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Season of birth predicts mortality in rural Gambia

We present evidence that events in early life strongly influence the adult survival prospects of rural Africans. Our analysis of births and deaths in three Gambian villages dating back to 1949 shows that people born during the annual 'hungry season' are up to 10 times more likely to die prematurely in young adulthood. A permanent effect of malnutrition on the development of the immune system during fetal growth seems a likely explanation.

Patterns of nutrition and disease in rural communities from sub-Saharan Africa are heavily influenced by a clear divide between wet and dry seasons. In the Gambia, the wet season (July–October) coincides with an annual hungry period when staple foods from the previous harvest are seriously depleted¹. This is compounded in adults by an intensive agricultural workload, and in young children by diarrhoeal disease and malaria which peaks during the rains².

These stresses combine to cause intra-uterine growth retardation³, severe growth faltering in infancy and early childhood², and weight loss in adults¹ during this season. Impaired fetal growth reduces birth-weight by roughly 200–300 g and doubles the incidence of low-birthweight babies (< 2.5 kg), but can be reversed by supplementing maternal diet³. This seasonality has been documented for over 40 years⁴, the intensity varying according to rainfall, disease patterns and crop yields.

Since 1949 detailed records of births and deaths have been collected in three rural

subsistence-farming villages (Keneba, Kantong Kunda and Manduar)⁴. These records provide data on month of birth for 3,102 individuals, born between 1949 and 1994, for whom current fate (number of deaths, 1,077, and date of death) is known with certainty up to the end of 1994.

Analysis of variance in this data set revealed highly significant month-of-birth effects with highest mortality in births from July to December, two months longer than the usual hungry season divide. At an early age, deaths were similar in groups born between January and June and between July and December, but from the age of 15 those born in the hungry season had a greater mortality (Fig. 1).

When examined for deaths at all ages the season-of-birth effect was not significant (hungry, 581/1,627; harvest, 496/1,475; log-rank $\chi^2 = 2.3$, $P = 0.13$), but for those surviving to the age of 15 the odds ratio for premature death was 3.65 (38/460 against 10/415; log-rank $\chi^2 = 15.3$, $P < 0.0001$). This increased consistently to reach 10.4 for deaths past the age of 35 (9/68 against 1/69; logrank $\chi^2 = 6.2$, $P = 0.013$). Classification of the 48 deaths occurring after the age of 15 (based on clinic records or verbal autopsies) revealed: 17 infections, eight maternal deaths (at least two infection-related), three cancers, four renal failures, three epilepsy-related, five accidents and three other causes, with five unknown.

These results indicate that prenatal or early postnatal events affect the future health of rural Gambians in a manner first manifested around puberty and amplified with increasing age. The linkage between early life events and later viability has clear parallels with the 'infant and fetal origins of disease' hypothesis proposed by Barker for chronic diseases of affluence⁵. However, in the present findings, mortality was dominated by infections and pregnancy-related deaths with none being related to chronic degenerative disease.

Nutritional programming during fetal life seems the most likely causal factor (although early infections can have permanent effects on immune function⁶). Obser-

vations on the acute effects of protein-energy malnutrition suggest a likely involvement of cell-mediated immunity⁷. As early as 1810 Menkell linked malnutrition with lymphoid-tissue atrophy (especially of the thymus), and 'nutritional thymectomy' became a common medical term⁸. Several components of the human immune system mature early in fetal life⁹; deficits in organ growth and development occurring *in utero* are more serious and long-lasting than those caused by later malnutrition¹⁰. Low-birthweight babies may have sustained impairment of immune competence as infants and children⁹. In animals the effects of fetal undernutrition on immunological function have even been recorded in F₂ and F₃ offspring¹¹.

The early, *in utero*, sensitivity of the immune system to malnutrition would fit with our current observation that babies born up to two to three months after the peak of the hungry season remain vulnerable suggesting that fetal growth impairment in mid-pregnancy may have a carry-over effect even when maternal nutrition improves in late pregnancy. Likewise there is an intriguing similarity between the deviation of the Kaplan–Meier survival plots, the natural onset of thymic involution at puberty, and the well-documented post-pubertal decline in immune function.

Our current finding has emerged from a unique setting combining a seasonal experiment of nature with detailed longitudinal demographic records, but the general principle of fetal programming of immune function is likely to be of broad significance in other populations, especially those with marginal nutrition and high levels of exposure to disease.

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Figure 1 Kaplan–Meier survival plots for rural Gambians divided by season of birth. Harvest season, dotted line; hungry season, solid line.

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