

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Hawkesworth, S; Prentice, AM; Fulford, AJ; Moore, SE (2008) Maternal protein-energy supplementation does not affect adolescent blood pressure in The Gambia. *International journal of epidemiology*, 38 (1). pp. 119-27. ISSN 0300-5771 DOI: 10.1093/ije/dyn156

Downloaded from: <http://researchonline.lshtm.ac.uk/7381/>

DOI: [10.1093/ije/dyn156](https://doi.org/10.1093/ije/dyn156)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

Maternal protein-energy supplementation does not affect adolescent blood pressure in The Gambia

Sophie Hawkesworth,^{1*} Andrew M Prentice,^{1,2} Anthony JC Fulford^{1,2} and Sophie E Moore²

Accepted 7 July 2008

Background Birthweight, and by inference maternal nutrition during pregnancy, is thought to be an important determinant of offspring blood pressure but the evidence base for this in humans is lacking data from randomized controlled trials.

Methods The offspring from a maternal prenatal protein-energy supplementation trial were enrolled into a follow-up study of chronic disease risk factors including blood pressure. Subjects were 11–17 years of age and blood pressure was measured in triplicate using an automated monitor (Omron 705IT). One-thousand two-hundred sixty seven individuals (71% of potential participants) were included in the analysis.

Results There was no difference in blood pressure between those whose mothers had consumed protein-energy biscuits during pregnancy and those whose mothers had consumed the same supplement post-partum. For systolic blood pressure the intention-to-treat regression coefficient was 0.46 (95% CI: –1.12, 2.04). Mean systolic blood pressure for control children was 110.2 (SD ± 9.3) mmHg and for intervention children was 110.8 (SD ± 8.8) mmHg. Mean diastolic blood pressure for control children was 64.7 (SD ± 7.7) mmHg and for intervention children was 64.6 (SD ± 7.6) mmHg.

Conclusions We have found no association between maternal prenatal protein-energy supplementation and offspring blood pressure in adolescence amongst rural Gambians. We found some evidence to suggest that offspring body composition may interact with the effect of maternal supplementation on blood pressure.

Keywords Blood pressure, maternal supplementation, The Gambia, DOHaD

¹ MRC International Nutrition Group, London School of Hygiene and Tropical Medicine, London, UK.

² MRC Keneba, MRC Laboratories, Fajara, The Gambia.

* Corresponding author: MRC International Nutrition Group, Nutrition and Public Health Intervention Research Unit, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.
E-mail: sophie.hawkesworth@lshtm.ac.uk

Introduction

The inverse association between birth weight and blood pressure in later life, first demonstrated in the 1980s,¹ has been replicated many times. A number of reviews of the literature have been conducted;^{2,3} one comprising over 444 000 subjects and covering the years 1996–2000, concluded that a 1-kg increase in birth weight was associated with approximately

2 mmHg decrease in systolic blood pressure.³ More recent studies have also reported a modest inverse association between birth weight and systolic blood pressure.⁴ Although the evidence base has been criticized for publication bias and inappropriate statistical methods,⁵ the concept that susceptibility to raised blood pressure can be traced back to development in early life remains firmly on the research agenda.

Birth weight in this context is used as a proxy measure of fetal nutrition and more direct measures are desirable. Studies of the maternal diet as an exposure are scarce however, partly due to the inherent difficulty of collecting accurate dietary data; the studies that are available provide an inconsistent picture. In Filipino adolescent boys, a maternal diet low in percentage energy from protein was associated with higher blood pressure at 16 years of age.⁶ A recent publication from the Avon Longitudinal Study of Parents and Children (ALSPAC) however, showed no association between diet in pregnancy and offspring blood pressure at 7.5 years of age.⁷ In Guatemala, a balanced protein-energy supplement provided during pregnancy and in early life was also unrelated to blood pressure in young adulthood.⁸

Exposure to the severe food shortages of the Dutch Hunger Winter of 1944 is often used as a pseudo-experiment with which to investigate the importance of maternal undernutrition in the development of chronic disease. Data from different Dutch Hunger Winter cohorts has been inconsistent; one showing no association with blood pressure at 50 years,⁹ whilst another reported that famine exposure during gestation was associated with higher blood pressure and a higher rate of hypertension at 59 years of age.¹⁰

In contrast to human studies, there is a wealth of animal experimental data in this field. Global food restriction, either during part or all of pregnancy, has been associated with raised blood pressure in both sheep and rat offspring.^{11,12} In pregnant rats, the extensively studied low-protein diet has consistently been related to raised offspring blood pressure, despite a normal postnatal diet.¹³

Applying an experimental design to human studies may help to clarify some of the controversy in this area. We therefore present data on blood pressure amongst adolescents whose undernourished rural Gambian mothers took part in a randomized controlled trial of prenatal protein-energy supplementation that significantly increased birth weight.

Methods

The present follow-up study took place from November 2005 to August 2006 in The Gambia, West Africa. Subjects were the offspring of a maternal protein-energy supplementation trial, conducted previously in the region and described briefly later.

Original trial

Between 1989 and 1994, pregnant women in the rural West Kiang region of The Gambia took part in a food supplementation trial to improve birth weight.¹⁴ Using a cluster design with 28 villages, all pregnant women were randomized to receive two protein-energy biscuits a day, either from 20 weeks gestation until delivery (intervention villages) or for 20 weeks post-partum (control villages). The two biscuits provided a maximum daily intake of 4250 kJ energy, 22 g protein, 56 g fat, 47 mg calcium and 1.8 mg iron and were produced from local ingredients. Birth weight was the primary outcome and was measured using a portable spring balance and tared sling (CMS Weighing Equipment, London). There were 2047 live singleton births during the 5 years of the trial and the intervention was found to improve both birth weight (+136 g over the whole year and +201 g when analysed over hungry season months) and neonatal mortality.¹⁴

Present study

At the time of follow-up, the offspring from this trial were 11–17 years of age. Data were missing for 44 children (23 interventions and 21 controls), thus reducing the potential sample size for follow-up to 2003. Children were invited to take part if they were still resident in West Kiang or if they had moved to urban/peri-urban areas at the coast, provided they were within 1-h drive from the Medical Research Council (MRC) laboratories. Full informed consent was obtained from the parents or guardians of the children and community support was sought through meetings with village elders and school head teachers. Scientific approval for the study was granted by MRC The Gambia Scientific Coordinating Committee (SCC) and ethical permission was granted by the joint Gambian Government and MRC Ethics Committee as well as the London School of Hygiene and Tropical Medicine Ethics Committee.

Measurements were conducted in the subject's village of residence as far as this was possible, to minimize disruption to their day. All fieldworkers were fully trained and were unaware of which treatment group the child's mother had belonged to. Blood pressure was measured in triplicate using the automated Omron 705IT device (Omron, UK) and following the manufacturer's instructions. In an effort to improve the accuracy of the readings, fieldworkers were asked to continue taking measurements until three were within 5 mmHg of each other.¹⁵ Children with unusually high blood pressure readings, as defined by the United States National Heart, Lung and Blood Institute guidelines,¹⁶ were seen again on a different day and referred to a physician if readings remained high. If the blood pressure readings on the second visit were within the normal range these new values were entered into the database and used in the analysis.

Height, weight, mid-upper arm circumference (MUAC) and triceps skinfold thickness were measured by a single fieldworker in the majority (99%) of cases to minimize observer bias. Standard techniques were used for each measurement. Weight was measured to the nearest 0.1 kg using daily calibrated, digital scales (Tanita Corporation, Japan). Height was measured using a daily calibrated stadiometer (Leicester height measure, Seca 214, UK) to the nearest 0.1 cm and body mass index (BMI) was defined as $\text{weight}(\text{kg})/\text{height}(\text{m})^2$. Body composition was further assessed by bioelectrical impedance analysis using the Tanita BC-418MA (Tanita Corporation, Japan) segmental analyser. We previously generated population-specific equations for this device, to convert impedance measurements into an estimate of % fat-free mass (%FFM) that was more accurate than the Tanita's inbuilt equations in this setting.¹⁷

Our equation:

$$\%FFM = \exp(7.659 + 0.709 * \ln(\text{ht}) - 0.311 * \ln(z) - 0.402 * \ln(\text{wt}) - 0.044 * \ln(\text{triceps}) + 0.024 * \text{sex} + 0.007 * \text{age})$$

where z is impedance (Ω), ht is height (m), wt is weight (kg) and $triceps$ is triceps skinfold thickness (mm).

%FFM was used to calculate % fat mass (%FM = $100 - \%FFM$). It was not possible to create prediction equations for the segmental impedance readings and therefore the Tanita's own results for % trunk fat were used as an indication of central fat distribution.

Statistical analysis

All statistical analysis was conducted using Stata 9 (Stata Corporation, College Station, TX, USA) and all outcome variables were found to be normally distributed. In the original trial, gestational age was assessed by the Parkin score¹⁸ and only children with a gestational age estimated as over 37 weeks have been included in the analysis. Mean blood pressure fell from the first to third measurement although all three readings were highly correlated ($r > 0.94$ for all) and the variance of the residuals for all three blood pressure measurements were very similar. We therefore took the mean of all three measurements as the estimate of systolic and diastolic blood pressure. Pulse pressure was defined as systolic – diastolic pressure, whilst mean arterial pressure (MAP) was defined as $\text{diastolic} + (1/3 \times \text{pulse pressure})$.

Independent t -tests were used to assess any differences in characteristics from the original trial between those recruited and those not recruited into the follow-up. Generalized estimating equations¹⁹ were used to take the cluster design of the original trial into account when investigating the impact of maternal supplementation on offspring blood pressure. Models were adjusted for covariates relating to blood pressure but unrelated to supplementation: age, sex, rural or urban location and season of birth (fitted as Fourier terms²⁰). Models were fitted firstly without

interactions and then looking at any interaction between supplementation and age, sex, location, season of birth or current body composition. In a separate analysis we had found that body composition in adolescence was unrelated to maternal supplementation (Hawkesworth *et al.*, unpublished). We fitted the body composition variables (BMI, % body fat and % trunk fat) as quartiles to look at any interaction with supplementation on blood pressure; using a multi-level regression model fitted with the maximum likelihood method. Interaction terms were fitted separately and likelihood ratio tests were used to assess any improvements in the models once the interaction had been added.

Data on the number of biscuits consumed was available for women in the intervention arm and this was used to define two groups of women: those eating less than the median number of biscuits and those eating more. A per-protocol analysis was conducted utilising generalized estimating equations to assess the association between biscuit group (control, low, high) and offspring blood pressure.

A further analysis was conducted to investigate the effect of season of birth on blood pressure in adolescence. Linear regression models were fitted with factors relating to current blood pressure: age, sex, % body fat and rural or urban location. This model was then compared, using a likelihood ratio test, to one also containing seasonality of birth fitted as Fourier terms (sin, cos, sin2 and cos2).²⁰

Results

One-thousand three-hundred seventeen children were recruited into the follow-up study, representing 72% of children who were still alive. A modified version of the CONSORT²¹ diagram is shown in Figure 1 and demonstrates that loss-to-follow-up rates were very similar between the intervention and control arms. Table 1 depicts characteristics from the original trial, compared between those who were recruited into the follow-up and those who were not. Children recruited into the follow-up were on average almost 3 months younger than those not recruited; there were no other differences.

Characteristics of the 1267 subjects included in this analysis are shown in Table 2. Excluded individuals (from the 1317 recruited) were 46 preterm subjects, three individuals with implausible blood pressure readings and one with ambiguity about their treatment allocation. Mean systolic blood pressure for boys was 109.9 (SD ± 9.2) mmHg and for girls was 111.1 (SD ± 8.8) mmHg. Mean diastolic blood pressure for boys was 63.9 (SD ± 8.0) mmHg and for girls it was 65.5 (SD ± 7.2) mmHg.

Intention-to-treat analysis

There was no effect of prenatal compared to postnatal maternal protein-energy supplementation on either

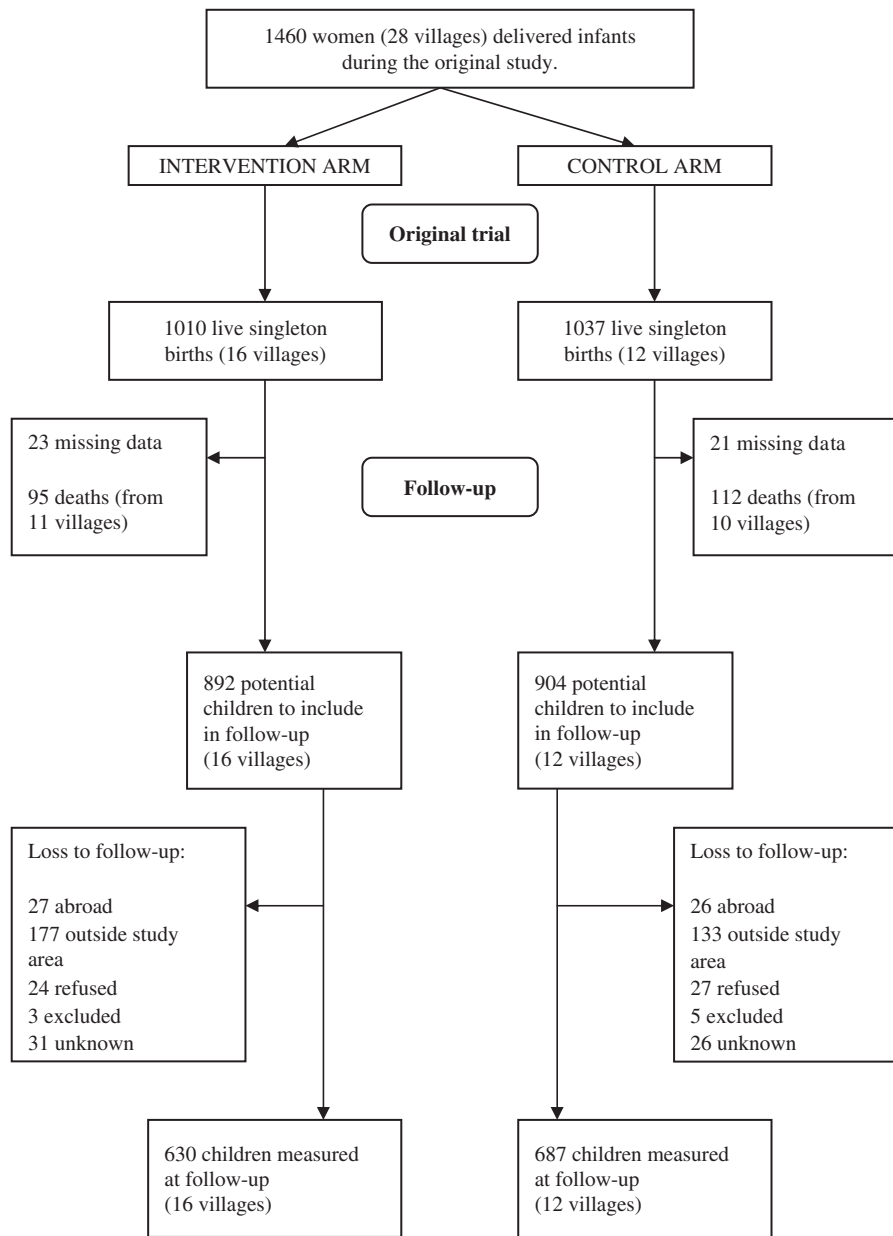


Figure 1 Flow diagram displaying subjects recruited into the follow-up study from the original trial

offspring systolic blood pressure, diastolic blood pressure, pulse pressure or MAP in adolescence (Table 3).

There were no interactions between treatment group and age, sex, location (rural or urban) or season of birth for any of the blood pressure outcomes (data not shown). The effect of supplementation on blood pressure was not modified by BMI but was affected by both % body fat and % trunk fat. For quartiles of % body fat an interaction was present for systolic (LR test χ^2 : 18.77; P -value: 0.002), diastolic (LR test χ^2 : 12.72; P -value: 0.026) and MAP (LR test χ^2 : 16.34; P -value: 0.006) but not for pulse pressure (LR test χ^2 : 10.31; P -value: 0.067). There was a

similar pattern of interactions with supplementation and quartiles of % trunk fat, these were present for systolic (LR test χ^2 : 13.22; P -value: 0.021), diastolic (LR test χ^2 : 17.43; P -value: 0.004) and MAP (LR test χ^2 : 17.44; P -value: 0.004) but not for pulse pressure (LR test χ^2 : 7.40; P -value: 0.193). Figure 2 demonstrates the interaction of % body fat and the effect of the intervention on systolic blood pressure. Amongst individuals who were relatively lean at follow-up, prenatal supplementation was associated with raised systolic blood pressure. The pattern of the interaction was similar for both diastolic and MAP (data not shown).

Table 1 The difference in trial characteristics between those recruited and those not-recruited into the follow-up study

| | Not recruited but with data available ^a | | Recruited into follow-up | | P-value ^b |
|---------------------------|----------------------------------------------------|-------------------------|--------------------------|-------------------------|----------------------|
| | N | Mean (SD) or percentage | N | Mean (SD) or percentage | |
| Age at start of follow-up | 686 | 14.0 (1.5) | 1317 | 13.8 (1.5) | 0.001 |
| % male | 686 | 49.3 | 1317 | 52.1 | 0.231 |
| Birth weight (g) | 686 | 2921.2 (414.8) | 1317 | 2895.9 (436.2) | 0.210 |
| Birth length (cm) | 575 | 49.4 (2.1) | 1179 | 49.4 (2.3) | 0.720 |
| Maternal weight (kg) | 685 | 53.2 (7.1) | 1315 | 53.0 (7.0) | 0.518 |
| Maternal height (m) | 524 | 1.6 (0.1) | 1060 | 1.6 (0.1) | 0.212 |
| % term infants | 568 | 97.4 | 1168 | 96.1 | 0.168 |
| % mothers with parity 1 | 637 | 11.8 | 1257 | 12.3 | 0.763 |

^aData was missing on 44 children from the original study.

^bP-value refers to *t*-tests for continuous data or chi-squared for categorical.

Table 2 Descriptive data (means and SD in parentheses) for the offspring of the protein-energy supplementation trial, enrolled into the follow-up

| | Control | | Intervention | |
|--------------------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| | Males (<i>n</i> = 338) | Females (<i>n</i> = 321) | Males (<i>n</i> = 321) | Females (<i>n</i> = 287) |
| Birth weight (g) | 2923 (425) | 2822 (402) | 3011 (439) | 2924 (374) |
| Birth length (cm) | 49.7 (2.2) ^{#35} | 49.1 (2.1) ^{#41} | 49.8 (2.1) ^{#24} | 49.2 (2.1) ^{#37} |
| Age (y) | 14.1 (1.5) | 14.1 (1.5) | 14.1 (1.5) | 14.2 (1.5) |
| Systolic BP (mmHg) | 109.4 (9.5) | 111.0 (8.9) | 110.5 (8.9) | 111.1 (8.7) |
| Diastolic BP (mmHg) | 63.7 (8.1) | 65.8 (7.0) | 64.2 (7.8) | 65.2 (7.4) |
| Pulse pressure (mmHg) ^a | 45.7 (7.4) | 45.2 (6.5) | 46.3 (7.0) | 45.9 (6.5) |
| Mean arterial pressure (mmHg) ^b | 78.9 (7.9) | 80.9 (7.1) | 79.6 (7.5) | 80.5 (7.2) |
| Height (cm) | 150.1 (11.0) | 152.8 (9.4) | 150.7 (10.5) | 151.6 (9.2) |
| Weight (kg) | 36.8 (9.0) | 41.2 (9.7) | 37.5 (8.0) | 41.3 (10.5) |
| HAZ ^c | -1.5 (1.1) | -0.8 (1.1) | -1.5 (1.1) | -1.0 (1.0) |
| BMI z-score | -1.6 (1.1) | -1.1 (1.2) | -1.4 (1.0) | -1.0 (1.2) |
| Body fat (%) | 12.6 (3.0) ^{#1} | 19.3 (4.3) | 12.6 (2.8) ^{#6} | 19.5 (4.7) ^{#2} |
| Trunk fat (%) ^d | 12.0 (3.0) ^{#1} | 14.8 (4.6) ^{#1} | 11.9 (2.7) ^{#6} | 15.2 (5.0) ^{#3} |

^aCalculated as systolic—diastolic blood pressure.

^bCalculated as diastolic + (1/3 × pulse pressure).

^cHeight for age z-score estimated from UK 1990 reference data³¹.

^dEstimated by the Tanita inbuilt equations, not from population-specific equations.

[#]Incomplete data: ^{#1} = *n* - 1, ^{#2} = *n* - 2, ^{#3} = *n* - 3 and so on.

Per-protocol analysis

For most of the blood pressure outcomes there remained no association with the intervention when investigated with a per-protocol analysis. There was a suggestion however, that children whose mothers had consumed less than the median number of biscuits during the trial had a higher pulse pressure compared to control children. The difference in pulse pressure between the low-biscuit category and control group was 0.99 mmHg (95% CI: 0.31, 1.67, *P* = 0.004).

Birth weight and later blood pressure

There was no association between birth weight and blood pressure (adjusted for age, sex and season

of birth) in this cohort (regression coefficient = -0.001, 95% CI: -0.002, 0.001, *P* = 0.39) even after adjustment for current body size (regression coefficient = -0.001, 95% CI: -0.002, 0.000, *P* = 0.06). We observed the same lack of association if we adjusted birth weight for gestational age (data not shown).

Season of birth and later blood pressure

Season of birth was found to be associated with systolic blood pressure in adolescence (LR test χ^2 : 7.89, *P*-value: 0.019). Individuals who had been born in July had lower systolic blood pressure than individuals born during the remainder of the year (Figure 3) after adjustment for age, sex, location and

Table 3 Effect of maternal supplementation on offspring blood pressure; intention-to-treat analysis

| | Unadjusted regression coefficient ^a (95% CI) | P-value | Adjusted regression coefficient ^b (95% CI) | P-value |
|------------------------------------|---------------------------------------------------------|---------|-------------------------------------------------------|---------|
| Systolic (mmHg) | 0.46 (−1.12, 2.04) | 0.570 | 0.47 (−1.14, 2.08) | 0.566 |
| Diastolic (mmHg) | 0.09 (−1.31, 1.13) | 0.890 | −0.01 (−1.24, 1.23) | 0.994 |
| Pulse pressure (mmHg) ^c | 0.69 (−0.03, 1.41) | 0.060 | 0.64 (−0.06, 1.33) | 0.072 |
| MAP (mmHg) ^d | 0.10 (−1.20, 1.40) | 0.881 | 0.16 (−1.16, 1.48) | 0.814 |

^aCoefficient from generalised estimating equations (gee) with original village of residence (cluster) modelled as a random effect.

^bCoefficient from generalised estimating equations (gee) modelled with original village cluster and adjusted for age, sex, rural or urban location and season of birth.

^cCalculated as systolic—diastolic blood pressure.

^dMean arterial pressure calculated as diastolic + (1/3 × pulse pressure).

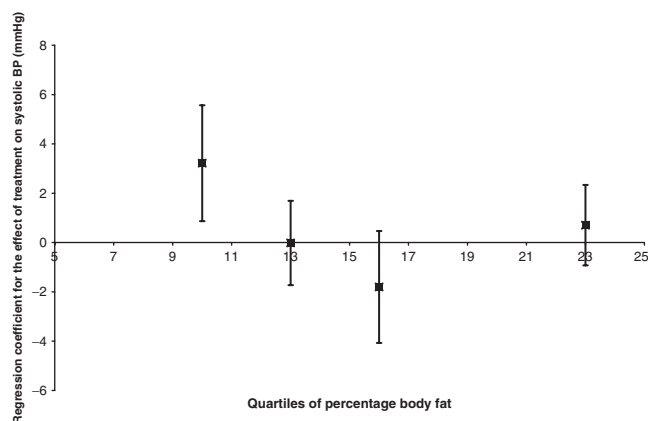


Figure 2 Interaction between current percentage body fat and the effect of prenatal supplementation on systolic blood pressure in adolescence. Regression coefficient (error bars = $\pm 2 \times \text{SE}$) for the effect of supplementation on systolic blood pressure is displayed for each quartile of percentage body fat separately

current body fat percentage. This pattern was not repeated for the other blood pressure outcomes: season of birth was unrelated to diastolic blood pressure, pulse pressure and MAP (data not shown).

Discussion

Amongst Gambian adolescents aged 11–17 years there was no difference in blood pressure between those whose mothers had received protein-energy dense biscuits during pregnancy and those who received the same biscuits during lactation. This is one of the first studies to investigate the impact of the maternal diet on the programming of disease risk from the standpoint of a randomized controlled trial. The sample size for the study was large and we have reported results with very tight confidence intervals.

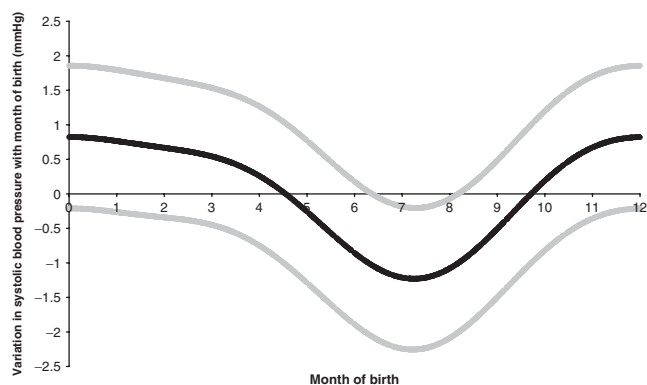


Figure 3 Association between month of birth and systolic blood pressure in adolescence. Middle line represents the variation in systolic blood pressure with month of birth. Upper and lower lines represent 95% confidence interval

Although we found no evidence of an overall association between maternal supplementation and offspring blood pressure, we observed an interaction with current body composition. Amongst individuals who were in the lowest quartile for % body fat, and therefore relatively lean at follow-up, the intervention was associated with raised systolic blood pressure. This interaction may reflect the concept, described by Gluckman and Hanson, that it is the mismatch between fetal and later exposures that confers the greatest risk.²² The fetuses of women taking protein-energy supplements may have received developmental cues from their fetal environment suggesting more favourable conditions than were experienced postnatally, for individuals who remained particularly lean. If replicated elsewhere, this type of interaction would highlight the importance of nutrition interventions throughout the life course and of fully understanding the implications of pregnancy interventions for health in later life.

Our per-protocol analysis suggested that women who consumed fewer than the median number of biscuits during pregnancy had children with higher pulse

pressure compared with control children. However, this finding was not reflected in women who consumed *more* than the median number of biscuits. Thus we can assume that this is a spurious finding or one that demonstrates a major flaw of this type of analysis: namely that randomization is lost.

The main weakness of the current study is that the control group received the protein-energy supplement during lactation. This was provided for ethical reasons during the original trial and our follow-up could therefore be interpreted as comparing the effects of improved nutrition during pregnancy with improved nutrition during lactation. However, data from a trial previously conducted in this same region found little evidence that providing protein-energy and multi-vitamin supplements to lactating women affects their breast milk quantity or quality^{23,24} and data from elsewhere supports this view.²⁵ Furthermore, the lack of an association between birth weight and later blood pressure argues against the dilution of an effect of the pregnancy intervention; at least one mediated via size.

Another weakness is the difficulty of measuring blood pressure, particularly in children.¹⁵ We attempted to minimize this source of bias by using a validated (albeit in adults) automated device, a standard protocol recommended by the American Heart Association¹⁵ and the average of three readings. We therefore feel that we have produced a relatively accurate estimate of blood pressure in a field which often has to rely on data obtained from hospital and military records.⁴

The overall lack of association between pregnancy supplementation and offspring blood pressure reflects the findings of a Guatemalan community-based intervention where a balanced protein-energy supplement provided during pregnancy and in early life was not associated with blood pressure at 20–29 years of age.⁸ The individuals in our study were undergoing puberty at the time of follow-up which could potentially obscure a relationship between early life exposures and blood pressure: the inverse association with birth weight is often much weaker at this age.³ In contrast to our findings a recent follow-up study of Nepalese children whose mother's had received multiple micronutrient supplements during pregnancy reported a reduction in systolic blood pressure at 2.5 years of age.²⁶ One explanation is that multiple micronutrients are having an impact where protein-energy supplements are not. Alternatively, it may be that maternal supplementation produces early life differences, which are not maintained as the children grow and develop.

The lack of association observed in our study may reflect that the maternal diet is only one component of fetal nutrition, which also comprises placental sufficiency and maternal nutrient stores.¹ Birth weight was increased in the intervention arm of the original trial¹⁴ however, which suggests that the maternal diet did influence development to some extent. An alternative explanation may relate to the

timing of supplementation in the life-course. Data is beginning to emerge on the importance of inter-generational undernutrition, suggesting that it is the grandmother's diet during pregnancy that impacts on offspring development.²⁷

Independently of any intervention influence, season of birth was associated with systolic blood pressure in this group of adolescents. Systolic blood pressure was lowest for individuals who were born in July, and highest for individuals born in December and January. In rural areas of The Gambia such as this one there is a marked seasonality of food availability, with a more affluent period running from January to June; the so-called 'harvest season'.¹⁴ The prevalence of small for gestational age babies experiences a nadir in June and is thought to reflect more favourable conditions during gestation.²⁸ The seasonality of birth in relation to blood pressure may also reflect this more favourable gestation. It may be that individuals born at the middle of the year, after a gestation throughout the harvest season, exhibit body systems that have developed to their full potential and thus have lower blood pressure. In a previous study however, we failed to show an association between being born in the hungry and blood pressure in young adulthood.²⁹ In the current study the association was not present for diastolic blood pressure and we are therefore wary of over interpreting these findings.

In conclusion, we have found no evidence in The Gambia that maternal prenatal protein-energy supplementation is associated with offspring blood pressure in adolescence. This is in contrast to animal studies demonstrating that nutrient restriction during pregnancy is associated with raised blood pressure in the offspring.³⁰ In a field of research dominated by observational data from affluent populations,⁴ our findings represent an important addition to the knowledge base.

Acknowledgements

This study was supported by the European Union Sixth Framework Programme for Research and Technical Development of the European Union Community 'Early Nutrition Programming Project' (FOOD-CT-2005-007036) and by the UK Medical Research Council. We would like to acknowledge the mothers who participated in the original trial and the children who took part in this study. We are extremely grateful to Marijke Prins and Meaghan Kall for their help with running the study. We would particularly like to thank Yankuba Sawo for his help with setting up the study and Kabiru Ceesay, Morikebba Sanyang, Kalilu Sanneh, Saul Jarjou and Sheriff Kolley for their enthusiastic and tireless help when collecting data in the field. We are indebted to all of the staff at MRC Keneba for their help in assisting the fieldwork for this study.

KEY MESSAGES

- The prenatal environment is thought to be an important determinant of later disease but lacks data from randomized trials.
- Here we present a large follow-up study of adolescents in The Gambia whose mothers took part in a trial of protein-energy supplementation during pregnancy.
- In the original trial, supplementation in pregnancy resulted in a mean increase in birth weight of 136 g.
- We found no impact of improved maternal nutrition during pregnancy on offspring blood pressure at adolescence.

References

- ¹ Barker DJP. *Mothers, Babies and Health in Later Life*. 2nd edn. Edinburgh: Churchill Livingstone, 1998.
- ² Law CM, Shiell AW. Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertens* 1996;**14**:935–41.
- ³ Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. *J Hypertens* 2000;**18**:815–31.
- ⁴ Adair L, Dahly D. Developmental determinants of blood pressure in adults. *Annu Rev Nutr* 2005;**25**:407–34.
- ⁵ Huxley R, Neil A, Collins R. Unravelling the fetal origins hypothesis: is there really an inverse association between birthweight and subsequent blood pressure? *Lancet* 2002;**360**:659–65.
- ⁶ Adair LS, Kuzawa CW, Borja J. Maternal energy stores and diet composition during pregnancy program adolescent blood pressure. *Circulation* 2001;**104**:1034–39.
- ⁷ Leary SD, Ness AR, Emmett PM, Davey Smith G, Headley JE. Maternal diet in pregnancy and offspring blood pressure. *Arch Dis Child* 2005;**90**:492–93.
- ⁸ Webb AL, Conlisk AJ, Barnhart HX, Martorell R, Grajeda R, Stein AD. Maternal and childhood nutrition and later blood pressure levels in young Guatemalan adults. *Int J Epidemiol* 2005;**34**:898–904.
- ⁹ Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the Dutch famine and disease in later life: an overview. *Reprod Toxicol* 2005;**20**:345–52.
- ¹⁰ Stein AD, Zybert PA, van der Pal-de Bruin K, Lumey LH. Exposure to famine during gestation, size at birth, and blood pressure at age 59 y: evidence from the Dutch famine. *Eur J Epidemiol* 2006;**21**:759–65.
- ¹¹ Barker DJ, Bagby SP. Developmental antecedents of cardiovascular disease: a historical perspective. *J Am Soc Nephrol* 2005;**16**:2537–44.
- ¹² Vehaskari VM, Woods LL. Prenatal programming of hypertension: lessons from experimental models. *J Am Soc Nephrol* 2005;**16**:2545–56.
- ¹³ Langley-Evans SC, Welham SJ, Jackson AA. Fetal exposure to a maternal low protein diet impairs nephrogenesis and promotes hypertension in the rat. *Life Sci* 1999;**64**:965–74.
- ¹⁴ Ceesay SM, Prentice AM, Cole TJ *et al*. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *BMJ* 1997;**315**:786–90.
- ¹⁵ Pickering TG, Hall JE, Appel LJ *et al*. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. *Circulation* 2005;**111**:697–716.
- ¹⁶ Update on the 1987. Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. *Pediatrics* 1996;**98**:649–58.
- ¹⁷ Prins M, Hawkesworth S, Wright A *et al*. Use of bioelectrical impedance analysis to assess body composition in rural Gambian children. *Eur J Clin Nutr* 2007;doi:10.1038/sj.ejcn.1602830.
- ¹⁸ Parkin JM, Hey EN, Clowes JS. Rapid assessment of gestational age at birth. *Arch Dis Child* 1976;**51**:259–63.
- ¹⁹ Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;**73**:13–22.
- ²⁰ Fulford AJ, Rayco-Solon P, Prentice AM. Statistical modelling of the seasonality of preterm delivery and intrauterine growth restriction in rural Gambia. *Paediatr Perinat Epidemiol* 2006;**20**:251–59.
- ²¹ Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. *Br Med J* 2004;**328**:702–8.
- ²² Gluckman PD, Hanson MA. The developmental origins of the metabolic syndrome. *Trends Endocrinol Metab* 2004;**15**:183–87.
- ²³ Prentice AM, Roberts SB, Prentice A *et al*. Dietary supplementation of lactating Gambian women. I. Effect on breast-milk volume and quality. *Hum Nutr Clin Nutr* 1983;**37**:53–64.
- ²⁴ Prentice AM, Lunn PG, Watkinson M, Whitehead RG. Dietary supplementation of lactating Gambian women. II. Effect on maternal health, nutritional status and biochemistry. *Hum Nutr Clin Nutr* 1983;**37**:65–74.
- ²⁵ Adair LS, Pollitt E. Outcome of maternal nutritional supplementation: a comprehensive review of the Bacon Chow study. *Am J Clin Nutr* 1985;**41**:948–78.
- ²⁶ Vaidya A, Saville N, Shrestha BP, Costello AM, Manandhar DS, Osrin D. Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal: follow-up of a double-blind randomised controlled trial. *Lancet* 2008;**371**:492–99.

- ²⁷ Kuzawa CW, Quinn EA, Adair LS. Intergenerational predictors of fetal growth rate in generation 3 of the Cebu cohort. Oral presentation, 5th International Congress on Developmental Origins of Health & Disease. *Early Hum Dev* 2007;**83**:S44.
- ²⁸ 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**:134–99.
- ²⁹ 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**:646–53.
- ³⁰ Langley-Evans SC, Langley-Evans AJ, Marchand MC. Nutritional programming of blood pressure and renal morphology. *Arch Physiol Biochem* 2003;**111**:8–16.
- ³¹ Cole TJ. The LMS method for constructing normalized growth standards. *Eur J Clin Nutr* 1990;**44**:45–60.

Commentary: Can improving a mother's diet improve her children's cardiovascular health?

Caroline Fall

Accepted 3 September 2008

Nearly 20 years ago David Barker and colleagues¹ showed a surprising association between low birth-weight and an increased risk of adult hypertension, type 2 diabetes and death from cardiovascular disease. They put forward the controversial hypothesis that exposure to undernutrition in fetal life or infancy increases an individual's vulnerability to these disorders. Under-nutrition, it was suggested, forced the rapidly growing fetus/infant to make physiological adaptations that enabled short-term survival but 'programmed' permanent structural and metabolic changes that caused later disease.^{1,2} Implicit in the hypothesis is that since the mother's nutritional status influences the quality and quantity of nutrients reaching the fetus, improving maternal diets could prevent common chronic diseases in future generations. If true, this could be particularly important for developing countries, where maternal undernutrition is widespread and where diabetes and cardiovascular disease are becoming major problems.

Animal experiments have provided 'proof of principle' that maternal undernutrition can produce these outcomes in the offspring, and that the effects can be prevented by nutritional interventions. For example in rats, maternal protein restriction during pregnancy leads to elevated blood pressure in the offspring, and this is prevented by supplementing the mother's low-protein diet with folic acid.³ Animal studies have demonstrated mechanisms that could mediate

adverse outcomes, including effects of maternal undernutrition on offspring organ structure, endocrine pathways and epigenetic characteristics. In contrast, until recently, debate about the importance of maternal nutrition for *human* health has relied mainly on observational data. Blood pressure has been measured in people whose mothers' nutritional status or diet was recorded, or whose mothers were exposed to famine during pregnancy.⁴ The findings are inconsistent and confusing. While some studies showed higher blood pressure in offspring of women who were thinner, or famine-exposed, or had diets low in protein relative to energy, others showed no associations.⁴

We are now beginning to see the hypothesis tested in intervention studies, by following up the children of undernourished women who took part in nutrition supplementation trials in pregnancy. In this issue, Hawkesworth *et al.*⁵ report a study of blood pressure in Gambian adolescents whose mothers received high-energy biscuits, providing up to 4250 kJ of energy, 22 g of protein and micronutrients daily from 20 weeks gestation, in a cluster randomized trial. Control women received the same supplement during lactation (from 20 weeks post-partum). The intervention certainly influenced fetal nutrition, increasing birth-weight by 136 g, reducing the incidence of low birthweight by 40%, and halving perinatal mortality. However, in a rigorously carried out follow-up study, with high participation rates, the investigators found no difference in blood pressure between children of women in the intervention and control groups. The