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Early-Life Programming of Aging and Longevity

The Idea of High Initial Damage Load (the HIDL Hypothesis)

LEONID A. GAVRILOV AND NATALIA S. GAVRILOVA

Center on Aging, National Opinion Research Center (NORC) and University of Chicago, Chicago, Illinois 60637, USA

ABSTRACT: In this study, we test the predictions of the high initial damage load (HIDL) hypothesis, a scientific idea that early development of living organisms produces an exceptionally high load of initial damage, which is comparable with the amount of subsequent aging-related deterioration accumulating during the rest of the entire adult life. This hypothesis predicts that even a small progress in optimizing the early-developmental processes can potentially result in a remarkable prevention of many diseases in later life, postponement of aging-related morbidity and mortality, and significant extension of healthy life span.

KEYWORDS: high initial damage load (HIDL); aging; longevity; early-life; development; programming

INTRODUCTION

In 1991, we suggested a scientific idea that early development of living organisms produces an exceptionally high load of initial damage, which is comparable with the amount of subsequent aging-related deterioration accumulating during the rest of the entire adult life.[1]

This idea of high initial damage load (the HIDL hypothesis) predicts that even a small progress in optimizing the early-developmental processes can potentially result in a remarkable prevention of many diseases in later life, postponement of aging-related morbidity and mortality, and significant extension of healthy life span.[1–3] Thus, the idea of early-life programming of aging and longevity may have important practical implications for developing early-life interventions promoting health and longevity.

In this study, we tested the predictions of the HIDL hypothesis. Specifically, the HIDL hypothesis predicts that early-life events may affect survival in later adult life through the level of initial damage. This prediction is confirmed for such early-life factors as paternal age at a person's conception[4] and the month of a person's birth.[4,5]

Address for correspondence: Leonid A. Gavrilov, Center on Aging, NORC/University of Chicago, 1155 East 60th Street, Chicago, IL 60637-2745. Voice: 773-256-6359; fax: 773-256-6313.
gavrilov@longevity-science.org

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Another testable prediction of the HIDL hypothesis is a prevision of an unusual nonlinear pattern of life-span inheritance. This prediction is tested and confirmed: familial transmission of life span from parents to children follows a nonlinear (accelerating) pattern, with steeper slopes for offspring life span of longer-lived parents, as predicted.[6]

DISCUSSION OF THE IDEA OF HIGH INITIAL DAMAGE LOAD

The introductory section presented earlier is written as an abstract briefly summarizing the main ideas, findings, and conclusions of our studies. The purpose of this section is to provide a more detailed discussion of the idea of HIDL.

Reliability theory of aging predicts that a failure rate of simple redundant systems increases with age according to the Weibull (power) law.[1–3] This theoretical prediction is consistent with empirical observations that failure kinetics of technical devices follow the Weibull law.[7] However, biological systems "prefer" to fail according to the Gompertz (exponential) law,[1,8] which calls for explanations.

An attempt to explain exponential deterioration of biosystems in terms of the reliability theory led us to a paradoxical conjecture that biological systems start their adult life with a high load of initial damage.[1–3]

Although this idea may look like a counterintuitive assumption, it fits well with many empirical observations on massive cell losses in early development. For example, the female human fetus at 4–5 months of age possesses 6–7 million eggs (oocytes). By birth, this number drops to 1–2 million and declines even further. At the start of puberty in normal girls, there are only 0.3–0.5 million eggs, just only 4–8% of initial numbers (for review, see Ref. 3).

Massive cell losses in early development are creating conditions for a Poisson distribution of organisms according to the numbers of remaining cells, which in turn produce the exponential (Gompertzian) law of mortality increase.[1] Because the mathematical proof for this statement is already published elsewhere for a more general case of binomial distribution,[1] we can concentrate here on substantive discussion of the idea of HIDL in biological systems.

Biological systems are different from technical devices in two aspects. The first fundamental feature of biosystems is that, in contrast to technical (artificial) devices, which are constructed out of previously manufactured and tested components, organisms form themselves in ontogenesis through a process of self-assembly out of *de novo* forming and externally untested elements (cells). The second property of organisms is the extraordinary degree of miniaturization of their components (the microscopic dimensions of cells, as well as the molecular dimensions of information carriers like DNA and RNA), permitting the creation of a huge redundancy in the number of elements. Thus, we can expect that for living organisms, in distinction to many technical (manufactured) devices, the reliability of the system is achieved not by the high initial quality of all the elements, but by their huge numbers (redundancy).

The fundamental difference in the manner in which the system is formed (external assembly in the case of technical devices and self-assembly in the case of biosystems) has two important consequences. First, it leads to the macroscopicity of technical devices in comparison with biosystems since technical devices are assembled "top-down" with the participation of a macroscopic system (humans) and must be suitable for this macroscopic system to use (i.e., commensurate with humans). Organisms, on the other hand, are assembled “bottom-up” from molecules and cells, resulting in an exceptionally high degree of miniaturization of the component parts. Second, since technical devices are assembled under the control of humans, the opportunities to pretest components (external quality control) are incomparably greater than in the self-assembly of biosystems. The latter inevitably leads to organisms being “littered” with a great number of defective elements. As a result, the reliability of technical devices is assured by the high quality of elements, with a strict limit on their numbers because of size and cost limitations, while the reliability of biosystems is assured by an exceptionally high degree of redundancy to overcome the poor quality of some elements.

It follows from this concept of HIDL that even small progress in optimizing the processes of ontogenesis and increasing the numbers of initially functional elements can potentially result in a remarkable fall in mortality and a significant improvement in life span. This optimistic prediction is supported by experimental evidence of increased offspring life span in response to protection of parental germ cells against oxidative damage just by feeding the future parents with antioxidants.[9] Increased life span is also observed among the progeny of parents with a low resting respiration rate (proxy for the rate of oxidative damage to DNA of germ cells; see Ref. 1). The concept of HIDL also predicts that early life events may affect survival in later adult life through the level of initial damage. This prediction proved to be correct for such early-life indicators as parental age at a person’s conception[4] and the month of a person’s birth (see FIG. 1, TABLE 1, and earlier publications[4,5]).

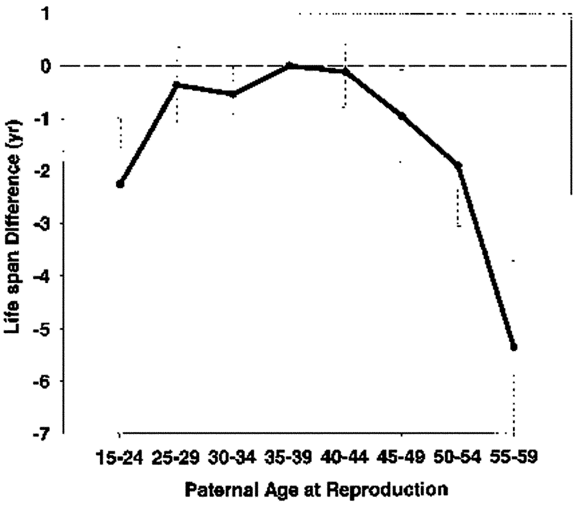

FIGURE 1. Daughters’ life span as a function of paternal age at daughter’s birth: 5063 daughters from European aristocratic families born in 1800–1880. Both parents lived 50+ years. Details of data analysis are described elsewhere.[4]

TABLE 1. Female life span as a function of month of birth

Month of birth	Net effect, in years (point estimate)	Standard error	*P* value
February	0.00	Reference level	
March	1.10	0.92	.2331
April	1.72	0.92	.0619
May	2.35	0.90	.0090
June	1.66	0.90	.0665
July	1.86	0.91	.0404
August	1.49	0.90	.0978
September	1.51	0.92	.0986
October	1.95	0.90	.0308
November	2.13	0.93	.0229
December	3.04	0.91	.0009
January	0.94	0.92	.3086
February	0.00	Reference level	

NOTE: Results are obtained through multivariate regression analysis of life-span data (outcome variable) for 6908 women born in 1800–1880 (extinct birth cohorts with life span known for each person), who survived by age 30 (focus on analysis of adult life span). The following additional predictor variables are also included in the final model because of their predictive value: (1) calendar year of birth, (2) ethnicity (Russian, British, and others), (3) loss of father during formative years of childhood (before age 15), (4) loss of mother during formative years of childhood (before age 15), (5) cause of death (violent vs. nonviolent), (6) early death of at least one sibling (before age 30), (7) high birth order (7+), (8) nobility rank of the father (indicator of social status), (9) large family size (number of siblings: 9+), (10) maternal life span, (11) paternal life span, (12) paternal age at person's birth, (13) late paternal age at first childbirth (50+ years), (14) birth of the first child by mother after age 30, and (15) death of mother from violent cause of death. The F value for the regression model is 18.12 ($P < .0001$). "Net effect" corresponds to additional years of life gained (or lost) compared to the reference category (life span for those born in February).

Women may be particularly sensitive to early-life exposures because they are mosaics of two different cell types (one with an active paternal X chromosome and another one with an active maternal X chromosome). The exact pattern of this mosaic is determined early in life. If early-life conditions affect the proportion (or distribution pattern) of cells with a given X chromosome, such conditions might have long-lasting effects in later life. Indeed, this conjecture of stronger female response to early-life exposures is confirmed for such early-life predictors of adult life span as paternal age at a person's conception[4] and the month of a person's birth.[4,5]

Another testable prediction of the HIDL hypothesis is a prediction of an unusual nonlinear pattern of life-span inheritance. Traditionally, it is assumed that the dependence of progeny life span on parental life span should follow a linear relationship, which is common to all other quantitative traits in classic quantitative genetics.[10] In other words, for each additional year of parental life span, the children are expected to have some fixed gain in their average life span too, as a result of polygenic inheritance of quantitative traits.[10] However, the HIDL hypothesis leads to a very different prediction of a nonlinear (accelerated) "concave-up" pattern of life-span inheritance. There should be virtually no life-span heritability (a negligible response of progeny life span to the changes in parental life span) when parental life span is below a certain age, and a much higher heritability (an increased response to parental life span) when parents live longer lives. This prediction follows from the hypothesis of HIDL among short-lived parents, whose bodies are damaged during early developmental processes, although their germ-cell DNA might be perfectly normal. (If the germ-cell DNA were damaged too, these short-lived parents would probably produce offspring who also live short lives. This category will thus be unlikely to distort the linear dependence of offspring life span on parental life span by a large amount.) Therefore, the progeny of some short-lived parents may have quite normal life spans, well beyond genetic expectations. This result would thus obstruct the classic linear offspring-on-parent dependence for life span. Only at some high parental life span, when most of the germ-normal/somatically damaged parents are eliminated because of their shorter length of life, will the classic linear pattern of life-span inheritance eventually reveal itself in its full capacity. This prediction of the HIDL hypothesis was tested and confirmed in humans: familial transmission of life span from parents to children proved to follow a nonlinear (accelerating) pattern, with steeper slopes for the life span of offspring born to longer-lived parents, as predicted.[6]

Thus, there is mounting evidence now in support of the idea of fetal origins of adult degenerative diseases, and early-life programming of aging and longevity.[4]

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REFERENCES

1. Gavrilov, L.A. & N.S. Gavrilova. 1991. The Biology of Life Span: A Quantitative Approach. Harwood Academic. New York.
2. Gavrilov, L.A. & N.S. Gavrilova. 2001. The reliability theory of aging and longevity. J. Theor. Biol. **213:** 527–545.
3. Gavrilov, L.A. & N.S. Gavrilova. 2003 (July 16). The quest for a general theory of aging and longevity. Science's SAGE KE (Science of Aging Knowledge Environment) **2003**(28)**:** 1–10 [available at http://sageke.sciencemag.org].
4. Gavrilov, L.A. & N.S. Gavrilova. 2003. Early-life factors modulating lifespan. *In* Modulating Aging and Longevity, pp. 27–50. Kluwer. Dordrecht.
5. Gavrilov, L.A. & N.S. Gavrilova. 1999. Season of birth and human longevity. J. Anti-Aging Med. **2:** 365–366.
6. Gavrilova, N.S. & L.A. Gavrilov. 2001. When does human longevity start? Demarcation of the boundaries for human longevity. J. Anti-Aging Med. **4:** 115–124.
7. Weibull, W.A. 1951. A statistical distribution function of wide applicability. J. Appl. Mech. **18:** 293–297.

8. GOMPERTZ, B. 1825. On the nature of the function expressive of the law of human mortality and on a new mode of determining life contingencies. Philos. Trans. R. Soc. London **A115:** 513–585.
9. HARMAN, D. & D.E. EDDY. 1979. Free radical theory of aging: beneficial effects of adding antioxidants to the maternal mouse diet on life span of offspring: possible explanation of the sex difference in longevity. AGE **2:** 109-122.
10. FALCONER, D.S. & T.F.C. MACKAY. 1996. Introduction to Quantitative Genetics. Longman. London.