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REVIEW

Determinants of longevity: genetic, environmental and medical factors

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Abstract. Christensen K, Vaupel JW (Odense University Medical School, Odense, Denmark; Sanford Institute, Duke University, Durham, NC, USA; and The Danish Epidemiology Science Centre, The Steno Institute of Public Health, Department of Epidemiology and Social Medicine, Aarhus University Hospital, Aarhus, Denmark). Determinants of longevity: genetic, environmental and medical factors (Review). *J Intern Med* 1996; **240:** 333–41.

This review focuses on the determinants of longevity in the industrialized world, with emphasis on results from recently established data bases. Strong evidence is now available that demonstrates that in developed countries the maximum lifespan as well as the mean lifespan have increased substantially over the past century. There is no evidence of a genetically determined lifespan of around 85 years. On the contrary, the biggest absolute improvement in survival in recent decades has occurred amongst 80+ year-olds. Approximately one-quarter of the variation in lifespan in developed countries can be attributed to genetic factors. The influence of both genetic and environmental factors on longevity can potentially be modified by medical treatment, behavioural changes and environmental improvements.

Keywords: centenarians, life expectancy, lifespan, mortality.

Introduction

The determinants of longevity might be expected to be well understood. The duration of life has captured the attention of many people for thousands of years; an enormous array of vital-statistics data are available for many centuries. Life-span is easily measured compared with other health phenomena, and in many countries data are available on whole populations and not just study samples. Knowledge concerning determinants of human longevity, however, is still sparse, and much of the little that is known has been learned in recent years. This review focuses on genetic, environmental and medical factors as determinants of longevity in developed countries and discusses alternative paradigms concerning human longevity.

How should longevity be measured?

Longevity can be studied in numerous ways; key questions include the following. How long can a human live? What is the average length of life? Are the maximum and average lengths of life approaching limits? Why do some individuals live longer than others? In addressing these questions, it is useful to

study the maximum lifespan actually achieved in various populations, the mean lifespan, and the variation in lifespan.

Estimating the maximum lifespan of human beings is simply a matter of finding a well-documented case report of a person who lived longer than other well-documented cases. The assessment of mean lifespan in an actual population requires that the study population is followed from birth to extinction. An alternative approach is to calculate age-specific death rates at some point in time for a population, and then use these death rates to determine how long people would live on average in a hypothetical population in which these death rates prevailed over the course of the people's lives. This second kind of mean lifespan is generally known as life expectancy. The life expectancy of the Swedish population in 1996 is the average lifespan that would be achieved by the 1996 birth cohort if Swedish mortality rates at each age remained at 1996 levels for the entire future life of this cohort.

Assessment of determinants of life expectancy and variation in lifespan amongst individuals rely on demographic comparisons of different populations and on such traditional epidemiological designs as follow-up studies of exposed or treated versus non-exposed or nontreated individuals. Designs from genetic epidemiology – such as twin, adoption and other family studies – are useful in estimating the relative importance of genes and environment for the variation in longevity.

Determinants of extreme longevity

Numerous extreme long-livers have been reported in various mountainous regions, including Georgia, Kashmir, and Vilcabamba. In most Western countries, including the Scandinavian countries, exceptional lifespans have also been reported. Examples are Drachenberg, a Danish–Norwegian sailor who died in 1772 and who claimed that he was born in 1626, and Jon Anderson, from Sweden, who claimed to be 147 years old when he died in 1729. There is no convincing documentation for these extreme long-livers. When it has been possible to evaluate such reports, they have proven to be very improbable [1, 2]. In countries, like Denmark and Sweden, with a long tradition of censuses and vital statistics, remarkable and sudden declines in the number of extreme long-livers occur with the introduction of more rigorous checking of information on age of death, as the result of laws requiring birth certificates, the development of church registers and the establishment of statistical bureaus [3, 4]. This suggests that early extreme long-livers were probably just cases of age exaggeration.

Today (March 1996), the oldest reported well-documented maximum lifespan for females is 121 years [5] and for males 113 years [6]. Both these persons are still alive. Analyses of reliable cases of long-livers show that longevity records have been repeatedly broken over past decades [3, 6]; this suggests that even longer human lifespans may occur in the future.

There has been surprisingly little success in identifying factors associated with extreme longevity. A variety of centenarian studies have been conducted during the last half century. As reviewed by Segerberg [7], most of the earlier studies were based on highly selected samples of individuals, without rigorous validation of the ages of reputed centenarians. During the last decade several more comprehensive, less selected centenarian studies have been carried out in Hungary [8], France [9], Finland [10] and Denmark [11].

A few specific genetic factors have been found to be associated with extreme longevity. Takata *et al.* [12] found a significantly lower frequency of HLA-DRw9 amongst centenarians than in an adult control group in Japan, as well as a significantly higher frequency of HLA-DR1. The HLA-antigens amongst the Japanese centenarians are negatively associated with the presence of autoimmune diseases in the Japanese population, which suggests that the association with these genetic markers is mediated through a lower incidence of diseases. More recently, both a French study [13] and a Finnish study [14] found a low prevalence of the e4 allele of apolipoprotein E amongst centenarians. The e4 allele has consistently been shown to be a risk factor both for coronary heart disease and for Alzheimer's dementia. In the French study [13], it was also found that centenarians had an increased prevalence of the DD-genotype of angiotensin-converting enzyme (ACE) compared with adult controls. This result is contrary to what was expected as the DD-genotype of ACE has been reported to be associated with myocardial infarction. Only a few genetic association studies concerning extreme longevity have been published;

Table 1 Determinants of extreme lifespan in the industrialized world

Genes coding for:	Human leukocyte antigens HLA-DR (?) Apolipoprotein E (?) Angiotensin-converting enzyme (ACE) (?)
Environment	Year of birth Smoking (?) Alcohol (?) Diet (?)
Medicine	Dehydroepiandrosterone (DHEA) (?)

the associations described above need to be replicated in future studies.

Amongst environmental factors, even such an obvious candidate as nonsmoking has failed to be associated with extreme longevity. For example, the world's oldest man has smoked for most of his life and still smokes cigars regularly [6]. This should not be taken as evidence of the harmlessness of smoking: the influence of many risk factors attenuates when studied in older people. For smoking, the underlying explanation is likely to be that individuals for whom smoking was a severe health hazard (due to genetic make-up or other risk factors) have died well before the most advanced ages. The individuals surviving to extreme ages are particularly robust and either are not very susceptible to the health hazards of smoking or have compensating characteristics [15, 16]. Studies of alcohol consumption and diet through life, as well as physical activity, have also failed to show consistent association with attainment of extreme age [8–11].

History provides numerous examples of medical treatments claimed to yield a long and healthy life. However, none of these claims has been proven. In recent years, studies of humans have indicated that blood level of dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) are inversely correlated to mortality. Furthermore, these 'weak androgens' have shown association with various objective and subjective health measurements in elderly persons [17, 18]. Clinical trials are now under way to test this medication and its influence on ageing. The discussed determinants of extreme lifespan are listed in Table 1.

Determinants of mean lifespan

Amongst the lifespan measurements discussed here, mean lifespan is the one most important to social-security and health-care systems in the western world. Demographers and epidemiologists agree that life expectancy has been increasing during the last century in the industrialized world (Table 2). The question has been whether this increase in life expectancy will continue. Until a few years ago, most researchers in demography, epidemiology and gerontology believed that life expectancy would not increase much more (for example, see Refs 19–21). This 'limited lifespan paradigm' goes back to Buffon, in the 18th century [22], who hypothesized that a biological clock determines the maximum lifespan of an individual. The limited lifespan view has had many supporters over the years [23–29]. The underlying axiom is that deaths at older ages are natural deaths due to intrinsic, intractable ageing processes, whereas deaths at younger ages are generally extrinsic and potentially preventable.

The most prominent advocate of this hypothesis has been Fries [30–34]. Fries claimed that there is a genetically determined upper limit to the lifespan of every individual. This limit varies from person to person; for the average person it is about 85 years. Progress in living conditions and health would reduce death only at younger ages. The human survivorship

Table 2 Life expectancy in the Nordic countries[a]

	Males						Females					
Country	1910	1930	1960	1970	1985	1993	1910	1930	1960	1970	1985	1993
Island	49.9	58.1	70.7	71.1	74.0	76.9	54.7	62.3	75.5	76.9	80.2	80.7
Norway	55.0	62.8	71.2	71.2	72.8	74.2	58.8	65.7	75.7	77.1	79.6	80.3
Denmark	55.6	61.5	70.4	70.7	71.6	72.3	58.5	63.2	74.1	75.8	77.5	77.6
Sweden	55.2	62.3	71.4	72.2	73.8	75.5	57.6	64.4	75.2	77.1	79.7	80.8
Finland	45.4	52.9	65.2	66.4	70.1	72.1	48.1	57.3	72.3	74.6	78.5	79.5

[a] From Caselli G, Meslé F, Vallin J. *Le triomphe de la médicine*. Paris: Institut National d'Études Demographiques, 1995; and Nordic Statistical Secretariat, eds. *Yearbook of Nordic Statistics 1995*. Copenhagen: Nordic Council of Ministers, 1995.

curve would show increasing rectangularization with a dramatic drop in survival at around age 85.

A number of researchers have disputed this view and have argued that there is no biological or genetic barrier to longer life expectancy [35–41]. They believe that mortality rates can be reduced at all ages and that life expectancy could considerably exceed 85.

Until recently, it was impossible to test these alternative views because very few published life tables provide age-specific data after age 85. Through a substantial effort during the last decade, death counts and population counts by individual year of age up to the highest ages and by individual year of time back at least 4 decades are now available in the *Odense Archive of Population Data on Ageing* for most developed countries [42–47]. The comprehensive data bases in this archive provide very strong support for the 'mortality reduction paradigm': evidence from 27 countries show a dramatic decline in death rates at older ages [42, 44]. In fact, the older the age category the greater the absolute reduction in death rate [43]. The number of centenarians has roughly doubled every 10 years in developed countries over the past half century, and most of this rapid rise can be attributed to the marked increase in survival from age 80 to age 100 [48]. Rates of mortality improvement at older ages in countries with the longest life expectancy are not, on average, slower than rates of improvement in countries with shorter life expectancies [44]. Rates of improvement for women, who generally enjoy substantially longer life expectancy than men, are more rapid than for men. These findings suggest that life expectancy in developed countries is not currently coming close to an upper limit.

Why is life expectancy increasing? Genetic factors have been shown to play an important role in determining lifespans in various animals. For example, a single mutation in the nematode *Caenorhabditis elegans* doubles lifespan [49]. In humans, gross genetic abnormalities like trisomy have proven the influence of genetic factors in shortening longevity and, as discussed above, some genetic factors appear to be associated with exceptional longevity. However, the dramatic change in life expectancy within a few generations cannot be due to change in the genetic composition of the population.

Life expectancy is clearly influenced by environmental and public-health factors. Up until 1950 or so, most of the gain in life expectancy was because of reductions in infant, childhood, and early adult mortality, as the result of rising standards of living, public-health interventions and medical developments that reduced deaths from infectious diseases. Since 1950, however, the increase in life expectancy in developed countries is largely attributable to reductions in mortality at older ages [50]. Thus, the key question is: why are death rates declining, even at and, indeed, especially at advanced ages?

It is well known that socio-economic status, education and occupation influence mortality patterns throughout life [51]. However, the causal pathways by which social status, wealth, education and occupation influence mortality are not well understood. Part of the problem is that it is difficult to unravel the intricate web of causality linking socio-economic factors and longevity. For instance, both wealth and health at older ages are influenced by both wealth and health at younger ages and, through both genetic and environmental influences, by the wealth and health of one's parents. A person who is healthy when young may get a better education and a better first job. The health in youth may carry over to health (and longevity) in old age, which may also be influenced by education and occupation.

In today's western world, cigarette smoking is the most prominently known environmental factor that influences lifespan. In a large study of English doctors it was found that the age at which half of cigarette smokers had died was 8 years less than the age for nonsmokers, and for heavy cigarette smokers 10 years less [52]. The influence of cigarette smoking on longevity is probably mainly mediated through an increased risk for cardiovascular and lung diseases, as well as for cancer. Declining cigarette smoking as well as changes in diet and physical activity may be important factors in rising life expectancy in at least some countries.

Recent research has confirmed the increased risk associated with excessive alcohol consumption, but has also showed reduced mortality amongst individuals with moderate daily wine consumption compared to teetotallers [53]. Comprehensive population studies of height and weight have shown that high and low body-mass-index (weight divided by height squared) is associated with increased mortality [54].

A long-standing debate concerns the extent to which intrauterine and perinatal exposures influence

late life morbidity and hence lifespan. In particular, nutrition and infection early in life have been claimed to be a strong determinant of late life mortality. In a series of papers Barker and co-workers have reported a follow-up of the individuals found in a large UK source of detailed birth and infant records from the beginning of the century [55, 56]. These studies have indicated that low growth rates *in utero* and during infancy are associated with adverse health outcomes at adult ages. In particular, a strong relationship between reduced growth early in life and high death rates for cardiovascular diseases has been reported. Based on these observations, Barker and co-workers have proposed 'the fetal-origins hypothesis', which asserts that a baby's nourishment before birth and during infancy programme its susceptibility to diseases and mortality later in life. A number of studies, however, have failed to support this hypothesis. For example, Swedish and Danish studies have shown no increased mortality in adulthood amongst large samples of twins, although twins experience severe growth retardation *in utero* during the third trimester [57, 58].

A significant proportion of the increase in life expectancy might be attributable to medical progress. However, it is hard to disentangle the effect of the simultaneous improvement in living conditions and medical treatment. In the industrialized world, the classical example is tuberculosis incidence and mortality, which has declined steadily through the first 8 decades of this century with no increased decline after the introduction of antibiotics after World War II [59, 60].

Because many new treatments are being introduced following evidence of increased survival in a clinically controlled trial, it seems likely that medical treatment has, at least in recent decades, reduced death rates at older ages and that such improvements will continue. An example of a promising development is that large randomized trials have demonstrated that fibrinolytic therapy can reduce mortality in patients with suspected acute myocardial infarction (AMI) [61]. Improved treatment of frequent and potentially fatal diseases, such as AMI and serious infections, can be expected to increase life expectancy. Furthermore the emergence of geriatric medicine, with emphasis on both prevention and intervention initiatives amongst elderly persons, is likely to reduce the number of premature deaths amongst elderly persons [62].

Table 3 Determinants of mean lifespan in the industrialized world

Genes	Probably multiple
Environment	Year of birth
	Socio-economic status
	Education
	Occupation
	Smoking
	Alcohol
	Body-mass index
	Diet (?)
	Physical activity (?)
	Intra-uterine conditions (?)
Medicine	Probably multiple

In the USA, an activist approach towards medical treatment of elderly persons seems to be more prevalent than in Europe and Japan. This is a possible explanation of the recent finding that survival after age 80 in the USA is considerably greater than in Europe and Japan [46]. If this explanation is verified, then more intensive medical treatment of the elderly may lead to substantial increases in mean lifespans. The discussed determinants of extreme lifespan are listed in Table 3.

Determinants of variation in lifespan

Whatever mean lifespans are, some individuals live longer than others. Why? The correlation in lifespan between different kinds of relatives can shed light on the importance of genetic and environmental factors in variation of lifespan. Folk wisdom suggests that if you want to live long you should choose two long-lived parents. Family studies, however, have generally found only small correlations of between 0.01 and 0.15 in lifespan between parents and offspring whilst the correlation between siblings has been found to be considerably higher, in the range of 0.15–0.35 [24, 63, 64]. Correlation within families can be due either to genetic factors or to shared environment. The finding of a higher correlation between siblings compared to the parent–offspring correlation could either be due to a higher degree of shared environment amongst siblings (perhaps because they belong to the same generation) or to nonadditive genetic factors.

The concept of nonadditive genetic factors can be described by an example. Assume that a gene is associated with longevity; for simplicity, suppose two different alleles, A_1 and A_2, exist for this gene.

Hence, a person can be A_1A_1, A_1A_2 (or, equivalently A_2A_1), or A_2A_2. Further assume that the effect of A_x depends on the other allele, that is to say the effect of A_1 is not the same for an A_1A_1 individual as for an A_1A_2individual. Suppose the father is A_1A_1 and the mother is A_2A_2. Then the children will all have the genotype A_1A_2, but none of the children will have the same genotype as either parent. In such a situation, nonadditive genetic factors are not transmitted from one generation to another but they will generate some similarity between siblings. More generally, the interaction between genes is not necessarily limited to one locus but can also be between different gene loci.

Nonadditive genetic factors are of special interest in studies of longevity. In 1930, Fisher described what he called the fundamental theory of natural selection for 'fitness traits' [65]. Fisher pointed out that reproduction is the key feature in evolution and hence there has been a strong selection pressure on fitness traits such as survival to reproduction. Such selection pressure tends to minimize variance in additive genetic factors. If a specific additive genotype is very important to survival to reproduction, there will be a tendency for only those who have this genotype to pass on their genes to the next generation. After many generations of selection, all individuals in the population will have the genotype (except for new mutations). Therefore, there will be little or no variation in additive genetic factors for fitness traits but there will still be variation because of nonadditive genetic factors. Longevity might be such a trait if it is highly correlated with the chance of surviving to reproduction.

The correlation in lifespan described above – with higher correlation between siblings compared with parent offspring correlations – suggests the influence of nonadditive genetic factors. To disentangle the effect of shared genetic and environmental factors, twin and adoption studies are required.

Both twin and adoption studies have demonstrated a strong genetic component of premature death. The only adoption study published shows a correlation between Danish adoptees and their biological parents, especially for death due to infection and vascular causes. In contrast, death from cancer appears to be influenced by the family environment [66]. A Swedish twin study showed that death from coronary heart diseases was influenced by genetic factors both in women and in men, but that the influence of genetic effects on cardiovascular mortality decreased at older ages [67].

Most studies of lifespan in twins have been based on populations in which many twins were still alive, in which there was only a short period of observation, and in which no information was available about the zygosity (fraternal or identical) of the twins [64, 68, 69]. A recent study by Herskind *et al.* [70] (also see McGue *et al.* [71]) followed more than 2800 twin-pairs with known zygosity, born between 1870 and 1900, from birth to death. This study showed that approximately one-quarter of the variation in lifespan in this population could be attributed to genetic factors, whilst the remaining three-quarters was due to nonshared environmental factors. As expected from the fundamental theory of natural selection, the genetic factors were found to be nonadditive.

Twin and adoption studies do not shed light on which environmental and genetic factors influence the variation in lifespan. It seems plausible that the candidates are the same as those described above as determinants of mean lifespan (for example smoking, nutrition, medical treatment, socio-economic conditions and various candidate genes). Probably, a large number of environmental and genetic factors interact to determine lifespan. A recent analysis by our group suggests that only 1% of the variation in lifespan can be explained by the variation in the genetic factor apolipoprotein E, the most potent 'longevity gene' yet uncovered in humans.

It should be noted that the one-quarter or so of the variation in lifespan due to genetic factors is not necessarily beyond intervention. Insight into the function of genes can immediately open up possibilities for modifying adverse genetic effects if gene–environment interaction plays a part in the aetiology. A classic example of such an interaction is phenylketonuria, an autosomal recessive trait with elevated blood and urine phenylalanine, caused by a defect in a locus, on chromosome 12, coding for phenylalanine hydroxylase. Normal development is obtained in homozygous individuals with a diet low in phenylalanine and supplemented with tyrosine. Mental retardation appears if the individuals consume an ordinary diet (Fig. 1).

Another example is the Smith–Lemli–Opitz syndrome (SLOS), first described in 1964. SLOS is an autosomal recessive disorder with variable expressivity. Craniofacial anomalies are predominant, in addition to limb and genital anomalies, failure to

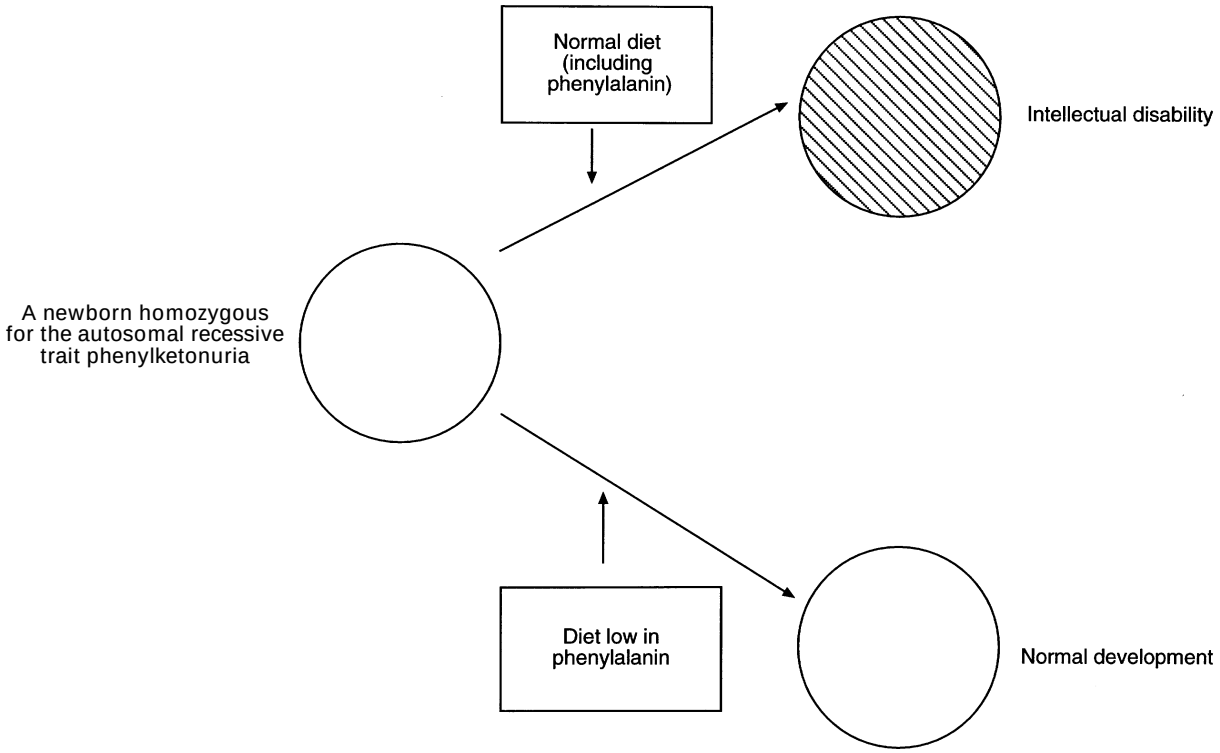

Fig. 1 Phenylketonuria: an example of gene–environment interaction.

thrive and mental retardation. SLOS is thought to be the second most common autosomal recessive disorder amongst white North Americans after cystic fibrosis, with a carrier frequency of 1–2%. Recent research has shown that SLOS results in an error in cholesterol synthesis. Insight into the aetiology of this genetically determined disease has induced a medical treatment that may reduce some of the postnatal symptoms. The treatment is a diet *high* in cholesterol [72].

Conclusion

Knowledge of the determinants of human longevity is still sparse. On the population level, a number of factors associated with mortality can be identified. On the individual level, however, these associations are too weak to be reliable predictors of a person's lifespan. This can be illustrated by a case history. A Danish woman, who was born in 1890 and who grew up in a poor family, was sent away from home when she was 17 because she had severe tuberculosis that was a potential hazard to the rest of the family. The infection was treated with an operation. At the age of 48 she got breast cancer, first in one breast and 6 years later in the other, and had both breasts removed. In her 80s she had three minor strokes. The woman herself told this story, which was verified, in 1996 shortly after her 105th birthday.

The prospects for deeper understanding of the determinants of longevity may, however, be good. Rapid progress in genetics may add considerably to our understanding of survival. Because processes of ageing in such species as yeast, worms, insects, and rats are similar in some ways to processes of ageing for humans, advances in experimental gerontology may prove to be informative (for example see Refs 73–78). Demographic and epidemiological studies of human populations may also play an important role as more reliable and more extensive data are collected and analysed. Mortality is changing in different regions and countries: life expectancy is declining in Russia and parts of Eastern Europe, and rapidly increasing in Japan and some other developed countries. Mortality change in Denmark is following a different pattern than in the other Nordic countries [79]. In many countries, the changes in mortality rates vary substantially at different ages.

The variety and speed of mortality change provides excellent opportunities for identifying underlying

mechanisms and causal factors if appropriate data are gathered, especially data on the specific characteristics of individuals. The development, particularly in the Nordic countries, of large registers of health-related information about individuals – including such special populations as twins, adoptees, and centenarians, as well as the general population – may permit significant breakthroughs in knowledge about the determinants of the duration of life.

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