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Parental History of Moderate to Severe Infantile Malnutrition is Associated with Cognitive Deficits in their Adult Offspring^{1,2}

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Abstract

Objectives—We compared the IQ and academic achievement of the young adult offspring of parents malnourished in infancy and those of a healthy control group in order to test the hypothesis that the offspring of previously malnourished individuals would show IQ and academic deficits that could be related to reduced parental socioeconomic status.

Methods—We conducted a group comparison study based on a community sample in Barbados (Barbados Nutrition Study). Participants were adult children 16 years of age whose parents had been malnourished during first year of life (N=64; Mean age 19.3 years; 42% male) or whose parents were healthy community controls (N=50; Mean age 19.7 years; 48% male). The primary outcome was estimated IQ (Wechsler Abbreviated Scale of Intelligence); a secondary outcome was academic achievement (Wide Range Achievement Test – Third Edition). Data were analyzed using PROC MIXED with and without adjusting for parental socioeconomic status (Hollingshead Index of Social Position).

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Results—IQ was reduced in the offspring of previously malnourished parents relative to offspring of controls (9.8 point deficit; $p < 0.01$), but this difference was not explained by parental socioeconomic status or parental IQ. The magnitude of the group difference was smaller for basic academic skills and did not meet criteria for statistical significance.

Discussion—The deleterious impact of infant malnutrition on cognitive function may be transmitted to the next generation; however, this intergenerational effect does not appear to be explained by the reduced socioeconomic status or IQ of the parent generation.

Keywords

Malnutrition; Intergenerational; IQ; Socioeconomic status

INTRODUCTION

Malnutrition in infancy and early childhood remains a major public health challenge in many parts of the developing world. In 2014, there were an estimated 667 million children under age 5 in the world. Of these, 159 million (23.8%) experienced growth stunting and 50 million (7.5%) were wasted.¹ Early childhood growth faltering is estimated to cause a total loss of 69.4 million years of educational attainment and an economic cost of \$176.8 billion per birth cohort.²

Because of its impact on brain development, malnutrition in infants carries the risk for lifelong impairment. Early malnutrition has been repeatedly associated with impaired cognition, evident throughout childhood and adolescence,^{3–5} and persisting into adulthood.^{6,7} This cognitive impairment can result in lowered educational attainment and diminished social status.⁸ As these affected adults themselves become parents, the impact of this early nutritional insult may extend beyond the individual who was malnourished.

Socioeconomic status is a powerful predictor of intellectual functioning and academic achievement.⁹ Moreover, neuroimaging studies have demonstrated that poverty is associated with changes in brain morphology that could underlie cognitive effects.¹⁰ Intergenerational effects of parental socioeconomic circumstances on the cognitive functioning of their children have also been documented. The childhood neighborhood environment of the parent, for example, has been linked to cognitive functioning in the next generation¹¹. Thus, the diminished social status of previously malnourished parents could translate to intellectual compromise in their children, even though the children themselves were adequately nourished throughout their development. Such a finding would have major implications in terms of the potential social significance of malnutrition in infants and young children.

Along these lines, a recent study from Jamaica found that the preschool age children of parents whose growth had been stunted showed lower developmental quotients (DQ) than offspring of non-stunted parents.¹² The investigators were not, however, able to document differences between the children of previously stunted and non-stunted parents across a number of environmental factors, including parental intelligence, educational attainment, socioeconomic status or quality of the home environment, nor did these factors account for

the developmental differences in their children. The children of the stunted parents were also shorter, but the children's heights were not related to the developmental differences either.

We examined this question of cognitive functioning in the next generation by assessing the adult offspring of previously malnourished parents and of healthy control parents in the context of the Barbados Nutrition Study (BNS). The BNS is a decades-long and now multi-generational study based on a community sample of children who had normal birth weights but subsequently were hospitalized for moderate to severe malnutrition in the first year of life. Thus, for the affected individuals, the exposure to malnutrition was restricted to the first year of life.

As adults, the affected individuals in the original BNS cohort demonstrated prominent cognitive deficits.⁷ These previously malnourished adults had significantly lower IQ, approximately one standard deviation in magnitude, relative to unaffected peers, after adjusting for the effects of childhood socioeconomic circumstances. In addition, prevalence of IQ in the range of intellectual disability was significantly elevated in the previously malnourished individuals, observed in about a quarter of the sample and approximately nine times more frequently in the previously malnourished than in the control group.

The cognitive impairment, moreover, had consequences for the social outcomes of the BNS study participants. Individuals who had been malnourished in infancy had poorer socioeconomic outcomes relative to those of the control group.⁸ Moreover, the gap in weekly household income between the two groups increased considerably over their life span. The socioeconomic circumstances of both groups improved during the period from childhood to adolescence, but that of the controls had improved to a greater extent. These socioeconomic differences were substantially mediated by their cognitive functioning. Although it is certainly plausible that socioeconomic differences in the households of the malnourished individuals also influenced IQ outcomes, group differences in IQ throughout childhood and adolescence were robust, even after controlling for multiple environmental factors.^{5,13}

In the most recent phase of the BNS, we assessed intellectual functioning in the adult offspring (Generation 2, G2) of the previously malnourished individuals and of the healthy comparison group. We reasoned that the children of the previously malnourished adults would have experienced the effects of their parents' lowered socioeconomic status and hence could themselves have cognitive deficits relative to offspring of the healthy control parents. We thus hypothesized that the offspring of these previously malnourished individuals would show deficits in their IQ and academic achievement relative to offspring of the healthy comparison group and further that this deficit would be related to reduced parental socioeconomic status. We further included parental IQ as a covariate to explore an indicator of more proximal experiential influences.

METHODS

Site

Participants were born in Barbados, an English-speaking Caribbean country. The majority of the population is of African origin (92%) and lower-middle class, with obligatory school attendance to 16 years and a 99% literacy rate. Although Barbados currently has a relatively high standard of living compared with other developing countries,¹⁴ during the era when the BNS sample was born (1967–1972), the infant mortality rate was 46 per 1,000 live births, compared with 11.6 today. Malnutrition was common in Barbados when the participants were born, but is now virtually eliminated due to an improved economy and an island-wide program to eradicate malnutrition.^{15,16}

Design

Adult children (16 years of age, G2) of the Generation 1 (G1) BNS participants were invited to participate in a study of their cognitive, psychiatric, and psychosocial outcomes.

Participants

The G1 parents had been born in Barbados between 1967 and 1972. The previously malnourished parents (MAL) had been hospitalized for moderate to severe malnutrition during the first year of life, and the healthy control parents (CON) were recruited from the same communities and schools. Birth weight exceeded 2500 grams for all participants in both groups. The index children had been admitted to Queen Elizabeth Hospital in their first year of life with grade II or III protein energy malnutrition (marasmus or kwashiorkor) based on the Gomez Scale, which classifies degree of malnutrition on the basis of expected weight for age. These children were subsequently enrolled in a government-supported intervention program that provided health care, growth monitoring, nutrition education, subsidized foods, and regular home visits, and were followed in the program until age 12.

Although the previously malnourished children had achieved complete catchup in their physical growth by adolescence,¹⁷ their cognitive and behavioral development remained adversely affected.⁵ Both the index and control groups had been evaluated as children, adolescents, and young adults on multiple occasions between 1977 and 1991, and again as adults between 2006 and 2010.⁷ As children and adolescents, the previously malnourished group showed deficits in their cognition, attention, and academic performance, as well as increased internalizing symptoms and externalizing behaviors.^{5,7,13,18–20}

Figure 1 shows the derivation of the G2 sample. A detailed description of the derivation of the G1 sample has been previously reported.⁷ From the original 312 participants in the G1 cohort, 249 were eligible for the adult follow-up study. The rest were ineligible because they were deceased, incarcerated or no longer residing on the island. One hundred sixty-eight (67%) of these 249 completed neuropsychological testing. Further recruitment and data collection was constrained by funding limitations. Nevertheless, prior analyses indicated that the G1 participants did not differ from non-participants in terms of gender, age, childhood and adolescent socioeconomic status, or childhood IQ.²¹

The offspring of these G1 individuals were potentially eligible for the present study. Inclusion criteria were age and having a biological parent who had been a participant in the BNS; exclusion criteria included biological conditions with a significant impact on cognition (e.g., Down Syndrome).

A total of 156 G2 individuals were 16 years of age or older and thus eligible for the present study. Of these, 121 were enrolled, of whom 114 were able to be scheduled to complete the testing. The final sample included 64 G2 offspring of 34 G1 parents from the MAL group and 50 G2 offspring of 33 G1 parents from the CON group. These individuals were evaluated between 2013 and 2016.

This study was approved by the Ministry of Health, Barbados. Written informed consent was provided by all participants under the oversight of the Judge Baker Children's Center Human Research Review Committee (Assurance No. FWA 00001811). Participants were compensated for travel and time taken off from work.

Measures

Standardized screening tests of intelligence and academic achievement were administered. These tests are not normed in Barbados, and so U.S. norms were applied. Since the design included a local control group, however, group comparisons can be deemed valid. These tests were previously used successfully to assess the G1 sample.⁷

IQ—Wechsler Abbreviated Scale of Intelligence (WASI)²² – Vocabulary and Matrix Reasoning subtests. This 2-test version can be used to estimate Full Scale IQ. The correlation with the full (4-subtest) WASI is reported to be 0.95 and the correlation with the Wechsler Adult Intelligence Scale-III is 0.92.

Academic Achievement—Wide Range Achievement Test, 3rd Edition (WRAT-III)²³ – Reading, Spelling and Calculation subtests. These are brief screening measures of single word reading, single word spelling, and calculation, however. As such, they can fail to assess significant aspects of academic functioning, such as reading comprehension or mathematical concepts.

Socioeconomic Status—Social position was measured by the Hollingshead Scales,²⁴ which rank social position based on occupation and educational attainment. The Occupation and Education scores yield scores ranging from 1 to 7, with higher scores reflecting lower social status. Items are weighted (Occupation score $\times$ 7, Education score $\times$ 4) and summed to produce an Index of Social Position Score (ISP, possible range of scores 11–77), classified into five categories, with higher scores indicating lower status.

Procedure

Testing was carried out in a single session at the study laboratory in Bridgetown, Barbados by a trained local psychometrician who was blind to group membership in the context of a more detailed neuropsychological assessment, lasting approximately 3 hours. Parental Hollingshead ISP was assessed at the same time.

Statistical Methods

Data were analyzed using SAS statistical software, Version 9.3.²⁵ Group differences in age and parental Hollingshead ISP were evaluated by t-tests; chi-squared tests assessed differences in sex distribution. Nutrition group differences in cognitive outcomes were assessed using PROC MIXED, adjusted for gender, with and without adjusting for Hollingshead ISP and then subsequently adjusting for Hollingshead ISP and also parental IQ. This series of analyses appropriately accounted for the clustering (or correlation) of observations within a family due to the repeated measures arising from multiple offspring from the same parent. Specifically, statistical tests and confidence intervals from these analyses were based on the empirical or so-called “sandwich” estimator of the standard errors; the latter ensures that the positive correlation among measures from offspring of the same family was appropriately adjusted for in the analyses. The significance level was set at $p < 0.05$ and we did not control for experiment-wise error.

RESULTS

Participant Characteristics

Table 1 shows the demographic and anthropometric characteristics of the participants by nutrition group, as well as the characteristics of their G1 parents. The parental ISP score for the CON group was lower (meaning *higher* socioeconomic status). There were no group differences for height, weight, or body mass index for either the parents or their adult offspring. Among the G2 offspring, there were no differences in the proportion who attended preschool or in total years of schooling. Significantly, the majority of the G2 offspring (72% overall) still resided with their parents and only 8% were married, again with no difference between nutrition groups. Thus, the parental ISP can be considered a reasonably valid indicator of the socioeconomic environment of the G2 offspring.

IQ and Achievement

Table 2 shows the unadjusted means, standard deviations, and parameter estimates for effects of malnutrition group on IQ and achievement scores for the G2 adult offspring, with and without adjusting for the G1 ISP score. Mean IQ is also shown for the G1 parent generation, with differences consistent with those reported previously for the larger G1 cohort.⁷ The primary focus of this study, however, was the G2 offspring. They demonstrated a significant effect of nutrition group for Full Scale IQ, with a difference of nearly 10 points (two-thirds of a standard deviation), approaching that exhibited by their parents (12 points). Contrary to our hypothesis, the magnitude of these effects for the G2 offspring was not reduced when adjusted for parental ISP. Nor was it meaningfully reduced when parental IQ was also adjusted for.

The achievement tests were submitted to a parallel set of analyses. Although the mean scores for the G2 CON group were higher than those of the MAL group, the difference was smaller and did not reach statistical significance, with or without adjusting for parental ISP.

DISCUSSION

The primary finding of this study is that adult children of parents who had experienced an episode of moderate to severe malnutrition during the first year of life showed intellectual deficits relative to adult children of parents who had been well-nourished throughout their development. The magnitude of these differences approached that demonstrated by their parents. Moreover, although the previously malnourished parents had lower socioeconomic status and lower IQ as adults than did the healthy control parents, these variables did not account for cognitive outcomes in their adult children. The adult children of previously malnourished parents also achieved lower scores on a screening measure of basic academic skills in their offspring, but the differences were smaller in magnitude and did not reach an acceptable level of statistical significance.

Several other observations are noteworthy. First, for both nutrition groups, the scores of the G2 offspring are consistently higher than those of their parents; and second, whereas adjusting for parental ISP did not reduce the effect sizes for the G2 participants, it did reduce the size of these effects for the parent generation, presumably because those with lower IQ had trended to lower social position.

These findings are consistent with and thus extend those of a Jamaican study of early developmental outcomes in preschool aged children whose parents had experienced growth stunting.¹² Specifically, we demonstrated intergenerational effects of parental malnutrition history on their children's cognition, but we could not link this effect to experiential variables. Our findings indicate, moreover, that these intergenerational effects can persist into adulthood.

Intergenerational effects of childhood malnutrition have been seen in other settings. The grandchildren of a Swedish population that was exposed to a limited food supply between 1915 and 1929 had elevated mortality rates.²⁶ Intergenerational effects were also seen in a trial of protein supplementation during childhood in a nutritionally at-risk Guatemalan cohort, whose offspring showed improved growth.²⁷ In the present study, however, the nutritional insult was confined to the first year of life and neither the parent generation nor the adult children experienced long-term stunting.

The effects demonstrated here could certainly reflect the potential effects of many experiential influences, such as parenting practices or opportunities and support for learning that may not be captured by the socioeconomic status measure and that we did not measure. The Jamaican study cited above, however, assessed preschool age children and collected detailed information on their environmental circumstances.¹² Although they did document group differences between children whose parents had been stunted and had not been stunted, they could not relate these differences to any of these environmental variables.

The differences in IQ in the G2 generation could also, however, reflect a more biological mechanism. Preclinical studies in rat models have documented intergenerational effects of malnutrition; offspring of mothers who had been prenatally malnourished themselves showing adverse effects in terms of both brain and behavior.^{28,29} This finding points to a potential biological mechanism, such as epigenetic changes in response to the nutritional

insult. In humans, nutritional deprivation in the periconceptional period has been associated with epigenetic changes in the offspring^{30,31} that may then persist over the life span.³²

Recently reported epigenetic data from the BNS cohort in fact document a significant increase in DNA methylation changes, with a greater than 40-fold overrepresentation of methyl-CpG changes for imprinted loci in G1 adults who had been malnourished as infants compared to controls.³³ Some of these changes, moreover, could be related to their deficits in IQ and attention. There was also evidence for intergenerational transmission of these epigenetic changes to their offspring, although it was less striking. Moreover, in an animal model, adult rats that had been exposed to malnourishment early in their development exhibited attention deficits on behavioral testing. Analysis of RNA from the prefrontal cortex of these rats revealed that expression of *Ifng*, a gene associated with a hypermethylated differentially methylated region in the G1 previously malnourished participants, was significantly decreased.

The present study also had limitations. First, IQ results from a complex of environmental and genetic influences, and as mentioned, unmeasured variables other than the malnutrition itself, could account to an unknown extent for the observed phenomena. Second, there was considerable sample attrition from the original 312 in the G1 cohort. G1 participants did not differ significantly from non-participants on basic demographic characteristics or childhood IQ, however. Moreover, many G1 participants were not included in this study because they did not have adult children. Nevertheless, we successfully recruited and studied the majority of the eligible G2 individuals. Finally, we used only a brief screening measure of academic skills, and more comprehensive assessment could have revealed group differences not detected by this brief measure.

In sum, this study confirmed cognitive deficits in the adult children of parents who experienced malnutrition early in life. We were not, however, able to link these effects to the reduced socioeconomic circumstances of the parents, as we had hypothesized. These findings raise concerns that infantile malnutrition can have meaningful and deleterious impacts extending well beyond the generation that was directly impacted, with major public health implications. The source of this phenomenon merits further investigation. Both environmental and biological mechanisms, including epigenetic changes, should be explored.

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Figure 1.

Derivation of G2 sample from G1 sample. A total of 167 G1 adults were enrolled in the follow-up study. Of these, 150 (89%) completed neuropsychological testing. These individuals had 156 G2 offspring who were within the age range for the present study. Of these, 121 (80%) were enrolled in the study, of whom 114 (94%) were able to be scheduled and completed testing. MAL, Previously Malnourished; CON, Control; G1, Generation 1 Parent; G2, Generation 2 Offspring.

Table 1Demographic and anthropometric characteristics of G1 parents and their G2 adult offspring¹.

	Generation 1		Generation 2	
	CON	MAL	CON	MAL
Total, N	33	34	50	64
Male, N (%)	16 (48.5)	10 (29.4)	24 (48.0)	27 (42.2)
Age at evaluation (Years)	38.2 ± 2.7	38.7 ± 1.7	19.7 ± 3.1	19.3 ± 3.3
Range	34–44	35–43	16–27	16–30
Hollingshead ISP [*]	3.9 ± 1.0	4.4 ± 0.7	-	-
Education [*]	4.5 ± 1.0	4.9 ± 0.3	-	-
Occupation [*]	5.1 ± 1.6	6.0 ± 1.3	-	-
Total Years Schooling	-	-	13.7 ± 1.9	13.7 ± 1.9
Attended preschool, N (%)	-	-	14 (28.0)	17 (26.6)
Living with Parents, N (%)			37 (74.0)	44 (68.8)
Married, N (%)			5 (10.0)	4 (6.3)
Height (cm)	169.1 ± 9.0	167.0 ± 7.5	166.2 ± 10.6	168.7 ± 7.4
Weight (kg)	83.0 ± 17.7	83.4 ± 18.1	68.4 ± 17.7	68.9 ± 20.6
Body Mass Index	29.3 ± 7.2	29.9 ± 6.5	25.1 ± 7.7	24.3 ± 7.4

¹Values are means ± SDs for continuous variables or n (%) for categorical variables.^{*}*t* test, Hollingshead ISP, Education, Occupation, *p* < 0.02.

CON, Control; MAL, Previously Malnourished; ISP, Index of Social Position

G1 and G2 IQ and Achievement scores and nutrition group differences for G1 and G2 participants adjusted by for covariates¹.

Table 2

		Adjusted for Gender				Adjusted for Gender+ISP				Adjusted for Gender, ISP+Parent IQ			
		CON	MAL	β	SE	p	B	SE	p	B	SE	p	p
Generation 1		N=33	N=34										
WASI Full Scale IQ		94.5 $\pm$ 14.3	82.3 $\pm$ 13.9	-11.6	3.5	0.002	-8.6	3.3	0.01				
Generation 2		N=50	N=64										
WASI IQ													
Full Scale IQ		99.1 $\pm$ 15.0	89.6 $\pm$ 15.1	-9.8	3.1	0.002	-9.7	3.1	0.003	-9.0	3.3	0.007	
Vocabulary (T-Score)		49.8 $\pm$ 11.9	44.7 $\pm$ 11.4	-5.4	2.5	0.040	-5.4	2.6	0.050	-5.4	2.6	0.050	
Matrix Reasoning (T-Score)		47.6 $\pm$ 9.5	41.1 $\pm$ 12.9	-6.6	2.1	0.002	-6.0	2.1	0.006	-6.0	2.1	0.006	
WRAT-III													
Reading (Standard Score)		94.5 $\pm$ 18.3	89.2 $\pm$ 17.9	-5.6	3.7	0.133	-5.3	3.6	0.150	-5.3	4.2	0.212	
Spelling (Standard Score)		94.7 $\pm$ 16.8	89.7 $\pm$ 18.1	-5.5	3.4	0.103	-4.9	3.2	0.132	-4.2	4.0	0.294	
Calculation (Standard Score)		84.4 $\pm$ 14.9	79.9 $\pm$ 13.3	-4.7	2.8	0.155	-3.8	2.7	0.155	-2.4	2.9	0.418	

¹Values are means $\pm$ SDs, unstandardized parameter estimates, and standard errors of the estimates. Outcome variables include the WASI, Wechsler Abbreviated Scale of Intelligence and WRAT-III, Wide Range Achievement Test – Third Edition.

CON, Control Group; MAL, Previously Malnourished Group. ISP, Hollingshead Index of Social Position.