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## Supplementary appendix

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**Growth faltering in rural Gambian children after four decades of interventions: a retrospective cohort study**

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**Supplementary material- contents**



## 1. Supplementary study population

The UK Medical Research Council has supported a research centre in the remote rural Gambian village of Keneba since 1949. Studies initially consisted of demographic records of births, deaths, marriages and migrations collected by village recorders and an annual survey of health and nutritional status in Keneba and 3 nearby villages: Manduar, Kantong Kunda and Jali.[1] In 1974 the Dunn Nutrition Unit commenced more intensive research and provided full-time clinical services to 3 of the villages (Jali declined to participate).

## 2. Supplementary methods

*Anthropometry*

The anthropometry measurements were performed in the clinic by trained clinic staff. Weight measurements were performed with the infants unclothed and recorded in kilograms to two decimal places. In the early decades, birth weights and subsequent weights were recorded using manual Salter spring balance and tared sling (Salter Industrial Measurements Ltd, West Bromwich, United Kingdom) and Todd Scales, Cambridge, UK. In the later decades electronic Seca 336 high precision portable baby weighing scales were used. All the weighing scales were calibrated regularly. Lengths were measured on Holtain infantometer (Holtain, Crymmych, UK) in the early decades but more recently on Kiddimetre (Raven Equipment, Great Dunmow, Essex, UK). The Leicester plastic stadiometer was used to measure maternal heights in the later years. Tape measures were used to measure the infants' mid upper arm circumferences and head circumferences. Sex and age-adjusted z-scores for weight for age (WAZ), length for age (LAZ), weight for length (WLZ), mid upper arm circumference (MUACZ), head circumference (HCZ) and birth weight (BWTZ) were calculated by comparison to the WHO 2006 growth standards.[2] Stunting, wasting and underweight are defined respectively as height-for-age, weight-for-length, weight-for-age of 2 or more standard deviations below the WHO reference median.

We define growth faltering in terms of the fall in z-scores between 3 and 21 months in order to avoid both the complications of catch-up growth in the first 3 months and the inevitably poorer estimates of the curves at the extremes of the data range.

*Statistical Methods*

Effects of age and season on repeated growth parameters were fitted using random effects models. Models for males and females and each decade were fitted separately. To describe secular changes in growth by decade i.e. rates of stunting, wasting and underweight in 2 year olds plotted in Figure 4, we fitted random effects logistic regression of the binary variable on the first four orthogonal polynomials in age and the first pair of Fourier terms for season (see below).

To describe the effect of season on growth, seasonal patterns of body size were obtained by "Fourier regression". [3,4] Briefly, Fourier regression represents the seasonal pattern as a Fourier series whose higher order terms are regarded as high-frequency noise and discarded. The resulting truncated series is a linear combination of trigonometric functions of $\theta$, the angle representing the phase of the year when the measurement was made, and whose coefficients are readily estimated as part of the regression model. We fitted the first three pairs of Fourier terms and controlled for age by including the first three orthogonal polynomials in age (*age*1, *age*2, *age*3) in the model. Thus the $j^{th}$ observation for the $i^{th}$ individual is given by:

$$Y_{ij} = \beta_0 + \beta_1 age1_{ij} + \beta_2 age2_{ij} + \beta_3 age3_{ij} + \sum_{k=1}^{3} \left[\alpha_k \sin\left(k\theta_{ij}\right) + \beta_k \cos\left(k\theta_{ij}\right)\right] + \tau_i + \varepsilon_{ij}$$

where the $\alpha_k$ and $\gamma_k$ are the coefficients for the Fourier terms and the $\beta$s the remaining regression coefficients; $\tau_i$ is the random effect due to the $i^{th}$ individual and $\varepsilon_{ij}$ is the error term. We appreciate that seasonal patterns may themselves vary with age. Allowing for this would have unduly complicated the analysis and is unnecessary for the purpose of this paper. The seasonal patterns we estimate are therefore averaged across all age groups.

In order to quantify the children's susceptibility to seasonal changes (as plotted in Figure 5) we estimated the amplitude of the seasonal pattern, which we define as the square root of half the sum of the squared Fourier coefficients:

$amplitude = \sqrt{\sum_k [\alpha_k^2 + \gamma_k^2] / 2}$.[5]

The delta method was used to estimate the standard error of these estimates (employing Stata's post-estimation command *nlcom*).

To describe the changes in body size with age, plots of mean z-score versus age (Figure 2) were produced by fitting age with 10-knot cubic regression splines and controlling for season by including the first pair of Fourier terms.

Estimates of mean values and their standard errors calculated at particular ages for each sex and decade were taken from the predicted values yielded by the above regression models. We quantify growth faltering as the drop in z-score over the 18-month interval starting at 3 months of age. These estimates are all simple linear combinations of the regression coefficients and their standard errors calculated using the variance-covariance matrix for the regression coefficients i.e. the Fisher information matrix (employing Stata's post-estimation command *lincom*).

The estimation of age specific disease incidence over the different decades was done by dividing the total number of children diagnosed with the disease in each age group as numerator, by total number of children 2 years of age or under who were seen in the clinic.

We perform no formal statistical hypothesis tests. With such large volumes of observational data almost any difference examined would be significant so statistical significances provide poor means of discriminating between important and trivial patterns in the data. Instead we focus on estimating effect sizes and their confidence intervals. All analysis was performed using Stata 12. (StataCorp, College Station,TX).

## 3. Supplementary tables

### Table 1: Summary of previous studies that have assessed trends in growth faltering in African children

| Study | Study design (interval) | Country | N (age group) | Main findings |
|---|---|---|---|---|
| **Said-Mohammed et al. 2015**[6] | Systematic review (1970-2013) | South Africa | 50 studies (under 6 years) | NCHS reference, from 1993 to 2003 the prevalence of stunting increased by 2.9 % (z-test, $p < 0.05$). WHO standard, the prevalence of stunting decreased by 5.9 % between 1999 and 2013 (z-test, $p < 0.001$). However, the 2008 National Income Dynamic Study (NIDS) showed an increase of 6.8 % from the 2005 National Food Consumption Survey (z-test, $p < 0.001$). |
| **Gray S et al. 2010**[7] | Longitudinal study (1998-2004) | Uganda | 123 | Noticeable declines in weight velocity occurred in the fourth month and after the sixth month. Weight gain was static after the second year, when upward of 40% of children were clinically underweight. |
| **Kalanda BF et al. 2005**[8] | Longitudinal study | Malawi | (0-1 y) | Low birthweight infants were shorter and lighter throughout infancy than either normal birthweight or international reference values.<br><br>At 12 months, placental or peripheral malaria at delivery (adjusted odds 1.8; 1.0, 3.1), number of infant illness episodes (AOR = 2.1; 1.2, 3.6) and maternal illiteracy (AOR = 2.7; 1.5, 4.9) were independently associated with low weight for age.<br><br>Maternal short stature (AOR = 1.8; 1.1. 3.2), male sex (AOR = 2.4; 1.4, 4.1), number of infant illness episodes (AOR = 2.6; 1.5, 4.4), and birth in the rainy season (2.1; 1.2, |

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| | | | | 3.7) were independently associated with stunting.<br><br>Placental or peripheral malaria at delivery (AOR = 2.2; 1.1, 4.4) and number of illness episodes (AOR = 2.2; 1.1, 4.5) were independently associated with thinness. |
| **Hauspie RC et al 1989**[9] | Longitudinal study | Democratic Republic of Congo | 4030<br><br>(0-4 y) | Growth weight velocity slows down below average in the rainy seasons. |

## Table 3: Summary of randomised trials of nutrition interventions in The Gambia aimed at improving growth

| Study | Study design | Country | N<br><br>(mother/ infant/children or mother-infant pairs) | Main findings |
|---|---|---|---|---|
| **Johnson et al. 2016**[10] | RCT | The Gambia | 620 | Despite evidence of between-arm differences in some fetal biometry, z-scores at birth were not greater in the intervention arms than the FeFol arm (e.g., birth weight z-scores: FeFol -0.71, MMN -0.63, PE -0.64, PE + MMN -0.62; group-wise p = .796). In regression analyses, intervention associations with birth weight and head circumference were modified by maternal weight gain between booking and 30 weeks gestation (e.g., PE + MMN associations with birth weight were +0.462 z-scores (95% CI [0.097, 0.826]) in the highest quartile of weight gain but -0.099 z-scores (-0.459, 0.260) in the lowest). |
| **Goldberg et al. 2013**[11] | RCT | The Gambia | 525 | No significant effect of calcium supplementation on infant growth.<br><br>(Not designed with birth weight as an outcome therefore, it wasn't powered to look at birthweight.) |
| **van de Merwe et al. 2013**[12] | RCT | The Gambia | 172 | PUFA supplementation resulted in a significant increase in plasma n-3 LC-PUFA concentrations (P < 0.001 for both DHA and EPA) and mid upper arm circumference (MUAC) (effect size: 0.31 z scores; 95% CI: 0.06, 0.56; P = 0.017) at 9 mo of age. At 12 mo, MUAC remained greater in the intervention group, and we observed |

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| | | | | significant increases in skinfold thicknesses (P ≤ 0.022 for all). No other significant differences between treatment groups were detected for growth or LMRs at 9 mo or for secondary outcomes. |
| **Unger S [13] 2013 (Thesis)** | RCT | The Gambia | 1101 | Multiple micronutrient supplementation was associated with a small increase in height-for-age z-scores 24wk after recruitment (effect size for MMN groups combined: 0·084 SD/24wk, 95%CI: 0·005, 0·168; p=0·037; equivalent to 2-5mm depending on age). |
| **Williams et al. 2007[14]** | RCT | The Gambia | 93 | Gambian infants showed a seasonal deterioration in growth and persistently elevated acute phase protein concentrations and intestinal permeability. Oral supplementation with glutamine did not improve growth (x +/- SE: weight gain, 60 +/- 19 and 69 +/- 20 g/mo; length gain, 1.01 +/- 0.05 and 0.95 +/- 0.03 cm/mo) or intestinal permeability [lactulose:mannitol ratio: 0.29 (95% CI: 0.23, 0.35) and 0.26 (95% CI: 0.21, 0.32)] in the glutamine and placebo groups, respectively. |
| **Darboe et al. 2007[15]** | RCT | The Gambia | 197 | Apart from a transient diff erence in length between the treatment groups at 6 months (in favour of WHO dose of Vitamin A), there was no detectable effect of the supplementation regimen on growth. |
| **Jarjou et al. 2006[16]** | RCT | The Gambia | 125 | No significant differences were detected between the groups in breast-milk calcium concentration, infant birth weight, or growth or bone mineral status during the first year of life. |
| **Krähenbühl et al. 1998[17]** | RCT | The Gambia | 90 | Neither the high fat nor the high carbohydrate supplement had an effect on weight or height gain. The high fat supplement did slightly increase adipose tissue mass. |
| **Ceesay et al. 1997[18]** | RCT | The Gambia | 2047 | Maternal weight gain increased by 201 g (P < 0.001) in the hungry season, by 94 g (P < 0.01) in the harvest season (November to May), and by 136 g (P < 0.001) over the whole year. The odds ratio for low birthweight babies in supplemented women was 0.61 (95% CI 0.47 to 0.79, P < 0.001). Head circumference was significantly increased (P < 0.01), but by only 3.1 mm. Birth length and duration of gestation were not affected. |
| **Hoare S et al. 1996[19]** | RT | The Gambia | 40 | With a 50% increase in energy intake and a 100% increase in protein intake there was a |

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| | | | | rapid and highly significant (P < 0.001) gain in weight within a fortnight whether the supplement was given immediately or 2 weeks after presentation. Rates of weight increase were similar whether supplementation was provided early or late, but over the full 28 d (of intervention and non-intervention) children who received late supplementation had greater overall weight gain (P < 0.02) than those supplemented early. |
| **Bates et al. 1993[20]** | RCT | The Gambia | 110 | Body weights and arm circumferences showed a linear increase, plus a seasonal effect (rainy season faltering). For body weight there was no significant overall effect of the supplement. For arm circumference, a very small (2%) but significant (P < 0.01) difference favoured the supplemented group. |
| **Prentice AM et al. 1987[21]** | RCT | The Gambia | 379 | Supplementation was ineffective during the dry season but highly effective during the wet season: +225 +or- 56 grams, p=0.001 (unadjusted) or +200 +or- 53 grams, p=0.001 (adjusted for sex, season, and parity) by between-child multiple regression analysis; +231 +or- 65 grams, p=0.001 by within-mother analysis. The proportion of babies of low birthweight (2501 grams) decreased from 23.7 to 7.5%, p=0.002. |

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