Early-Life Nutritional Programming of Health and Disease in The Gambia

Sophie E. Moore

Division of Women's Health, King's College London, London, UK and MRC Unit The Gambia, Banjul, The Gambia

Keywords

Developmental origins of health and disease · Gambia · Immunology and inflammation · Reproduction/pregnancy/lactation · Human nutrition

Abstract

Background: Exposures during early life are increasingly being recognised as factors that play an important role in the aetiology of chronic non-communicable diseases (NCDs). The “Developmental Origins of Health and Disease” (DOHaD) hypothesis asserts that adverse early-life exposures – most notably unbalanced nutrition – leads to an increased risk for a range of NCDs and that disease risk is highest when there is a “mismatch” between the early- and later-life environments. Thus, the DOHaD hypothesis would predict highest risk in settings undergoing a rapid nutrition transition. **Summary:** We investigated the link between early-life nutritional exposures and long-term health in rural Gambia, West Africa. Using demographic data dating back to the 1940s, the follow-up of randomised controlled trials of nutritional supplementation in pregnancy, and the “experiment of nature” that seasonality in this region provides, we investigated the DOHaD hypothesis in a population with high rates of maternal and infant under-nutrition, a high burden from infectious disease, and an emerging risk of NCDs. **Key Messages:** Our work in rural Gambia suggests that in popula-

tions with high rates of under-nutrition in early life, the immune system may be sensitive to nutritional deficiencies early in life, resulting in a greater susceptibility to infection-related morbidity and mortality.

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Since the conception of the Developmental Origins of Health and Disease (DOHaD) hypotheses, a major focus has been on understanding the possible links between nutrition during fetal life and early infancy and subsequent risk of non-communicable disease. Initial work focused on birth weight as a proxy for intrauterine growth retardation, and the concept of “mismatch” defined that the highest risk would be among individuals exposed to nutritional deprivation during early life but nutritional excess later [1]. Such a theory would put many low- and middle-income countries at greatest risk; within such populations, and as a consequence of the very rapid nutrition transition, we are seeing, within a single generation, the transition from early-life malnutrition (foetal growth retardation leading to small-for-gestational age [SGA] and growth faltering in early post-natal life) to over-nutrition in later life [2, 3]. Understanding the link between early-life nutrition and health across the life-course is thus critical, so appropriate interventions can be developed.

Over the past 2 decades, we have been investigating the relationship between nutrition in early-life and long-term health risk among a population of rural Gambians. Here, I summarise the work completed to date. Since the late 1940s, the UK Medical Research Council (MRC) has been conducting a health and nutrition research programme among the rural West Kiang population of The Gambia [4]. As part of this programme, demographic records have been collected on the residents of three villages (Keneba, Kantong Kunda and Manduar), providing the longest documented continuous surveillance of a rural African population. Coupled with this long-term record keeping, this population is exposed to an “experiment of nature” as a consequence of the pronounced seasonality, affecting many aspects of diet, health and behaviour. November to June is a long, hot and dry season characterised by low levels of active infection, and good growth is observed in infants and young children and a positive energy balance seen in adults. From July to October, the annual rains result in high levels of infection, growth faltering in children, and a negative energy balance is observed among adults. Pregnant women are not exempt from the effects of this annual “hungry” season, and a seasonal increase in SGA and preterm infants is observed [5]. We have used these demographic records and the well-documented effects of seasonality to investigate the effects of the early-life nutritional environment on long-term health.

Initial work used the season of birth as a proxy measure for early-life nutritional exposures. We hypothesised that individuals born during the annual hungry season would have a greater risk of adverse cardio-metabolic outcomes as adults. However, in a study of 219 rural Gambian adults, we were unable to show any association between either the season of birth or the nutritional status in infancy, and adult risk of cardiovascular disease [6]. However, this lack of an effect was possibly a consequence of the excellent metabolic health profile observed among these rural Gambians, rather than a sign that metabolic programming does not operate in this population. In parallel to this work, we also asked the question if season of birth would predict adult mortality, and the observed results were most surprising. Using a survival analysis of 3,162 individuals (2,059 alive/1,103 dead), analysed according to season of birth, we showed that individuals born during the annual hungry season had a 10-times increased risk of premature adult mortality (death before >25 years of age) [7, 8] (Fig. 1). The cause of death was ascertained in 77% of the group, and demonstrated that these deaths were from infections, or infection-related causes, and not from chronic degenerative diseases. This

Fig. 1. Kaplan–Meier survival plots by season of birth. Figure adapted from [7]. HR, hazards ratio.

observation led us to hypothesise that among populations with high rates of under-nutrition in early life and a high burden of infectious disease, the immune system is programmed during early life, resulting in a greater susceptibility to infection-related morbidity and mortality.

Work that followed focused on the thymus as a potential target for early-life nutritional programming. The rationale for this was threefold: first, the thymus is central for the early development of adaptive immunity, with thymic development known to start early in the first trimester of pregnancy; second, thymic development is disproportionately affected by both maternal and infant under-nutrition, a fact leading to the thymus being termed a “barometer of malnutrition” long before any role for the thymus gland in immunological memory was known [9]; and, third, post-natal development of the thymus can be assessed sonographically using a non-invasive validated method to estimate the thymic index (TI) [10].

While little data exist to support TI as a robust measure of immunocompetence, TI has been shown to correlate with thymus weight at autopsy [10], has been correlated with mode of feeding in early infancy [11], and has been used previously in both The Gambia and Bangladesh to show that the human thymus is sensitive to environmental influences during infancy [12, 13]. Further, in populations with a high burden of infectious disease, a small thymus in infancy is an independent risk factor for subsequent mortality in childhood [14–16]. However, the role of early-life nutrition on thymic development remains to be determined.

To further our understanding, we established a prospective birth cohort of 138 Gambian infants, with TI

Fig. 2. Percentage (standard error) difference in mean thymic index between hungry and harvest season births (a), and between hungry and harvest season measurements, adjusted for gender, gestation and current weight (b). Figure adapted from [12].

assessed sonographically across the first year of life [12]. We demonstrated that TI varies significantly with season of birth and subsequently (and more strongly) with season of measurement [12] (Fig. 2). Characteristic tracking of an individual's TI (even after adjustment for body size) was observed, consistent with a possible role for the thymus in long-term programming. A seasonal influence was also observed in lymphocyte subpopulation counts from the same cohort [17], indicating a corresponding disruption to T-cell numbers and consistent with the hypothesis that permanently programmed defects in thymic function may affect adult cell-mediated immunity.

Of particular interest was the observation that the seasonal effect on TI was greatest when the infant was 8 weeks of age. Since, in this community, infants at this age are exclusively breast fed, are growing well and have minimal incidence of active infections, this observation could suggest the involvement of breast milk factors on thymic development. Using breast milk samples collected at the same time that TI was measured, Ngom et al. [18] tested for the presence of a candidate breast milk immune factor interleukin (IL)-7; a cytokine critical for thymic and T-cell development. Despite considerable monthly variation, breast milk IL-7 concentrations were significantly lower in the hungry/wet season compared with the harvest/dry season, suggesting a putative role for breast milk factors in thymic development [18]. However, the observational nature of this birth cohort study limited our ability to show causality, so work that followed focused on randomised trials.

In the first study, we followed up a group of 472 children aged between 6 and 9 years who were born during a trial of maternal nutritional supplementation [19]. In the original trial, pregnant women in the intervention group and in the control group were randomised to a high protein-energy

(PE) biscuit supplement (providing a maximum daily intake of 4,250 kJ energy and 22 g protein) from 20 weeks of gestation until delivery and from delivery until 20-weeks post-partum respectively [20]. At follow-up, the outcome variables tested in the children were naïve responses to rabies and pneumococcus vaccine, delayed-type hypersensitivity skin reactions, and mucosal defence (secretory immunoglobulin A and dual-sugar permeability). Despite this comprehensive battery of assessment tests, we found no consistent evidence for linkage between immune function and either season of birth, size at birth or maternal prenatal dietary supplementation [19], suggesting that these exposures in early life did not predict a measurable defect in immune response in children at this age.

More recent work has focused on a proof-of principle intervention trial employing comprehensive multiple micronutrient (MMN) and PE supplements [21]. The Early Nutrition and Immune Development (ENID) trial (ISRCTN49285450) is a randomised, partially blind trial to assess whether nutritional supplementation to pregnant women (from <20 weeks gestation to term) and their infants (from 6 to 12 months of age) can enhance infant immune development). Pregnant women were randomised to 4 intervention groups (iron-folate, MMNs, PE, PE + MMN), and from 6 months of age, infants are further randomised to a lipid-based nutritional supplement with or without additional MMNs. The primary outcome measures of the ENID Trial are thymic development during infancy, and antibody response to vaccination. At the time of writing, analysis of antibody response to vaccination was ongoing, and will be reported later. However, while supplementation in pregnancy did not have any measurable effect on thymic development, supplementation with MMNs from 6 to 12 months of infant

age resulted in a modest (8%, $p = 0.002$) increase in TI at 12 months of age (SE Moore, unpublished observations).

In summary, our work to date in The Gambia has demonstrated that (a) seasonal/nutritional effects on immune outcomes can be readily detected in the first year of life in Gambian infants [12]; a finding also subsequently replicated among a larger contemporary cohort of Bangladeshi infants [13], appear undetectable in later childhood [19], but again detectable in later life [22, 23]; (b) the detectable defects (thymic contraction, deviations in markers of thymic function [12, 17, 18]) all appear to be related to adaptive immunity. However, while our initial observational work suggested evidence of pre-natal influences given that differences in size adjusted TI are detectable at 1 and 7 days post-partum [12, 13], results from our more recent randomised trial do not support a pre-natal nutritional influence on thymic development but do provide evidence that supplementary micronutrients in infancy may confer benefit to thymic development. The functional consequences for infant immune responses are currently being investigated.

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Disclosure Statement

The author has no conflicts of interest to declare.

References

- Hanson MA, Gluckman PD: Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev* 2014;94:1027–1076.
- Corvalan C, Kain J, Weisstaub G, Uauy R: Impact of growth patterns and early diet on obesity and cardiovascular risk factors in young children from developing countries. *Proc Nutr Soc* 2009;68:327–337.
- Prentice AM, Rayco-Solon P, Moore SE: Insights from the developing world: thrifty genotypes and thrifty phenotypes. *Proc Nutr Soc* 2005;64:153–161.
- Hennig BJ, Unger SA, Dondeh BL, Hassan J, Hawkesworth S, Jarjou L, et al: Cohort profile: the Kiang West Longitudinal Population Study (KWLPS) – a platform for integrated research and health care provision in rural Gambia. *Int J Epidemiol* 2015;pii: dyv206.
- Rayco-Solon P, Fulford AJ, Prentice AM: Differential effects of seasonality on preterm birth and intrauterine growth restriction in rural Africans. *Am J Clin Nutr* 2005;81:134–139.
- Moore SE, Halsall I, Howarth D, Poskitt EM, Prentice AM: Glucose, insulin and lipid metabolism in rural Gambians exposed to early malnutrition. *Diabet Med* 2001;18: 646–653.
- Moore SE, Cole TJ, Collinson AC, Poskitt EM, McGregor IA, Prentice AM: Prenatal or early postnatal events predict infectious deaths in young adulthood in rural Africa. *Int J Epidemiol* 1999;28:1088–1095.
- Moore SE, Cole TJ, Poskitt EM, Sonko BJ, Whitehead RG, McGregor IA, et al: Season of birth predicts mortality in rural Gambia. *Nature* 1997;388:434.
- Prentice AM: The thymus: a barometer of malnutrition. *Br J Nutr* 1999;81:345–347.
- Hasselbalch H, Nielsen MB, Jeppesen D, Pedersen JF, Karkov J: Sonographic measurement of the thymus in infants. *Eur Radiol* 1996;6: 700–703.
- Hasselbalch H, Jeppesen DL, Engelmann MD, Michaelsen KF, Nielsen MB: Decreased thymus size in formula-fed infants compared with breastfed infants. *Acta Paediatr* 1996;85: 1029–1032.
- Collinson AC, Moore SE, Cole TJ, Prentice AM: Birth season and environmental influences on patterns of thymic growth in rural Gambian infants. *Acta Paediatr* 2003;92: 1014–1020.
- Moore SE, Prentice AM, Wagatsuma Y, Fulford AJ, Collinson AC, Raqib R, et al: Early-life nutritional and environmental determinants of thymic size in infants born in rural Bangladesh. *Acta Paediatr* 2009;98:1168–1175.
- Aaby P, Marx C, Trautner S, Rudaa D, Hasselbalch H, Jensen H, et al: Thymus size at birth is associated with infant mortality: a community study from Guinea-Bissau. *Acta Paediatr* 2002;91:698–703.
- Garly ML, Trautner SL, Marx C, Danebod K, Nielsen J, Ravn H, et al: Thymus size at 6 months of age and subsequent child mortality. *J Pediatr* 2008;153:683–688, 688.e1–e3.
- Moore SE, Fulford AJ, Wagatsuma Y, Persson LA, Arifeen SE, Prentice AM: Thymus development and infant and child mortality in rural Bangladesh. *Int J Epidemiol* 2014;43:216–223.
- Collinson AC, Ngom PT, Moore SE, Morgan G, Prentice AM: Birth season and environmental influences on blood leucocyte and lymphocyte subpopulations in rural Gambian infants. *BMC Immunol* 2008;9: 18.
- Ngom PT, Collinson AC, Pido-Lopez J, Henson SM, Prentice AM, Aspinall R: Improved thymic function in exclusively breastfed infants is associated with higher interleukin 7 concentrations in their mothers' breast milk. *Am J Clin Nutr* 2004;80: 722–728.
- Moore SE, Collinson AC, Prentice AM: Immune function in rural Gambian children is not related to season of birth, birth size, or maternal supplementation status. *Am J Clin Nutr* 2001;74:840–847.
- Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM, et al: Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *BMJ* 1997;315: 786–790.

- 21 Moore SE, Fulford AJ, Darboe MK, Jobarteh ML, Jarjou LM, Prentice AM: A randomized trial to investigate the effects of pre-natal and infant nutritional supplementation on infant immune development in rural Gambia: the ENID trial: early nutrition and immune development. *BMC Pregnancy Childbirth* 2012;12:107.
- 22 Moore SE, Jalil F, Ashraf R, Szu SC, Prentice AM, Hanson LA; Birth weight predicts response to vaccination in adults born in an urban slum in Lahore, Pakistan. *Am J Clin Nutr* 2004;80:453–459.
- 23 Ngom PT, Solon J, Moore SE, Morgan G, Prentice AM, Aspinall R; Thymic function and T cell parameters in a natural human experimental model of seasonal infectious diseases and nutritional burden. *J Biomed Sci* 2011;18:41.