Neonatal adiposity increases the risk of atopic dermatitis during the first year of life

Sinéad M. O'Donovan, PhD,[a] Jonathan O'B. Hourihane, MD,[b] Deirdre M. Murray, PhD,[b,c] Louise C. Kenny, PhD,[c,d] Ali S. Khashan, PhD,[c,e] Carol ní Chaoimh, PhD,[a] Alan D. Irvine, MD,[f,g,h] and Mairead Kiely, PhD[a,c]

Cork and Dublin, Ireland

Background: Early nutrition and adiposity have been linked to atopic dermatitis (AD) development.

Objective: We sought to describe risk factors for AD in the first year of life in infants participating in the Cork BASELINE birth cohort study (n = 1537).

Methods: Prospective data on early-life events, infant feeding, and nutritional and environmental exposures were collected at 15 weeks' gestation, birth, and 2, 6, and 12 months of age. Body composition was assessed by using air displacement plethysmography at day 2 and 2 months. The primary outcome, persistent AD, was determined if the UK Working Party Diagnostic Criteria were satisfied at both 6 and 12 months.

Results: At 6 and 12 months, the point prevalence of AD was 14.2% (99% CI, 10.5% to 17.8%) and 13.7% (99% CI, 10.3% to 17.6%), respectively; 7.5% (99% CI, 5.0% to 9.9%) of infants had AD at both 6 and 12 months of age. At hospital discharge, 35% of infants were exclusively breast-fed, decreasing to 14% by 2 months. Complementary feeding was commenced at a median of 19 weeks (interquartile range, 17-22 weeks; 19% at <17 weeks and 6% at ≥26 weeks). Median fat mass at day 2 was 0.35 kg (interquartile range, 0.25-0.48 kg). A parental history of atopic disease was self-reported by 43% of mothers and 34% of fathers. Risk factors for AD at 6 and 12 months were maternal atopy (adjusted odds ratio, 2.99; 99% CI, 1.35-6.59; $P = .0004$) and fat mass of the 80th percentile or greater at day 2 (adjusted odds ratio, 2.31; 99% CI, 1.02-2.25; $P = .009$).

Conclusion: This is the first report of neonatal adiposity as a predictor of AD at 6 and 12 months of age in a well-characterized atopic disease–specific birth cohort. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Atopic dermatitis, eczema, infant, body composition, vitamin D, infant feeding*

Atopic dermatitis (AD) is the most common inflammatory disease of childhood,[1] affecting around 1 in 5 children in the developed world[2]; however, it is also a disease of urbanization within developing nations.[3] Although research efforts have intensified to try and identify the cause and preventive strategies for AD, the cause of AD has yet to be firmly established.[4] These factors are likely to be complex given that AD is a multifaceted disease. There is a well-recognized inherited component to the expression of AD[4,5]; however, environmental factors, including nutrition, can also contribute to the increasing prevalence.

The role of environmental factors in AD development has been studied, including rural and urban living, infections, antibiotic use, farm residence, pet ownership, mode of delivery, day care attendance, and pollution.[6,7] The results from these studies have been inconsistent.

Maternal and infant nutrition studies have focused on maternal avoidance and restrictive diets during pregnancy and lactation[8,9]; early infant feeding practices, such as breast-feeding[10]; use of hydrolyzed infant formula[11,12]; and timing of complementary feeding[13-17] or the specific role of potential immunomodulatory nutrients, such as vitamin D,[18-20] long-chain polyunsaturated fatty acids,[21,22] antioxidants,[23,24] and folic acid,[25] in AD development. Data from these studies have been inconsistent, but as highlighted recently by Grimshaw et al,[26] focusing on single aspects of early infant nutrition might be an oversimplification of the complex interactions contributing to the development of food allergy. These observations could also be applied to AD.

Obesity is more common among asthmatic children,[27-29] and recent data suggest that obesity might also play a role in the development of AD.[30-32] However, these studies were primarily in school-aged children and used body mass index (BMI) as a proxy for adiposity. Association studies are very difficult to

From [a]the Vitamin D Research Group, School of Food and Nutritional Sciences, [b]the Department of Paediatrics and Child Health, [c]the Irish Centre for Fetal and Neonatal Translational Research, and the Departments of [d]Obstetrics and Gynaecology and [e]Epidemiology and Public Health, University College Cork; [f]the Department of Clinical Medicine, Trinity College, Dublin; [g]the Department of Paediatric Dermatology, Our Lady's Children's Hospital, Dublin; and [h]the National Children's Research Centre, Dublin.

The National Children's Research Centre (NCRC) is the primary funding source for the ongoing Cork Babies After SCOPE: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints (BASELINE) birth cohort. Additional support came from the UK Food Standards Agency (FSA) (grant no. T07060). The SCOPE Ireland Study was funded by the Health Research Board of Ireland (CSA 02/2007). L.C.K., M.K., and D.M.M. are PIs in the Science Foundation Ireland funded INFANT Research Centre (grant no. 12/RC/2272). S.M.O'D. is supported by a grant to M.K. from the European Commission under the Seventh Framework (ODIN, GA 613977 Food-based Solutions for Optimal Vitamin D Nutrition and Health through the Life-cycle) and by a grant to M.K. and J.O'B.H. from the European Commission under the Seventh Framework (iFAAM; GA 312147 Integrated Approaches to Food Allergen and Allergy Risk Management).

Disclosure of potential conflict of interest: S. M. O'Donovan has received research support from the European Union FP7 (ODIN, GA 613977; iFAAM; GA 312147). J. O'B. Hourihane has received research support from the Food Standards Agency and the National Children's Research Centre Ireland and has received lecture fees from Thermo Fisher. L. C. Kenny has provided expert testimony in several ongoing medical negligence cases, has received research funding to support the Centre that she directs (www.infantcentre.ie), and has received royalties as the editor of several textbooks (www.infantcentre.ie). M. Kiely has received research support from the National Children's Research Centre, Crumlin, Dublin, for establishment of the cohort; from iFAAM (EC grant no. 312147) for serving as a coinvestigator; and from ODIN (EC grant no. 613977) for serving as principal investigator and project coordinator. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 16, 2015; revised May 6, 2015; accepted for publication May 6, 2015.

Corresponding author: Mairead Kiely, PhD, University College Cork, Food and Nutritional Sciences, Vitamin D Research Group, School of Food and Nutritional Sciences, Cork, Ireland. E-mail: m.kiely@ucc.ie.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.05.035

Abbreviations used
AD: Atopic dermatitis
BASELINE: Babies After SCOPE: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints
BMI: Body mass index
IQR: Interquartile range
25(OH)D: 25-Hydroxyvitamin D
OR: Odds ratio
SCOPE: Screening for Pregnancy Endpoints
UKWPDC: UK Working Party Diagnostic Criteria

interpret because obesity itself is a multifactorial disease and AD has uncertain pathogenesis. A lack of studies in early childhood (0-2 years), the period with the highest incidence of AD, represents an area that should be further explored.

Therefore in this well-characterized birth cohort study (Cork Babies After SCOPE: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints [BASELINE] birth cohort study) targeted at growth, nutrition, and atopic disease outcomes, we conducted an integrated analysis of factors that have been reported to be associated with development of AD throughout the first year of life, including familial tendency, body composition, infant feeding, and nutritional and environmental exposures.

METHODS

Study design

From August 2008 to November 2011, 2137 infants were recruited to the ongoing Cork BASELINE birth cohort study. The Cork BASELINE birth cohort study is a noninterventional, single-center birth cohort; a complete cohort description was previously provided.[33] All women participating in the Screening for Pregnancy Endpoints (SCOPE) study were invited to partake in the Cork BASELINE birth cohort, and 1537 provided consent. SCOPE is a global multicenter longitudinal cohort study of low-risk primiparous women, with the main aim of developing screening tests for the major diseases of late pregnancy.[34-36] An additional 600 infants were enrolled after delivery from the postnatal wards of Cork University Maternity Hospital; however, these infants were not included in the current analysis because prospective antenatal data and umbilical cord blood were not collected.

The Cork BASELINE birth cohort study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures were approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (ref ECM5[9] 01/07/2008). BASELINE is registered with the National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov, ID: NCT01498965). SCOPE is registered at the Australian New Zealand Clinical Trials Registry (ACTRN12607000551493). Written informed consent for the Cork BASELINE birth cohort was obtained at 20 weeks' gestation or at birth.

For details on the Cork BASELINE birth cohort study stratified by infants with and without persistent AD at 6 and 12 months of age, see Table I.

Nutritional and clinical assessments

Information on study participants was gathered by using interviewer-led detailed questionnaires and clinical assessments at day 2 and at 2, 6, and 12 months. Questionnaires captured details on demography, maternal and paternal self-reported atopy (rhinitis, house dust mites, animals, latex, AD, bee/wasp, and asthma), environment during pregnancy, and the baby's early-life environment.

With respect to early infant nutrition, detailed information on feeding method (breast-fed, formula fed, or combination fed), frequency of feeds, name and brand of infant formula, solid food, feeding behavior, and provision of supplements was collected at each time point. Definitions for the current article include the following: *exclusive breast-feeding*, human milk only, with infants receiving no water, infant formula, or supplementary fluids; *fully breast-feeding*, human milk is the main source of nutrition, with infants occasionally receive infant formula or other drinks, although not on a regular basis; and *any breast-feeding*, infant receives any volume of human milk.

Anthropometric measures of weight, length, and abdominal circumference were measured by using standard operating procedures. Age- and sex-specific weight-for-length SD scores were calculated by using the LMS method[37] and World Health Organization growth reference data.[38] Based on the cohort-specific results, regional percentiles were calculated. BMI percentiles for weight at birth and 2 and 6 months were calculated, and cutoffs that represent the 91st and 98th percentiles were used in estimating the odds of AD. However, for abdominal circumference at day 2, percentiles that represent the 85th and 95th percentiles were created. Body composition analysis was performed at day 2 and 2 months in an infant-sized air displacement plethysmography system, the PEA POD Infant Body Composition System (COSMED USA, Concord, Calif), which was developed and validated for the assessment of infant body composition from birth to approximately 6 months of age.[39,40] Fat mass, fat mass index, fat-free mass, and fat-free mass index were considered continuous measures of risk, but for estimating the odds of AD defined by the UK Working Party Diagnostic Criteria (UKWPDC), cutoffs that represent the 80th and 85th percentiles for these measures at day 2 and 2 months were created from participants in this study.

AD diagnosis

Possible AD was identified at 6 and 12 months by using serial allergy questionnaires obtained from the EuroPrevall study,[41] and AD was then formally diagnosed by using the UKWPDC.[42] The primary outcome in the current analysis was persistent AD, which was diagnosed if infants satisfied the UKWPDC at both 6 and 12 months. Secondary outcomes included AD at 6 months that achieved remission at 12 months and late-onset AD at 12 months.

Biomarker analysis

Serum 25-hydroxyvitamin D (25[OH]D) concentrations were quantified in maternal serum 25(OH)D at 15 weeks' gestation and in umbilical cord blood by using a liquid chromatography–tandem mass spectrometry method that is traceable to the National Institute of Standards Technology reference measurement procedure and accredited by the Centers for Disease Control Vitamin D Standardization Certification Program.[43,44]

Statistical analysis

Statistical analysis of the data was conducted with IBM SPSS for Windows, version 21 (2012; IBM, Armonk, NY). Data are presented by using descriptive statistics, including means with SDs, medians with interquartile ranges (IQRs) for continuous variables, and frequencies with percentages for categorical variables. For comparisons between categorical variables, χ^2 or Fisher exact tests were used, whereas independent *t* tests or nonparametric tests were used for continuous variables depending on their distribution.

To date, no reference intervals have been established specifically for pregnancy or umbilical cord 25(OH)D concentrations, and therefore current thresholds for children and adults were used; the minimum threshold for vitamin D deficiency is a 25(OH)D concentration of less than 30 nmol/L, and 97.5% of the population requirements should be met at 50 nmol/L or greater.[45] In addition, serum 25(OH)D concentrations at 10 nmol/L increments were explored. An exploratory analysis of the various anthropometric and body composition measures was performed (weight percentiles, fat-free mass [in kilograms], fat mass [in kilograms], and fat mass index [fat mass in kilograms/length in meters squared] at day 2 and 2 months) examining the relationship with AD.

All potential risk factors for AD (hereditary, demographic, anthropometric, body composition, and environmental and nutritional exposures) were explored in univariate analyses for persistent AD (Table II), late-onset AD

TABLE I. Description of the Cork BASELINE birth cohort study stratified by infants with and without persistent AD at 6 and 12 months

Variable	Cohort (n = 709)	No AD (n = 573)	AD at 6 and 12 mo (n = 53)	*P* value
Maternal factors				
Age (y), mean (SD)	31.1 (4)	30.9 (4.1)	32 (3.3)	.059*
≥35 (%)	98 (14)	72 (13)	10 (19)	.193†
Education, university (%)	342 (48)	277 (48)	25 (47)	.861†
Marital status, married (%)	536 (75)	424 (74)	43 (81)	.254†
BMI at 15 wk, ≥30 kg/m^2 (%)	85 (12)	65 (11)	7 (13)	.684†
Smoker at 15 wk (%)	46 (7)	43 (8)	3 (6)	.788‡
Domestic pet kept during pregnancy (%)	285 (40)	226 (39)	20 (38)	.808†
25(OH)D at 15 wk (nmol/L), median (IQR)	58 (39-78)	58 (39-78)	55 (43-79)	.771‡
<30 (%)	107 (15)	86 (15)	8 (15)	.991†
<50 (%)	286 (40)	229 (40)	19 (36)	.551†
Vitamin D supplement in pregnancy (%)	335 (48)	260 (46)	29 (55)	.216†
Delivery, vaginal (%)	519 (73)	427 (75)	35 (75)	.172†
Family history of atopy§				
Maternal (%)	304 (43)	230 (40)	35 (66)	.0003†
Paternal (%)	242 (34)	179 (32)	24 (45)	.043†
Neonatal factors				
Sex, female (%)	3441 (48)	276 (48)	23 (43)	.506†
Season of birth, summer (%)	289 (41)	235 (41)	26 (49)	.256†
Birth weight (kg), mean (SD)	3.5 (0.5)	3.4 (0.5)	3.6 (0.5)	.139*
Fat mass, day 2				
Fat mass (kg)				
≥80th percentile (%)	142 (20)	103 (18)	18 (34)	.006†
Fat mass index (kg/m^2)				
≥80th percentile (%)	142 (20)	105 (19)	16 (30)	.043
Fat mass, 2 mo				
Fat mass (kg)				
≥80th percentile (%)	112 (20)	89 (20)	6 (15)	.414
Fat mass index (kg/m^2)				
≥80th percentile (%)	109 (20)	90 (20)	5 (12)	.219
Cord 25(OH)D (nmol/L), median (IQR)	33 (21-46)	32 (20-46)	36 (23-48)	.662‡
<30 (%)	314 (44)	262 (46)	20 (38)	.263†
<50 (%)	562 (79)	454 (79)	42 (79)	.998†
Vitamin D supplement at 6 mo (%)	350 (49)	274 (48)	30 (57)	.221†
Breast-fed				
Exclusive discharge (%)	245 (35)	194 (34)	17 (32)	.786†
Exclusive 2 mo (%)	101 (14)	80 (14)	6 (11)	.581†
Complementary feeding				
With concurrent breast-feeding (%)	229 (32)	178 (31)	17 (32)	.879†
Age of introduction				
<17 wk (%)	126 (19)	101 (18)	9 (18)	.959†
>26 wk (%)	39 (6)	9 (2)	1 (2)	.520‡
Domestic pets kept at 6 mo	271 (38)	209 (37)	22 (42)	.467†

*Independent *t* test.
†χ^2 Test.
‡Fisher exact test.
§Self-reported diagnosis of asthma, allergic rhinitis, AD, food allergy, bee/wasp, latex, house dust, or animals.

(Table III), and AD that achieved remission (Table IV). Potential predictors of the primary outcome, persistent AD, were retained in the regression model if they were at a *P* value of less than .1 in the univariate analysis. On the basis of these analyses, we performed a multivariate logistic regression for persistent AD (Table V), late-onset AD, and AD that achieved remission (Table VI), including maternal and paternal atopy, fat mass at the 80th or greater percentile at day 2, vitamin D postnatal supplementation, and season of birth. Analyses were adjusted for multiple testing, with 5 variables included in the multivariate logistic regression; a *P* value of less than .01 was considered statistically significant. Results are interpreted by using this multiple testing–adjusted *P* value.

Results of all logistic regression models are reported as odd ratios (ORs) with 99% CIs. Interactions between the significant risk factors were explored. *Post hoc* analysis was performed to explore whether increased fat mass modified the association between 25(OH)D concentration and AD; we tested the interaction between maternal and cord 25(OH)D concentrations and fat mass at the 80th percentile or greater at an α value significance level of .01.

RESULTS

Participants

Maternal-infant dyads recruited through the SCOPE study (n = 1537), with cord serum available (n = 1050), and who attended and completed the 12-month assessment

(n = 709) were included in the current analysis. Maternal and neonatal characteristics are detailed in Table I. Several prenatal exposures reported in the literature as risk factors for AD development were incorporated into the analysis, which included maternal age (>35 years [14%]), smoking (7%), obesity (BMI >30 kg/m^2 [12%]), maternal 25(OH)D concentration at 15 weeks' gestation (median, 58.5 nmol/L; interquartile range, 38.7-78.1 nmol/L) and vitamin D supplementation (48%). Early postnatal factors, including cesarean section delivery (27%), summer season of birth (41%), cord serum 25(OH)D concentration (median, 32.7 nmol/L; interquartile range, 20.7-46.2 nmol/L), and the keeping of domestic pets at 6 months (38%) were also considered (Table I).

Primparous women with a singleton pregnancy were recruited exclusively from the Cork region, and therefore the birth cohort is not nationally representative. Although more tertiary educated mothers were recruited than groups reported elsewhere,[46,47] other sociodemographic and infant feeding characteristics compared well with national reports, as previously described.[33]

Feeding practices

Breast-feeding was initiated in 71% of infants; 35% were exclusively breast-fed. At 2 months, 47% of infants were still receiving any breast milk, of whom 14% and 33% were exclusively and fully breast-fed, respectively. By 6 months, 1% were exclusively breast-fed, with 22% still receiving any breast milk in combination with infant formula, solid food, or both. Overall, 49% of infants were provided with a vitamin D–containing supplement at 6 months. Median age of complementary feeding for the cohort (n = 709) was 19 weeks (interquartile range, 17-22 weeks), with 19% introduced to solid food before 17 weeks (early) and 6% after 26 weeks (late).

Anthropometry and body composition

Mean birth weight was 3.5 kg (SD, 0.5 kg). Median abdominal circumference at day 2 was 34 cm (interquartile range, 32-35 cm), with 8% above the 95th percentile. Median fat mass at day 2 was 0.35 kg (interquartile range, 0.25-0.48 kg), with a range of 0.036 to 1.1 kg. Median fat mass index at day 2 was 1.47 kg/m^2 (interquartile range, 1.01-1.87 kg/m^2), with a range of 0.15 to 3.81 kg/m^2. By 2 months, median fat mass and the fat mass index were 1.19 kg (interquartile range, 0.98-1.4 kg) and 3.46 kg/m^2 (interquartile range, 2.93-4.03 kg/m^2), respectively.

AD

At 6 and 12 months, the point prevalence of AD was 14.2% (99% CI, 10.5% to 17.8%) and 13.7% (99% CI, 10.3% to 17.6%), whereas the cumulative prevalence of AD in the first year of life was 20.5% (99% CI, 16.7% to 24.4%). The prevalence of persistent AD at 12 months was 7.5% (99% CI, 5.0% to 9.9%). The prevalence of late-onset AD and AD at 6 months that achieved remission by 12 months was 6.2% (99% CI, 4.0% to 8.6%) and 6.8% (99% CI, 4.5% to 9.4%), respectively. The prevalence of maternal (66% vs 40%) and paternal (45% vs 32%) atopic history was higher in infants with persistent AD. Infants with persistent AD had a higher fat mass of greater than the 80th percentile (27% vs 15%) compared with infants who never had AD ($P < .05$).

Factors associated with persistent AD

Prenatal exposures not associated with the development of persistent AD were maternal smoking (OR, 0.55 [99% CI, 0.12-2.62]), BMI greater than 30 kg/m^2 (OR, 1.33 [99% CI, 0.52-3.38]), and vitamin D supplementation (OR, 1.12 [99% CI, 0.58-2.15]). Early postnatal factors not associated with the development of persistent AD were breast-feeding (exclusive or fully at hospital discharge and 2 months), cesarean section delivery (1.32 [OR, 99% CI, 0.65-2.69]), and keeping of domestic pets (OR, 1.37 [99% CI, 0.71-2.66]; Table II). Neither maternal nor cord serum 25(OH)D concentrations were associated with AD risk. The main risk factors for persistent AD were self-reported maternal atopy (OR, 2.99 [99% CI, 1.35-6.59], $P = .0004$) and fat mass (in kilograms) at the 80th percentile or greater at day 2 (OR, 2.31 [99% CI, 1.02-5.25], $P = .009$; Table V). No significant risk factor was identified for late-onset AD and AD that achieved remission (Table VI).

Other anthropometric measures, including birth weight percentiles and abdominal circumference at day 2, were not associated with persistent AD. Fat-free mass and fat mass index at day 2 or any measure of body composition at 2 months were also not associated with persistent AD. This indicates that neonatal fat mass rather than body size at birth or during infancy is associated with the development of persistent AD. Among infants with a maternal atopic history, fat mass at day 2 remained a risk factor for persistent AD (OR, 2.71 [99% CI, 0.98-1.79], $P = .012$). The interactions between maternal atopy and fat mass at day 2 and between fat mass and maternal/cord serum 25(OH)D concentrations were not significant (all $P > .05$), and therefore no effect modifier was described for persistent AD.

Considering that some of the increased ORs were not statistically significant, we calculated *post hoc* statistical power for each nonsignificant association, as presented in Table V. For the association between paternal atopy and AD, the statistical power was 45% and 24% at the 5% and 1% significance level, respectively. For vitamin D supplementation at 6 months and AD association, the available statistical power was 6% and 18% at the 5% and 1% significance level, respectively. For the season of birth and AD association, the statistical power was 16% and 5% at the 5% and 1% significance level, respectively.

DISCUSSION

These data show for the first time that neonatal adiposity is positively associated with AD. Using a well-characterized, disease-specific, prospective birth cohort, we have shown that in our cohort a number of proposed risk factors for atopic disease, including maternal sociodemographic factors, smoking, BMI, mode of delivery, domestic pets, early infant feeding, age of complementary feeding, and vitamin D status during pregnancy and at delivery were not associated with the infant's risk of persistent AD and that maternal atopic history and infant fat mass were independently predictive of persistent AD as diagnosed by using a clinically validated assessment.

Adiposity is suggested to induce systemic inflammation, which might negatively influence the immature immune system and atopic outcomes. Although the precise link between obesity and AD remains to be elucidated, the hypothesis is plausible. Adipokine levels are reportedly altered in patients with AD with reduced levels of visfatin and adiponectin[48,49] and increased levels of resistin and apelin.[48] Emerging evidence has

TABLE II. Univariate predictors of persistent AD

	AD, no. (%)	OR (99% CI)	*P* value
Persistent AD	53 (7.5)		
Maternal factors			
Maternal age (≥35 vs <35 y)	10 (12.2)	1.61 (0.69-3.76)	.146
University education (vs none)	25 (8.3)	0.93 (0.49-1.80)	.787
Married (vs single)	43 (9.2)	1.26 (0.56-2.76)	.448
Cesarean section delivery (vs vaginal)	18 (11)	1.32 (0.65-2.69)	.319
BMI at 15 wk (≥30 vs <30 kg/m^2)	7 (9.7)	1.33 (0.52-3.38)	.434
Smoker at 15 wk (vs nonsmoker)	3 (6.5)	0.55 (0.12-2.62)	.322
Domestic pet kept during pregnancy (vs none)	20 (8.1)	1.13 (0.58-2.18)	.647
25(OH)D status at 15 wk (nmol/L)			
<30 (vs ≥30)	8 (8.5)	0.90 (0.35-2.32)	.776
<50 (vs ≥50)	19 (7.7)	0.94 (0.43-2.07)	.834
Vitamin D–containing supplement at 15 wk (vs none)	29 (10)	1.12 (0.58-2.15)	.666
Alcohol consumption at 15 wk (vs none)	6 (6.1)	0.91 (0.37-2.20)	.906
Rural living environment (vs urban)	26 (8.9)	1.11 (0.58-2.14)	.675
Family history of atopy*			
Maternal (vs none)	35 (13.2)	2.87 (1.44-5.72)	.00008
Paternal (vs none)	24 (11.8)	1.61 (0.83-3.13)	.063
Neonatal factors			
Sex, female (vs male)	23 (7.7)	0.80 (0.41-1.54)	.376
Summer season of birth (vs winter)	26 (10)	1.62 (0.84-3.13)	.058
Anthropometry†			
Birth weight			
>91st percentile (vs <91st percentile)	5 (9.1)	1.07 (0.41-2.81)	.890
Weight at 2 mo			
>91st percentile (vs <91st percentile)	3 (6.7)	0.71 (0.21-2.38)	.583
Weight at 6 mo†			
>91st percentile (vs <91st percentile)	4 (7.8)	0.86 (0.30-2.46)	.778
Abdominal circumference at day 2			
>85th percentile (vs <85th percentile)	5 (9.1)	0.99 (0.313-3.15)	.988
>95th percentile (vs <95th percentile)	4 (8.0)	0.89 (0.26-3.12)	.818
Body composition			
Fat mass ≥80th percentile (vs <80th percentile)			
Day 2	18 (14.8)	2.31 (1.04-5.13)	.007
2 mo	6 (6.3)	0.69 (0.28-1.69)	.416
Fat mass index (kg) ≥80th percentile (vs <80th percentile)			
Day 2	16 (13.2)	1.89 (1.01-3.53)	.045
2 mo	5 (5.3)	0.55 (0.21-1.44)	.225
Cord 25(OH)D status (nmol/L)			
<30 (vs ≥30)	20 (7.1)	0.85 (0.36-2.04)	.639
<50 (vs ≥50)	42 (8.5)	1.07 (0.44-2.56)	.851
Vitamin D–containing supplement at 6 mo (vs no)	30 (9.9)	1.61 (0.83-3.13)	.064
Exclusive breast-feeding (vs no)			
At hospital discharge	17 (8.1)	0.88 (0.42-1.79)	.635
At 2 mo	6 (7.3)	0.89 (0.32-2.45)	.768
Any breast-feeding (vs none)			
At hospital discharge	41 (9.2)	1.56 (0.70-3.48)	.154
At 2 mo	28 (9.6)	1.35 (0.71-2.60)	.238
At 6 mo	14 (10.4)	1.52 (0.73-3.17)	.145
Age of solid food introduction (vs 17-26 wk)			
<17 wk	9 (8.2)	0.88 (0.36-2.15)	.720
>26 wk	4 (11.8)	1.09 (0.27-4.43)	.881
Domestic pet at 6 mo (vs none)	22 (9.5)	1.37 (0.71-2.66)	.216

*Self-reported diagnosis of asthma, allergic rhinitis, AD, food allergy, bee/wasp, latex, house dust, or animals.
†Based on cohort-specific percentiles.

demonstrated a positive association between adiposity, more recently central adiposity, and AD, although most studies have focused on school-aged children and used BMI, which is an indirect measure of adiposity.[30-32,40-52] Intrauterine exposure to maternal obesity[53] and gestational diabetes mellitus,[54,55] which have been linked to fetal macrosomia, might increase the risk of infant adiposity. Our data showed no association between maternal BMI or infant birth weight and AD. The independent association with fat mass at birth specifically requires further exploration.

Exclusive breast-feeding for 4 months is suggested to reduce AD risk.[10,56] We found no association between breast-feeding and

TABLE III. Univariate predictors of late-onset AD

	AD, no. (%)	OR (99% CI)	*P* value
Late-onset AD	44 (7.2)		
Maternal factors			
Maternal age (≥35 vs <35 y)	10 (12.2)	1.75 (0.70-4.37)	.118
University education (vs none)	21 (7.0)	0.98 (0.47-2.02)	.929
Married (vs single)	33 (7.2)	1.25 (0.52-2.99)	.512
Cesarean section delivery (vs vaginal)	9 (5.8)	0.94 (0.40-2.19)	.839
BMI at 15 wk (≥30 vs <30 kg/m^2)	9 (12.2)	1.75 (0.68-4.54)	.130
Smoker at 15 wk (vs nonsmoker)	41 (7.2)	1.21 (0.34-4.28)	.696
Domestic pet kept during pregnancy (vs none)	24 (9.6)	1.51 (0.73-3.14)	.144
25(OH)D status at 15 weeks (nmol/L)			
<30 (vs ≥30)	7 (7.5)	0.93 (0.33-2.57)	.844
<50 (vs ≥50)	18 (7.3)	1.19 (0.57-2.48)	.536
Vitamin D–containing supplement 15 wk (vs none)	19 (6.8)	0.95 (0.46-1.97)	.848
Alcohol consumption at 15 wk (vs none)	5 (5.1)	0.48 (0.14-1.65)	.125
Rural environment (vs urban)	16 (5.7)	0.64 (0.30-1.37)	.131
Family history of atopy*			
Maternal (vs none)	21 (8.6)	1.17 (0.56-2.44)	.572
Paternal (vs none)	19 (9.6)	1.76 (0.85-3.67)	.047
Neonatal factors			
Sex, female (vs male)	21 (7.1)	1.07 (0.52-2.22)	.807
Summer season of birth (vs winter)	16 (7.2)	1.17 (0.57-2.43)	.576
Anthropometry†			
Birth weight			
>91st percentile (vs <91st percentile)	3 (5.7)	0.75 (0.23-2.52)	.644
Weight at 2 mo			
>91st percentile (vs <91st percentile)	4 (8.7)	1.25 (0.43-3.67)	.684
Weight at 6 mo†			
>91st percentile (vs <91st percentile)	3 (6.0)	0.77 (0.23-2.59)	.676
Abdominal circumference at day 2			
>85th percentile (vs <85th percentile)	5 (9.1)	1.05 (0.30-3.68)	.925
>95th percentile (vs <95th percentile)	5 (9.8)	1.15 (0.33-4.06)	.776
Body composition			
Fat mass ≥80th percentile (vs <80th percentile)			
Day 2	10 (8.8)	1.32 (0.50-3.48)	.459
2 mo	4 (4.3)	0.54 (0.18-1.58)	.253
Fat mass index (kg) ≥80th percentile (vs <80th percentile)			
Day 2	11 (9.5)	1.46 (0.71-3.0)	.302
2 mo	3 (3.2)	0.38 (0.12-1.28)	.120
Cord 25(OH)D status (nmol/L)			
<30 (vs ≥30)	23 (8.1)	1.0 (0.48-2.07)	.989
<50 (vs ≥50)	36 (7.3)	1.18 (0.46-3.00)	.651
Vitamin D–containing supplement at 6 mo (vs no)	20 (6.9)	1.05 (0.51-2.17)	.869
Exclusive breast-feeding (vs no)			
At hospital discharge	16 (7.6)	1.24 (0.58-2.63)	.469
At 2 mo	5 (5.9)	0.84 (0.26-2.64)	.686
Any breast-feeding (vs none)			
At hospital discharge	31 (7.1)	1.27 (0.53-2.98)	.461
At 2 mo	22 (7.7)	1.39 (0.67-2.89)	.242
At 6 mo	11 (8.4)	1.51 (0.66-3.42)	.198
Age of solid food introduction (vs 17-26 wk)			
<17 wk	12 (10.6)	1.50 (0.63-3.57)	.233
>26 wk	3 (9.1)	1.55 (0.37-6.46)	.425
Domestic pet at 6 mo (vs none)	26 (11.1)	2.02 (0.97-4.20)	.013

*Self-reported diagnosis of asthma, allergic rhinitis, AD, food allergy, bee/wasp, latex, house dust, or animals.
†Based on cohort-specific percentiles.

AD; however, our low prevalence of breast-feeding and very short breast-feeding duration[57] might have compromised our ability to elucidate the potential effect of breast-feeding on AD development in this cohort. The appropriate age to introduce solid food is continuously debated, with both the early and late introduction of food associated with an increased risk for atopic outcomes.[58,59] In the present study solid food introduction, irrespective of whether concurrent with breast-feeding or before 17 or after 26 weeks, was not associated with AD development. A recent systematic review stated that there is no need to avoid introducing complementary foods beyond 4 months, irrespective of atopic heredity[57]; our data support this statement. Clear and

TABLE IV. Univariate predictors of AD that achieved remission

	AD, no. (%)	OR (99% CI)	*P* value
AD that achieved remission	48 (7.8)		
Maternal factors			
Maternal age (≥35 vs <35 y)	8 (10)	1.42 (0.57-3.49)	.321
University education (vs none)	24 (8)	0.99 (0.50-1.93)	.959
Married (vs single)	38 (8.2)	1.17 (0.52-2.57)	.619
Cesarean section delivery (vs vaginal)	19 (11.6)	1.55 (0.77-3.16)	.117
BMI at 15 wk (≥30 vs <30 kg/m^2)	6 (8.5)	1.26 (0.48-3.34)	.542
Smoker at 15 wk (vs nonsmoker)	0	—	—
Domestic pet kept during pregnancy (vs none)	17 (7.0)	0.79 (0.39-1.61)	.396
25(OH)D status at 15 wk (nmol/L)			
<30 (vs ≥30)	7 (7.5)	1.00 (0.37-2.73)	.998
<50 (vs ≥50)	23 (9.1)	1.52 (0.72-3.23)	.152
Vitamin D–containing supplement at 15 wk (vs none)	29 (10)	1.26 (0.64-2.47)	.377
Alcohol consumption at 15 wk (vs none)	5 (5.1)	0.58 (0.20-1.67)	.182
Rural environment (vs urban)	22 (7.7)	1.07 (0.44-2.12)	.790
Family history of atopy*			
Maternal (vs none)	24 (9.7)	1.38 (0.70-2.71)	.219
Paternal (vs none)	20 (10.1)	1.69 (0.86-3.34)	.046
Neonatal factors			
Sex, female (vs male)	24 (8.0)	0.89 (0.45-1.75)	.650
Summer season of birth (vs winter)	14 (5.7)	0.62 (0.30-1.27)	.086
Anthropometry†			
Weight at birth			
>91st percentile (vs <91st percentile)	5 (9.1)	1.20 (0.45-3.16)	.719
Weight at 2 mo			
>91st percentile (vs <91st percentile)	7 (14.3)	2.13 (0.90-5.06)	.086
Weight at 6 mo†			
>91st percentile (vs <91st percentile)	6 (11.3)	1.47 (0.59-3.64)	.404
Abdominal circumference at day 2			
>85th percentile (vs <85th percentile)	6 (10.7)	1.97 (0.76-5.12)	.066
>95th percentile (vs <95th percentile)	5 (9.8)	1.67 (0.59-4.72)	.204
Body composition			
Fat mass ≥80th percentile (vs <80th percentile)			
Day 2	11 (9.6)	1.34 (0.53-3.37)	.422
2 mo	13 (12.7)	2.09 (1.03-4.25)	.041
Fat mass index (kg) ≥80th percentile (vs <80th percentile)			
Day 2	10 (8.7)	1.15 (0.56-2.38)	.706
2 mo	11 (10.9)	1.62 (0.77-3.38)	.203
Cord 25(OH)D status (nmol/L)			
<30 (vs ≥30)	16 (5.8)	0.95 (0.38-2.36)	.881
<50 (vs ≥50)	38 (7.7)	1.18 (0.47-2.97)	.639
Vitamin D–containing supplement at 6 mo (vs no)	29 (9.6)	1.65 (0.83-3.27)	.060
Exclusive breast-feeding (vs no)			
At hospital discharge	19 (8.9)	1.10 (0.54-2.24)	.726
At 2 mo	10 (11.1)	1.26 (0.49-3.21)	.524
Any breast-feeding (vs none)			
At hospital discharge	36 (7.7)	1.12 (0.52-2.39)	.708
At 2 mo	21 (7.3)	0.84 (0.42-1.68)	.524
At 6 mo	14 (10.4)	1.31 (0.60-2.85)	.381
Age of solid food introduction (vs 17-26 wk)			
<17 wk	6 (5.6)	0.96 (0.39-2.34)	.896
>26 wk	2 (6.3)	1.17 (0.29-4.80)	.770
Domestic pet at 6 mo (vs none)	17 (7.5)	0.91 (0.45-1.85)	.736

*Self-reported diagnosis of asthma, allergic rhinitis, AD, food allergy, bee/wasp, latex, house dust, or animals.
†Based on cohort-specific percentiles.

concise guidelines for complementary feeding are required, and the data presented in this article should be considered in future recommendations.

Several studies examining vitamin D intake, supplementation, and status during pregnancy and in the immediate postnatal period have suggested associations between low vitamin D intake and status and atopic disease, including AD.[19,20,60-64] Other studies have described possible adverse or reverse J-shaped associations between vitamin D supplementation[65,66] and/or high serum 25(OH)D concentrations[18,67] on the infant's atopic disease risk. There is considerable heterogeneity among these studies, both from the design and analytic perspectives, as well

TABLE V. Multivariate prediction of persistent AD

	AD, no. (%)	OR (99% CI)	*P* value
Sample for complete multivariate analysis (n = 617)	7.4		
Maternal atopy (vs none)	35 (14.5)	2.99 (1.35-6.59)	.0004
Fat mass (kg) ≥80th percentile (vs <80th percentile)	18 (14.9)	2.31 (1.02-5.25)	.009
Paternal atopy (vs none)	24 (11.8)	1.86 (0.86-4.02)	.040
Vitamin D–containing supplement at 6 mo (vs none)	30 (10.0)	1.58 (0.73-3.42)	.126
Summer season of birth (vs winter)	26 (10.0)	1.50 (0.70-3.23)	.171

R^2 value for complete multivariate analysis = 9.8%.

TABLE VI. Multivariate prediction of AD that achieved remission by 12 months and late-onset AD at 12 months

	AD, no. (%)	OR (99% CI)	*P* value
AD that achieved remission (n = 621)	6.7		
Maternal atopy (vs none)	24 (9.7)	1.56 (0.71-3.42)	.145
Fat mass (kg) ≥80th percentile (vs <80th percentile)	11 (9.6)	1.27 (0.50-3.25)	.513
Paternal atopy (vs none)	20 (10.1)	1.52 (0.69-3.39)	.175
Vitamin D–containing supplement at 6 mo (vs none)	29 (9.7)	1.77 (0.80-3.95)	.065
Summer season of birth (vs winter)	14 (5.7)	0.59 (0.25-1.39)	.114
Late-onset AD (n = 617)	6.1		
Maternal atopy (vs none)	21 (8.6)	1.33 (0.59-3.00)	.369
Fat mass (kg) ≥80th percentile (vs <80th percentile)	10 (8.8)	1.25 (0.47-3.32)	.553
Paternal atopy (vs none)	19 (9.6)	1.58 (0.69-3.60)	.153
Vitamin D–containing supplement 6 months (vs none)	20 (6.9)	0.94 (0.42-2.13)	.855
Summer season of birth (vs winter)	16 (7.2)	0.83 (0.36-1.93)	.572

as the validity of the clinical outcome. We observed no association between vitamin D supplementation in either the prenatal or postnatal period and AD. Neither did we detect an effect of serum 25(OH)D concentration during pregnancy or in cord blood on the infant's risk of persistent AD.[19,20,65,68] A marginally significant seasonal variation was observed; however, we could not attribute this to serum 25(OH)D concentrations. Therefore an independent effect of sunlight *per se* on AD should be further explored.[69]

The main strength of this study is its prospective design, along with the use of standardized allergy questionnaires and clinically validated outcomes, such as the UKWPDC for AD diagnosis and extremely high-quality repeated prospective data collection and analysis of body composition and vitamin D status. The main limitation of the study is that parental atopy was self-reported. Another limitation is the lack of direct measures for body composition beyond 2 months; because such measures do not exist, this is more a limitation of the study of body composition. Despite the large cohort, the study had a small number of infants with persistent AD, and several statistical analyses lacked adequate statistical power. This has likely caused the lack of significance between paternal atopy and persistent AD.

In conclusion, we have prospectively generated the first association of neonatal body composition with AD at 6 and 12 months. To date, there have been indirect observations that increased adiposity can increase the risk and severity of AD, but this has not been demonstrated directly or during the neonatal period. Future studies should determine whether impaired immune responses are exhibited early in life among infants with a high fat mass. Early identification of at-risk subjects might enhance the prediction of AD and could provide an opportunity for early preventative measures for these infants.

We thank all the families who took part in the Cork BASELINE birth cohort and the midwives and nurses of Cork University Maternity Hospital and Cork University Hospital for their support of the study and all the BASELINE staff (D. Sheehan, E. Cobbe, E. McCarthy, J. Connolly, H. A. Smith, L. O'Connell, G. Hannon, C. Cullinane, and A. Gallagher).

Clinical implications: Neonatal adiposity is a risk factor for AD. This finding might help identify those at high risk of AD and suggests possible mechanistic pathways in the development of AD.

REFERENCES

1. Irvine AD, McLean WH, Leung DY. Filaggrin Mutations Associated with Skin and Allergic Diseases. N Engl J Med 2011;365:1315-27.
2. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS One 2012;7:e39803.
3. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol 2009;124:1251-8.e23.
4. McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. J Allergy Clin Immunol 2013;131:280-91.
5. Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. J Allergy Clin Immunol 2010;125:16-29.e11.
6. Prescott S, Nowak-Węgrzyn A. Strategies to prevent or reduce allergic disease. Ann Nutr Metab 2011;59(suppl 1):28-42.
7. Strachan DP. Hay fever, hygiene, and household size. BMJ 1989;299:1259-60.
8. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract 2013;1:29-36.
9. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child, Cochrane Database Syst Rev. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000133.pub3/abstract. Accepted May 25, 2013.
10. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. Br J Dermatol 2009;161:373-83.
11. von Berg A, Filipiak-Pittroff B, Krämer U, Hoffmann B, Link E, Beckmann C, et al. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol 2013;131:1565-73.e5.
12. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. J Allergy Clin Immunol 2011;128:360-5.e4.
13. Grulee CG, Sanford HN. The influence of breast and artificial feeding on infantile eczema. J Pediatr 1936;9:223-5.
14. Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. JAMA 2001;285:413-20.
15. Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, Dudenhausen JW, et al. Breastfeeding duration is a risk factor for atopic eczema. Clin Exp Allergy 2002;32:205-9.
16. Benn CS, Wohlfahrt J, Aaby P, Westergaard T, Benfeldt E, Fleischer Michaelsen K, et al. Breastfeeding and risk of atopic dermatitis, by parental history of allergy, during the first 18 months of life. Am J Epidemiol 2004;160:217-23.

17. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. Lancet 1995;346:1065-9.
18. Weisse K, Winkler S, Hirche F, Herberth G, Hinz D, Bauer M, et al. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. Allergy 2013;68:220-8.
19. Baïz N, Dargent-Molina P, Wark JD, Souberbielle JC, Annesi-Maesano I. Cord serum 25-hydroxyvitamin D and risk of early childhood transient wheezing and atopic dermatitis. J Allergy Clin Immunol 2014;133:147-53.
20. Jones AP, Palmer D, Zhang G, Prescott SL. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. Pediatrics 2012;130:e1128-35.
21. Calder PC. Fishing for allergy prevention. Clin Exp Allergy 2013;43:700-2.
22. Kremmyda LS, Vlachava M, Noakes PS, Diaper ND, Miles EA, Calder PC. Atopy risk in infants and children in relation to early exposure to fish, oily fish, or long-chain omega-3 fatty acids: a systematic review. Clin Rev Allergy Immunol 2011;41:36-66.
23. Allan K, Kelly FJ, Devereux G. Antioxidants and allergic disease: a case of too little or too much? Clin Exp Allergy 2010;40:370-80.
24. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. J Allergy Clin Immunol 2011;127:724-33.e30.
25. Crider KS, Cordero AM, Qi YP, Mulinare J, Dowling NF, Berry RJ. Prenatal folic acid and risk of asthma in children: a systematic review and meta-analysis. Am J Clin Nutr 2013;98:1272-81.
26. Grimshaw KE, Maskell J, Oliver EM, Morris RC, Foote KD, Mills EN, et al. Diet and food allergy development during infancy: Birth cohort study findings using prospective food diary data. J Allergy Clin Immunol 2014;133:511-9.
27. Liu PC, Kieckhefer GM, Gau BS. A systematic review of the association between obesity and asthma in children. J Adv Nurs 2013;69:1446-65.
28. Forno E, Acosta-Pérez E, Brehm JM, Han YY, Alvarez M, Colón-Semidey A, et al. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. J Allergy Clin Immunol 2014;133:1308-14.e5.
29. Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. Obes Rev 2013;14:222-31.
30. Murray CS, Canoy D, Buchan I, Woodcock A, Simpson A, Custovic A. Body mass index in young children and allergic disease: gender differences in a longitudinal study. Clin Exp Allergy 2011;41:78-85.
31. Silverberg JI, Kleiman E, Lev-Tov H, Silverberg NB, Durkin HG, Joks R, et al. Association between obesity and atopic dermatitis in childhood: a case-control study. J Allergy Clin Immunol 2011;127:1180-6.e1.
32. Kusunoki T, Morimoto T, Nishikomori R, Heike T, Ito M, Hosoi S, et al. Obesity and the prevalence of allergic diseases in schoolchildren. Pediatr Allergy Immunol 2008;19:527-34.
33. O'Donovan SM, Murray DM, Hourihane JO, Kenny LC, Irvine AD, Kiely M. Cohort profile: the Cork BASELINE Birth Cohort Study: Babies after SCOPE: Evaluating the Longitudinal Impact on Neurological and Nutritional Endpoints. Int J Epidemiol 2014 Aug 7. [Epub ahead of print].
34. Groom KM, North RA, Stone PR, Chan EH, Taylor RS, Dekker GA, et al. Patterns of change in uterine artery Doppler studies between 20 and 24 weeks of gestation and pregnancy outcomes. Obstet Gynecol 2009;113(2 Pt 1):332-8.
35. Chappell LC, Seed PT, Myers J, Taylor RS, Kenny LC, Dekker GA, et al. Exploration and confirmation of factors associated with uncomplicated pregnancy in nulliparous women: prospective cohort study. BMJ 2013;347:f6398.
36. North RA, McCowan LM, Dekker GA, Poston L, Chan EH, Stewart AW, et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. BMJ 2011;342:d1875.
37. Cole TJ, Green PJ. Smoothing reference centile curves: the lms method and penalized likelihood. Stat Med 1992;11:1305-19.
38. WHO Mutlicentre Growth Reference Study Group WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass-index-for-age: Methods and development. Geneva: World Health Organization; 2006. p. 312. Available at: http://who.int/childgrowth/pinlications/en.
39. Ellis KJ, Yao M, Shypailo RJ, Urlando A, Wong WW, Heird WC. Body-composition assessment in infancy: air-displacement plethysmography compared with a reference 4-compartment model. Am J Clin Nutr 2007;85:90-5.
40. Ma G, Yao M, Liu Y, Lin A, Zou H, Urlando A, et al. Validation of a new pediatric air-displacement plethysmograph for assessing body composition in infants. Am J Clin Nutr 2004;79:653-60.
41. Keil T, McBride D, Grimshaw K, Niggemann B, Xepapadaki P, Zannikos K, et al. The multinational birth cohort of EuroPrevall: background, aims and methods. Allergy 2010;65:482-90.
42. Williams HC, Jburney PG, Hay RJ, Archer CB, Shipley MJ, Ahunter JJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. Br J Dermatol 1994;131:383-96.
43. Cashman KD, Kiely M, Kinsella M, Durazo-Arvizu RA, Tian L, Zhang Y, et al. Evaluation of vitamin D standardization program protocols for standardizing serum 25-hydroxyvitamin D data: a case study of the program's potential for national nutrition and health surveys. Am J Clin Nutr 2013;97:1235-42.
44. Sempos CT, Vesper HW, Phinney KW, Thienpont LM, Coates PM. Vitamin D status as an international issue: national surveys and the problem of standardization. Scand J Clin Lab Invest 2012;243:32-40.
45. Institute of Medicine. Dietary reference intakes for calcium and vitamin D. Date published 2011. Available at: http://www.ncbi.nlm.nih.gov/books/NBK56070/. Accessed January 30, 2015.
46. The Economic Social and Research Institute Department of Health and Children. Perinatal Statistics Report 2010. Available at: http://www.esri.ie/news_events/latest_press_releases/perinatal_statistics_repo_4/. Accessed January 30, 2015.
47. Central Statistics Office. Census 2006: education and qualifications. Available at: http://census.cso.ie/census/ReportFolders/ReportFolders.aspx. Accessed September 21, 2014.
48. Machura E, Szczepanska M, Ziora K, Ziora D, Swietochowska E, Barc-Czarnecka M, et al. Evaluation of adipokines: apelin, visfatin, and resistin in children with atopic dermatitis. Mediators Inflamm 2013;2013:760691.
49. Nagel G, Koenig W, Rapp K, Wabitsch M, Zoellner I, Weiland SK. Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. Pediatr Allergy Immunol 2009;20:81-8.
50. Yao TC, Ou LS, Yeh KW, Lee WI, Chen LC, Huang JL. Associations of age, gender, and BMI with prevalence of allergic diseases in children: PATCH study. J Asthma 2011;48:503-10.
51. Suarez-Varela MM, Alvarez LG, Kogan MD, Ferreira JC, Martinez Gimeno A, Aguinaga Ontoso I, et al. Diet and prevalence of atopic eczema in 6 to 7-year-old schoolchildren in Spain: ISAAC phase III. J Investig Allergol Clin Immunol 2010;20:469-75.
52. Silverberg JI, Simpson EL. Association Between obesity and eczema prevalence, severity and poorer health in US adolescents. Dermatitis 2014;25:172-81.
53. Modi N, Murgasova D, Ruager-Martin R, Thomas EL, Hyde MJ, Gale C, et al. The influence of maternal body mass index on infant adiposity and hepatic lipid content. Pediatr Res 2011;70:287-91.
54. Page KA, Romero A, Buchanan TA, Xiang AH. Gestational diabetes mellitus, maternal obesity, and adiposity in offspring. J Pediatr 2014;164:807-10.
55. Crume TL, Ogden L, Daniels S, Hamman RF, Norris JM, Dabelea D. The impact of in utero exposure to diabetes on childhood body mass index growth trajectories: the EPOCH study. J Pediatr 2011;158:941-6.
56. de Silva D, Geromi M, Halken S, Host A, Panesar SS, Muraro A, et al. Primary prevention of food allergy in children and adults: systematic review. Allergy 2014;69:581-9.
57. O'Donovan SM, Murray DM, Hourihane J, Kenny LC, Irvine AD, Kiely M. Adherence with early infant feeding and complementary feeding guidelines in the Cork BASELINE Birth Cohort Study. Public Health Nutr 2015 Feb 18:1-10. [Epub ahead of print].
58. Tarini BA, Carroll AE, Sox CM, Christakis DA. Systematic review of the relationship between early introduction of solid foods to infants and the development of allergic disease. Arch Pediatr Adolesc Med 2006;160:502-7.
59. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Primary prevention of food allergy. Allergy 2014;69:590-601.
60. Allen KJ, Koplin JJ, Ponsonby AL, Gurrin LC, Wake M, Vuillermin P, et al. Vitamin D insufficiency is associated with challenge-proven food allergy in infants. J Allergy Clin Immunol 2013;131:1109-16.e6.
61. Rothers J, Wright AL, Stern DA, Halonen M, Camargo CA Jr. Cord blood 25-hydroxyvitamin D levels are associated with aeroallergen sensitization in children from Tucson, Arizona. J Allergy Clin Immunol 2011;128:1093-9.
62. Miyake Y, Sasaki S, Tanaka K, Hirota Y. Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. Eur Respir J 2010;35:1228-34.
63. Camargo CA Jr, Ganmaa D, Sidbury R, Erdenedelger K, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. J Allergy Clin Immunol 2014;134:831-5.e1.

64. Peroni DG, Piacentini GL, Cametti E, Chinellato I, Boner AL. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. Br J Dermatol 2011;164:1078-82.
65. Back O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy? Acta Dermatovenereol 2009;89:28-32.
66. Hyppönen E, Sovio U, Wjst M, Patel S, Pekkanen J, Hartikainen AL, et al. Infant Vitamin D Supplementation and Allergic Conditions in Adulthood: Northern Finland Birth Cohort 1966. Ann N Y Acad Sci 2004;1037:84-95.
67. Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al. Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr 2008;62:68-77.
68. Camargo CA Jr, Ingham T, Wickens K, Thadhani R, Silvers KM, Epton MJ, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics 2011;127:e180-7.
69. Vähävihu K, Ala-Houhala M, Peric M, Karisola P, Kautiainen H, Hasan T, et al. Narrowband ultraviolet B treatment improves vitamin D balance and alters antimicrobial peptide expression in skin lesions of psoriasis and atopic dermatitis. Br J Dermatol 2010;163:321-8.