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Killing Me Softly: The Fetal Origins Hypothesis

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In the late 1950s, epidemiologists believed that a fetus was a "perfect parasite" that was "afforded protection from nutritional damage that might be inflicted on the mother" (Susser and Stein, 1994). The placenta was regarded as a "perfect filter, protecting the fetus from harmful substances in the mother's body and letting through helpful ones" (Landro, 2010). Nonchalance existed with regard to prenatal nutrition. During the 1950s and 1960s, women were strongly advised against gaining too much weight during pregnancy (Paul, 2010). During the baby boom, "pregnant women were told it was fine to light up a cigarette and knock back a few drinks" (Landro, 2010). Roughly half of U.S. mothers reported smoking in pregnancy in 1960 (Aizer, Stroud, and Buka, 2009).

But what if the nine months *in utero* are one of the most critical periods in a person's life, shaping future abilities and health trajectories—and thereby the likely path of earnings? This paper reviews the growing literature on the so-called "fetal origins" hypothesis. The most famous proponent of this hypothesis is David J. Barker, a British physician and epidemiologist, who has argued that the intrauterine environment—and nutrition in particular—"programs" the fetus to have particular metabolic characteristics, which can lead to future disease (Barker, 1990). For

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example, Barker argued that individuals starved *in utero* are more likely to become overweight as adults, and that they are more likely to suffer from diseases associated with obesity, including cardiovascular problems and diabetes.

The fetal origins hypothesis combines several key ideas: First, the effects of fetal conditions are persistent. Second, the health effects can remain latent for many years—typically heart disease does not emerge as a problem until middle age, for example. Third, the hypothesized effects reflect a specific biological mechanism, fetal "programming," possibly through effects of the environment on the epigenome, which are just beginning to be understood. The epigenome can be conceived of as a series of switches that cause various parts of the genome to be expressed—or not. The period *in utero* may be particularly important for setting these switches (Petronis, 2010).

The fetal origins hypothesis also broadened the conventional focus on health behaviors of adults, such as smoking, exercise, and diet, to include earlier environmental factors that might affect the well-being of the fetus. The hypothesis has been controversial. Much of the early evidence was mainly correlational and did not effectively address potential confounders. Perhaps surprisingly, some of the most convincing evidence in favor of a broader version of the hypothesis comes from recent work in economics. Economists have also been active in demonstrating that various environmental factors can have negative impacts on the developing fetus, even at levels previously thought harmless. Later-life impacts extend to "bread and butter" economic outcomes, including educational attainment and wages.

This paper offers an overview of the epidemiological literature and Barker's place within it, a more detailed discussion of the contribution from economics, and some promising directions for future research. Clearly, a full acceptance of the fetal origins hypothesis idea would have radical implications for individual decisions and policy alike, suggesting for example that the optimum time to intervene to improve children's life chances is before they are born—and perhaps before mothers even realize that they are pregnant.

Epidemiology

Effects Apparent at Birth

Although isolated examples of the adverse health consequences of events *in utero* had been recorded earlier (such as congenital rubella syndrome, which was first recognized in 1941 by Norman Gregg),[1] the thalidomide episode in the late 1950s and early 1960s was a watershed event in establishing the importance of the *in utero* period. Thalidomide was licensed in 1957 and widely prescribed to pregnant women for morning sickness until 1961, when it was identified as the cause of an epidemic of severe birth defects such as missing arms and legs (McBride, 1961, Von Lenz and Knapp, 1962). As Dr. Philip Landrigan (cited in Roan, 2007), Chair

[1] Mothers infected with rubella in the first trimester of pregnancy have a 50 percent chance of delivering a baby with a problem such as cataracts, deafness, or heart disease (Dunn, 2007).

of the Department of Community and Preventive Medicine at Mount Sinai School of Medicine in New York City, has said, "Thalidomide was the first episode that made the medical profession and public realize that the placenta is not some sort of impervious barrier."

There were other examples of fetal exposures that could lead to severe and permanent abnormalities at birth. In 1973, Jones, Smith, Ulleland, and Streissguth described a pattern of anomalies common in children of alcoholic mothers, and labeled it "fetal alcohol syndrome." The facial features and behaviors typical of fetal alcohol syndrome had been recognized for a long time, but had been attributed to heredity. For example, Goddard (1912)'s monograph on the Kallikak family is subtitled "A Study in the Heredity of Feeble-Mindedness." Karp, Qazi, Moller, Angela, and Davis (1995) were the first to suggest that the characteristics of this family could be explained well by alcoholism and fetal alcohol syndrome.

Latent Effects

A distinct strand of medical and epidemiological literature develops the more subtle idea that events *in utero* can alter the infant in a way that leads to later disease, even in infants who are apparently healthy at birth. Kermack, McKendrik, and McKinlay (1934) explored the idea that the long-term effects of health shocks might remain latent for long periods of time. A series of studies of the Dutch "Hunger Winter" of 1944 set out to test this hypothesis. This famine was precipitated by the Nazi occupation of the Netherlands, in which many Dutch were reduced to eating tulip bulbs in a desperate attempt to forestall starvation.

Nutrition in the Netherlands had been adequate up to October 1944; however, the Nazis had occupied the country and cut off food shipments after that date. By November 1944, official rations had fallen below 1,000 dietary calories per day, and by April 1945, they were down to 500 calories per day. The famine was known to have affected fertility, weight gain during pregnancy, maternal blood pressure, and infant birthweight. Stein, Susser, Saenger, and Marolla (1975) examined the relationship between prenatal exposure to famine and the conscription records of over 400,000 18-year-old men. Famine exposure was defined using birth date and place of birth. No effects were found on IQ scores, but the obesity rate was doubled among those who had been exposed in the first trimester (Ravelli, Stein, and Susser, 1976). A limitation of this study was that it dealt with 18 year-olds, a group too young to provide evidence about any effects of fetal origins on the types of chronic degenerative conditions that typically manifest themselves later in life.

Clearly, the idea of latent health effects stemming from the prenatal period preceded the work of David Barker.[2] However, Barker brought three important

[2] In the preface to *The Fetal Matrix*, Gluckman and Hanson (2005) observe that: "most ideas in science just seem to evolve—no single person is the real inventor—rather multiple groups of researchers converge on a problem, offering thoughts and insights and experimental data, and the theory gradually develops." More pointedly, Lynch and Smith (2005) refer to Barker and Osmond (1986) as "the most influential replication" of Forsdahl (1977) and Forsdahl (1978).

perspectives to the table. First, he is credited with the specific hypothesis that "events early in life might be linked to such chronic degenerative diseases as non-insulin dependent diabetes mellitus (NIDDM) and cardiovascular disease (CVD), which do not usually appear until mid-life or later" (Rasmussen, 2001). Second, he obtained and analyzed new data, through no small amount of old-fashioned "shoe leather" (Freedman, 1991). For example, his sample of 16,000 men and women born between 1911 and 1930 in Hertfordshire, near London, "came to light as a result of the Medical Research Council's systematic search of the archives and records offices of Britain" (Barker, 1995). Finally, Barker brought an effective proselytizing zeal that helped make his name synonymous with the fetal origins hypothesis.

In contrast to the natural experiment employed in studying the "Hunger Winter," Barker's empirical work was essentially correlational. For example, in Barker and Osmond (1986), he analyzed extracts from Britain's Office of Censuses and surveys all death certificates from 1968 to 1978. The basic analysis involved presenting correlation coefficients between adult mortality rates over that period and the 1921 to 1925 infant mortality rates by geographical area. There are no controls for confounders, nor is there any discussion of how partial correlations might differ from the raw correlations presented. Rather, it is blandly stated that "Other environmental influences suspected as causes of ischemic diseases [that is, diseases related to reduced supply of blood to a certain organ, like the heart] . . . are not known to have the same geographical variations as past infant mortality." Moreover, congenital and infectious causes of infant death show similar correlations with adult mortality whereas one might have expected the latter to have weaker effects under the fetal origins hypothesis. Barker (1995) presents two basic cross-tabulations between birthweight categories and later-life morbidity/mortality and comments that "the associations between birth measurements and coronary risk factors are found to be unchanged after even the most potent adult determinants of risk are allowed for"; but he does not elaborate further about the control variables used to address confounding.

This approach provoked sharp criticism. For example, Paneth and Susser (1995) write:

> Indeed, it is easy to see the barrage of papers from Barker's group as an inductionist's delight. Example is piled on example, each somewhat consistent with the hypothesis but none seriously testing it. . . . What is missing in this work so far is the rigorous testing by rejections and exclusions—that is, by deliberate attempts at refutation.

Their more specific complaints are that anthropometric measures like low birthweight are weak indicators of fetal nutrition and that the observed relationships between anthropometrics and future health outcomes could reflect many other potential confounders. Nevertheless, Barker has shown a genius for synthesizing and explicating the fetal origins hypothesis in a way that has grasped the imagination of both scientists and lay people.

Subsequent studies used data from national Dutch psychiatric registries and found an increase in schizophrenia among those affected by the famine *in utero* (Hoek, Brown, and Susser, 1998). This finding has been replicated for the Chinese famine of 1959–61 (St. Clair et al., 2005), but not for famines associated with the seige of Leningrad (Stanner et al., 1997) nor the 1866–68 famine in Finland (Kannisto, Christensen, and Vaupel, 1997). However, in both Leningrad and Finland, mortality was high and conditions "so severe it is possible that only the healthy individuals survived" (Rasmussen, 2001). For example in Finland the infant mortality rate was 40 percent (Kannisto, Christensen, and Vaupel, 1997). The possible bias in estimated "fetal effects" due to this type of extreme selection is discussed further below. In the Netherlands, the affected cohort has now been followed to age 59, and significant changes in fat deposition have been found for women (though not for men), and in blood pressure for both men and women (Stein, Zybert, van der Paul–de Bruin, and Lumey, 2006; Stein, Khan, Rundle, Zybert, van der Pal–de Bruin, and Lumey, 2006).

How Latent?

In recent years, many studies have shown that birthweight can be affected by a variety of subtle and less-subtle shocks during the fetal period; in Currie (2011) and Almond and Currie (2011), we provide surveys of this literature. However, although birthweight is the most widely available and most studied measure of fetal health, it may not be a particularly comprehensive or sensitive measure, and the exclusive focus on birthweight may have retarded recognition of the importance of fetal effects. In the seminal study by Stein, Susser, Saenger, and Marolla (1975), cohorts who were exposed to famine during the first half of pregnancy had relatively normal birthweight but later showed more evidence of health effects such as incipient heart disease. In contrast, cohorts affected later in pregnancy suffered greater reductions in birthweight but were relatively healthier in later life. Thus, "One of the important observations from the Dutch Hunger Winter Study was that intrauterine exposures that have long-lasting consequences for adult health do not necessarily result in altered birth weight" (Schultz, 2010).[3]

That said, there has been no convergence on an alternative, superior metric to birthweight. Of course, it may be unsurprising that is hard to find a single comprehensive measure of latent fetal health impacts at the time of birth. Nevertheless, it is problematic for what Douglas Miller of the University of California-Davis has referred to as the "science fiction" problem in analyzing the fetal origins hypothesis: absent time-travel, we have to wait a generation for the effects of a prenatal intervention of interest to be observed in adulthood. A reliable metric for health at birth would obviate the need for time-travel. Otherwise, we are compelled to analyze historical shocks, which may have limited comparability to present conditions.

An ideal measure would be sensitive for fetal insults at all stages of pregnancy, be easy to measure, and be available for all mothers (or at least a large sample of

[3] Kelly (forthcoming) notes a similar disconnect between birthweight and fetal origins effects for the 1957 "Asian Flu" in Britain.

mothers) in a cohort. Barker observes that "from studies of children it should be possible to develop better biochemical markers of fetal undernutrition" (Barker, 1995). However, to our knowledge none have been suggested. Most recently, Barker has advocated using placental shape as a marker. But as Gluckman and Hanson (2005, p. 58) caution, "We have to be extremely careful not to view body size and shape at birth as measures of developmental outcome . . ."

The lack of an ideal measure of fetal health has not prevented economists from addressing the fetal origins hypothesis. This may be because economists are accustomed to considering many variables to be latent—like the potential wages of nonworkers. On a practical level, economists' focus on identification strategies has often enabled them to sidestep the question of finding a better measure of fetal health.

Conceptual Framework

One reason economists have become interested in the fetal origins hypothesis is that it holds important implications for the modeling of human capital development. In the now-standard Grossman (1972) model of the development of health capital, the equation of motion of the health stock is often written as:

$$H_t = (1 - \delta)H_{t-1} + I_t,$$

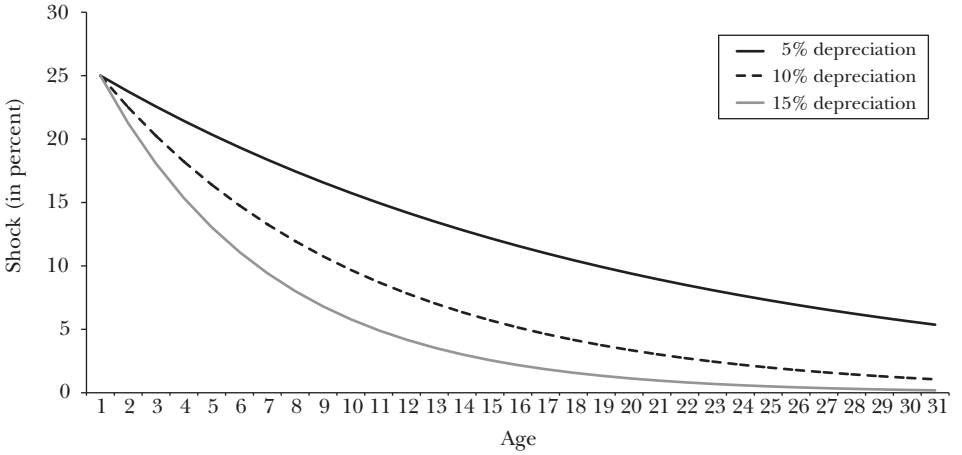
where I_t represents investments in health capital and δ represents the depreciation rate. This workhorse model builds in the "fade out" of early-life health shocks. That is, if health capital depreciates, then the effects of shocks to health capital must also depreciate over time, so events further in the past will have less-important effects than more recent events. As Smith (1999) observed, "How could short exposures matter if health is a stock?"[4]

Figure 1 shows how persistent a 25 percent negative shock to the birth endowment would be given alternative annual depreciation rates δ. Even under the lowest annual depreciation rate of 5 percent, half of the endowment shock is gone by the mid-teen years. For the higher depreciation rates of 10 and 15 percent, we would be hard-pressed to detect any lingering effects of the shock after age 30.

Heckman (2007) outlines a capacity formation model that is well-suited to consider fetal origins. A basic insight is to use a conventional constant elasticity of substitution production function to produce health, but to consider the inputs to be health investments at different developmental stages of childhood. In the simplest

[4] If investments in all periods subsequent to the shock are affected by the shock, then prenatal exposures could be important for adult health in the Grossman (1972) framework. However, the fetal origins literature posits an important and persistent biological effect of the prenatal period—that is, holding investments fixed.

Figure 1
Shock Persistance by Age in the Grossman Framework



Note: Figure 1 shows how persistent a 25 percent negative shock to the birth endowment would be given alternative annual depreciation rates.

two-input model, instead of having capital and labor inputs, we could have investments *in utero* and those occurring during the rest of childhood:

$$H_{adult} = A\left[I_{prenatal}^{\Phi} + (1 - \gamma) I_{postnatal}^{\Phi}\right]^{1/\Phi}.$$

One implication of these models is that the effects of prenatal investment shocks may be non-monotonic in age. Thus, they liberate us from the "fade out" of early shocks inherent in the Grossman formulation (Almond and Currie, 2011). The potential for complementarities between prenatal shocks and subsequent investments underscores the persistent importance of a "good start."[5] Furthermore, "dynamic complementarities" would imply that investments in period t are more productive when there is a high *level* of capability in period $t - 1$ (Heckman, 2007).

Second, "self-productivity" implies that higher levels of capacity in one period create higher levels of capacity in future periods (which is noteworthy when capacity is multidimensional, for example, if baseline health facilitates cognition). Cunha and Heckman (2008) and Cuhna, Heckman, and Schennach (2010) simulate models of this type and suggest that capabilities measured in early childhood can explain much of the variation in adult accomplishments. The intuition is that early shocks have had a longer time to feed through the dynamic system while late shocks have not yet had time to dissipate. Currie, Stabile, Manivong, and Roos (2010)

[5] The constant elasticity of substitution production function employed does not impose complementarity, but rather allows a full range of elasticities of substitution, from Leontieff through perfect substitutability (Heckman, 2007; Almond and Currie, 2011).

provide some empirical evidence consistent with this hypothesized time pattern, finding evidence that health at birth, health in early childhood, and health in the late teen years have larger effects on educational attainment and use of welfare than health in early adolescence. To date, there has been no similar empirical exercise considering the impact of fetal shocks.

Before turning to empirical evidence from economics on the fetal origins hypothesis, it is important to consider what studies of fetal origins can actually hope to measure. For example, if exposing a fetus to rubella at a specific time in pregnancy results in deafness, then it might be reasonable to view this as a "biological" effect. However, the long-term impacts of being born with fetal alcohol syndrome may be very different depending on whether or not the child is institutionalized, or whether the child is "mainstreamed" at school. At a more subtle level, parents may try to help children overcome disabilities, or they may decide to focus their efforts on siblings without disability (Behrman, Rosenzweig, and Taubman, 1994; Almond, Edlund, and Palme, 2009; Datar, Kilburn, and Loughran, 2010; Bharadwaj, Eberhard, and Neilson 2010; Adhvaryn and Nyshadham 2011).) Hence, when examining longer-term outcomes, it is important to keep in mind that these can represent both biological and social factors (Royer, 2009; Almond and Currie, 2011). Even in the short term, people may act to mitigate the effects of shocks. For example, in a famine, family members might try to give a pregnant woman a larger share of food rations. Such actions would make it harder to draw inferences based on average food rations.

Empirical Contributions from Economics

Barker's fetal origins hypothesis has spawned a large and growing empirical literature both within health economics and more broadly (Currie, 2009). Development economics has been especially active in exploring the fetal origins hypothesis; examples include Shultz and Strauss (2008) and observational studies by Bleakley (2007), Chen and Zhou (2007), Field, Robles, and Torero (2009), Maccini and Yang (2009), Cutler, Fung, Kremer, Singhal, and Vogl (2010), and Bhalotra and Rawlings (2011). Furthermore, environmental economics (Deschenes, Greenstone, and Guryan, 2009), economic history (Fogel and Costa, 1997), family economics (Del Bono and Ermisch, 2009), and even the economic growth field (Birchenall, 2007) have been influenced by the fetal origins hypothesis. We will not attempt to summarize this voluminous literature. Instead, we will describe four thematic contributions economists have made to the fetal origins hypothesis: 1) analysis of nonhealth endpoints; 2) improved identification strategies; 3) consideration of relatively mild and more-varied prenatal exposures; and 4) formalization of the tension between "scarring" and selective mortality in ecological data.

Nonhealth Endpoints

Currie and Hyson (1999) broke new ground in economics by exploring whether fetal origins effects might extend not just to measures of health, but also to

measures of human capital. Using the British National Child Development Survey, they found that low-birthweight children (children with birthweight less than 2,500 grams) were more than 25 percent less likely to pass English and math O-level tests (equivalent to high school exit exams) and were also less likely to be employed at age 33. While this study was primarily descriptive, the finding that test scores were lower in low-birthweight children was surprising as epidemiologists had routinely posited fetal "brain sparing" mechanisms, whereby adverse *in utero* conditions were parried through a placental triage that prioritized neural development over the body (for example, Scherjon, Oosting, Ongerboer de Visser, de Wilded, Zondervan, and Kok, 1996).

Since then, a substantial empirical literature has developed analyzing within-family (and within-twin-pair) differences in birth outcomes and their relationship to educational attainment, often using large samples of data from birth registries. Although as discussed above, birthweight is a relatively crude measure of fetal health, such studies typically find significant effects of birthweight on educational and/or labor force outcomes, as in Currie and Moretti (2007), Oreopoulos, Stabile, Walld, and Roos (2008), Black, Devereux, and Salvanes (2007), and Royer (2009). For example, Black, Devereux, and Salvanes (2007) find that a 10 percent increase in birthweight increases high school graduation by 1.2 percent, IQ (of men) by 1.2 percent, earnings by 0.9 percent, and height by 0.3 percent.

Besides human capital and labor market outcomes, various other outcomes have been found to respond to *in utero* shocks, as well. For example, marital status is negatively impacted by early childhood exposure to the 1959–61 China famine (Almond, Edlund, Li, and Zhang, 2010; Brandt, Siow, and Vogel, 2008). Welfare dependency is higher following *in utero* shocks (Almond, 2006; Oreopoulos, Stabile, Walld, and Roos, 2008; Nilsson, 2008), and neighborhood characteristics in adulthood are also compromised (Almond, 2006).

Improving Identification

Economists have risen to the challenge posed by Paneth and Susser (1995) of subjecting the fetal origins hypothesis to "rigorous testing by rejections and exclusions—that is, by deliberate attempts at refutation." The fact that the hypothesis applies to a well-defined developmental period lends itself to "severe" hypothesis testing (see Dinardo, 2007, and references therein). Cohorts potentially affected by a particular shock *in utero* can be compared to cohorts born just before or just after the shock. The fetal origins hypothesis offers the prediction that later-life health outcomes should be worse only for those cohorts whose pregnancies overlapped with the shock.[6]

To be sure, in some contexts it can be challenging to disentangle the *in utero* effects of the fetal origins hypothesis from the effects of shocks that occur in early childhood. For a fetal shock, we often have sharp comparisons between the affected cohort in the 10 months before birth, and two other cohorts: the cohort that was

[6] The qualitative predictions of the fetal origins hypothesis are stronger than the quantitative predictions, a point we return to in the "Future Research" section.

about to be conceived when the shock occurred (and is therefore too young to be affected) and the cohort that was already born at the time of the shock (and is therefore too old to be affected prenatally). In contrast, it may be difficult to define such sharp comparisons for developmental periods after birth. For example, suppose that air pollution has negative effects on the developing fetus, but also harms young children. The effects on very young children might increase with age as the children spend more time outdoors. The effects may eventually decrease with age as the children mature and their metabolisms slow (children are thought to be particularly sensitive to pollution because their systems are still developing and they have rapid metabolisms). A smooth change in the effects of air pollution with age will make it difficult to disentangle the effects of pollution from other age and period effects. However, given a shock to pollution it may still be possible to find a sharp contrast, for example, between the affected cohort and children who were not yet conceived at the time of the shock.[7] Alternatively, many "severe tests" of the fetal origins hypothesis can be interpreted as capturing the *additional* effect of fetal exposure on top of those stemming from (smoother) early-childhood effects.

However, seeking to quantify *in utero* effects through comparisons with those born just earlier or later gives rise to several problems. First, most birth cohorts are neither exposed to an identifiable shock *in utero*, nor were born just before or just after such a shock (and thus cannot serve as good controls). Rather than looking at all the data on births, the researcher is immediately pushed to looking at particular episodes in which an identifiable shock occurred and then attempting to draw defensibly generalizable conclusions from these episodes. Second, we need to be able to link data on adult outcomes to data on the affected cohorts. But many prominent datasets, such as the Current Population Survey, do not include information on where someone was born or precise date of birth. As a result, many interesting and policy-relevant experiments linked to a certain time and place may never be analyzed.

Economists have been creative in linking large-sample cross-sectional datasets back to ecological conditions around the time of birth. Most often, they have used information on when and where a respondent was born to link that person back to *in utero* health conditions. This has enabled economists to consider historical events featuring relatively well-defined start and/or end points. Economists have also shown a willingness to focus on exogenous sources of variation in fetal health that are well measured at the aggregate level but not at the individual level.

In this spirit, the 1918 Influenza Pandemic offers an appealing identification strategy because it was unexpected, short, and surprisingly arbitrary in whom it affected (Almond, 2006). While the infection status of individual women is unobserved, roughly one one-third of those born in early 1919 had mothers who contracted influenza while pregnant. As a control group, we can consider those born in early 1918, who had essentially zero prenatal exposure to the 1918 pandemic.

[7] On the other hand, if the one-off shock affects the composition of births (the parents who conceive after the shock may be different from those who conceived earlier), this comparison may be less clean than if we just consider effects among those already conceived at the time of the shock.

Furthermore, we can use variation across U.S. states in the severity of the pandemic to construct a second, difference-in-differences estimate of the pandemic's effect (using information on state of birth from the U.S. Census). Both approaches yield large estimates of long-term effects. Despite the brevity of the health shock, children of infected mothers were about 20 percent more likely to be disabled and experienced wage decreases of 5 percent or more, as well as reduced educational attainment (Almond, 2006).[8, 9]

Banerjee, Duflo, Postel-Vinay, and Watts (2010) consider the nineteenth-century blight to French vineyards from the phylloxera insect. During the late 1800s, phylloxera spread slowly from the southern coast of France northward, affecting production and thereby income in different regions in different years. They use data on military recruits at age 20 for each *département* in each year to assign the phylloxera conditions in the year of birth and examine effects on the recruits. Male children born to wine-growing families and born in the years and regions affected by the crisis were 0.5 to 0.9 centimeters shorter in adulthood, which is large relative to the 2 centimeter secular increase in heights over the nineteenth century. In contrast, no long-term impacts were detected for male morbidity at age 20 or female life expectancy (from vital statistics records).

Likewise, Field, Robles, and Torero (2009) evaluate the diffusion of a prenatal shock in Tanzania during the 1980s, but here a beneficial one: iodine supplementation during pregnancy. Moreover, maternal supplementation is thought to remain effective for two years, so delays in resupply constitute a second part of the identification strategy. The authors' data further enable them to consider siblings of those exposed to the sporadic iodization efforts, thereby removing the effect of selective take-up by families. They find large and robust educational impacts—on average about a half a year of schooling, with larger improvements for girls. Health, by contrast, appeared unaffected. In view of the low cost of iodine supplementation and persistence of iodine deficiency in poor countries, the authors conclude that prenatal supplementation offers an efficient, cost-effective means of improving human capital.

Finally, Almond and Mazumder (forthcoming) consider the coincidence of pregnancy and the dawn to dusk fast during Ramadan, which shifts forward approximately 11 days each year. With cohorts born across multiple birth years, Ramadan's effect can be disentangled from seasonal effects on health (Doblhammer and Vaupel, 2001). Furthermore, Almond and Mazumder (forthcoming) leverage the fact that away from the equator, daylight fasts are longer during summer months. A point of departure from previous analyses is to allow for pregnant mothers who

[8] Brown (2011) argues that parental characteristics may have deteriorated for the *in utero* cohort. Insofar as cohort differences are concerned (U.S. regional variation is not analyzed), when Brown (2011) controls for a vector of parental characteristics in the National Longitudinal Study sample, estimates of damage to children are qualitatively similar and statistically indistinguishable from those without this adjustment.

[9] Nelson (2010), Kelly (forthcoming), Neelsen and Stratmann (2011), and Lin (2011) find similar long-term damage for prenatal exposure to pandemic influenza in Brazil, Britain, Switzerland, and Taiwan, respectively.

reported fasting to be different from those who did not report fasting, potentially in unobserved ways. Indeed, Almond and Mazumder do not observe whether mothers fasted and instead construct an intent-to-treat estimate based on whether a child was *in utero* during Ramadan. Interestingly, they find no evidence that Muslims time births relative to Ramadan's occurrence. Nevertheless, being exposed to Ramadan in early pregnancy has large health effects. Daytime fasting in early pregnancy increases the likelihood of adult disability by over 20 percent among Iraqis and Uganda's Muslims, with substantially larger effects for mental/learning disabilities. The fact that Ramadan is also a relatively mild health shock leads us to consider other more commonly experienced exposures.

Mild and Non-Nutritional Early-Life Exposures

Economists have utilized the power of large-sample datasets to detect effects of relatively mild fetal insults. This extension is key as exposure to relatively mild pathogens is common. Hence, estimates of the effects of mild exposures may be more relevant to policy than estimates of the effects of disasters. Because the immediate mortality and economic disruption from the 1918 flu or the China famine are sufficient to imply that any reasonable measure to prevent such catastrophes is likely to pass a cost–benefit calculation, showing that there was additional damage to fetal health from these disasters merely "makes the rubble bounce." However, a practical danger in focusing on mild exposures is that identification may suffer. Economists have been skillful at analyzing relatively mild exposures (compared to famine and pandemic) while leveraging the sharp predictions of the fetal origins hypothesis regarding timing of pregnancy relative to shocks.

Infectious disease offers one example. Infections were mentioned in early work by Barker, but this idea was subsequently neglected in the epidemiological literature (Finch, 2007). Infections can affect fetal health by diverting maternal energy towards fighting infection, by restricting food intake, or through negative consequences arising from the body's own inflammatory response (Crimmins and Finch, 2006). Examples of economic investigations exploiting variations in infectious disease include seasonal variation in infections (Costa and Lahey, 2005), improvements across U.S. states in reducing the burden of infectious disease (Case and Paxson, 2009, for the case of typhoid and measles), and early-life malaria exposure in the U.S. South (Barreca, 2010). Despite the fact that the infections considered are seasonal and endemic (as opposed to pandemic), these effects can still be large. For example, Barreca (2010) estimates that schooling falls approximately half a year with ten additional malaria deaths per 100,000 and that early-life malaria "can account for as much as 25 percent of the difference in long-term educational attainment between cohorts born in malaria-afflicted states" and non-afflicted areas in the early twentieth-century United States.

Pollution is another commonly experienced and potentially important source of fetal health insults. Recent research shows that low-level exposures to such everyday contaminants as automobile exhaust and cigarette smoke have negative effects on fetal health (Currie, 2011). Yet there has been little research to date

linking fetal exposures to future outcomes. An exception is Sanders (2011), who builds on Chay and Greenstone (2003), who treated the recession of the early 1980s as a natural experiment that reduced pollution (just as the current recession has reduced the production of greenhouse gases). He finds that high school test scores in Texas improved for the cohort *in utero* at the time.

Finally, a number of interesting papers consider the effects of economic shocks around the time of birth on fetal health. Here, health in adulthood tends to be the focus (rather than human capital), and findings are less consistent than in the studies of nutrition and infection described above. One problem may be that the shocks are more diffuse in terms of timing so comparisons are less sharp. A second issue is that the mechanism is not entirely clear. Presumably economic downturns could affect fetal health through multiple pathways including effects on nutrition, smoking, drinking, stress, and stress-related disease. As one example, van den Berg, Lindeboom, and Portrait (2006) found that those born during economic downturns in the Netherlands lived "a few years less" than those born during a boom. In contrast, Cutler, Miller, and Norton (2007) use data from the Health and Retirement Survey to look for long-term effects on the health of cohorts born during the Dust Bowl era of the 1930s. They do not find any effects, but this may be a case where the timing of the shock is somewhat diffuse. Baten, Crayen, and Voth (2007) related variations in grain prices in the decade of birth to adult numeracy using an ingenious measure based on "age heaping" in the British Censuses between 1851 and 1881. Persons who are more numerate are less likely to round their ages to multiples of five or ten. They find that children born in decades with high grain prices were less numerate by this index.

The fact that the estimated effects of milder fetal health shocks often remain large suggests that it may be possible to go further and consider still milder and more common exposures. For example, there is considerable interest in the possible effects of maternal stress on infant health (for instance, Aizer, Stroud, and Buka, 2009). Stoecker (2011) examines the impact of extreme cold during pregnancy and finds some small but statistically significant negative effects on adult test scores in vulnerable populations.

Fetal Origins versus Culling

Adverse events experienced *in utero* may do more than "scar" survivors. These events may also increase fetal mortality as well as early-life mortality rates. Survivors exposed to these circumstance are thus a potentially selected sample, where selection is endogenous to the same adverse event as the "scarring" effect. The challenge to inference posed by selective mortality has been recognized both in epidemiology and economics.

A first pass at this issue is to consider the direction and scale of the selective mortality. Because mortality tends to remove those in poor health, survivors of negative fetal events are generally positively selected. Thus, in order to be detected, the negative scarring effects have to be sufficiently strong among the survivors to overwhelm the positive effect of selection. Hence, estimates of the effects of fetal health shocks are generally conservative when the shock also increases mortality. It may be

possible to use the estimated increase in the mortality rate to bound the magnitude of the bias from selective mortality. For example, if neonatal mortality increases by 2 percentage points due to an adverse *in utero* event, and we assume that this 2 percent would have had, for example, the best (and alternatively, worst) outcomes observed among survivors, this would yield lower (and upper) bounds on scarring. A much larger scope for selective mortality may exist if fetal mortality is affected.

The scope for selective mortality is generally larger in the more extreme natural experiments, such as those provided by famines or pandemics. It may also be more important in situations where baseline health is poor, and a relatively modest shock can have accentuated mortality effects. The latter case is relatively likely in developing countries or with historical episodes in developed countries.

Economists have modeled this mortality selection process. For example, Almond (2006) assumes that unobserved, unidimensional health is sufficient for survival to adulthood if it remains above some mortality threshold. An early-life shock can raise mortality by either reducing the mean of population health, or by raising the mortality threshold (people die at higher levels of health; this could occur, for instance, if the healthcare infrastructure deteriorates during the health shock). To the extent that some of the former effect (reducing the mean of population health) is permanent and stronger than the effect of an increased mortality threshold, we will observe damage among survivors in accordance with the fetal origins hypothesis. In addition to the severity of the health insult, the fraction of the population that is unaffected or asymptomatic will also determine mortality rates.[10] Almond also shows how infection rates, the key exogenous variable in this type of study, can be recovered from aggregate mortality rates without making assumptions on the distribution of health—which by definition is unobserved.

Bozzoli, Deaton, and Quintana-Domeque (2009) consider the tension between culling and scarring effects of infection in determining health. They use adult height as a measure of health, arguing that in populations, it is a sensitive index of the disease environment (conditional on nutrition). One innovative feature of their work is that they consider both relatively developed, low-mortality countries and higher-mortality developing countries. A second is that they show how much further it is possible to get in terms of inference if we assume that health is distributed normally. Their basic finding is that culling may dominate scarring for very high mortality levels, making survivors taller.

Neither Almond (2006) nor Bozzoli, Deaton, and Quintana-Domeque (2009) allow the early-childhood mortality threshold to increase with the virulence of the disease outbreak, which as we mentioned could occur if the healthcare infrastructure deteriorates during the health shock (perhaps the healthcare workers also get sick). To the extent that this effect increases early-life mortality, a positive bias on later-life outcomes remains, and future work might explore the importance of relaxing this assumption.

[10] Thanks to Larry Katz for making this point.

Future Research

Despite the proliferation of research on the fetal origins hypothesis, a host of promising avenues for future research remain. We highlight five.

First, many papers have documented that a wide array of natural experiments had effects on newborn health, but the long-term effects of these experiments have not been determined, for example, Currie and Gruber (1996) or Hoynes, Page, and Stevens (2011). With appropriate data, such analyses constitute low-hanging fruit. There have been a few pioneering attempts to follow the long-term effects of interventions in early childhood on long-term outcomes. For example, Garces, Thomas, and Currie (2002) and Ludwig and Miller (2007) consider the long-term effects of Head Start, while Chetty et al. (forthcoming) and Muennig, Johnson, and Wilde (2011) examine the long-term effects of assignment to different kindergarten classrooms in the Tennessee STAR experiment. But studies that consider long-term effects of real-world policies (rather than rare disasters) touching fetal health have been relatively rare. Short of conducting actual policy evaluations, if economists can identify the effects of less-extreme episodes on long-term outcomes, this will be extremely useful for policy.

Second, one of the most radical implications of the fetal origins hypothesis may be that one can best help children (throughout their life course) by helping their mothers. That is, we should be focusing on pregnant women or perhaps even women of child-bearing age if the key period turns out to be so early in pregnancy that many women are unaware of the pregnancy (Almond and Mazumder, forthcoming). Such pre-emptive targeting would constitute a radical departure from current policies that steer nearly all healthcare resources to the sick, i.e., the "pound of cure" approach. That said, the existing evidence is not sufficient to allow us to rank the cost-effectiveness of interventions targeted at women against more traditional interventions targeted at children, adolescents, or adults. For example, broadening the target population to women who might get pregnant would reduce the set of policies that are cost effective. Moreover, there are relatively few "shovel-ready" policies that have been shown to affect fetal health at the population level. Prenatal iodine supplementation (Field, Robles, and Torero, 2009), Food Stamps (Almond, Hoynes, and Schanzenbach, 2011), and the Supplemental Feeding Program for Women, Infants, and Children (WIC) are important exceptions.

A third area for future research involves the integration of work on son preference with work on fetal origins. Prior to the advent of prenatal sex determination, girls *in utero* were protected from gender bias, both in terms of birth outcomes and a spectrum of fetal effects.[11] With the diffusion of technologies that allow determining the sex of the fetus earlier, such protection has eroded (Lhila and Simon, 2008). Dahl and Moretti (2008) find, for example, that among mothers who have ultrasounds, those carrying girls are less likely to be married at the time of the birth.

[11] Gender discrimination in postnatal investments has been well documented, for example, Das Gupta (1987).

On the other hand, increased sex-selective abortion may imply that families who carry a girl to term may be less-biased against girls, which should improve postnatal investments. The initial evidence suggests that health investments respond to sex determination and sex selection. In India, Hu and Schlosser (2010) find that fewer girls are born and that they are less likely to be malnourished. In contrast, Bharadwaj and Nelson (2010) find that Indian mothers pregnant with sons have more prenatal care visits and tetanus shots than those pregnant with girls. In China, Almond, Li, and Meng (2010) find no change in investment measures, but that neonatal mortality, an indicator of prenatal environment, increases for girls after ultrasound becomes available. A new chapter in the literature on fetal origins will consider the ramifications of sex discrimination that can now commence *in utero*.

Fourth, future work on the fetal origins hypothesis should consider the rising obesity rates in both developed and developing countries. Maternal obesity has been associated with poor birth outcomes and with premature birth in particular (McDonald, Han, Mulla, and Beyene, 2010). Currie and Ludwig (2010) show that higher maternal weight gain during pregnancy is related to a higher probability of birthweight over 4,000 grams, which is also thought to lead to a greater probability of obesity, diabetes, and heart disease later in life. To date, there has been little explanation of how increased obesity may affect the fetus and thus have long-term health effects. Gluckman and Hanson (2005, p. xii) observe that "for the first time in our evolutionary history, humans now inhabit an environment in which we have not evolved to live." One alarming possibility is that the trends in obesity may erode the historical gains in cohort health caused by the reduced disease burden and improved nutrition.

Finally, a major limitation in current research is our inability to make quantitative predictions as to how much a given fetal insult will affect later-life outcomes. To this end, it will be important to uncover which measures of maternal health, health at birth, or early-childhood health best capture incipient fetal origins effects. At present, this is an open question; to a surprising degree pregnancy remains a "black box." Obviously, doctors and epidemiologists may need to take the lead in devising new measures. Promising possibilities include research in epigenetics, which aims to decipher when and how various genes are switched "on" and "off" and, as a fallback, to find better measures of proximate maternal factors such as stress levels or maternal nutrition. Progress in measurement will help delineate mechanisms by which fetal origins effects are generated. Economists can help by evaluating whether such measures indeed lie along the causal pathway. Progress on measurement will not only allow fetal origins research to move beyond its qualitative predictions, but also to construct stronger falsification tests.

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