Received: 15 October 2019 | Revised: 17 November 2020 | Accepted: 5 January 2021

DOI: 10.1002/hec.4231

RESEARCH ARTICLE

Health Economics WILEY

Fetal origins—A life cycle model of health and aging from conception to death

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Funding information
Open Access funding enabled and organized by ProjektDEAL. WOA Institution: GEORG-AUGUST-UNIVERSITAET GOTTINGEN; Blended DEAL: ProjektDEAL

Abstract

The fetal origins hypothesis suggests that health and nutrition shocks in utero are causally related to health deficits in old age. It has received considerable empirical support, both within epidemiology and economics but so far it has not been integrated into a life cycle theory of human aging and longevity. The present study shows that the health deficit model, based on the frailty index developed in gerontology, generates shock amplification consistent with the hypothesis. In order to discuss human health over the life cycle from conception to death, we develop a theory of ontogenetic growth and health in utero and during childhood, unify it with the health deficit model of adult aging, and discuss the transmission of early-life shocks to late-life health deficit accumulation.

KEYWORDS
fetal origins, health deficits, in utero development, ontogenetic growth

JEL CLASSIFICATION
JEL, I10, J13, D91

1 | INTRODUCTION

In this paper, we propose a new theory of human aging and longevity that takes child development and development in utero into account. Half a century ago, epidemiologists would tend to view the fetal state as a protected one. Since then epidemiological evidence has been accumulating that this appears not to be the case, which has spawned the fetal origins hypothesis. The fetal origins hypothesis suggests that health deficits in utero may cause morbidities in old age though without being directly visible for most of the life course (e.g., Almond & Currie, 2011a). Within economics, research has considerably strengthened the case that in utero (or early-in-life) shocks indeed appear to impact on late-in-life health (e.g., Almond, 2006; Almond & Mazumder, 2011; Bhalotra & Rawlings, 2011; Kesternich, Siflinger, Smith, & Winter, 2015; Lin & Liu, 2014; Scholte, Van Den Berg, & Lindeboom, 2015; Van Den Berg, Lindeboom, & Portrait, 2006). In addition, research has demonstrated effects beyond late-in-life health, including human capital and labor market outcomes (e.g. Almond, Edlund, & Palme, 2009; Bleakley, 2007; Nelson, 2010; Bhalotra & Venkataramani, 2016; Scholte et al., 2015); welfare dependence (Almond, 2006; Oreopoulos, Stabile, Walld, &

Roos, 2008), and even investment behavior (Cronqvist, Previtero, Siegel, & White, 2016). From a broader perspective, the fetal origins hypothesis thus seems to be a promising avenue through which to gain further insights into the causes and intergenerational transmission of inequality (e.g., Currie, 2011). For surveys from economists' perspective on the vast literature of fetal or developmental origins, see Almond and Currie (2011b) Almond, Currie, and Duque (2018), and Conti, Mason, and Poupakis (2019).

The first contribution of this paper is to provide a general mechanism, based on principles of human aging established in medical science and gerontology, that allows for a discussion of the consequences of differences in fetal origins in health economics. We argue a new mechanism is needed in order to explain the process by which shocks in utero are amplified during the course of life. In the health capital model (based on Grossman, 1972), initial differences are depreciated away as individuals grow older. In contrast, in the health deficit model (Dalgaard & Strulik, 2014), initial health deficits are conducive to faster development of new deficits. Consequently, initial health differences become larger as individuals grow older: small initial differences that are perhaps only visible at the cellular level are amplified to be visible as differences in biomarker quality in young adults (Belsky et al., 2015), and further amplified to be visible as differences in diagnosed diseases and frailties in old age (Mitnitski et al., 2002a; Mitnitski & Rockwood, 2016).

While the underlying mechanism of aging applies at all ages, the health deficit model has been so far only available for adults. Accordingly, the second contribution of this paper is to extend it by a childhood period, which provides a health economic model for the whole human life cycle, from conception to death. This unified theory makes it possible to explain early-life origins of late-life health challenges. For that purpose we first develop a theory of in-utero and childhood development in terms of body growth and health and then integrate it with the health deficit model.[1]

The theory of health deficit accumulation is built on two basic features imported from gerontology: the frailty index and the reliability theory of aging. The frailty index measures the number of health deficits that a person has, relative to the number of potential deficits (Mitnitski et al., 2002a; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). Reliability theory explains aging by the loss of function through accumulating damage in the redundant building blocks and elements of the body, such as organs, tissue, bones, cells etc. (Gavrilov & Gavrilova, 1991). While (cellular) damage occurs throughout life, from the time when the first cells and tissue begin to form until death (Kirkwood, 2005), the in-utero and childhood period are distinct from adulthood because the body grows. We conceptualize ontogenetic growth as the build-up period of redundancy in body cells and biological aging as accumulated damage of redundant body cells (in organs, tissue, bones, etc.). In terms of the frailty index, growth in utero and childhood increase the denominator (the number of potentially damageable cells) while health deficit accumulation increases the numerator.

Our unified model of human aging makes it possible to discuss how specific shocks of nutrition and health damage in utero and childhood affect adult health and longevity. Health deficits, if they remain unrepaired, have always a more severe impact on subsequent health the earlier in life they occur. The reason is the quasi-exponential nature of health deficit accumulation (Abeliansky & Strulik, 2018a; Mitnitski et al., 2002a; Mitnitski & Rockwood, 2016). The exponential (or, more generally, convex) association of health deficits with age is a formal expression of the generality of biological aging understood as "intrinsic, cumulative, progressive, and deleterious loss of function that eventually culminates in death" (Arking, 2006). According to the terminology developed in Dragone and Vanin (2020), the accumulation of health deficits is a self-productive process: the presence of many health deficits is conducive to the faster development of new deficits. It is a natural outcome of theories of aging built on the redundancy and interdependence of health deficits such as reliability theory (Gavrilov & Gavrilova, 1991) and network theories of aging (Rutenberg, Mitnitski, Farrell, & Rockwood, 2018). Here, we show that the feature of self-productivity in health deficit accumulation explains how invisibly small damages in utero or childhood are amplified over the human life cycle to be expressed in large (visible) health deficits in old age.

Our modeling of childhood development has also a foundation in human biology. While there are several purely statistical approaches to formally represent ontogenetic growth (for a review, see Karkach, 2006), West, Brown, and Enquist (2001) provide a theory that derives the growth curve of humans (and other animals) from first principles in thermodynamics, that is the energy needs to create and maintain body cells. The integration of this theory of childhood growth into the model of human aging allows us to discuss nutritional shocks in utero as well as in childhood and their impact on child growth and adult health in a unified and scientifically founded way (based on West et al, 2001). We show that growth dynamics imply a natural separation of childhood into two distinct periods; an early period, in which initial differences in body size and frailty are amplified by child growth; and a later period, in which initial differences are dampened by child growth. This provides a micro-foundation of the frequent assumption in economic models of

child development that such distinct periods exist (Almond & Currie, 2011a, 2011b; Heckman, 2007). Health damages, in contrast, are amplified everywhere along the human life cycle, from conception to death.

The paper proceeds as follows. In Section 2, we re-investigate the basic model of health deficit accumulation in adulthood with special focus on the impact of initial conditions on lifetime health outcomes when investments are optimally determined. In Section 3, we set up the model of ontogenetic growth and derive its implication for the transmission of health and nutrition shocks during childhood. In the Supplementary Appendix we apply the model to discuss the role of various shocks and other problems of childhood development. In Section 4, we unify the childhood period with the health deficit model for adults and use the new theory to discuss fetal- and early-life origins of late-life health. In Section 5, we conclude.

2 | SHOCK PERSISTENCE AND AMPLIFICATION IN THE HEALTH DEFICIT MODEL

In this section we review the health deficit model of Dalgaard and Strulik (2014) with a special focus on the persistence and amplification of early-life health shocks, which were not addressed in the original contribution. A crucial feature for early life shocks to matter for late-life health is shock persistence or shock amplification. It is emphasized in the medical literature as well as by economic scholars of fetal origins that shock transmission operates through a biological channel, independent from investments (Almond & Currie, 2011a; Barker, 1995). Formally, this means that the transition operates through the variable capturing the state of health of an individual. It is easy to see that the popular model of health capital accumulation, based on Grossman (1972), fails to provide such a mechanism. In continuous time, health capital H accumulates according to $\dot{H} = I - \delta H$, in which I are investments and δ is the rate of health capital depreciation, which could be age-dependent. The equation of motion implies that individuals of better health (represented by greater H) experience a faster deterioration of their health (greater δH). This feature of self-depreciation (Dragone & Vanin, 2020) provides convergence: initial differences in health are depreciated away as individuals grow older such that differences in early-life development fade away and (asymptotically) do not matter in old age.

The health deficit model, in contrast, provides shock amplification. It captures the empirically observable process of health deficit accumulation as $\dot{D} = \mu(D + E)$, in which D is health deficits, μ is the force of aging, and E measures influences on deficit accumulation that are not captured by the current state of health. The crucial feature is that the health deficit model is self-productive (Dragone & Vanin, 2020): the presence of many health deficits is conducive to the faster development of new deficits. This feature implies shock amplification: individuals with (small) initial health differences experience faster aging and develop more health deficits earlier in old age. Health deficits are measured by the frailty index, which is the relative number of health deficits that a person has out of a long list of potential deficits. The frailty index has an established methodology in gerontology (Searle et al., 2008) and the underlying parameters have been estimated with great precision (Abelisansky and Strulik, 2018; Mitnitski et al., 2002a). Empirically the feature of self-productivity is confirmed by the exponential (or, more generally, convex) association of health deficits with age (Abeliansky, Erel, & Strulik, 2020; Abeliansky & Strulik, 2018a, 2018b; Harttgen, Kowal, Strulik, Chatterji, & Vollmer, 2013; Mitnitski et al., 2013; Mitnitski and Rockwood, 2016; Mitnitski et al., 2002a; Searle at al., 2008; Shi et al., 2011). In Supplementary Appendix A and B we discuss the features of shock depreciation and shock amplification in more detail and introduce the background literature.

The economic health deficit model of Dalgaard and Strulik (2014) separates E into the impact of health investment h on health deficit accumulation and a remaining residual ϵ. This allows the accumulation of health deficits to be not strictly exponential even in the absence of health investments or in case of inefficacy of health spending. The residual captures influences on health deficit accumulation that are not explicitly modeled, that is that do neither result from the current state of individual health nor from health investments. Specifically, it is assumed that health deficits accumulate according to

$$\dot{D}(t) = \mu(D(t) - Ah(t)^{\gamma} + \epsilon). \tag{1}$$

The parameters $A > 0$ and $0 < \gamma < 1$ reflect the state of the health technology. While A refers to the general power of health expenditure in maintenance and repair of the human body, the parameter γ specifies the degree of decreasing returns of health expenditure. The larger γ the larger the relative productivity of cost-intensive high-technology medicine in maintaining and repairing deteriorated human bodies.[2] Bad health promotes death such that

individuals die when $\bar{D}$ health deficits have been accumulated. Formally, this defines a free terminal time problem: the conditions for death are given but the length of life is variable and death occurs as an endogenous event, depending on life cycle choices.

Individuals are interested only in maximizing their lifetime utility from consumption:

$$\int_{\tau}^{T} \mathrm{e}^{-\rho(t-\tau)} u(c(t))\mathrm{d}t, \tag{2}$$

with $u(c) = (c^{1-\sigma} - 1)/(1-\sigma)$ for $\sigma \neq 1$ and $u(c) = \log(c) + b$ for $\sigma = 1$. The parameter σ is the inverse of the elasticity of intertemporal substitution and ρ is the rate of time preference.[3]

Besides spending income on final goods, individuals may save or borrow at a net interest rate r. Individuals take all prices as exogenously given. The law of motion for individual wealth k is thus given by (3):

$$\dot{k}(t) = w + rk(t) - c(t) - ph(t), \tag{3}$$

in which w is the (annual) wage, r is the interest rate, and p is the price of health goods. The problem is to maximize (2) subject to the accumulation Equations (1) and (3), the initial conditions $D(\tau) = D_{\tau}$, $k(\tau) = k_{\tau}$, and the terminal conditions $k(T) = \bar{k}$, $D(T) = \bar{D}$. At the very basic level the problem is to trade off the benefits and costs of health investments over the life cycle. The benefits consists in, by slowing down the process of aging, a longer life which allows for more consumption along the extensive margin. However, by increasing health investments, individuals forego consumption in the current period. In Supplementary Appendix C, we provide the details on the analytical solution of this free terminal time problem. Here, we present the numerical solution of a calibrated version.

We take the calibration of the model for an average 20 years old male US American in the year 2000 from Dalgaard and Strulik (2014). This means that we set the rate of aging μ to 0.043, which is the rate of health deficit accumulation estimated for Canadian men by Mitnitski et al. (2002a). Rockwood and Mitnitski (2007) stress the similarity of their results for United States and Canadian populations but they do not report the detailed results for the US analysis. Recently, Abeliansky et al. (2020, Tab 6) found that US American men living in the North East age at the same rate as Canadians in the Mitnitski et al. (2002a) study. We set the interest rate to 6%, following Barro, Mankiw, and Sala-i-Martin (1995), and we set $\gamma = 0.19$ to capture the growth of health spending at an annual rate of 2% over the life cycle (Keehan, Lazenby, Zezza, & Catlin, 2004). From the estimates of Mitnitski et al. (2002a) we set $D(0) = 0.0274$ as the relevant initial value at age 20 and $\bar{D} = 0.1005$, that is 55.2 years later since the life-expectancy of a 20 year old US American in the year 2000 was 55.2 years. We set $\epsilon = -0.013$ such that the model predicts a life-expectancy at age 20 of 42 for $A = 0$, corresponding to the life expectancy in the late 19th century when adult life expectancy was only modestly affected by medical technology (Fries, 1980). We set $\rho = r$ such that the age-consumption profile is constant over the life as obtained by Browning and Ejrnæs (2009) for childless households. We take GDP per worker in the United States in the year 2000 (PPP$ 77,003) and assume a capital share of 1/3, which implies an annual labor income (in international dollars) of $ 51,335. We normalize $p = 1$ and set $\sigma = 1$ in order to obtain a value of life at age 20 consistent with the estimate of Murphy and Topel (2006). Finally, we estimate $A = 0.00139$ such that the individual dies with deficits $\bar{D}$ at age 75.2, according to the life-expectancy of 20 years old US Americans in the year 2000.[4]

In Figure 1 we replicate the benchmark run of Dalgaard and Strulik (2014), represented by blue (solid lines). We then look at an individual that is initially 10% less healthy than the Reference American, represented by red (dash-dotted) lines, and an individual that is initially 10% healthier than the Reference American. These differences in initial health deficits at age 20 can be thought of as resulting from negative health shocks earlier in life (and perhaps in utero). The model predicts that unhealthier individuals spend more on health, in line with observations in De Nardi, Pashchenko, and Porapakkarm (2017). But the higher health expenditure is not powerful enough to equalize initial health differences. In fact, initial health differences get amplified over time: as individuals age, the vertical distance between the individuals' deficit trajectories becomes larger, see the panel on the left-hand side of Figure 1. The underlying reason for this pattern is that initial deficits influence the effectiveness of health investments: the greater the health deficits the smaller the impact of a given amount of health investments in prolonging life. In this sense the model involves dynamic complementarities akin to those found in the human capability theory (Heckman, 2007).

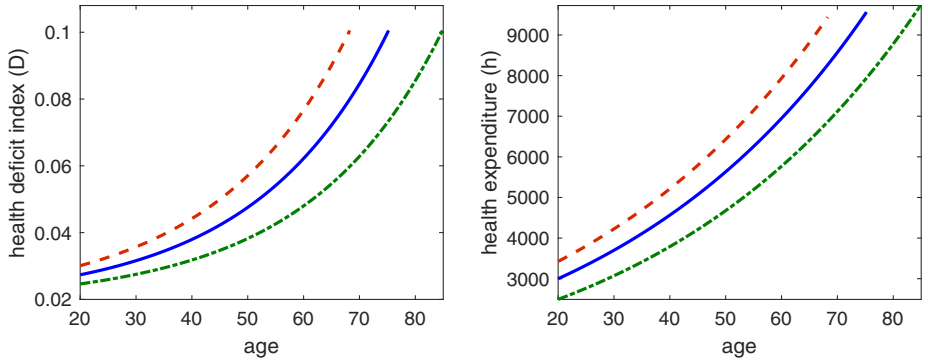

FIGURE 1 Initial health and health deficit accumulation. Blue (solid) lines replicate results for the Reference American in Dalgaard and Strulik (2014). Green (dashed) lines: individual with 10% less initial health deficits at age 20. Red (dash-dotted) lines: individual with 10% more initial health deficits at age 20 [Colour figure can be viewed at wileyonlinelibrary.com]

3 | ONTOGENETIC DEVELOPMENT AND CHILDHOOD HEALTH AND FRAILTY

3.1 | Basic principles: accumulation and depletion of redundancy

The baseline health deficit model tracks the evolution of health deficits, health expenditure, and consumption over the life cycle of adults, starting from about the age of 20. Hence, in a strict sense, the analysis does not fully capture fetal origins. Fetal origins are "only" represented as initial values of health deficits in adulthood. In this section we extend the theory to include a childhood period and an embryonic period.

There are at least two main differences between health development of embryos and children compared to adults. (i) There is no rational health investment from the side of the fetus or child. Instead the fetus receives nutrients and perhaps negative health shocks from the mother, and children receive nutrition and health investments from their parents. (ii) There is body growth. Child development can be understood as the accumulation of body cells such that an initially nonviable fetus gets healthier over time. Here we propose a model of ontogenetic growth that is naturally unified with the model of human aging through the notion of redundancy. Growth in utero and in childhood can be understood as the build-up of body-cell redundancy and organ reserve. Aging, in gerontology, is understood as depletion of redundancy in (functioning) body cells, that is as accelerated loss of organ reserve such that individuals become increasingly frail. It has been estimated that for young adults the functional capacity of human organs is tenfold higher than needed for survival (Fries, 1980). Gavrilov and Gavrilova (1991) provide a micro-foundation of human aging from reliability theory, understood as the gradual loss of functionality of basic elements (such as body cells), which causes the loss of organ functionality and, eventually, death. By combining the periods of childhood (build-up of redundancy) and adulthood (depletion of redundancy) we arrive at a novel unified theory of human development from conception to death.

The frailty index has been developed to measure visible health deficits in elderly persons. However, in line with basic principles of reliability theory, damage and depletion of functioning body cells occurs at any age (Kirkwood, 2005). In animal studies it has been shown that loss of redundancy at the cellular level is positively associated with the frailty index (Rockwood, Mitnitski, & Howlett, 2015). A study by Belsky et al. (2015) extends the measurement of aging to young adults, aged 26 to 38. Since in this cohort only 1% of members had been diagnosed with an age-related chronic disease, the study used biomarkers to measure physiological deterioration of multiple organ systems (pulmonary, periodontal, cardiovascular, renal, hepatic, and immune function). Biological age at chronological age 38 was computed from biomarker function and found to be normally distributed ranging from age 28 to 61. In line with the health deficit model it was found that biologically older individuals aged at a faster rate. On average, each year increase of biological age was associated with a 5% larger deterioration of biomarkers, implying that deficits in organ systems grow exponentially at a rate of about 5%, similar to the growth of health deficits in elderly persons, which were found to grow between 3% and 5% (Abeliansky et al., 2020; Mitnitski et al., 2002a; Mitnitski & Rockwood, 2016).

In order to apply the health deficit model to individuals of all ages, we thus interpret the frailty index as a measure of the relative number of health deficits at the organ or cellular level, that is as the number of damaged

body cells (or organs) divided by the number of potentially damageable cells (or organs). We associate the beginning of adulthood with the end of ontogenetic growth (at about age 20). For adults, the denominator of the frailty index is given. Fetal and childhood development, in contrast, are characterized as the period of body cell accumulation, in which the denominator of the frailty index increases through the build-up of organ reserve and redundancy through ontogenetic growth. Formally, the frailty index is defined as $D = D_A/P$, in which P are potential deficits (at the cellular level) and D_A is the number of actual deficits. The frailty index for children and adults thus evolves as:

$$\left(\frac{\dot{D}_A}{P}\right) = \frac{\dot{D}_A}{P} - \frac{D_A}{P}\frac{\dot{P}}{P}. \tag{4}$$

Notice that the second term on the right hand side of (4) is zero in adulthood because (by assumption) body growth and thus the accumulation of organ and cell redundancy stops at entry to adulthood. Using the new notation we rewrite Equation (1), governing the accumulation of health deficits, as

$$\frac{\dot{D}_A}{P} = \mu\left(\frac{D_A}{P} - Ah^{\gamma} - A\bar{h}^{\gamma} + \varepsilon\right), \tag{5}$$

in which $\bar{h}$ are health investments received in childhood and h is health expenditure in adulthood.

3.2 | A simple theory of ontogenetic growth

A theory of ontogenetic growth has been proposed by West et al. (2001). It is based on thermodynamic regularities and produces empirical observable age-growth patterns for humans and other animals. The growth equation originates from an energy balance stating that the energy consumed is equal to the energy used for the creation and maintenance of body cells such that $B = bm + e_c\dot{m}$, in which B is the energy consumed, m is the number of body cells, b is the energy needed to maintain a cell and e_c is the energy needed to create a cell. Assuming that a cell has unit weight and that $e_c = 1$, the number of cells and thus the weight of the individual evolves as:

$$\dot{m} = B - bm. \tag{6}$$

Energy flow per unit of time is given by:

$$B = \min\{am^{\beta}, \bar{B}\}, \tag{7}$$

in which $\bar{B}$ is an energy supply constraint and a is a thermodynamic constant (reflecting metabolic efficiency). If $B = am^{\beta}$, energy supply is unconstrained and Equation (7) states that the metabolic rate scales with the body mass of the child. This allometric relationship between energy consumption B and body mass m is known as Kleiber's Law (Kleiber, 1932). The scaling parameter β is estimated with high precision as 3/4 for mammals and almost all terrestrial animals, yielding the famous "mouse-to-elephant curve" (Brody, 1945). West, Brown, and Enquist (1997) provide a microfoundation of the scaling law by showing that organisms, viewed as energy transporting networks that minimize energy dissipation, fulfill Kleiber's law with $\beta = 3/4$. The fact that $\beta < 1$ implies that larger bodies are more energy-efficient in the sense that they need less energy to maintain a body cell.

Inserting $B = am^{\beta}$ into (6) and solving the resulting Bernoulli differential equation provides the von Bertalanffy equation for body size (von Bertalanffy, 1957):

$$m(t) = \left\{a/b - \left[a/b - m(\tau)^{1-\beta}\right]e^{-(1-\beta)b(t-\tau)}\right\}^{\frac{1}{1-\beta}}, \tag{8}$$

in which τ is the initial time and $m(\tau)$ is the initial body mass. Empirically, the von Bertalanffy equation is a good approximation of body growth if food supply is abundant and it is frequently used to describe ontogenetic growth of humans and other animals in biology and related natural sciences (Karkach, 2006; Kooijman, 2000). Graphically, the von Bertalanffy equation has a sigmoid shape. If growth would never stop, body size would converge toward $m = (a/b)^{1-\beta}$, as can be read off from (8) for $t \to \infty$. However, human growth is determinate, which means that it stops at a certain age $t = T$. While T is idiosyncratic it is typically reached a few years after sexual maturity.[5]

The sigmoid shape implies that there exists an inflection point (at age t_I) at which the shape of the growth curve changes from convex to concave. In order to develop this feature in more detail, consider the differential equation $\dot{m} = am^{\beta} - bm$ that follows from (6) and (7) in the case of no energy supply restrictions. Taking the second derivative we obtain $\ddot{m} = \beta a m^{\beta-1} - b$. Noticing that the age-growth pattern is convex for $\ddot{m} > 0$, we conclude a convex growth for:

$$m(t) < m_I \equiv \left(\frac{\beta a}{b}\right)^{\frac{1}{1-\beta}}, \tag{9}$$

in which m_I is body size at the inflection point. Inserting m_I for $m(t)$ in (8) and solving for age, we obtain age at the inflection point (t_I) and conclude that human growth follows a convex pattern at ages:

$$t < t_I \equiv \frac{1}{(1-\beta)b} \log\left[\left(\frac{a/b - m(\tau)^{1-\beta}}{a/b}\right)\frac{1}{1-\beta}\right] + \tau, \tag{10}$$

in which $m(\tau)$ is initial body size at age $\tau < t_I$. Since $\ddot{m} > 0$ for $t < t_I$, initial differences in body weight are amplified by body growth at ages smaller than t_I, whereas initial differences at ages larger than t_I are dampened. Notice that there exists at most one inflection point. If growth stops before m_I is reached, the growth curve is always convex and if initial size is larger than m_I, the growth curve is always concave. See Supplementary Appendix D for a detailed formal discussion of shock amplification.

The literature usually analyzes in-utero growth and childhood growth separately, captured by two distinct growth curves. This distinction is intuitively plausible since the embryo is connected to the metabolism of the mother in an ambient temperature of about 37 degrees Celsius. These conditions change drastically with birth when the child depends on its own metabolism, loses energy through heat dissipation etc. Consequently in utero growth requires less energy for cell maintenance and creation (b and e_c are smaller in the model of ontogenetic growth). In other words, in utero growth is more energy efficient and faster. We thus consider both periods separately.

3.3 | In utero development

In Figure 2, the panel on the left-hand side shows a calibration of the model for in-utero development when energy supply is unconstrained and there are no shocks. Parameters are $a = 1.08$, $b = 0.07$, $\beta = 3/4$ and $m(0) = 0.0001$. Body weight is measured in grams. The blue solid line shows the model prediction for body weight by week of gestation, the red dotted line shows the data for American boys from Kiserud et al. (2017). The age–growth curve is clearly convex during in-utero growth, implying that initial differences in body weight (and fetus frailty) will be amplified as the fetus develops.

Next consider energy constraints. If food is not abundant, fetal growth is constrained by maternal supply of energy (or, more generally, nutrients), $B = \bar{B}$. Naturally, if the fetus is energy-constrained, a larger share of energy is used for maintenance and less is available for cell creation such that growth is retarded in these periods. Suppose energy supply in utero is proportional to the metabolic rate of the mother and that the mother's metabolic rate scales with her size according to Kleiber's law such that $\bar{B} \propto M^{3/4}$ where M is the size of the mother and $M^{3/4}$ is the metabolic rate of the mother (Kleiber, 1932; West et al., 1997). We then conclude that, ceteris paribus, fetuses with larger mothers are less likely (or less frequently) energy-constrained and are thus larger at birth. More generally, we conclude from Equations (6)–(8) that (i) fetuses who are less frequently energy-constrained in utero are bigger at any time in utero and thus also at birth, and (ii) individuals who are born too early, that is at low t, are smaller at birth.

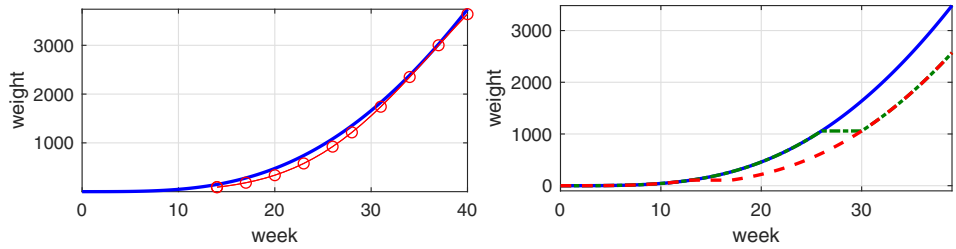

FIGURE 2 Ontogenetic human growth in utero. Left: solid blue line: model prediction; circled red line: data from Kiserud et al. (2017) for male fetal weight during gestation. Right: nutritional constraint binding at $\bar{B} = bm(\tau)$ for 4 weeks (Ramadan) with onset at $\tau = 13$ (red dashed lines) and $\tau = 26$ (green dash-dotted lines) [Colour figure can be viewed at wileyonlinelibrary.com]

As an example application, consider a women who is pregnant during the Ramadan (Almond & Mazumder, 2011). We model this in a drastic sense such that for the four weeks during Ramadan there is no child growth and consider an onset of Ramadan at the beginning of the second or third trimester. Formally, we normalize the nutritional shock such that the nutritional constraint binds at $\bar{B} = bm(\tau)$ for 4 weeks with $\tau = 13$ and $\tau = 26$. The panel on the right hand side of Figure 2 shows the results. The solid line reiterates again the growth trajectory for unconstrained energy supply. Dashed lines show results for Ramadan onset at $\tau = 13$ and dash-dotted lines for $\tau = 26$. Since all body cells are treated equally, there is no impact of the timing of Ramadan during pregnancy. In order to explain a greater impact of early-life nutrition shocks one could differentiate between the importance of body cells and introduce a mechanism why energy constraints have more severe impact early in the gestation period or one could argue that inferior nutrition does not only retard body growth but also induces health damages, a feature that we discuss in Section 3.5. Alternatively, one could argue that the energy constraint (10) is more likely to be binding if the fetus is already large. This feature would imply that the last trimester is more important for body growth and nutritional constraints. Such an outcome would be consistent with the finding of Doblhammer and Vaupel (2001) and Abeliansky and Strulik (2020) that individuals born in autumn (for whom fresh fruits have been abundant in summer) age slower than individuals born in spring.

3.4 | Childhood development

From birth onwards, humans rely on their own metabolism and the values of the metabolic parameters e_c and b change. Simple thermodynamics suggest that ontogenetic growth is still captured by the differential Equation (6) and the nutrition constraint (7). Although the supply of energy (nutrients) in childhood is no longer determined by the metabolism of the mother, it is still determined by the provision of food by the parents. In Dalgaard and Strulik (2015; 2016) we developed a theory of human growth where nutritional investments were conceptualized as a choice variable of parents. Here, for simplicity, we take the position of the developing child for whom nutrition is exogenous. In case of sufficient food supply, $\bar{B} > am^b$, and child growth is still captured by the von Bertalanffy Equation (8) with $\beta = 3/4$. However, the size of the parameters a and b changes, compared to in utero growth, due to the new metabolic conditions. Moreover, for child growth, it is more convenient to measure age in units of years and body mass in kilograms.

The panel on the left-hand side of Figure 3 shows a calibration of the growth curve that starts at average birth weight ($m(0) = 3.4$ kg) and a and b are targeted to match weight at age 5 and 20. This leads to the estimates $a = 1.52$ and $b = 0.50$. Dots show the actual average weight of US boys in the year 2000 according to CDC (2000). We assume that ontogenetic growth stops at age 20, as indicated by the end of the solid line. The dashed line indicates how growth would proceed if growth would be indeterminate and would never stop. The growth trajectory is mildly convex-concave with an inflection point at about age 7. This means that there is small amplification initial differences in body weight (and implied child frailty) in early childhood until about age 7 followed by a period of small dampening of initial differences in body weight until the onset of adulthood.

The final step is to map body weight m into organ redundancy P. Here we venture into uncharted terrain since the frailty index has not yet been applied to children. As discussed above, in symptomless young adults, biomarkers measuring functionality of multiple organ systems decline at about the same rate at which measurable health deficits are accumulated among the elderly. The reliability theory of aging suggests that damages are accumulated at the same

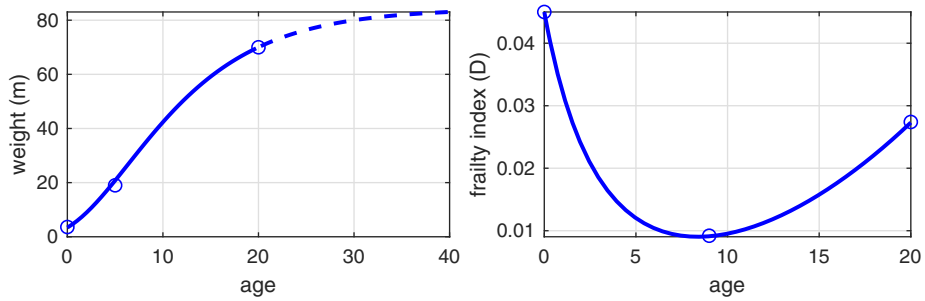

FIGURE 3 Ontogenetic growth in childhood and the frailty index. Left-hand side: Solid line: calibrated model; dots: weight for age data for boys from CDC (2000); dashed line: hypothetical growth if growth were indeterminate. Right hand side: predicted frailty index; dots: constructed frailty index from mortality data [Colour figure can be viewed at wileyonlinelibrary.com]

rate irrespective of age. We thus assume that the parameter of deficit accumulation are the same for children and adults. The numerical values are those from Section 2.

We assume that there are decreasing returns of redundancy. While this feature is obvious for some organs and tissues whose size is clearly limited by functionality (e.g. eyes and ears) it is perhaps less obvious for bone mass and muscle size. The mapping from size to functionality is thus coarse-grained and does not capture organ specifics. We assume that $P = \kappa m^{\alpha}$ and calibrate κ and α such the implied path of D approximates the evolution of a constructed frailty index for childhood.

In order to construct the frailty index, we exploit the feature that, for adults, it has been shown that the frailty index is a very good predictor of the mortality rate. The prediction of mortality can be so accurate that chronological age adds insignificant explanatory power when added to the regression (Rockwood & Mitnitski, 2007). At the population level, Mitnitski, Mogilner, MacKnight, and Rockwood (2002b) obtain an R^2 of 0.99 in a simple log-log regression of the frailty index and the mortality rate. We thus hypothesize that a similar association exists between the frailty index of infants and children and their mortality rate. We use US mortality by age in the year 1999 for the calibration (cf. Figure 2 in Goldsmith, 2014).

For adults, mortality increases exponentially with age, a regularity known as Gompertz law. For children, however, mortality evolves nonmonotonically. At birth it is as high as at age 50 (in the United States). For infants and small children, mortality declines quickly with age and starts rising again at about age 10. A similar age-pattern is observed for the burden of chronic disease, measured by disability-adjusted life years: at birth the DALY is about as high as at age 50, it then declines quickly and starts rising again at about age 10 (see Belsky et al., 2015, Figure 1). We thus calibrate the remaining parameters κ and α in the following way. We take the parameters μ, A, ϵ, and γ as calibrated by Dalgaard and Strulik for adults. We feed into Equation (5) average expenditure on child health care per year in the year 2000 (of \$1939) and then determine initial deficits and α and κ such that the solution of system (5)–(8) originates at a frailty index of 0.0450 at birth (equaling the calibrated frailty index at age 50), declines until age 10 and then rises again to a value of 0.0272 at age 20 (matching the actual value at age 20, stemming from the calibration of adults). This leads to the estimates $\alpha = 0.30$ and $\kappa = 0.18$.

The evolution of the constructed frailty index is shown in the panel on the right-hand side of Figure 3. Although health damages at the cellular level start immediately when the first somatic cells are formed in utero (Kirkwood, 2005), ontogenetic growth and the formation of new body cells dominates during early childhood such that the frailty index declines and the young child becomes healthier and more robust as it grows. This process ends around puberty (at about age 11), the period, in which physiological functions gradually start to decline (Kirkwood & Mathers, 2009). In this period, body growth slows down and new damage accumulates faster than new cells and tissue are formed.

Although we argued that deficits are measured at the cellular level and thus their impact on diagnosed health impairments is only expressed when sufficient damage has been accumulated, it is interesting to note that infants and small children are also frail in the original meaning of the index. Several items that are frequently included in the frailty index applied to the elderly, apply to infants and small children as well. For instance, infants and small children have "difficulties walking," "difficulties lifting weight," and have low grip strength. However, in contrast to the elderly they have a period of ontogenetic growth ahead, during which these difficulties are eliminated by the accumulation of redundant muscle and bone mass or, more generally, the accumulation of more healthy body cells.

3.5 | Two types of shocks and childhood frailty

In utero and childhood shocks affect the frailty index in two distinct ways. Nutritional shocks affect the denominator of the frailty index through retarded ontogenetic growth and slower build-up of healthy body cells. Health shocks (infections and accidents) affect the numerator of the index by reducing the number of functioning body cells. We could also imagine a combination of both shocks, for example if fighting infections needs energy and thus reduces the energy available for body growth. This could be conceptualized as an increase in the energy needed to maintain body cells, that is a larger b during the infection period.

Figure 4 illustrates the two types of shocks. Blue (solid) lines reiterate benchmark development from Figure 3. Red (dashed) lines show the evolution of body growth and frailty when constrained nutrition in utero lowered birth weight by 1 kg (to 2.4 kg). Green (dash-dotted) lines show the development when the child is born with normal weight (3.4 kg) but in utero health shocks increased health deficits at birth by 20%.

In case of low birth weight, the frailty index mildly diverges from the benchmark case during the convex growth phase of the body (which, as explained above, amplifies initial differences) and converges mildly toward benchmark in the concave growth phase (where initial differences are dampended). This pattern is distinct from the one obtained for birth with additional health deficits. Health deficits accumulate in a quasi-exponential way at any age and thus there is no convergence phase. Throughout life, the distance to benchmark gets larger, a feature that becomes salient in the second phase of childhood. For the qualitative result that early life shocks matter for adult health, however, the type shock as well as the assumed functional form is irrelevant. The only feature needed for "fetal origins" is that shocks are at least partly preserved during childhood, that is, diagrammatically, that the red and green curves do not converge fully back to the unshocked blue curve. In Supplementary Appendix E we discuss shocks in early and middle childhood and compare with Heckman (2007) capability approach. In Supplementary Appendix F we apply the model to explain the widening socioeconomic gradient of childhood health.

4 | FROM BIRTH TO DEATH: GROWTH, AGING, AND LATE-LIFE HEALTH

Finally, we fit the pieces together and propose a unified model of child development and health at all ages from birth to death. In utero development is represented in terms of initial values of birth weight m (0) and health deficits at birth D_A (0) such that the model captures the whole human life cycle outside the womb by a unique set of equations and parameters. Some equations apply only in childhood or only in adulthood because we assume that children receive no income and that adult body size does not grow. Table A1 in Supplementary Appendix G summarizes the model's equations. The childhood indicator function 11 assumes the value of 1 in childhood and zero in adulthood. We take all parameter values as calibrated above, that is we take the values from Dalgaard and Strulik (2014) and add the childhood parameter values as calibrated in Section 4. Supplementary Table A2 summarizes the model's parameters. The model is solved with the unique set of parameters in one go. However, with entry into adulthood (at age 20) several things happen: ontogenetic growth ceases, the person receives an income and he starts consuming, saving, and spending on health care in order to maximize lifetime utility.

Results for the benchmark run are shown by blue (solid) lines in Figure 5. Life cycle health and aging unifies the two periods that were previously explained by two separate models for adults (Dalgaard & Strulik, 2014, and Section 2) and for children (Section 3). The upper left panel is a zoom into the lower left panel, showing the first 20 years of development. The frailty index fits the actual data for adult men (from Mitnitski et al. (2002a) and the curvature follows closely the curvature of the mortality rate (Goldsmith, 2014, Figure 2). It increases in a quasi-exponential way (following Gompertz law) in adulthood and is u-shaped in childhood.

Red (dashed) lines in Figure 5 show the development of an identical individual that enters life with 10% more health deficits at birth than the benchmark individual. Due to the self-productive nature of deficit development the trajectory diverges from benchmark already in childhood, although this is hardly visible from lifetime perspective (of the lower left panel). At age 20, health deficits exceed the benchmark by 20%. As the adult individual grows older, the divergence of the frailty index becomes more visible. In young adulthood, we can imagine these developments as differences in organ and tissues redundancy and biomarker quality as observed in the study of Belsky et al. (2015). In elderly individuals, health differences become visible as diagnosed health deficits (such as cardiovascular diseases or arthritis). Eventually, sufficiently many health deficits have been accumulated and death occurs, about 10 years earlier than in the benchmark case. Since adults behave fully rational, are endowed with the same preferences, receive the same income,

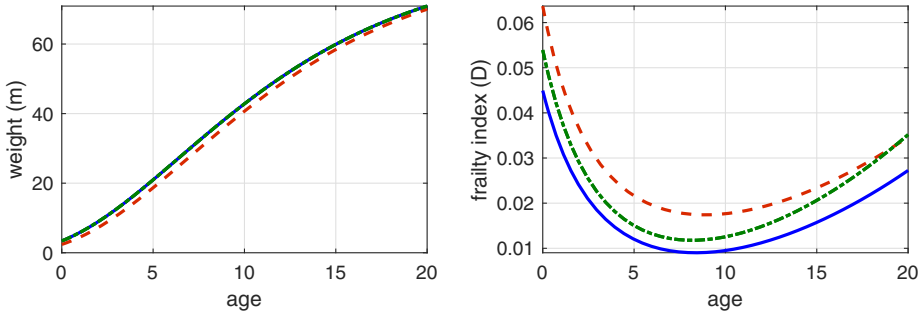

FIGURE 4 Fetal origins: In utero shocks and childhood frailty index. Blue (solid) lines: reiteration of benchmark case (Figure 3). Red (dashed) lines: 1 kg lower birth weight. Green (dash-dotted) lines: 20% more health deficits at birth [Colour figure can be viewed at wileyonlinelibrary.com]

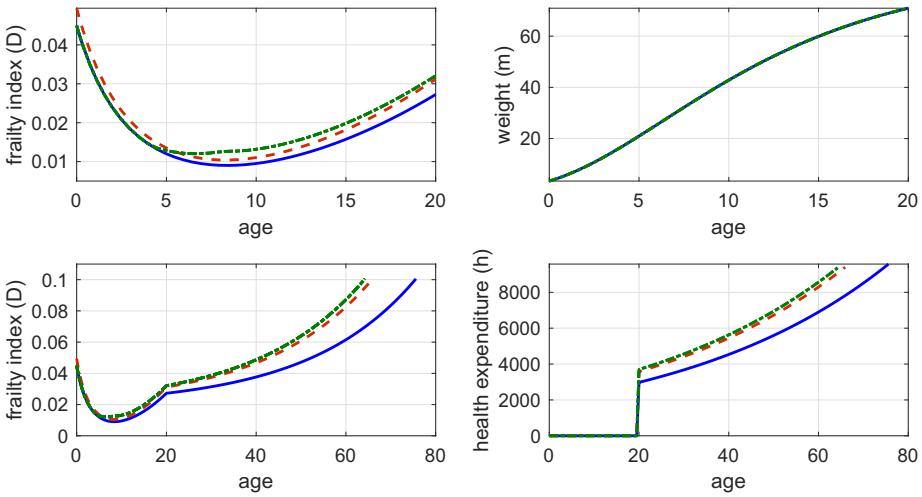

FIGURE 5 Child development and adult aging blue (solid) lines: unshocked (optimal) growth in utero and childhood (death at 75.2). Red (dashed) lines: in utero health damage $\Delta D\,(0) = 10\%$. Green (dash-dotted) lines: Health shock in middle childhood: $\Delta\epsilon = 1\%$ from age 4 to 8. Parameters as for Figures 1 and 3 (see Supplementary Table A2). h endogenous health expenditure of adults [Colour figure can be viewed at wileyonlinelibrary.com]

and received the same nutrition and health expenditure in childhood, we identify fetal origins as the cause of adult differences in health and longevity.

Green (dash-dotted) lines in Figure 5 reflect development of an individual who experienced a period of exposure to unhealthy environment in childhood such that ϵ is 1% higher, compared to benchmark, from age 4 to 8. As result, health deficits are about 20% higher than benchmark at entry into adulthood. Subsequent development is similar as for the in-utero shock.

The panel on the right hand side of the figure shows the associated optimal health expenditure. Fetal- or childhood origins of inferior health are one possibility to motivate a negative association between health and health care expenditure. The standard health deficit model (as well as the health capital model) would predict the oppositive (with reversed causality), that is individuals that spend more on health are healthier. Here, we see that, for given age, less healthier individuals spend more on health in order to reduce their faster aging. The higher expenditure, however, does not fully remediate the initial disadvantage. In other words, the health difference between individuals diverges *despite* optimal countermeasures. Without the additional health investments of the shocked individuals, divergence would be greater.

A remaining question is whether individuals are able to observe slight deteriorations of health. Alternatively, these damages may go unnoticed in young and middle adult age and are only diagnosed in old age when the associated health deficits become sufficiently visible. Given such a visibility threshold, health deficit become earlier diagnosed in old age if they were initially larger. These perceptibility issues may explain why aging related health problems are diagnosed in

old age although they are de facto always present and originate from sub-optimal development in young age and perhaps in utero. While health deficits are slowly accumulating (from e.g., mild hypertension to difficulties running or lifting weight to more severe cardiovascular problems), the empirical association between early-life health shocks and late life-life health outcomes is in many studies only observed when health problems became sufficiently severe. In this sense, the health deficit model, fills the "invisible" gap from early-life health shocks to health outcomes in old age.

5 | DISCUSSION AND CONCLUSION

An influential strand of literature has provided convincing evidence in favor of the fetal origins hypothesis: in utero shocks have the ability to influence late-in-life outcomes. Relevant outcomes involve both health issues as well as a range of socio-economic outcomes. In this study we have argued that the health capital model based on Grossman (1972) is incapable of accounting for such effects. Indeed, since the notion of health—health capital—is analogous to physical capital, the model posits that health status depreciates more when the health status of individuals is high and less when the health status is low. These features imply that the health capital model generates the prediction that individuals with different initial conditions, prompted by in utero shocks, converge in health status during life, holding investments fixed.

The health deficit model offers radically different predictions. At its core the model conceptualizes aging as a continual process of loss of function—increasing frailty—that culminates in death. The notion of reduced functionality is captured by way of the frailty index: as humans age (health declines) the relative fraction of potential age-related health conditions climbs steadily upward. This underlying process, which can be slowed down by health investments, is exponential in nature. By implication, small differences in initial conditions at young ages are amplified during life. The exponential nature of increasing deficits during life has been confirmed repeatedly by empirical work within gerontology. Overall, the deficit model seems well positioned to account for the type of dynamics implied by the fetal origins hypothesis.

Our study clarifies how an empirical researcher can discriminate between the health capital model and the health deficit model. Indirectly, any evidence of late-life health repercussions that can be causally related to early-life health shocks rejects the health capital model. This is so because the inherent mechanism of the health capital model is self-depleting: the loss of health is large when the state of health is good. Shock amplification, however, needs a self-productive process. The health deficit model is built on a self-productive process: the loss of health is large when health is bad. The health deficit model is thus not rejected by the observation that early-life health shocks matter for late-life health. Direct evidence in favor of the health deficit model, however, would employ a measure of health that can be tracked over time for individuals and ideally it would be based on the same metric to measure health deficits as the theoretical model, that is the frailty index.

A discriminating test between the two models is to check if the health effects of an environmental shock in utero or during childhood are increasing during adulthood. This is, of course, somewhat data demanding in that it requires that the affected and nonaffected individuals are observed more than once in adulthood (i.e., a panel of individuals). Yet first evidence along these lines is available. Abeliansky and Strulik (2018b) show that individuals exposed to hunger episodes during childhood diverge year-by-year during adulthood, in terms of health deficits, from comparable nonexposed individuals. Abeliansky and Strulik (2020) investigate a very mild health shock, namely the season of birth. They show that individuals born in autumn develop less health deficits than those born in spring and that the difference in health deficits gets larger with advancing age. This corresponds with the finding of Doblhammer and Vaupel (2001) that individuals born in autumn live longer than individuals born in spring.

In order to investigate the transition from early-life health to late-life health we have extended the health deficit model by a childhood period. The unified model combines a period of aging and health deficit accumulation (originating from a loss in redundancy in organ reserve) with a period of ontogenetic growth (conceptualized as the build-up of cell redundancy and organ reserve). The model of ontogenetic growth model has been developed in a collaboration between biologists and physicists (West et al., 2001) and is based on energy needs for cell creation and maintenance. The model of ontogenetic growth naturally divides childhood in two distinct periods, a period of convex growth in utero and early childhood, in which initial differences in body weight and frailty are amplified by ontogenetic growth and a later period where initial differences are dampened. Health damage, in contrast, is always amplified in the course of human development. We have shown how early-life shocks are transmitted during childhood and how they affect health, aging, and longevity of adults. Taken together, we have thus proposed a new

model of human development from conception to death, which motivates the fetal origins hypothesis of late-life health deficits.

ACKNOWLEDGMENTS

We would like to thank three anonymous reviewers for useful comments.

Open Access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

This is a theory paper. No data was collected.

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ENDNOTES

[1] The basic model of health deficit accumulation has been adapted to study, among other things, the link between health and education (Strulik, 2018), years in retirement (Dalgaard & Strulik, 2017), the gender-gap in mortality (Schüenemann, Strulik, & Trimborn, 2017b), and the health gap between married and unmarried individuals (Schüenemann, Strulik, & Trimborn, 2020).

[2] We treat the expressions "health expenditure" and "health investments" synonymously. In the calibration, h is measured by (annual) medical care expenditure.

[3] Allowing for death to be a stochastic event and considering health as an element in the utility function leads to some further interesting results but does not change the basic insight on the accumulation of health deficits (see Schüenemann, Strulik, & Trimborn, 2017a; Strulik, 2015). We thus focus on the simpler model here.

[4] Prior life cycle models with endogenous longevity have been proposed by, among others, by Ehrlich and Chuma (1990), Forster (2001), Laporte and Ferguson (2007), Strulik (2015b), and Galama and Van Kippersluis (2019) within the health capital framework and by Strulik (2019), Strulik and Trimborn (2018), Dragone and Strulik (2020), and the studies referenced in footnote 1 within the health deficit framework.

[5] In this study, we focus on lean body mass and assume that with the growth stop in terms of height the body stops also growing in terms of width, that is we neglect the feature of obesity. An extension of the health deficit model with respect to self-control problems in eating behavior and obesity is provided in Strulik (2019).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Dalgaard CJ, Hansen CW, Strulik H. Fetal origins—A life cycle model of health and aging from conception to death. *Health Economics*. 2021;30:1276–1290. https://doi.org/10.1002/hec.4231