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Prenatal and early postnatal environments are significant predictors of total immunoglobulin E concentration in Filipino adolescents

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Summary

Background Recent evidence suggests that atopic disease may in part be mediated by fetal growth, as well as exposure to infectious disease early in life. Few studies have been able to evaluate these associations simultaneously, or to investigate prospectively the long-term effects of early environments while adequately controlling for potentially confounding variables.

Objective To examine how prenatal growth and infectious disease in infancy are related to total IgE production in adolescence.

Methods Ninety-nine adolescents (aged 14–15 years) were selected from a larger cohort study according to the following criteria: full-term birth, currently healthy, and small-for-gestational age ($N = 53$) or appropriate-for-gestational age ($N = 46$). Plasma total IgE was measured with ELISA, and analysed in relation to anthropometric, nutritional, and environmental quality data collected prospectively beginning in the third trimester prior to birth.

Results Each episode of infectious morbidity recorded at bimonthly intervals in the first 6 months of life was associated with a 0.12 log IU/mL reduction in total IgE in adolescence ($P = 0.004$). Prenatal undernutrition was associated with increased adolescent IgE, but only under conditions of an unsanitary household environment ($P = 0.002$). Each additional kilogram gained per month in the first 6 months of life was associated with an increase in adolescent IgE of 0.74 log IU/mL ($P = 0.03$). Each quartile increase in weekly household income at the time of blood sampling was associated with a 0.10 log IU/mL reduction in total IgE ($P = 0.02$).

Conclusion Infectious disease in infancy, as well as interactions between prenatal and postnatal environments, appear to have long-term effects on adolescent total IgE production. Future research should investigate the mechanisms behind these effects, and their implications for symptoms of atopic disease.

Keywords: adolescents, atopy, growth and development, immune system, infection, nutrition, prenatal exposure delayed effects

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Introduction

Evidence continues to grow in support of the hypothesis that prenatal and early postnatal environments are significant determinants of adult risk for a range of cardiovascular and metabolic diseases [1–4]. Recent research has indicated that human immune function may in part be programmed by early experiences [5–8], with potential implications for the development of infectious, neoplastic, autoimmune, and atopic diseases later in life. In this study we investigate the long-term effects of prenatal and early postnatal environments on IgE production in adolescence, using data from an ongoing longitudinal study of health in the Philippines.

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Atopic diseases such as asthma, hayfever, and eczema are mediated by IgE responses to predominantly innocuous, common environmental allergens, and elevated concentrations of total IgE are consistently found in atopic individuals [9, 10]. In previous research, elevated IgE in childhood and adulthood has been linked to larger head circumference at birth [11–14], leading to speculation that prenatal undernutrition may compromise the development of the thymus and bias the production of thymus-derived T lymphocytes in favour of the Th2 phenotype, thereby promoting the production of IgE. However, contrary to this hypothesis, a positive association between head circumference and thymus size at birth has recently been reported [15]. Although the physiological mechanisms are far from clear, a number of studies have reported significant associations between measures of fetal growth and later risk for elevated IgE, allergy, asthma, and obstructive airways disease [11, 16–19].

A parallel line of inquiry has indicated that exposure to infectious disease early in life may have a protective effect on the subsequent development of atopic disease. This 'hygiene hypothesis' has received support from reports of negative associations between infectious morbidity and IgE production and symptoms of allergy and asthma [20–23], although some findings are inconsistent [24, 25].

Few studies have been able to evaluate simultaneously the effect of prenatal undernutrition and postnatal infectious morbidity on later IgE production, even though it is likely that these factors are related. Previously, we reported that prenatal undernutrition as well as aspects of postnatal experience in the first year of life – duration of exclusive breastfeeding, height and weight gain, and infectious morbidity – were significantly associated with reduced vaccine responsiveness and thymic hormone production in Filipino adolescents [5, 6]. In this study we extend our analyses to include an investigation of the prenatal and postnatal factors that predict production of IgE in adolescence.

Subjects and methods

Study participants and protocol

Methodological background on the Cebu Longitudinal Health and Nutrition Study (CLHNS) has been presented elsewhere [26]. This population-based survey of maternal and child health in the Philippines began in 1983 with the recruitment of 3327 pregnant women. Detailed data on child and maternal health, anthropometry, patterns of breastfeeding, dietary intake, rates of diarrhoea and respiratory disease, household socio-economic status and demographics, and environmental quality were collected during in-home interviews conducted prior to and immediately following birth, and every subsequent 2 months for 2 years. The prospective design of this study provides a unique opportunity to evaluate a number of pre- and early postnatal factors that may influence IgE production later in life.

In 1998–99, 2089 CLHNS participants – 14 or 15 years of age at the time – remained in the cohort and were contacted for follow-up data collection. A subsample of these participants ($N = 107$) was selected for a more intensive study of the relationships between early environments and adolescent immune function. Sample size was restricted to accommodate a vaccination protocol requiring multiple blood draws [5]. Individuals were eligible for selection into this subsample if they were currently healthy, and were born at full term ($\geqslant 37$ weeks). Gestational age was determined from maternal recall of the date of her last menstrual period, or by clinical assessment [27] for low birthweight infants, for those who had pregnancy complications, and for those mothers who could not recall their last menstrual period.

Approximately equal numbers of small-for-gestational age (SGA: defined as <10th percentile of birthweight-for-gestational age) and appropriate-for-gestational age (AGA: $\geqslant 10$th percentile) [28] individuals were randomly selected from the population of SGA and AGA individuals remaining in the cohort. As in many developing countries, maternal undernutrition during pregnancy is common in the Philippines, and in the CLHNS the prevalence of intrauterine growth retardation (IUGR) was 20.9% [29]. The subsample of SGA individuals recruited for this study was representative of SGA individuals in the larger CLHNS cohort, except that the average birthweight of 2362 g was significantly lower than the average of 2494 g for all SGA individuals in the CLHNS ($P < 0.001$). By restricting the sample to full-term births, we eliminated the potentially confounding effect of preterm delivery, and focused on IUGR that is more reflective of prenatal undernutrition.

Total IgE concentration was analysed in blood samples collected as part of a protocol investigating antibody response to vaccination [5]. Upon enrollment in the antibody study, approximately 5 mL of EDTA plasma was collected and immediately frozen, followed by vaccination against typhoid fever. Two weeks and 3 months later, follow-up blood was drawn. Total IgE concentration was assayed in baseline plasma samples collected prior to vaccination. Samples were shipped on dry ice to the United States and stored at $-20\,^{\circ}C$ prior to analysis. Informed consent was obtained from all participants and their guardians, and the study protocol was approved by the University of North Carolina School of Public Health Institutional Review Board for research involving human subjects.

Total IgE ELISA

Plasma total IgE concentration was determined by ELISA (Bethyl Laboratories, Montgomery, TX, USA). Microtitre plate wells were pre-coated with affinity-purified anti-human IgE, and each sample was added in duplicate (100 μL, diluted 1 : 50 in 50 mM Tris, 0.15 M NaCl, 1% BSA, 0.05% Tween 20, pH 8.0). Plates were incubated at room temperature for 1 h and washed. Affinity-purified anti-human IgE detection antibody (conjugated with HRP) was added, plates were incubated for 1 h, and washed. TMB substrate solution was added to induce colour development, the reaction was stopped with 2 M H_2SO_4, and absorbance was read at 450 nm (Dynatech MR5000, Chantilly, VA, USA). The concentration of total IgE in each sample was determined with a five-parameter logistic standard curve constructed from IgE calibrators of known concentration (Statlia, Brendan Scientific, Grosse Point Farms, MI, USA). Low and high control samples were included with each assay, and between-assay coefficients of variation were less than 10%.

Data analysis

Complete nutritional, anthropometric, morbidity, environmental, and sociodemographic data were available for 99 individuals. The distribution of total IgE was positively skewed, and values were log-transformed to normalize the distribution prior to multiple linear regression analysis (Stata Version 7.0, Stata Corporation, College Station, TX, USA). IUGR and infectious morbidity in the first year of life were the primary independent variables of interest, but aspects of the prenatal environment (maternal nutritional status during pregnancy, maternal age, parity, season of birth), postnatal environment (household size and socio-economic status, number of siblings, duration of breastfeeding, pathogen exposure, maternal smoking during the third trimester), and growth (length, weight) were also considered as potential

predictors of total IgE in adolescence. Detailed data on breastfeeding and the introduction of supplemental foods were collected during bimonthly in-home interviews [30]. In addition, data on nutritional status at age 10–11 years and at the time of blood sampling were evaluated. These data were derived from standard anthropometric measurement procedures [31]. Pubertal status – as assessed by self-reports of menarche (girls) and pubic hair growth (boys) – was also considered.

Infectious morbidity was assessed during the first year of life at each of six bimonthly home visits, at which time mothers were asked if their infant had experienced diarrhoeal or respiratory symptoms in the week preceding the visit. An overall morbidity variable was constructed that sums the presence of diarrhoeal and/or respiratory symptoms at each of these time points. The maximum possible score for this variable is 12, representing the situation where a mother reported symptoms of diarrhoea and respiratory infection every 2 months for the first year of the infant's life. As a result of this interview schedule, the morbidity variable is not a complete morbidity history during the first year of life, but rather a composite of 6 weeks spaced equally throughout the year. Variables were also constructed that summed separately the presence of symptoms of diarrhoea or respiratory infection at each of the six home visits.

Variables assessing the cleanliness of the household environment were combined into two variables representing the degree of pathogen exposure in the first year of life. A baseline pathogen exposure variable included the following, recorded immediately following the infant's birth: quality of the household's water source, adequacy of facilities for excreta disposal, degree of crowding (more than three people/room), frequency of infant bathing (less than daily), and an overall judgement by the interviewer regarding the cleanliness of the household. Each item was coded 0 or 1, and the items were summed such that a higher score indicated a higher degree of baseline pathogen exposure (potential range: 0–5)

Data collected at the six bimonthly home visits were used as indicators of pathogen exposure in the first year of life. At each time point, information was collected on the following: the presence of domestic animals under the house (primarily pigs and goats), an unhygienic food storage area, and the unsanitary preparation of infant food. Each item was coded 0 or 1, and items were summed for each time point to provide an overall measure of pathogen exposure in the first year of life, with a higher score indicating a less sanitary environment (potential range: 0–18).

We hypothesized that IUGR would be associated with higher concentrations of total IgE, and that more frequent episodes of infectious morbidity in the first year of life would be associated with lower IgE. We recognize that undernutrition and infectious morbidity are frequently linked, and we therefore considered their effects independently and simultaneously in regression models to evaluate potential confounding. Similarly, the pattern and duration of breastfeeding was carefully evaluated as a potential covariate due to likely associations with both IUGR and infection.

We pursued the following model building approach to increase our confidence that significant associations with IgE were due to the direct effects of these variables, rather than correlated aspects of postnatal experience [32]: (1) Evaluate the crude association between IUGR and IgE, and between first-year morbidity and IgE. (2) Add variables representing the pattern of breastfeeding, measures of postnatal growth, and aspects of the postnatal environment to multivariate models including birthweight-for-gestational age and first-year morbidity. Interaction terms were included when appropriate. In particular, previous analyses of this data set have suggested the importance of interactions between aspects of the pre- and postnatal environment [5, 6], and between gender and postnatal exposures [33, 34]. A probability (P) less than 0.05 was considered as the criterion for statistical significance. Regression diagnostics were performed to ensure no violations in regression assumptions.

Results

Descriptive statistics are presented in Table 1. Adolescents who were born (SGA) differed significantly from (AGA) adolescents in expected ways: they had lower birthweight, a higher frequency of diarrhoea in the first year, slightly higher weight gain in the first year, and smaller body mass index (BMI) as adolescents. In addition, they were more likely to be first-born children, to be born to mothers with lower BMI, and to have lower current household incomes.

The geometric mean IgE concentration for the entire sample was 54.2 IU/mL (95% CI: 41.7, 70.4). Boys had

Table 1. Descriptive statistics for small-for-gestational age (SGA) and appropriate-for-gestational age (AGA) girls and boys with complete data; mean (SD) values are presented for continuous variables

	SGA ($N = 53$)	AGA ($N = 46$)
Female (%)	50.9	63.0
Gestational age (weeks)	39.4 (1.9)	40.1 (1.9)
Birth weight (g)	2374 (210)***	3294 (381)
Maternal BMI (kg/m^2)	21.1 (2.1)*	22.3 (2.7)
First pregnancy (%)	29.8**	8.3
Growth in length, 1st year (cm)	21.0 (2.8)	20.4 (2.7)
Weight gain, 1st year (kg)	4.98 (0.91)*	4.57 (1.07)
No. of episodes of diarrhoea, 1st year†	1.5 (1.2)*	1.0 (1.0)
No. of episodes of respiratory infection, 1st year	4.6 (1.1)	4.7 (1.3)
Pathogen exposure, 1st year‡	7.5 (3.5)	6.5 (4.0)
Duration of exclusive breastfeeding (days)	48.8 (31.7)	46.7 (43.3)
Weekly household income at birth (pesos)§	197.5 (194.9)	278.1 (230.6)
Current age (year)	14.5 (0.5)	14.6 (0.5)
Current BMI (kg/m^2)	18.1 (1.8)*	19.1 (2.5)
Current weekly household income (pesos)	2645 (1710)***	4493 (3321)

SD, standard deviation; BMI, body mass index.
*$P < 0.05$ (χ^2 test for independence of categorical variables; Student's t-test for continuous variables). **$P < 0.01$. ***$P < 0.001$. †Morbidity episodes were assessed at bimonthly intervals (possible range: 0–6). ‡Summary measure of pathogen exposure as indicated by the presence of animals under the house, unsanitary food storage area, and unsanitary infant food preparation at each of six bimonthly intervals (possible range: 0–18). §One peso = US$0.05 in 1983–84.

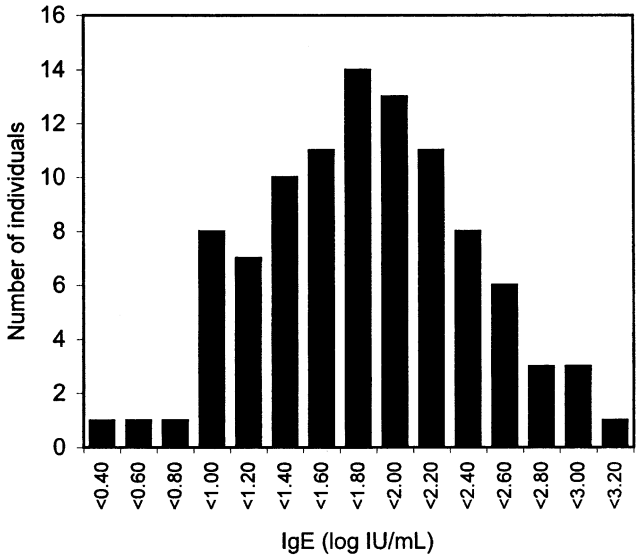

Fig. 1. Distribution of log-transformed total IgE ($N = 99$).

higher geometric mean concentrations (72.8 IU/mL; 48.0, 110.2) than girls (43.2 IU/mL; 30.9, 60.3), and the difference in log-transformed IgE was statistically significant (Student's $t = 1.99$, $P = 0.049$). Fig. 1 presents the distribution of log-transformed total IgE concentration in this population.

Intrauterine growth restriction was not significantly associated with log-transformed IgE ($\beta = 0.072$, $P = 0.53$) in a linear regression model including sex. In a separate regression model including sex, infectious morbidity in the first year of life was found to be negatively related to IgE ($\beta = -0.067$, $P = 0.039$). The same pattern of results was found in a regression model including IUGR, morbidity, and sex. IUGR infants did not differ significantly from non-IUGR infants in the duration of exclusive breastfeeding (48.8 vs. 46.7 days, Student's $t = 0.28$, $P = 0.78$), and infants above the median duration of exclusive breastfeeding (47.8 days) did not have significantly lower rates of first-year morbidity than those below the median (5.7 vs. 6.1 episodes; Student's $t = 1.14$, $P = 0.26$). The duration of exclusive breastfeeding (defined as a median split, 1 = more than 51 days) was not significantly associated with adolescent IgE, and did not alter coefficients for IUGR and first-year morbidity.

Next, variables representing aspects of the prenatal environment, early postnatal environment, size at age 10 or 11 years, current nutritional status, pubertal status, and current environment were evaluated in regression models including sex, IUGR, and first-year morbidity. The following variables were significant predictors of IgE: sex, infectious morbidity, IUGR, pathogen exposure, weight velocity in the first 6 months, and current household income (Table 2). Significant interactions were found for pathogen exposure and IUGR, and pathogen exposure and sex.

On average, mothers reported 5.9 episodes of diarrhoeal and/or respiratory morbidity in their infants during the first year after birth. Higher levels of infectious morbidity in the first year were significantly associated with reduced IgE concentration in adolescence ($\beta = -0.065$, $P = 0.022$). In order to evaluate the potential importance of the timing of infectious morbidity, the first-year morbidity variable was split into two variables representing the first 6 months and second 6 months following birth, respectively. When added simultaneously to a regression model including significant covariates, infectious morbidity during the first 6 months of life was strongly associated with IgE concentration ($\beta = -0.12$, $P = 0.005$) (Fig. 2), whereas morbidity in the second 6 months was not significantly associated with IgE ($\beta = 0.00$, $P = 0.99$). Infants whose mothers reported only one episode of morbidity in the first 6 months ($N = 10$) had an average adjusted log-transformed IgE concentration of 2.06 IU/mL (SD = 0.45) in adolescence, compared with an average of 1.51 IU/mL (SD = 0.48) for those with four morbidity episodes ($N = 20$). These values correspond to untransformed IgE concentrations of 114.8 and 32.4 IU/mL, respectively – almost a fourfold difference.

We further investigated the independent effects of diarrhoea and respiratory infection in the first 6 months. As with the overall morbidity measure, both variables were negatively associated with adolescent IgE concentration, although the effect of diarrhoea only approached statistical significance (diarrhoea: $\beta = -0.10$, $P = 0.16$; respiratory infection: $\beta = -0.13$, $P = 0.03$).

The variable representing the pathogenicity of the household at the time of birth was not found to be significantly

Table 2. Multiple linear regression model with significant predictors of log-transformed adolescent IgE concentration in 14–15-year-olds

	Adj. $R^2 = 0.331$			
$F_{8,90} = 7.05$, $P < 0.0001$	Unadjusted β	Adjusted β	Std. err.	*P*-value
Sex (female = 0, male = 1)	0.603	0.654	0.202	0.002
Pathogen exposure, 1st year	0.074	0.117	0.023	0.000
Sex × pathogen exposure	−0.052	−0.068	0.026	0.010
Birthweight-for-gestational-age (SGA = 1)	−0.552	−0.590	0.207	0.005
Birthweight-for-gestational-age × pathogen exposure	0.086	0.084	0.026	0.002
Morbidity, 1st 6 months	−0.113	−0.121	0.041	0.004
Wt velocity, 1st 6 months (kg/month)	0.726	0.741	0.338	0.031
Distribution of current weekly household income (quartiles)	−0.131	−0.105	0.044	0.020
Constant		0.836	0.307	0.008

Unadjusted β values represent the bivariate association between IgE concentration and each independent variable (variables with significant interaction terms were considered simultaneously). Adjusted β values control for the presence of the remaining variables in the model.

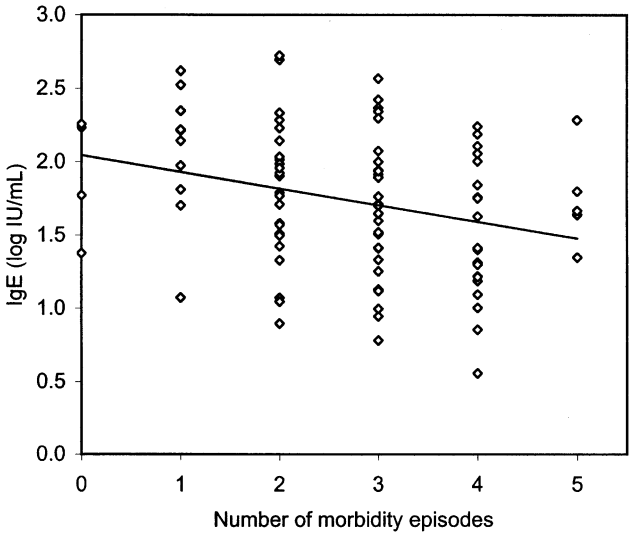

Fig. 2. Relationship between infectious morbidity in the first 6 months of life and total IgE concentration at age 14–15 years, after adjusting for sex, pathogen exposure in the first year of life, birthweight-for-gestational age, weight gain in the first 6 months, and current household income.

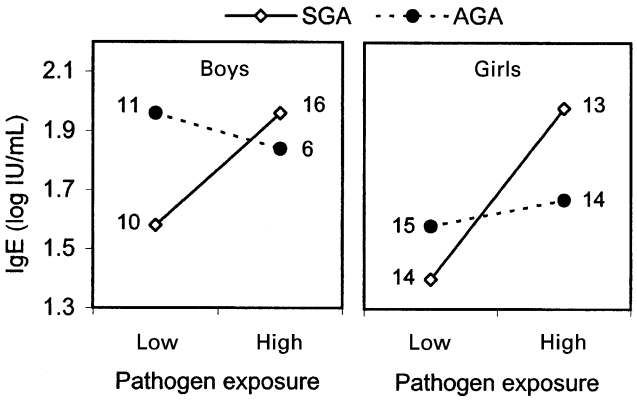

Fig. 3. Interaction between birthweight-for-gestational age and pathogen exposure during the first year of life in predicting total IgE concentration in 14–15-year-old boys and girls. A median split on pathogen exposure was used to define high and low levels of exposure. IgE concentrations were adjusted for morbidity and weight velocity in the first 6 months, and for current household income. The number of individuals in each sub-category is presented next to each data point. The interactions between sex and pathogen exposure and birthweight-for-gestational age are significant at $P<0.01$ (Table 2).

associated with total IgE ($\beta = 0.044$, $P = 0.33$). However, exposure to unsanitary conditions during the first year of life was positively related to adolescent IgE in interaction with both sex and IUGR (Fig. 3). For both boys and girls with IUGR, a relatively unsanitary environment in the first year of life was positively related to adolescent IgE concentration. Average adjusted, untransformed IgE concentrations were more than three times higher for SGA individuals at the 75th percentile of pathogen exposure (91.2 IU/mL), compared with those at the 25th percentile (28.8 IU/mL). For AGA boys there was a slight decrease in untransformed IgE from the 25th percentile of pathogen exposure (81.3 IU/mL) to the 75th percentile (50.1 IU/mL), and for AGA girls, there was a slight increase (33.9 vs. 53.7 IU/mL).

These associations are independent of morbidity, as the relationships between IgE and household pathogenicity are essentially unchanged if morbidity is removed from the model. The timing of exposure was not found to be critical: the pattern of results was similar for both the first 6 months and the second 6 months after birth. Interactions between pathogen exposure and breastfeeding duration were not significant.

The rate of weight gain (kg/month) in the first year was positively, but not significantly, associated with adolescent IgE ($\beta = 0.76$, $P = 0.22$). When weight gain was divided into two periods – birth to 6 months, and 6 to 12 months – weight gain in the first 6 months was positively related to IgE (Table 2), while weight gain in the second 6 months was not significant ($\beta = -0.55$, $P = 0.28$). Height gain during the first year (or first 6 months) was not significantly related to adolescent IgE. The magnitude of the effect of weight gain in the first 6 months was modest: at the 25th percentile for weight velocity (0.53 kg/month), the average adjusted, untransformed IgE concentration was 44.7 IU/mL, compared with 60.3 IU/mL at the 75th percentile (0.70 kg/month).

Weekly household income at the time of blood sampling was the only measure of the current environment that was significantly associated with adolescent IgE production. Individuals from the lowest income quartile had average adjusted untransformed IgE concentrations that were more than double those of individuals from the highest quartile (75.9 vs. 36.3 IU/mL).

Discussion

In this population of Filipino adolescents, followed prospectively from birth to age 14–15 years, perinatal factors were found to be significant predictors of current total IgE production. These results are consistent with previous reports from this population linking adolescent vaccine responsiveness and thymopoietin production to prenatal undernutrition and postnatal infectious disease exposure [5, 6]. While a large body of research has documented the long-term effects of early environments on adult cardiovascular and metabolic systems, our findings add to growing evidence that development of the immune system may in part be similarly 'programmed' [8, 35, 36].

The negative association between adolescent IgE concentration and infectious morbidity in the first 6 months is consistent with a number of studies reporting a protective effect of infection in infancy or childhood [20–23, 37]. This finding is also consistent with our previous report of a positive association between diarrhoeal morbidity in the first year of life and typhoid vaccine responsiveness in adolescence [5]. The physiological and developmental processes linking early nutrition, infection, and later IgE production are not clear, and were not directly investigated in this study. Impaired thymic development and alterations in the balance of Th1/Th2 lymphocytes have been proposed as potential mechanisms [13], although a recent evaluation of head circumference, thymus size at birth, and the development of allergy failed to support this model [15].

Both respiratory infection and diarrhoea were negatively associated with adolescent IgE, although only the effect of

respiratory infection was statistically significant. In this relatively small sample, it is not possible to determine whether this indicates a more important role for respiratory infection, or a type II error with respect to diarrhoea. Furthermore, since morbidity information was collected at bimonthly intervals, we do not have a complete record of early infections, but instead an overall, relative index of early disease experience. Indeed, the positive association between IgE and weight velocity in the first 6 months may represent unexplained variance in early morbidity: infants with high levels of infection will gain less weight, and if there is an underlying positive association between early infection and subsequent IgE production, then this will be reflected in a positive association between weight velocity and IgE.

Although we cannot elaborate on the implications of specific numbers or types of infections, our association between early morbidity and adolescent IgE production remains significant even after controlling for a wide range of potentially confounding variables. As such, this finding lends support to the hygiene hypothesis that complements the large number of retrospective studies that report similar associations, but do not control for potentially confounding factors such as prenatal undernutrition and duration of breastfeeding. The absence of a significant effect of breastfeeding in our analysis is noteworthy, and suggests the possibility that previous associations between breastfeeding and IgE may in part be mediated by correlated aspects of perinatal experience.

The positive association between IgE and pathogen exposure during the first year appears to run counter to the hygiene hypothesis, although it is possible that this variable represents an overall measure of allergen, rather than pathogen, exposure. The presence of domestic animals has been positively associated with the development of allergy and contaminated foods may have sensitizing effects, although research in this area is currently inconclusive [38–40]. Alternatively, the implications of early pathogen exposure for IgE production may depend upon the type of micro-organism, the timing and dose of exposure, whether the exposure results in infection, and the severity of subsequent infection [20]. In addition, it is possible that our pathogen exposure variable may be related to parasitic infection, which is associated with elevations in total, but not allergen-specific, IgE [41]. Data on the prevalence of parasitic infection in our population are not available. However, a higher burden of parasitic infection could account for the relatively high concentration of total IgE compared with European populations [42].

The effects of pathogen exposure in this sample appear to be moderated by prenatal undernutrition. Overall, adolescents born SGA did not have significantly elevated concentrations of IgE compared with AGA adolescents. However, high pathogen exposure was associated with high levels of adolescent IgE only for individuals born SGA, whereas pathogen exposure in the first year was associated with only slightly higher IgE concentrations for AGA girls, and lower IgE concentrations for AGA boys. This increased sensitivity to postnatal exposures among SGA individuals is consistent with previous findings from this population [5, 6], and suggests that the long-term immunological consequences of postnatal infectious morbidity may in part be contingent upon the quality of the prenatal nutritional environment. This significant interaction between prenatal undernutrition and postnatal infection may clarify why prior tests of the hygiene hypothesis focusing solely on the postnatal environment have yielded inconsistent results.

Strengths of this study include a prospective research design, and the consideration of a wide range of prenatal, early postnatal, childhood, and adolescent variables that may confound or modify the relationships among prenatal undernutrition, early infection, and IgE production later in life. In particular, the large data set that comprises the CLHNS allows us to consider interactions between prenatal and postnatal factors that appear to be important in shaping the development of aspects of immune function.

Limitations of this study include a relatively small sample size, and associated reductions in statistical power. It is also possible that the effect of birthweight was overestimated, since the average birthweight for SGA individuals in our sample was 132 g lower than the average for SGA individuals in the entire CLHNS cohort. However, other socio-economic, lifestyle, and anthropometric differences were not significant. The clinical implications of the findings are not evident, since data on symptoms of allergy and/or asthma were not collected, and we have assayed only total IgE and not allergen-specific IgE.

We now have consistent evidence in this population for early life influences on three different parameters of adolescent immune function. Variations in antibody response to vaccination [5], thymic hormone production [6], and IgE production are each significantly associated with aspects of intrauterine and early postnatal environments. Future research should investigate these associations in larger samples, and explore potential associations between early environments and symptoms of asthma and other atopic diseases, as well as explore the potential mechanisms through which perinatal factors exert long-term effects on immune development [36].

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