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Prenatal or early postnatal events predict infectious deaths in young adulthood in rural Africa

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Background Research over the past decade has suggested that prenatal and early postnatal nutrition influence the risk of developing chronic degenerative diseases up to 60 years later. We now present evidence that risk of death from infectious diseases in young adulthood is similarly programmed by early life events.

Methods In three rural Gambian villages, affected by a marked annual seasonality in diet and disease, we have kept detailed demographic, anthropometric and health records since 1949. Fate was known with certainty for 3162 individuals (2059 alive/1103 dead, most dying in childhood). For this case-control analysis of antecedent predictors of premature mortality, all adult deaths (n = 61) were paired with two randomly selected controls matched for sex and year of birth.

Results Mean age at death was 25 (SD: 8) years. Adult death was associated with a profound bias in month of birth with 49 cases born in the nutritionally-debilitating hungry season (Jul–Dec) versus 12 in the harvest season (Jan–Jun). Relative to harvest season the hazard ratio for early death in hungry-season births rose from 3.7 (for deaths >14.5 years, $P = 0.000013$) to 10.3 (for deaths >25 years, $P = 0.00002$). Anthropometric and haematological status at 18 months of age was identical in cases and controls, indicating an earlier origin to the defect. Most deaths for which cause was known had a definite or possible infectious aetiology; none were from degenerative diseases of affluence.

Conclusions Early life exposures, correlated with season of birth, strongly influence susceptibility to fatal infections in young adulthood. The evidence suggests that nutritionally-mediated intrauterine growth retardation may permanently impair the development of immune function.

Keywords Adult mortality, infection, immunity, intrauterine growth retardation, maternal nutrition, placental function, seasonality

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The observation that the risk of developing certain chronic diseases (coronary heart disease, diabetes, hypertension) is related to an individual's size at birth has generated the 'fetal and infant origins of disease' theory.[1] Although such associations are not universally observed and have been questioned,[2] the basic premise is now supported by an impressive number of independent studies[3,4] including an analysis of cardiovascular disease in over 70 000 women from the Nurse's Health Study.[5]

It has been proposed that early metabolic programming of a 'thrifty phenotype' (physiologically adapted to fetal nutrient depletion)[6] may be particularly important in developing countries where gestational poverty is often followed by adult affluence.[7] We set out to investigate the thrifty phenotype hypothesis using birth records started in 1949 in three rural African villages characterized by severe seasonality in diet and disease patterns. This seasonality creates a natural experiment in which month of birth acts as a strong proxy measure of fetal and early post-natal nutrition, and of certain maternal and infant infections. In the course of this work we discovered that premature death from infectious diseases in young adulthood is

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extremely strongly related to early life events correlated with season of birth.

Methods

Elements of a natural ecological experiment

A unique demographic record of births and deaths has been maintained continuously in three isolated rural Gambian villages (Keneba, Kanton Kunda and Manduar) since 1949. From 1950 to 1974 this was supplemented by annual surveys of the health and anthropometric status of all villagers conducted each April or May, and from 1974 onwards by more detailed morbidity and growth records collected year-round by full-time resident paediatricians. The patterns of diet and disease in these communities have been described in detail elsewhere.[8–10]

In the present context the salient environmental features are as follows. A subsistence farming existence is heavily influenced by a monomodal annual rainy season (Jul–Oct) which affects many aspects of diet, health and behaviour. A hungry season (coinciding with the rains) occurs when the previous year's food crops become depleted prior to the current year's harvest.[9] This is compounded by the need for hard agricultural labour (especially by women) and creates a marked negative energy balance (greatest in Jul–Oct) in all adults including pregnant women in whom monthly weight gain drops from 1500 g/month to only 400 g/month.[9] Birthweight is 200–300 g lower in the hungry season and the prevalence of low birthweight (<2500 g) exceeds 25% in the worst months. Much of this intrauterine growth retardation is known to be nutritionally mediated since it can be reduced by maternal supplementary feeding.[11] Most maternal and infant diseases also peak in the hungry season, especially malaria and diarrhoea.[12] These seasonal patterns have been documented to occur for at least 50 years with varying intensity according to rainfall, disease patterns and crop yields.[13]

Subjects and Analysis

Using a database of 3162 individuals aged up to 48 years, for whom month of birth and current fate (dead or alive) were known with certainty we present a survival analysis for 1103 deaths from 1654 hungry and 1508 harvest season births (Statistical Sciences, S-PLUS, version 3.3, Seattle: mathsoft 1995). A preliminary note of these findings, based on fewer deaths, has been published elsewhere.[14] A case-control analysis of the premature adult deaths is also presented. Cases consisted of all deaths aged ⩾14.5 years (n = 61). Two controls matched for sex and year of birth were randomly selected from the database for each case (n = 122). Causes of death were ascertained for 47 cases from field clinic records (n = 19), hospital records following referral (n = 9), or by verbal autopsy from relatives (n = 19). Secure cause of death information was unobtainable on the remaining 14 cases. The prevalence of HIV so far remains low within these communities.

In order to investigate possible influences of infant malnutrition on adult mortality, data on weight, height and haemoglobin were extracted from the historical records using the measurement closest to 18 months of age. This age was selected for two reasons: first, as the most critical period for malnutrition; and second, because Z-scores decline rapidly in the first year of life making it inappropriate to compare children whose measurements are not all recorded at an exact age, whereas average Z-scores are stable from 12 to 24 months. The profound seasonal swings in nutritional status in this setting[10] do not influence this aspect of the current analysis since all measurements were performed in Apr/May (the time of optimum nutritional status). Z-scores were calculated using the WHO ANTHROP programme.[15]

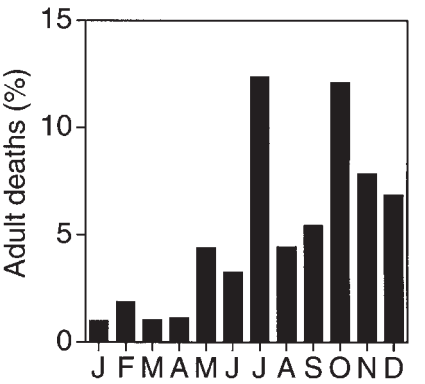

Figure 1 Seasonal distribution of births among premature adult deaths

Data are expressed as % of monthly births to adjust for seasonal differences in birth rate.

Results

The 61 premature adult deaths (mean age at death = 25.1 (SD: 8.4) years, range 14.7–47.0 years) occurred at an age when mortality in this community was generally low, and represented only 5.5% of all the deaths up to 48 years.

The sex ratio of 35 men to 26 women (1.35), though greater than for the overall population (0.97), was not significantly different (χ^2 = 1.30, NS). Exclusion of the nine maternal deaths (some of which could theoretically be related to a programmed phenomenon) and the five accidental deaths (all males) altered the residual sex ratio to 1.76 which remained non-significant (χ^2 = 2.02, NS).

Figure 1 shows a profound seasonal bias in month of birth for the cases with a large excess born during, and soon after, the hungry season (Jul–Dec, n = 49) compared to the harvest season (Jan–Jun, n = 12). This bias was not observed for the controls. Chi-squared analysis of season of birth in cases versus controls was highly significant (P = 0.0008). Division of the year into thirds yielded only five deaths for births Jan–Apr, against 21 for May–Aug, and 35 for Sep–Dec (log rank, P = 0.00007). With the relatively small number of adult deaths being analysed the apparent early peak in July may be an artifact.

Figure 2 shows Kaplan-Meier survival plots indicating the increasing hazard ratio for later deaths rising from 3.7 for deaths >14.5 years (log-rank, P = 0.000013) to 10.3 for deaths >25 years (log-rank, P = 0.00002).

Table 1 shows that, in spite of being assessed at the optimal time of year, anthropometric and haematological status at 18 months were very poor by well-nourished standards. Average weight-for-age and height-for-age were close to 2 standard

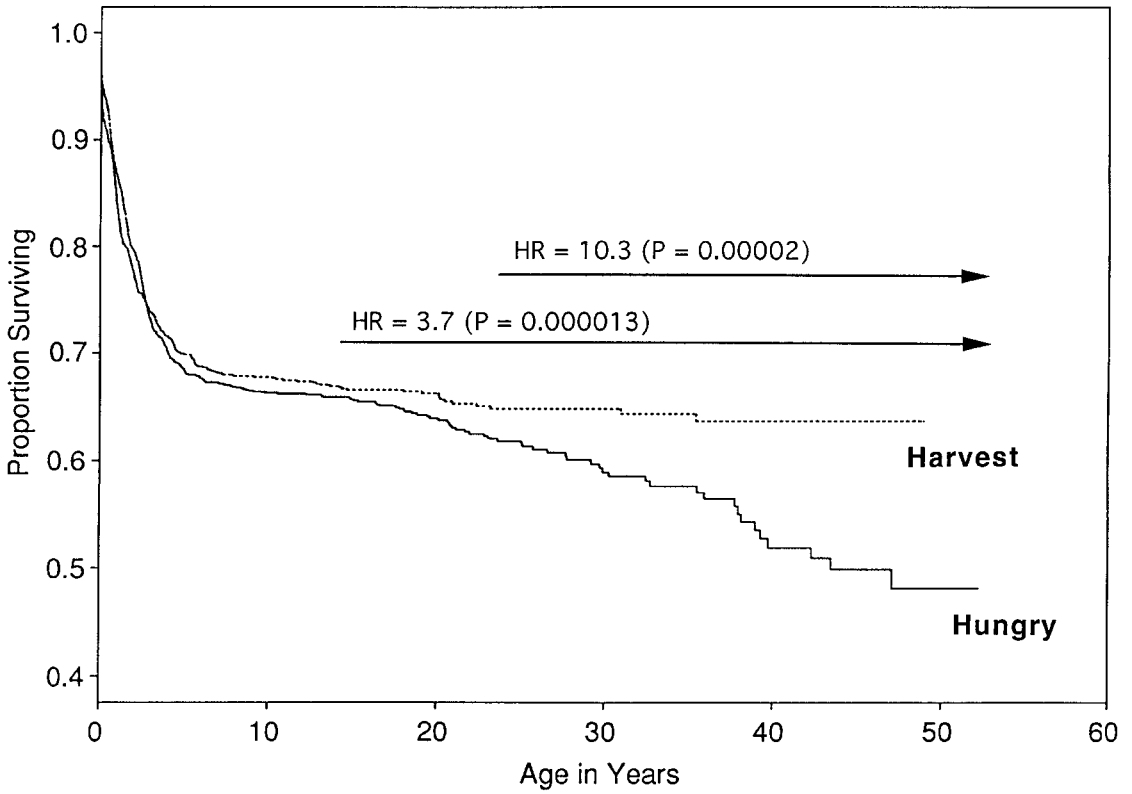

Figure 2 Kaplan-Meier survival plots by season of birth

Data for 1103 deaths from 3162 births. Upper (dotted) line = harvest season births (Jan–Jun); lower (solid) line = hungry season births (Jul–Dec).

Table 1 Nutritional status during infancy in cases and controls[a]

Variable	Cases	Controls	*P*-value
Mean age at measurement (years)	1.50 ± 0.54 (44)	1.49 ± 0.30 (110)	NS
Weight (kg)	8.99 ± 1.37 (44)	8.77 ± 1.36 (110)	NS
Weight-for-age (Z-score)	–1.99 ± 1.04 (44)	–2.04 ± 1.09 (110)	NS
Height (cm)	76.2 ± 5.6 (38)	74.7 ± 5.2 (101)	NS
Height-for-age (Z-score)	–2.04 ± 1.21 (38)	–2.27 ± 1.54 (101)	NS
Haemoglobin (g/100ml)	9.52 ± 1.60 (43)	9.36 ± 1.63 (107)	NS

[a] Plus-minus values are means ± SE with number of subjects in parentheses. Significance tests by ANOVA.

deviations below the CDC/WHO International Growth Reference. Mean haemoglobin was also low at 9.5 g/dl (normal range 11–14 g/dl). However, all of these averages were almost identical in the cases and controls.

Causes of the adult deaths are listed in Table 2 by season of birth. As anticipated for a rural African community there was an absence of deaths from chronic degenerative diseases, and a predominance of infectious (40%) and maternal deaths (15%). Many of the deaths in which infection was not identified as the primary cause had a likely infectious origin (e.g. hepatoma as a later outcome of hepatitis B infection). Including these with the known infections (but eliminating deaths with unknown cause) suggests that at least 60% of the non-accidental deaths had an infectious aetiology.

Discussion

This analysis shows that susceptibility to premature death in young adulthood is strongly related to early life events predicted by season of birth with a hazard ratio rising as high as 10.3. The predominance of deaths from infectious diseases suggests that one or more components of immune function have been permanently damaged. It is unknown whether the effect is confined to a subset of severely affected individuals or represents a graded premature immunosenescence.

This novel finding has emerged in an environmental setting characterized by a marked monomodal seasonality in many aspects of diet, nutritional status and disease. This makes the elucidation of the initial aetiological insult particularly

Table 2 Causes of death among cases by season of birth[a]

Category	Cause of death	Sex	Month and year of birth	Information source[a]
Hungry season births				
Infection	Wasting—suspected HIV	M	07–58	va
	HIV	M	09–55	hr
	Wasting—?TB-HIV	M	11–52	va
	Acute septicaemia-viraemia	F	09–50	cr
	Pneumonia[b]	F	10–50	cr
	Meningitis	M	10–67	va
	HIV	F	11–73	cr
	Fever with rash	M	08–71	va
	Fever	M	11–52	va
	Septic arthritis of hip	M	07–52	va
	Fever with rash	F	10–47	va
	Fever	M	10–48	va
	HIV	M	10–64	hr
	Chronic diarrhoea, wasting, acquired hemiplegia	M	12–74	va
Maternal	Pre-eclampsia	F	12–59	cr
	Pre-eclampsia	F	09–71	cr
	Puerperal tetanus	F	09–50	hr
	Maternal unspecified	F	07–50	va
	Hyperemesis gravidarum?	F	12–74	cr
	Maternal unspecified	F	10–47	va
	Maternal unspecified	F	10–77	cr
Cancer	Hepatoma[c]	M	07–53	cr
	Acute leukaemia	M	12–74	hr
	Cervical cancer	F	07–54	cr
Neurological	Severe uncontrolled epilepsy	F	10–54	cr
Renal	Nephrotic syndrome[d]	M	10–59	cr
	Renal failure	M	08–51	hr
	Chronic renal failure	F	09–63	hr
Cardiac	Rheumatic heart disease	M	10–49	hr
	Constrictive pericarditis[e]	F	11–63	hr
Other	Chronic generalized oedema and ascites	F	11–61	va
	Ascites	F	10–54	va
	Abdominal mass[f]	F	08–73	cr
Accident	Shot	M	10–51	va
	Drowned	M	11–70	va
	Unspecified	M	11–74	va
	Unspecified	M	12–57	va
Unknown	(Vesico-vaginal fistula)	F	07–54	(cr)
	(Epilepsy)	M	12–61	(cr)
	(Epilepsy)	M	07–51	(cr)
	(Chronic cervical spine pathology—suspected bone sepsis)	F	11–50	(cr)
	(Suspected systemic lupus erythematosus)[g]	F	07–49	(cr)
		M	10–62	–
		M	08–50	–
		M	10–51	–
		M	10–46	–
		F	07–48	–
		M	07–51	–
		F	12–71	–

continued

Table 2 Continued

Category	Cause of death	Sex	Month and year of birth	Information source[a]
Harvest season births				
Infections	HIV	M	05–59	cr
	Hepatitis	M	05–62	cr
	Typhoid	M	06–51	hr
	Fever	F	06–53	va
	Peritonitis	M	04–58	cr
Maternal	Unspecified	F	01–74	cr
	Pre-eclampsia	F	05–70	cr
Neurological	Profound acquired neurological impairment and epilepsy, cause unknown	M	03–63	cr
Other	Acute airways obstruction	M	06–77	cr
Accident	Car crash	M	02–50	va
Unknown	(Epilepsy)	M	05–59	(cr)
		M	02–61	–

[a] va = verbal autopsy; cr = clinic records; hr = hospital report.

[b] Longstanding bronchiectasis.

[c] Hepatitis B commonest risk factor in The Gambia.

[d] Evidence of sepsis at time of death.

[e] Tuberculous aetiology highly likely—father sputum-positive for TB bacilli.

[f] Probable carcinoma.

[g] Longstanding arthralgia, depressive psychosis, vasculitic malar rash, uveitis.

() = significant known pathology with uncertain contribution to cause of death.

challenging. However, several possibilities can be eliminated with some certainty, especially those proposing that the lower mortality in harvest season births might represent a 'survival of the fittest' phenomenon. Such selection might be conjectured to occur pre- or post-natally.

A pre-natal selection theory could be built around the fact that there is a significant seasonal fluctuation in birth rate, with an amplitude of approximately 30%. It could be argued that surviving fetuses at the time of lowest fertility represent a cohort selected for vigour at any time from implantation to delivery. However, the peak (Dec/Jan) and nadir (Jun/Jul) in births both cross the hungry-harvest season divide used in this analysis. Although there is an excess of births in the hungry season (as defined in this analysis) it amounts to only 9.7% and is unlikely to explain the very large differences in adult mortality.

Post-natal selection would require a higher infant and child mortality in harvest season births. This was not observed. Up to age 14.5 years hungry season births show a slightly higher mortality (HR = 1.05, $P < 0.437$), and the Kaplan-Meier survival curves never cross over as would be necessary to support a survival of the fittest theory.

The recent demonstration of genetic influences on fetal growth rate[16,17] has led to speculation that the observed association between fetal growth retardation and adult chronic disease might reflect a genetic linkage.[18] It is unlikely that genetic effects explain our current results since it would be necessary for polymorphisms linked to immune dysfunction also to predispose women to deliver in the hungry season.

Aflatoxins are powerful acute immunosuppressants and might cause permanent damage.[19] Transplacental transfer of aflatoxin is known to occur and fetal adduct levels correlate with maternal levels.[20] In The Gambia aflatoxin contamination caused by *Aspergillus* growth on long-stored foods peaks in April and May.[21] Thus any prenatal exposure effect would have to operate very early in gestation in order to affect births in November and December. Other environmental toxins might also be involved and follow-up studies are in progress.

Malaria infection in pregnancy represents another possibility. Figure 3 compares the seasonal birth distribution among the cases against 15-year aggregated data on the prevalence of maternal malaria and anaemia in this community. *Plasmodium falciparum* infection of the placenta (classified according to the presence of parasitized erythrocytes and distribution of malarial pigment in cells and fibrin in the intervillous space[22]) is

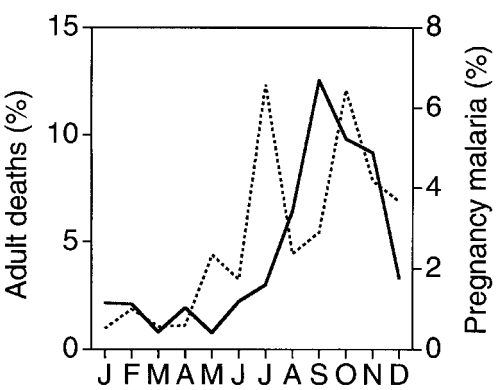

Figure 3 Seasonal distribution of births among cases compared to average prevalence of malaria in pregnant women

Data for malaria from same villages aggregated over 15 years. Solid line = malaria prevalence (%); broken line = monthly birth frequency among adult deaths.

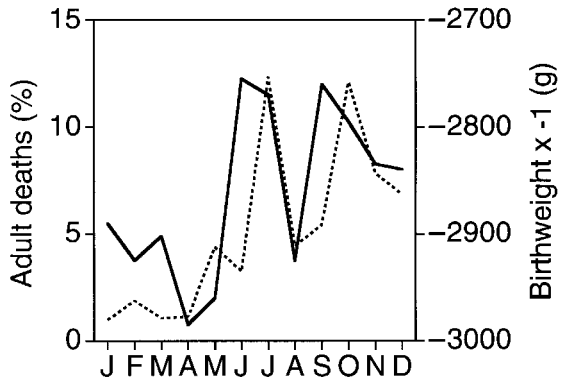

Figure 4 Seasonal distribution of births among cases compared to seasonal fluctuation in birthweight

Data for birthweights derived from a different dataset (n = 1027) as 5-year aggregate from 28 surrounding villages (including Keneba, Kantong Kunda and Manduar).[11] Solid line = inverted birthweight (g); broken line = monthly birth frequency among adult deaths.

common in this environment during the wet season. It is associated with low birthweight (especially in primigravida),[23,24] and biochemical evidence of fetoplacental dysfunction.[25] Immunological effects on the fetus include reduced placental antibody transfer,[26] and priming of cellular responses to subsequent infection.[27] These latter effects may not have a direct influence on programming later immunocompetence, but illustrate the potential of placental malaria infection in directing the functional capacity of fetal T-cells, and hence the infant's responses to early infections. It is possible that this could initiate a cascade of events resulting in lifelong effects on immune function. However, Figure 3 shows that malaria transmission appears to rise 2 months *after* the earliest affected months of birth. This diminishes the likelihood that maternal malaria is the causal factor, but does not exclude it since the relatively small number of adult deaths in this analysis precludes accurate identification of the peak months of susceptibility. It can be concluded that if malaria is the responsible agent then any imprinting on the baby's immune system would have to have the capacity to cause damage immediately pre-partum. Further studies of malaria and immune function of the offspring are underway in The Gambia.

Early post-natal exposures to seasonal infections in the infants themselves represent another possible mechanism. However, very young fully breastfed babies in this community tend to get few infections, and it is only after the introduction of weaning foods that infections escalate. Thus it is actually the harvest season babies that enter the period of peak infantile infections (Aug–Oct) at a more vulnerable time of life. On the other hand, rotavirus infection tends to show a sharp peak in January (in some but not all years)[28] which would affect hungry season births at 1–7 months of age. Exposure to certain viral and bacterial antigens in infancy has been shown to have long-term effects on immunity.[29–31]

Although these are all possibilities, Figure 4 indicates a very close inverse relationship between average birthweights in this community and the distribution of susceptible birth months for the adult deaths. Other evidence from the literature also favours the hypothesis that intrauterine growth retardation (caused in this case by maternal food shortages in the hungry season) slows cell division during sensitive periods in the ontogeny of the immune system. This would provide a mechanism by which early insults could be 'hard-wired' such that they had a permanent impact.

Lymphoid-tissue atrophy in malnutrition (especially of the thymus) has been recognized for almost two centuries, and nutritional thymectomy used to be a common medical term that is now largely forgotten.[32] Many components of the immune system develop early in fetal life[33] and deficits in organ growth and development *in utero* may be more serious and long-lasting than those caused by later malnutrition.[34] Maternal undernutrition is universally observed to have greater effects on thymic and lymphoid tissue growth than on other organs.[34,35] In addition to gross effects, the thymic microenvironment with diverse cellular content and complex structural organization is critical to its function[36] and might easily succumb to developmental damage.

Experimental neonatal thymectomy in animal models emphasizes the critical function of thymic lymphocyte processing in early life.[37] In mice, thymectomy within 24 hours of birth leads to profound leukopaenia and high later mortality. Thymectomy between 24 and 48 hours after birth causes autoimmune disease in susceptible strains suggesting a failure of negative selection of self-recognizing lymphocytes. It is thought that the development of tolerance happens pre-natally in humans indicating that the timing of critical events may differ from mice. Thus nutritionally-induced thymic dysfunction in early life could have multiple effects on the immune system including predisposition to auto-immune disease.[38] Possible links between birthweight and atopy[39] and autoimmune thyroid disease[40] have previously been described. The pulsatile nature of stem cell migration into the thymus during fetal life[41] further emphasizes how relatively short-term periods of fetal malnutrition could have a profound long-term impact.

There is evidence that low birthweight babies may have a sustained impairment of immune competence as infants and children[42–44] with hazards ratios for infectious deaths rising as high as 5.0 in Brazil,[44] though we are not aware of any longer term follow-up. The evidence in this respect remains weak in humans. In animals the effects of fetal undernutrition on immunological function (usually investigated with respect to single nutrient deficiencies) are well known[45] and have even been reported in F_2 and F_3 offspring.[46] If the defect in our Gambian population is nutritional in origin then the fact that nutritional status at 18 months of age was identical in cases and controls establishes the existence of an earlier critical window of development when malnutrition causes irreversible damage.

The recent finding that fasting cortisol levels are strongly related to birthweight in adult humans,[47] permits early speculation of another possible mechanism. Hypercortisolaemia impairs several facets of immune function, including lymphocyte and natural killer cell traffic and activity,[48] and also causes premature thymic atrophy.[49] Dexamethasone treatment of women at risk of pre-term delivery has been reported to reduce T-lymphocyte proliferation in cord blood, and later in childhood, compared to non-treated controls.[50] In The Gambian setting fetal exposure to excess glucocorticoids might result from maternal infectious or other stresses in the hungry season.

A nutritionally-mediated reduction in placental ability to deactivate cortisol might also be implicated. Protein deficient rat dams have low placental 11β-hydroxysteroid dehydrogenase-2 activity which increases fetal glucocorticoid exposure resulting in mild hypercortisolaemia in the offspring.[51] The mechanism of programmed hypercortisolaemia might be through a developmental reduction in glucocorticoid receptors in the hippocampus; an important centre for negative feedback control in later life.[52] Analysis of childhood deaths within this database (to be presented elsewhere) suggests that deaths from gastroenteritis and measles are programmed by season of birth, but that deaths from malaria and acute respiratory infections are not. Although such evidence does not yet permit firm conclusions as to the key affected components of specific or innate immunity, it implies a restriction of the programming effect to mechanisms of greater importance to defence against certain pathogens, with the suggestion that mucosal immunity and barrier defences may be implicated. It also helps to explain why childhood deaths appear not so strongly programmed as adult deaths since malaria and respiratory infections are the biggest killers and dilute out the effects of susceptibility to other infections.

The question arises as to whether these findings have a wider significance than in the rural African setting in which they emerged. If the fetal growth hypothesis proves to be correct this would be the case. Even in affluent countries fetal growth retardation can arise from many causes including poverty, maternal smoking, teenage pregnancy and poor placentation. If the programming of immunity is due to other early life events these may also occur widely.

Further studies are currently underway to try to identify the precise biological mechanisms involved in programming of immune competence. Early processes of immunological development, such as the establishment of T-lymphocyte subpopulations and repertoire, and setting of the Th1/Th2 response bias, represent potential candidates either by virtue of their known sensitivity to environmental influence or because of their fundamental role in determining the character of the host response to infection.

Acknowledgements

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