

Prenatal Undernutrition and Postnatal Growth Are Associated with Adolescent Thymic Function¹

Thomas W. McDade,^{*2} Melinda A. Beck,^{†**} Christopher W. Kuzawa[‡]
and Linda S. Adair^{**††}

^{*}Department of Anthropology, Northwestern University, Evanston, IL 60208-1310; Departments of [†]Pediatrics and ^{**}Nutrition and ^{††}Carolina Population Center, University of North Carolina, Chapel Hill, NC; and [‡]Department of Anthropology, Emory University, Atlanta, GA

ABSTRACT The fetal and early infant origins of a number of adult cardiovascular and metabolic diseases have received considerable attention, but the long-term consequences of early environments for human immune function have not been reported. We investigated the effects of pre- and postnatal environments on thymic hormone production in adolescents participating in an ongoing longitudinal study in the Philippines. Prospective data collected at birth, during y 1 of life, in childhood and in adolescence were used to predict plasma thymopoietin concentration in 14- to 15-y-old adolescents ($n = 103$). Thymopoietin concentration was compared for small-for-gestational-age and appropriate-for-gestational-age individuals while controlling for a range of postnatal exposures. Prenatal undernutrition was significantly associated with reduced thymopoietin production in interaction with the duration of exclusive breast-feeding ($P = 0.006$). Growth in length during y 1 of life was positively associated with adolescent thymopoietin production ($P = 0.002$). These associations remained significant after adjusting for a range of potentially confounding variables. These findings provide support for the importance of fetal and early infant programming of thymic function, and suggest that early environments may have long-term implications for immunocompetence and adult disease risk. *J. Nutr.* 131: 1225–1231, 2001.

KEY WORDS: • *thymic factor* • *immune system* • *prenatal exposure delayed effects*
• *growth and development* • *nutrition* • *humans*

Recent research suggests that many adult chronic, degenerative diseases are at least in part the result of fetal and early infant programming of cardiovascular and endocrine systems, and evidence is mounting for an association between low birthweight and adult hypertension, coronary heart disease and diabetes (1–3). However, the implications of early environments for the development and function of the immune system in adulthood are not known. This study addresses this question by investigating the long-term effects of prenatal and early postnatal experience on thymic hormone production in adolescence.

We found recently that prenatal undernutrition is associated with reduced antibody response to typhoid vaccination in adolescents from the Philippines, whereas postnatal diarrheal morbidity and rapid weight gain are positively associated with immunocompetence (4). This prospective study provides evidence in support of early programming of later immune function, complementing previous research on programming of cardiovascular and endocrine systems, and suggesting a possible mechanism for the recently reported association between

prenatal undernutrition and adult infectious disease mortality (5,6). This research also builds on previous work linking pre- and postnatal undernutrition to deficits in several aspects of immunity in infancy and early childhood (7–10).

A number of studies have drawn attention to the thymus as a potential mediator of the immunological consequences of undernutrition. The thymus is a primary lymphoid organ required for normal T-lymphocyte development and function, and for the production of a number of thymic hormones with peripheral immunoregulatory properties (11,12). Pre-T cells migrate from bone marrow to the thymus where they differentiate and mature into competent T-lymphocytes before their release into circulation. This process is critical for minimizing the potential for self-reactivity, for establishing the T-cell repertoire that populates peripheral lymphoid tissues and for maintaining the balance between subsets of T cells (13,14). Protein-energy malnutrition in infancy and early childhood has been associated with dramatic declines in thymic weight, lowered thymic hormone levels, reduced numbers of maturing T cells and alterations in the thymic microenvironment (9,15–20). The long-term consequences of early undernutrition for thymic development and function are not known, but the thymus has been hypothesized as a mediator of the associations between fetal undernutrition and symptoms of adult atopic and autoimmune disease (21,22).

Thymic hormones play important roles in T-cell develop-

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² To whom correspondence should be addressed.
E-mail: t-mcdade@northwestern.edu.

ment and peripheral T-cell function (23,24), and a number of studies have explored the clinical utility of thymic hormones as treatments for immune deficiency (25). Thymopoietin, one of the best characterized thymic hormones, is a 49–amino acid polypeptide that is produced primarily by thymic epithelial cells. It is involved in early T-cell differentiation, as well as the coordination of lymphocyte subsets and the peripheral regulation of mature T-cell function (26–28). It also appears to play an important role in cell cycle regulation in a number of tissues (29,30). Serum thymopoietin concentration correlates roughly with thymus size; it is highest at 15–30 y of age and declines in parallel with the age-related involution of the thymus (31).

The immunoregulatory properties of thymopentin, a synthetic peptide with the same biological properties as thymopoietin, have been investigated extensively. In vitro studies report enhanced T-cell differentiation, proliferation and cytokine production after thymopentin treatment, and in vivo murine studies demonstrate reduced tumor growth and restored T-cell activity after thymic involution (28). In human clinical studies, thymopentin treatment has been associated with increases in T-cell numbers, proliferation and interleukin-2 production, improved delayed-type hypersensitivity response to recall antigens, as well as improvement in the course of a number of autoimmune, neoplastic and infectious diseases (28,32).

In this study, we hypothesized that prenatal and early postnatal environments would have implications for thymic hormone production in adolescence. We investigated this issue in an ongoing, longitudinal study of maternal and child health in the Philippines with detailed information on a range of potentially confounding factors. To the best of our knowledge, this is the first study to report the long-term effects of early environments on the thymus, providing support for the potential importance of early programming of adult immune function.

SUBJECTS AND METHODS

Study participants and protocol. The Cebu Longitudinal Health and Nutrition Study (CLHNS)³ is an on-going population-based survey of maternal and child health in the Philippines that began in 1983 with the recruitment of 3327 pregnant women (33). In-home interviews were conducted before and immediately after birth, and every 2 mo for 2 y to collect in-depth data on child and maternal health, anthropometry, patterns of breast-feeding, dietary intake, rates of diarrhea and respiratory disease, household socioeconomic status and demographics, and environmental quality. Follow-up surveys were conducted in 1991, 1994–1995, and 1998–1999. The prospective design of this study provides a unique opportunity to explore a range of direct and indirect pathways through which early environments may affect later immune function.

In 1998–1999, 2089 CLHNS participants, 14 or 15 y old at the time, were contacted for follow-up data collection. From these remaining participants, a subsample of 103 individuals was selected for evaluation of the relationships between early environments and immune function in adolescence. Due to cost considerations and the nature of the protocol, a limited number of participants were recruited according to the following criteria: full-term birth (= 37 wk), currently healthy, and small-for-gestational age (SGA: defined as <10th percentile of birthweight for gestational age) vs. appropriate-for-gestational age (AGA: ≥10th percentile) (34).

SGA and AGA individuals were selected randomly from their

respective populations in the CLHNS cohort; we intentionally oversampled SGA individuals to evaluate the effects of intrauterine growth retardation (IUGR). We eliminated the potentially confounding effects of premature delivery by restricting our sample to full-term births, and focused on the small size assumed to be related to prenatal undernutrition. The subsample of SGA individuals recruited for this study is representative of SGA individuals in the larger CLHNS cohort, except that the average birthweight of 2347 g is significantly lower than the average of 2494 g for all SGA individuals in the CLHNS ($P < 0.001$).

Gestational age was determined from maternal recall of the date of her last menstrual period or by clinical (35) assessment of the newborn for those mothers who could not recall their last menstrual period, for low birthweight infants and for those who had pregnancy complications. As in many countries in the developing world, IUGR is common in the Philippines due to high rates of maternal undernutrition during pregnancy. In the CLHNS, the prevalence of IUGR is 20.9% (36).

Thymopoietin concentration was analyzed in blood samples collected as part of a protocol investigating antibody response to vaccination (4). Upon enrollment in the antibody study, ~5 mL of EDTA plasma were collected and immediately frozen, followed by vaccination against typhoid fever. Follow-up blood was drawn 2 wk and 3 mo later. Thymopoietin concentration was assayed in samples collected 2 wk after vaccination. The study protocol was conducted as approved by the University of North Carolina School of Public Health Institutional Review Board for research involving human subjects.

Thymopoietin ELISA. Samples were shipped on dry ice to the United States and stored at -20°C before analysis. Thymopoietin concentration was assayed using a commercially available high sensitivity solid-phase ELISA kit (R&D Systems, Minneapolis, MN). Microtiter plate wells were precoated with a polyclonal antibody specific for the first 19–amino acid sequence of human thymopoietin. Samples, standards and controls were added to wells in duplicate along with biotinylated monoclonal antibody (specific for amino acid sequences 29–50) and incubated at room temperature for 2.5 h. Wells were washed, followed by the addition of streptavidin-alkaline phosphatase. Wells were washed again, and an amplifier solution was added to facilitate color development. Sulfuric acid was added to stop the reaction, and absorbance was read at 490 nm (Dynatech MR5000, Chantilly, VA). The intensity of color development is directly proportional to the quantity of thymopoietin, and unknown values were determined on the basis of the standard curve constructed from thymopoietin calibrators (Statlia, Brendan Scientific, Grosse Pointe Farms, MI).

Data analysis. Four individuals with excessively high values due to sample hemolysis were excluded. Complete nutritional, anthropometric, morbidity and sociodemographic data were available for 96 individuals.

The distribution of thymopoietin was positively skewed, and values were log-transformed to normalize the distribution before multiple linear regression analysis (Stata, College Station, TX). Intrauterine growth retardation was the primary independent variable of interest, but aspects of the prenatal environment (maternal nutritional status during pregnancy and parity), postnatal environment (household socioeconomic status, pattern of breast-feeding, pathogen exposure and infectious morbidity) and growth (length and weight), and current status (pubertal status and nutritional status) were also considered as potential predictors of thymopoietin concentration (Table 1).

With one exception, each continuous variable approximated a normal distribution and was entered directly into linear regression models. Categorical variables were entered into linear regression models using indicator variable coding. The variable representing the duration of exclusive breast-feeding (no supplemental foods or liquids of any kind given before this point in time) was positively skewed, with a median of 51 d (25th percentile: 29.5 d; 75th percentile: 60 d). Therefore, this variable was dichotomized at the median, and individuals were classified as “short” or “long” exclusive breast-feeders accordingly.

The morbidity variable provides a measure of diarrheal and/or respiratory disease during y 1 of life. At each of the six bimonthly

³ Abbreviations used: AGA, appropriate-for-gestational age; BMI, body mass index; CLHNS, Cebu Longitudinal Health and Nutrition Study; HPA, hypothalamic-pituitary-adrenal; IUGR, intrauterine growth retardation; SGA, small-for-gestational age.

TABLE 1

Potential predictors of thymopoietin concentration in adolescence considered in addition to intrauterine growth retardation¹

Prenatal environment	
Maternal BMI, ² kg/m ²	21.7 (17.0, 28.1)
Mother's age, y	26.8 (15, 43)
Parity, n	First pregnancy (23.3%) Second + pregnancy (76.7%)
Season of birth	Wet (38.5%) Dry (25.0%) Other (36.5%)
Postnatal environment: y 1	
Duration of exclusive breast-feeding ³	Short (50.5%) Long (49.5%)
Exposure to pathogens	
Quality of water source	Good (26.9%) Poor (73.1%)
Food contamination	Moderate (56.7%) Low (43.3%)
Excreta disposal	Adequate (55.8%) Inadequate (44.2%)
Crowding, persons/room	3.0 (0.67, 9)
Morbidity ⁴	6.9 (2, 11)
Growth: birth to 1 y	
Length, cm	20.7 (13.6, 28.9)
Weight, kg	4.8 (2.1, 8.1)
Growth status at age 10 or 11 y	
Height, cm	134.1 (120.7, 154.3)
Weight, kg	28.1 (19.0, 48.0)
BMI, kg/m ²	15.5 (12.1, 23.0)
Total skinfolds (tricep + subscapular), mm	16.1 (9.0, 36.7)
Current status	
Nutritional/Growth status	
Height, cm	152.0 (136.5, 175.7)
Weight, kg	42.9 (29.0, 76.0)
BMI, kg/m ²	18.5 (14.6, 26.5)
Total skinfolds (triceps + subscapular), mm	21.5 (9.3, 43.7)
Hemoglobin, g/L	134 (73, 167)
Developmental status	
	Early puberty (29.8%) Late puberty (70.2%)
Exposure to pathogens	
Food contamination	Moderate (56.7%) Low (69.0%)
Excreta disposal	Adequate (69.0%) Inadequate (31.0%)

¹ Percentages are presented for categorical variables, and mean (range) values are presented for continuous variables.

² BMI, body mass index.

³ Duration of exclusive breast-feeding: short < 51 d; long ≥ 51 d.

⁴ Morbidity: episodes of diarrhea and respiratory infection reported by mothers in the week preceding bimonthly interviews during the infant's first year of life.

home visits after the birth of their infant, mothers were asked whether the infant had experienced diarrheal or respiratory symptoms in the week preceding the visit. The potential effects of diarrheal and respiratory disease were considered separately, as well as together in the summary variable.

Current nutritional status was assessed through standard anthropometric measures, as well as hemoglobin concentration. Hemoglobin was considered as a continuous variable, and as a dichotomous variable for which anemic individuals (hemoglobin <110 g/L) were compared with nonanemic individuals. Nine participants were identified as anemic.

Previous research suggests that thymic activity may be influenced by progression through puberty (12). Because participants in this study were peripubertal, an attempt was made to control for developmental status. Boys were classified as being in early or late puberty according to self-ratings of pubic hair growth, and girls were classified according to the stage of breast development.

We hypothesized that SGA individuals would have lower thymo-

poietin concentrations than AGA individuals. We used the model-building approach advocated by Lucas et al. (37) to increase our confidence in concluding that any association between IUGR and adolescent thymopoietin concentration was due to the quality of the prenatal environment rather than correlated aspects of postnatal experience. Our approach was as follows: 1) evaluate the crude association between SGA and thymopoietin; 2) add variables representing aspects of postnatal growth, morbidity and environment to multivariate models including birthweight-for-gestational-age; and 3) consider the effect of these variables without SGA in the model. Interaction terms were included when appropriate. $P < 0.05$ was taken as the criterion for statistical significance.

If the effect of SGA was reduced after adjusting for postnatal factors, we concluded that postnatal rather than prenatal environments were more likely to be causally related to adolescent thymopoietin production. However, we recognize that prenatal and postnatal effects may not be entirely independent, particularly with respect to growth, and that adjustment for postnatal factors may underestimate the importance of prenatal environments. If adjustment for postnatal factors amplified the effect of SGA, we concluded that both prenatal and postnatal influences were relevant. Significant interactions between SGA and postnatal factors were assumed to indicate that SGA modified the effect of later environments.

RESULTS

Characteristics of SGA and AGA individuals are presented in Table 2. Proportion of females, pubertal status, gestational age, postnatal growth in length and episodes of morbidity during y 1, the duration of exclusive breast-feeding and current age did not differ significantly between the two groups. As expected, SGA individuals had significantly lower birthweight, as well as lower body mass index (BMI) at age 14–15 y. They also gained significantly more weight in y 1 and were more likely to be born to mothers without a prior pregnancy and with lower BMI at the time of birth.

The median thymopoietin concentration for the entire sample was 17.5 pmol/L (25th percentile: 13.5; 75th percentile: 41.4). Median concentrations for boys (35.8 pmol/L) were more than twice as high as those for girls (14.9 pmol/L), and mean log-transformed thymopoietin concentrations differed significantly (Student's $t = 5.51$, $P < 0.001$). Sex was therefore included as a covariate in subsequent analyses. No significant association between birthweight-for-gestational-age and

TABLE 2

Descriptive statistics for small-for-gestational age (SGA) and appropriate-for-gestational age (AGA) girls and boys

	SGA (n = 51)	AGA (n = 45)
Female, %	58.8	66.7
Gestational age, wk	39.5 (38, 46)	40.2 (37, 45)
Birth weight, g	2347 (1814, 2863)***	3297 (2665, 4082)
Maternal BMI, kg/m ²	21.1 (17.0, 27.0)*	22.4 (18.3, 28.1)
First pregnancy, %	31.4**	9.1
Growth in length in y 1, cm	21.1 (13.6, 28.9)	20.2 (15.0, 25.8)
Weight gain in y 1, kg	5.0 (2.9, 7.7)*	4.5 (2.1, 8.1)
Morbidity	7.1 (2, 11)	6.8 (2, 11)
Duration of exclusive breast-feeding, d		
	53.1 (1, 154)	48.0 (1, 190)
Current age, y	14.6 (14, 15)	14.6 (14, 15)
Current BMI, kg/m ²	18.1 (14.8, 24.0)*	19.1 (14.6, 26.5)
Late/postpubertal, %	66.7	75.6

¹ Mean (range) values are presented for continuous variables.

* $P < 0.05$ (χ^2 test for independence of categorical variables; Student's t test for continuous variables); ** $P < 0.01$; *** $P < 0.001$.

TABLE 3

Multiple linear regression model with significant predictors of adolescent thymopoietin concentration in 14- to 15-y olds^{1,2}

	Adj. R ² = 0.338			
	Unadjusted β	Adjusted β	SEM	P-value
$F_{5,90} = 10.7$, $P < 0.0001$				
Sex (female = 0, male = 1)	0.325	0.290	0.058	0.000
Birthweight-for-gestational-age (SGA = 0, AGA = 1)	0.055	-0.033	0.077	0.667
Breastfeeding duration (short = 0, long = 1)	0.011	-0.095	0.075	0.206
Birthweight-for-gestational-age \times breastfeeding	0.153	0.304	0.108	0.006
Growth in length, birth to 12 mo, cm	0.041	0.032	0.010	0.002
Constant		0.585	0.220	0.009

¹ Unadjusted β values represent the bivariate association between thymopoietin concentration and each independent variable. Adjusted β values control for the presence of the remaining variables in the model.

² SGA, small-for-gestational age; AGA, appropriate-for-gestational age.

log thymopoietin concentration was found in multiple linear regression ($\beta = 0.078$, $P = 0.19$).

Next, variables representing aspects of the prenatal environment, postnatal environment, size at age 10 or 11 y and current status (Table 1) were added to models including sex and birthweight-for-gestational-age. The interaction between birthweight-for-gestational age and exclusive breast-feeding duration emerged as a significant predictor of adolescent thymopoietin concentration, as well as growth in length during y 1 of life (Table 3). Other variables (Table 1) did not approach statistical significance ($P > 0.15$), nor did they modify the effects of birthweight, breast-feeding or growth.

Overall, participants grew on average 20.7 cm in length during y 1 of life, and length increment was positively associated with thymopoietin concentration in adolescence (Fig. 1). Each additional centimeter of infant growth corresponded to ~7.5% increase in untransformed thymopoietin concentration, and adolescents who were 1 SD above the mean in 1-y length increment (23.4 cm) had thymopoietin concentrations that were 1.5 times higher than adolescents who were 1 SD below the mean (18.0 cm).

Growth was subsequently divided into two periods, i.e., birth to 6 mo and 6 to 12 mo, to explore the relative importance of early vs. later growth. Both variables were added to the model presented above. The slope of the relationship between growth in length and thymopoietin concentration was slightly higher from birth to 6 mo ($\beta = 0.035$, SEM = 0.012, $P = 0.005$), and slightly lower from 6 to 12 mo ($\beta = 0.028$, SEM = 0.015, $P = 0.060$), than that found for birth to 12 mo (Table 3). The results for birth to 6 mo are significant, whereas those for 6 to 12 mo are only marginally so. Although these differences are small, they suggest that the first 6 mo of life may be particularly important for thymic development.

The main effect of birthweight-for-gestational-age became significant ($\beta = 0.12$, $P = 0.044$) when length increment was added to the model. The adjusted R² for this model was 0.29. In addition, the duration of exclusive breast-feeding (<51 vs.

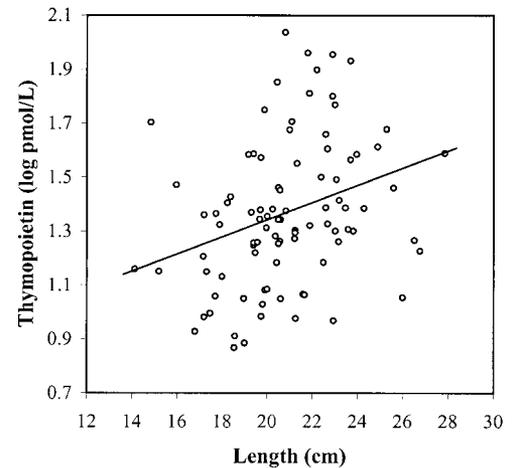


FIGURE 1 Relationship between growth in length during the first year of life and plasma thymopoietin concentration in 14- to 15-y olds, after adjusting for sex, birthweight-for-gestational age and duration of exclusive breast-feeding.

> 51 d) also emerged as an important predictor of adolescent thymopoietin production. The main effect of exclusive breast-feeding duration did not approach significance ($\beta = 0.047$, $P = 0.42$). However, the interaction between birthweight-for-gestational-age and duration of exclusive breast-feeding was significant, and the model including this term had a substantially higher adjusted R² value (Table 3), indicating that the effect of birthweight-for-gestational-age depended on the duration of exclusive breast-feeding.

Appropriate-for-gestational age individuals who were exclusively breast-fed for >50 d stood out with elevated thymopoietin concentrations in adolescence (Fig. 2). Small-for-gestational age individuals had lower concentrations regardless of exclusive breast-feeding duration, and short breast-feeding,

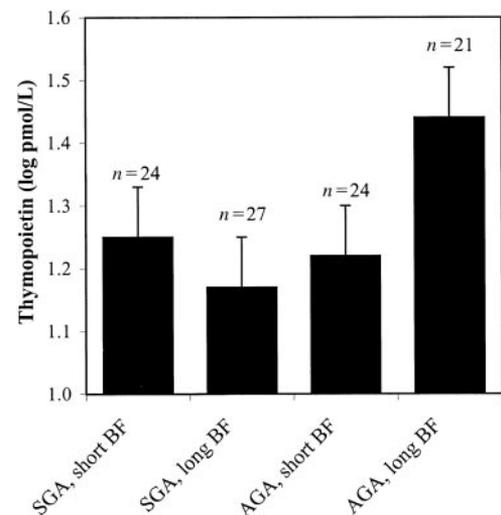


FIGURE 2 The interaction between birthweight-for-gestational age and duration of exclusive breast-feeding in predicting plasma thymopoietin concentration in 14- to 15-y olds ($P = 0.006$). Mean \pm SEM values are presented for each of the four groups: small-for-gestational age (SGA), short duration of exclusive breast-feeding (short BF); SGA, long duration of exclusive breast-feeding (long BF); appropriate-for-gestational age (AGA), short BF; AGA, long BF. Means are adjusted for sex and growth in length during the first year. The number of individuals in each group is presented above each bar.

AGA individuals had comparably low concentrations. The mean untransformed thymopoietin concentration of AGA, long exclusively breast-fed individuals was 50–90% higher than the thymopoietin concentration of individuals in the other three groups.

Last, the effects of sex, duration of exclusive breast-feeding and length increment in γ 1 were considered in a regression model without birthweight-for-gestational-age to facilitate interpretation of the relative importance of prenatal vs. postnatal influences on adolescent thymopoietin production. The effect of growth in length was comparable to the full model ($\beta = 0.030$, $P = 0.006$), whereas exclusive breast-feeding duration failed to reach statistical significance in the absence of an interaction term with SGA ($\beta = 0.040$, $P = 0.48$). The overall model was significant ($F_{3,93} = 12.45$, $P < 0.0001$), with an adjusted R^2 of 0.26. The amount of explained variance was substantially lower than the 34% accounted for by the full model, suggesting that prenatal undernutrition was an important predictor of adolescent thymopoietin concentration in addition to postnatal growth in length.

DISCUSSION

Prenatal undernutrition, duration of exclusive breast-feeding and length increment in γ 1 of life were found to be significantly associated with thymopoietin concentration in Filipino adolescents. These effects remained significant after we evaluated a wide range of potentially confounding variables, supporting our hypothesis that early environments may be causally related to adolescent thymic function. However, the specific nature of this causality is difficult to ascertain given the observational design of the study and also because low birthweight, duration of breast-feeding, infectious disease risk and postnatal growth have all been linked in the larger CLHNS cohort (38,39). Nonetheless, our findings are consistent with research in this population documenting relationships among IUGR, breast-feeding and weight velocity on adolescent antibody response to vaccination (4).

Limitations of this study include the relatively small sample size and its associated reduction in statistical power. In future research, we hope to take full advantage of the comprehensive CLHNS dataset. Furthermore, the possibility exists that the subsample chosen for this study was not representative of the CLHNS cohort and that findings reported here cannot be generalized. Participants were selected randomly from the pool of full-term SGA and AGA individuals, and, with the exception of birthweight, no significant differences were found between the subsample and the full cohort. In this study, the mean birthweight for SGA individuals was 147 g lower than the mean for remaining SGA individuals in the cohort, allowing for the possibility that results reported above may overestimate the effect of birthweight. In addition, this study cannot evaluate the significance of low birthweight combined with premature delivery because only full-term births were considered.

The study is also limited by challenges in the interpretation of thymopoietin concentrations. The absence of reference values prevents assessment of the clinical significance of our findings, even though the relative differences in thymopoietin concentration associated with birthweight-for-gestational-age, breast-feeding and growth in length demonstrate the importance of these variables. In addition, recent work has shown that thymopoietin is a ubiquitously expressed nuclear protein that is found in a range of tissues with high levels of proliferative activity (40). This raises the possibility that differences in thymopoietin concentra-

tions do not reflect differences in activity of the thymus as assumed. However, even though thymopoietin production is not limited to the thymus, the highest levels of mRNA are found in the thymic cortex (29), and circulating thymopoietin is generally believed to be of thymic origin (28,41). Future studies should consider evaluating additional thymic peptides (e.g., thymosins, thymulin, thymic humoral factor) as well as recent thymic emigrants (42) for a more complete picture of thymic activity.

Previous research on the thymus suggests that undernutrition and progression through puberty are negatively associated with thymic function (11,12,15), but in this study, only events early in life were found to be significantly related to adolescent thymopoietin production. This supports the hypothesis that early environments are important for later thymic function, and suggests a causal role for these environments rather than correlated aspects of childhood and adolescent environments. Additional research in a larger sample will be required to confirm and elaborate these findings. Results presented here also differ from those of our study on adolescent vaccine responsiveness in which current undernutrition was significantly related to a lower likelihood of mounting a positive antibody response in interaction with prenatal undernutrition (4).

Mature T cells are released from the thymus by wk 14 of gestation, and the rate of thymic tissue development increases dramatically during the last trimester, followed by rapid postnatal growth (13). As such, the prenatal and early postnatal periods are critical for the thymus, and insults during these periods may have more serious consequences than those experienced later in life. Growth in length during γ 1 of life may provide a proxy for organ growth in general and thymic growth in particular. Concordantly, recent sonographic assessments of thymic volume have reported positive associations with birthweight and body length in infancy (43,44). An infant who grows slowly during this critical period of thymic development may also grow a smaller thymus, with fewer epithelial cells for thymic hormone production in adolescence.

Impaired thymus growth may also account for the lower thymopoietin production in adolescents born SGA. This is consistent with previous research documenting lower thymus weights in SGA newborns (19) and reduced thymic hormone activity at 1 mo of age in SGA infants (9). The positive association between thymopoietin production and the duration of exclusive breast-feeding is also consistent with previous research reporting an association between exclusive breast-feeding through 4 mo of age and increased thymic volume at 10 mo (44). In addition to the macro- and micronutrients that minimize the likelihood of malnutrition, and the passive immunity that lowers the risk of infection, breast milk contains a number of molecules that facilitate immunological development in the newborn (45). Prolonged breast-feeding may promote thymic development directly or indirectly by improving the quality of the infant's postnatal environment. Breast-feeding was found to interact with prenatal growth such that AGA, long exclusively breast-fed individuals had the highest concentrations of thymopoietin in adolescence, suggesting that AGA infants are better prepared to benefit from prolonged exclusive breast-feeding. However, it is possible that analysis of a larger sample would reveal an additive, rather than interactive relationship between breast-feeding and birthweight-for-gestational-age.

Reduced thymopoietin production could also be the result of early programmed effects on the hypothalamic-pituitary-

adrenal (HPA) axis. The thymus is sensitive to HPA activity, i.e., in clinical populations, the excessive glucocorticoid production of Cushing's syndrome and the large doses of adrenocorticotropic hormone for ipsarythmia both result in thymic atrophy (15), and episodes of malnutrition, infection and psychological stress, all associated with HPA activation, appear to be causally related to transient thymic involution and reduced thymic hormone production (15,17,46). Inhibition of HPA activity and glucocorticoid production attenuates these effects (47,48). Birthweight has recently been associated with alterations in glucocorticoid production in 9-y-old children (49), and a number of primate studies have documented lasting irregularities in HPA and immune function in offspring of mothers stressed during pregnancy (50–53).

The association between early environments and adolescent thymic hormone production may provide a mechanism for recent reports linking fetal growth to symptoms of autoimmune and atopic disease in adults. Phillips et al. (22) discovered a negative association between birthweight and the proportion of women producing antibodies against thyroglobulin and thyroid peroxidase, whereas Godfrey et al. (21) found increased immunoglobulin E concentrations in men and women with disproportionate fetal growth of the head relative to the trunk and arms. Both groups speculate that impaired development of the thymus after fetal undernutrition may be responsible for these associations. Findings from this study support this hypothesis, but also emphasize the importance of the early postnatal environment to later thymic activity.

Additional research is required to establish the relevance of programming to the development and function of the immune system, and to explore the implications for atopic, autoimmune, infectious and neoplastic disease risk in adulthood. Although high rates of IUGR may make marginally nourished populations particularly vulnerable, the possibility of early programming of immune function will have important ramifications for other populations as well. Future studies should explore the moderators of early environment effects, the physiologic processes that link early environments to thymic development and function, and their specific immunologic consequences.

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