life-saving interventions but also by providing living organisms with additional resilience, redundancy, and robustness, which increases their ability to withstand stresses. Analyses of data on factors and conditions experienced by centenarians have led researchers to the same conclusion: High resilience makes a substantial contribution to exceptional longevity in humans.[30] Figure 4 shows that interventions that save lives once hypothetically applied to the U.S. population in 1950 would transform the 1950 mortality rate close to the U.S. 2007 pattern (sex-specific curves are shown in Fig. S7 in Supplemental Data).

Discussion

Demographers, studying trends in mortality and survival in populations of developed countries, have long had debates about "mortality compression" or "rectangularization of survival curve"—the process that took place in the first half of the 20th century. Although these changes were always linked to improvements in environmental and living conditions as well as advances in health care and medicine, there was no biological explanation of how these improvements got "under the skin" of the individuals in the populations to produce such rather specific trends in observed age patterns of mortality and survival. The biodemographic models described above provide useful insights: Biological systems responsible for the human body's resistance to stresses (*e.g.*, heat shock proteins) and resilience (*e.g.*, DNA repair) are likely to be involved. Myers and Manton[28] showed that in the second half of the 20th century the tail of the survival

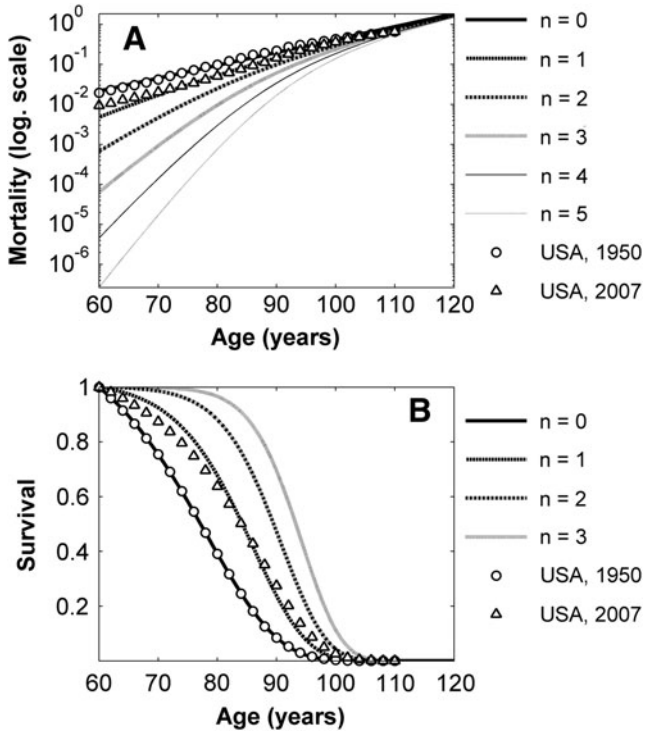

FIG. 4. Saving lives contributes to explanations of mortality and survival improvement. (**A**) Logarithms of mortality rates for U.S. total population (females and males) in 1950 (open circles) and in 2007 (open triangles). The 1950 mortality rate is approximated by the Gompertz function with $n=0$, where n is the number of times individual's life has been saved. The other curves correspond to mortality rates obtained by transforming the 1950 Gompertz mortality rate using the life saving equation with $n=1$, 2, 3, 4, and 5. (**B**) Survival functions for U.S. total population (females and males) in 1950 (open circles) and in 2007 (open triangles). Three other survival curves correspond to mortality rates obtained by transforming the 1950 Gompertz curve using the life saving equation with $n=1$, 2, and 3.

curve in the United States tended to increase across the older years of age. Horiuchi and Wilmoth[31,32] confirmed an increase of the tail of the life span distribution in the population of the United States. Wilmoth and Horiuchi[33] found that the decline in variability of life span, associated with a rectangularization pattern of changes in survival curves, came to an end around 1950 in Sweden and the United States, so the "compression of mortality" concept lost its ability to describe mortality trends. These findings were summarized in papers by Yashin et al.,[25,26] which found that the process of rectangularization of the survival curve that took place in the first half of the 20th century was later replaced by an almost parallel shift of the entire survival curve to the right (Fig. 1A).

The use of the SM model in analyses of genetic data shows that genetic factors may modify values and dynamic properties of variables describing aging-related transformations in the human body, and these modifications influence life span. Evidence for such influences is provided in a number of epidemiological studies. Port et al.[34] showed that the level of blood glucose affects mortality risk among subjects with cardiovascular disease. Yashin et al.[35] found associations between values of physiological indices at ages between 40 and 60 years and life span. Benetos et al.[36] found that dynamic properties of blood pressure affect mortality risk. Extending these analyses, Yashin et al.[37] also found that not only the values of these variables, but also their dynamic characteristics (*e.g.*, the rate of changes), are associated with life span, and healthy life span. These findings together with the insights from the SM analyses suggest that at least some of the detected associations may be caused by the joint influence of the number of genetic variants individually selected for their effects on health and survival outcomes.

The observed patterns in survival/mortality changes have important interpretations from the point of view of reliability theory. Indeed, the parallel shift of the mortality curve to the right corresponds to a proportional modification of the corresponding hazard rate. Such changes are expected in the series connection of N subsystems with similar age patterns of failure rates when one or several subsystems becomes invulnerable (*e.g.*, by providing them with high levels of redundancy, or repair capacity). The rectangularization (mortality counterclockwise rotation) pattern corresponds to providing a limited redundancy (or limited additional repair capacity) to one or more subsystems.[38] This analogy is consistent with systems biology approaches[39] to studying aging and longevity with identification of corresponding systems blocks, connections, reserve capacities, and repair mechanisms at different levels of an organism's biological organization. The presence of an "almost parallel shift" of survival curve to the right in Fig. 1A (showing changes in survival over time), and its absence in Fig. 1B (showing dependence of survival on genetic background), may indicate higher plasticity of mortality and survival in response to changes in external factors compared to changes in genetic background. The relatively low estimates of narrow-sense heritability in life span (about 25%) support this view and encourage the search for external factors capable of further improvement in human health and life span.

Improvements in environmental conditions (including changes in nutritional and living conditions, the use of new drugs, and new treatment procedures) are likely to activate new genes and modify metabolic pathways that contribute to increases in life span. Some of these genes may have large effects on life span; evidence to date from GWAS indicates that many others are likely to have small individual contributions. Accordingly, it could be hypothesized that the patterns shown in Fig. 1A reflect the contribution of genetic changes as well, resulting from the activation of a large number of small-effects longevity alleles in response to the changing environmental conditions across the past two centuries. Strehler and Mildvan[19] envisaged such a possibility by allowing the relative rate of vitality decline to depend on environmental factors as well. Being confirmed, this hypothesis will improve our understanding of how life span is regulated by external factors, and genetic analyses will help identify multiple genes that are likely to be collectively involved in such regulation. So the dependence of the parameters of the Gompertz mortality curves on characteristics of external stresses in the SM model is a useful simplification that was relevant for explaining SM correlation in the pregenomic era. New models capturing specific effects of gene–environment interactions and describing genetic

mechanisms mediating external influences on aging-related changes and health and survival outcomes are needed to properly explain the response of the body and phenotypic traits to changes in external factors.

Note that even if the patterns of differences in survival functions in the two panels in Fig. 1 look similar, and can be explained in terms of improved robustness and resilience, the mechanisms responsible for such changes are not necessarily the same. An improvement in survival over time involves the influence of advancing health care and medical technology (*e.g.*, proper access to emergency care, implantation of pacemakers, performing bypass surgery, etc.), which could extend life without affecting genetic mechanisms, for example, by increasing the reliability of functioning in certain biological organs or subsystems. Currently, more than 500,000 people in the United States have implanted pacemakers and over 100,000 people get new pacemakers implanted per year. The rate of implanting is higher in the elderly, with over 85% of implants received by those over age 65. The results of this paper provide researchers with new insights about the roles of advances in health care, medical technology, and medicine in survival improvements. Medical interventions today may substantially compensate for limitations of genetically based vitality mechanisms and increase life span.

The existence of additive genetic effect on life span explored in our study is in agreement with basic principles of quantitative genetics, considering complex traits as a function of many genetic and nongenetic factors. The additive genetic component of a phenotypic trait is responsible for transmission of a trait through generations and plays the key role in evolutionary theory of complex traits. It is also responsible for the narrow-sense heritability of such traits, which in the case of life span is about 25%.[40,41]

The additive joint influences of genetic variants on the risk of various diseases have been tested in several other studies using an aggregated index called "genetic or polygenic score."[42–47] Similar to our indices, the construction of genetic score functions involves weighted and unweighted sums of indicator functions of the genetic variants. These studies did not provide biological justifications for their score functions, and they used genetic variants detected in different studies and often in different populations. The results of such "meta-analyses," however, should be used with care, because the genes affecting the studied traits might be sensitive to external conditions. In GWAS of schizophrenia and a number of other psychiatric disorders, often none of genetic variants reached genome-wide significance. In such cases, substantially relaxed p value thresholds are often used in allele selection procedures.[48] Selected small-effect, low-significance genetic variants are used to construct genetic scores and test their influence on disease traits. Accordingly, more work is needed on the selection of influential alleles and the evaluation of regularities of their joint influence on health-related traits.

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Author Disclosure Statement

No competing financial interests exist.

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