Food allergy among low birthweight children in a national survey

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Abstract:

The aim of this paper was to investigate the association between birthweight and prevalence of food allergies using a national sample of US children. Adult report of birthweight and child food allergies were obtained for years 2005–2009 from the National Health Interview Survey (NHIS), a cross-sectional household survey of the US population. A total of 51,748 children aged 0–17 years were included in the analyses representing over 73 million children. Multivariable logistic regression analyses examined associations between birthweight categories and food allergies stratified by age and gender; accounting for the complex design of NHIS. Children aged 6–12 years who were born very low birthweight (500–1,499 g) were more likely to have reported food allergy compared to referent (3,000–3,499 g), OR = 1.72; 95% CI: 1.02–2.91. However, there was no clear trend of an association between birthweight and food allergy with increasing or decreasing birthweight across all ages. Estimates were generally stronger in younger male children as compared to estimates in females of the same age group. Marginal associations for respiratory allergy (OR = 1.52; 95% CI: 1.02–2.29) and hay fever (OR = 1.54; 95% CI: 0.93–2.54) were observed among very low birthweight children aged 0–5 years. There was limited evidence for a clear association between birthweight and food allergy. Marginal associations observed in children weighing 500–1,499 g at birth support efforts to minimize preterm births and very low birthweight given the increase in pediatric food allergies and the large number of children born low birthweight each year in the US.

Keywords: Food allergy | Birthweight | Children | Respiratory allergy | Hay fever

Article:

Introduction

The significance of food allergy research has been increasing in the United States (US), particularly among pediatric populations. Recent national survey estimates report a prevalence of

3.9% of food allergies among children 18 years or younger, affecting approximately 3 million children [1]. These data also suggest a significant increase in reported food allergies from 1997 to 2007. While a majority of affected children eventually outgrow their food allergies with age [2], for some children the condition continues into adult life.

The epidemiology of food allergies remains largely unknown. Although socioeconomic status, genetics, coexisting allergies, and even childhood obesity have been explored as potential risk factors [3, 4, 5, 6, 7], the impact of birthweight on food allergies remains speculative. A recent study of nearly 37 million newborns in the US from 1990 to 2005 reported a decreasing trend (by about 52 g) in average birthweight among term births [8]. Furthermore, the percentage of children classified as low birthweight (LBW) has also remained on the rise in recent years [9]. These findings underscore the importance of evaluating birthweight as a risk factor for child health. Some studies investigating birthweight as a potential risk factor for allergic disease have demonstrated an increased risk of atopic disease (allergic reactions) among preterm and otherwise LBW children [3, 10]. However, other studies have failed to find significant associations [5, 11] while some found that being preterm and of LBW were actually protective for allergies [4, 12, 13, 14, 15].

Thus, determining if low birthweight infants have a higher prevalence of food allergies could lead to improved prevention efforts for this population. In the present study, we examine the association between birthweight and food allergies using recent data from the National Health Interview Survey. To the best of our knowledge, this is the first study to investigate differences in reported food allergies by birthweight status using a nationally representative sample of US children.

Methods

Study Population

The National Health Interview Survey (NHIS) monitors the health of the US population through the collection of data on a broad range of health topics. The target population of NHIS is the civilian, non-institutionalized population of the US. NHIS is a cross-sectional household interview survey, and adopts a nationally representative multistage probability sampling design. We utilized information from the family, adult, and child files merging each of these data files by household and family identifiers if the record was also present in the child file. As the estimated prevalence for food allergy is about 4% [1], we combined 5 years (2005–2009) of NHIS data to obtain an adequate sample size for conducting multivariable and stratified analyses. Overall, a total of 51,748 children (0–17 years of age) comprised the 2005–2009 child files representing a weighted count of 73,561,535 children in the US. Since we used de-identified publicly available data, this study was exempt from ethics review.

Main Exposure and Outcome

The NHIS includes questions on birthweight and on food allergy. The adult respondent is asked if during the past 12 months, the sampled child had any kind of food or digestive allergy; the response was coded as ‘yes’/‘no’. The sampled adult also responds to the question “What was

sampled child's birthweight?" To obtain detailed evaluation of effects in all birthweight categories, birthweight was recoded into six categories: 500–1,499 g, 1,500–2,499 g, 2,500–2,999 g, 3,000–3,499 g, 3,500–3,999 g, and ≥4,000 g. Narrow categories such as these have also been employed in other studies [5, 16].

Covariates and Effect Measure Modifiers

Although certain food allergies are resolved by school age, others could continue beyond, and resolve at different ages [17, 18]. Hence, age was divided into three categories (0–5 years, 6–12 years, and 13–17 years) and treated as an effect measure modifier. Prior studies indicate that in younger children, males have a higher rate of reported food allergy while a reverse trend is observed in females [19]. Hence, differences in the prevalence of food allergy by gender were also assessed. An individual's socioeconomic status (SES) has been shown to relate to both birthweight and food allergy. SES has appeared to be significant as both a risk factor [20] and a protective factor [5] for allergy in children. For this study's analyses education of adult with the highest education in the family and income poverty ratio of the family were used as a proxy for SES. Income poverty ratio was calculated by NHIS as the quotient of household annual income and the US Census Bureau's poverty threshold for the survey year. As such, this variable provides a consistent appraisal of SES without being affected by inflation while accounting for family size and age structure (number of individuals in the family below 18).

Statistical Analyses

The NHIS consists of a complex, multistage sampling design, requiring the use of sample weights to calculate national estimates and accurately estimate standard errors. Furthermore, the present study combined data from years pertaining to two different sampling design periods (2005 and 2006–2009). Instructions for use of sample weights and variance estimation across these two study periods were obtained from the National Center for Health Statistics [21].

Main effects were analyzed using logistic regression models that adjusted for SES, age, race/ethnicity, and gender. The birthweight category of 3,000–3,499 g was used as the referent category not only due to its largest sample size, but also having been treated as referent in previous literature [22] and considered an optimal range for birthweight. Separate models were also fit to examine associations between birthweight and other allergies such as hay fever, eczema or skin allergy, and respiratory allergy. Approximately 4,975 children were missing information for birthweight or allergy outcomes, and were dropped in regression models. Statistical significance for each model was determined using 95% confidence intervals. All analyses were completed using SAS version 9.2 (SAS Institute, Cary NC) and SUDAAN v.10.0.1 (Research Triangle Institute, Research Triangle Park, NC) to account for the complex design of the survey and to provide national estimates of food allergy by birthweight category.

Results

On average, 4.5% of children aged 0–17 years in the study sample were found to have had a food or digestive allergy in the past 12 months. Table 1 presents the distribution of select characteristics of the child by food allergy prevalence. In general, a higher prevalence of food

allergy was reported in children who were younger (0–5 years) and in children with a family history of asthma or hay fever.

Table 1. Overall distribution of reported food allergies by select characteristics of study sample (0–17 years), N = 51,748 (weighted count: 73,561,535)

	N (%)	Food allergy prevalence—N (%)
Sampled child characteristics		
Age group		
0–5 years	17,518 (33.9)	828 (4.7)
6–12 years	18,434 (35.6)	812 (4.1)
13–17 years	15,796 (30.5)	688 (4.0)
Race		
Non-Hispanic White	23,577 (45.6)	1,130 (4.5)
Non-Hispanic Black	8,422 (16.3)	400 (4.3)
Hispanic	15,364 (29.7)	555 (3.3)
Other Races	4,385 (8.5)	243 (4.9)
Family history of asthma or hay fever		
Yes	7,069 (16.8)	568 (7.5)
No	35,025 (83.2)	1,353 (3.6)
Year of survey		
2005	12,523 (24.2)	515 (4.0)
2006	9,837 (19)	431 (4.4)
2007	9,417 (18.2)	378 (4.0)
2008	8,815 (17)	424 (4.5)
2009	11,156 (21.6)	580 (5.2)
Adult characteristics associated with sampled child		
Education		
Less than high school	6,701 (13)	206 (3.2)
High school	11,775 (22.9)	411 (3.5)
Some college	16,631 (32.3)	814 (4.2)
College and above	16,366 (31.8)	896 (5.1)
Income poverty ratio		
Under 1.00	8,195 (15.8)	343 (4.2)
1.00–1.99	9,986 (19.3)	448 (4.2)
2.00–3.99	12,996 (25.1)	621 (4.6)
4.00 and above	11,791 (22.8)	612 (4.6)
Unknown	8,780 (17)	304 (3.4)

Table 2 presents crude estimates from the logistic model for food allergy and birthweight stratified by age along with estimates adjusted for education, income poverty ratio, gender, and race/ethnicity. A statistically significant increased odds of having food allergy in the last 12 months was observed for children aged 6–12 years with very low birthweight of 500–1,499 g (OR = 1.72; 95% CI: 1.02–2.91) as compared to the referent category. However, in this age group, marginal associations were also reported in the birthweight categories of 2,500–2,999 g (OR = 1.29; 95% CI: 0.97–1.70) and 3,500–3,999 g (OR = 1.32; 95% CI: 1.03–1.69), both adjacent categories to referent, indicating no clear pattern of increased risk with increasing or decreasing birthweight. No clear trend of an association between birthweight and food allergy with increasing or decreasing birthweight was observed in children aged 0–5 years and 13–17 years as well.

Stratified results by age and gender are reported in Table 3. The odds ratios for male children in the very low birthweight category (500–1,499 g) remained higher in these age groups: 0–5 years

(OR = 1.46; 95% CI: 0.80–2.65) and 6–12 years (OR = 2.02; 95% CI: 1.01–4.02) than those observed in females in these same groups.

Table 2. Association between food allergy and birthweight stratified by age, N = 46,773 from NHIS data, 2005–2009

Age (years)	Birthweight (g)					
	500–1,499	1,500–2,499	2,500–2,999	3,000–3,499	3,500–3,999	≥4,000
0–5						
N (%)	454 (2.7)	1,241 (7.3)	3,174 (17.6)	6,220 (36.6)	4,190 (27)	1,235 (8.9)
OR[a]	1.08	1.30	1.41	1.00 (Ref)	1.21	1.05
95% CI[a]	0.65–1.78	0.84–2.01	1.05–1.89		0.92–1.59	0.71–1.56
OR[b]	1.05	1.32	1.46	1.00 (Ref)	1.16	0.98
95% CI[b]	0.64–1.72	0.86–2.05	1.09–1.96		0.88–1.52	0.65–1.47
6–12						
N (%)	661 (3.9)	1,174 (6.8)	3,013 (17)	5,921 (35.7)	4,206 (26.7)	1,505 (9.9)
OR[a]	1.68	1.06	1.29	1.00 (Ref)	1.34	1.05
95% CI[a]	1.00–2.84	0.73–1.54	0.97–1.71		1.05–1.71	0.69–1.61
OR[b]	1.72	1.05	1.29	1.00 (Ref)	1.32	1.03
95% CI[b]	1.02–2.91	0.72–1.53	0.97–1.70		1.03–1.69	0.68–1.56
13–17						
N (%)	557 (3.7)	876 (6)	2,435 (16.9)	4,895 (34.9)	3,684 (27.8)	1,332 (10.6)
OR[a]	1.18	1.16	1.28	1.00 (Ref)	1.02	1.17
95% CI[a]	0.67–2.07	0.69–1.98	0.92–1.77		0.78–1.33	0.79–1.73
OR[b]	1.20	1.16	1.29	1.00 (Ref)	1.02	1.19
95% CI[b]	0.68–2.12	0.68–1.97	0.93–1.79		0.78–1.33	0.81–1.75

[a]Unadjusted

[b]Adjusted for education, income poverty ratio, race/ethnicity, and gender

Table 3. Association between food allergy and birthweight stratified by age and gender (adjusted for education and income poverty ratio), N = 46,773 from NHIS data, 2005–2009

Gender	Age (years)	Birthweight (g)					
		500–1,499	1,500–2,499	2,500–2,999	3,000–3,499	3,500–3,999	≥4,000
M	0–5						
	OR	1.46	1.23	1.67	1.00 (Ref)	1.22	0.86
	95% CI	0.80–2.65	0.61–2.49	1.10–2.54		0.85–1.74	0.52–1.43
	6–12						
	OR	2.02	1.52	1.02	1.00 (Ref)	1.16	1.14
	95% CI	1.01–4.02	0.96–2.39	0.67–1.55		0.83–1.61	0.65–2.00
	13–17						
	OR	1.23	1.42	1.11	1.00 (Ref)	1.09	1.30
	95% CI	0.54–2.80	0.73–2.78	0.64–1.95		0.75–1.58	0.77–2.19
F	0–5						
	OR	0.46	1.42	1.24	1.00 (Ref)	1.09	1.23
	95% CI	0.19–1.09	0.81–2.49	0.80–1.92		0.71–1.68	0.66–2.30
	6–12						
	OR	1.35	0.64	1.52	1.00 (Ref)	1.49	0.80
	95% CI	0.61–2.96	0.32–1.29	1.06–2.19		1.05–2.10	0.45–1.43
	13–17						
	OR	1.20	1.04	1.42	1.00 (Ref)	0.94	1.05
	95% CI	0.57–2.51	0.46–2.36	0.95–2.12		0.64–1.38	0.59–1.88

Age-stratified results for birthweight and other allergy outcomes are presented in Table 4. Increased odds for hay fever were mainly observed in children aged 0–5 years who had a

birthweight of less than 1,500 g (OR = 1.54; 95% CI: 0.93–2.54) while 52% greater odds were also observed for respiratory allergy in this age group (95% CI: 1.02–2.29), when compared to children born at 3,000–3,499 g. No specific trends were observed for eczema or other skin allergy. Associations remained unchanged even after adjusting for SES, gender, and race/ethnicity (data not shown).

Table 4. Association between hay fever, respiratory allergy, and eczema and birthweight stratified by age, N = 46,773 from NHIS data, 2005–2009

	Age (years)	Birthweight (g)					
		500–1,499	**1,500–2,499**	**2,500–2,999**	**3,000–3,499**	**3,500–3,999**	**≥4,000**
Hay fever	0–5						
	OR	1.54	0.92	1.05	1.00 (Ref)	0.88	1.06
	95% CI	0.93–2.54	0.62–1.37	0.81–1.35		0.68–1.13	0.73–1.55
	6–12						
	OR	0.86	1.24	0.90	1.00 (Ref)	1.03	0.94
	95% CI	0.59–1.25	0.94–1.65	0.75–1.08		0.87–1.22	0.74–1.21
	13–17						
	OR	0.75	0.81	0.93	1.00 (Ref)	1.18	1.20
	95% CI	0.51–1.09	0.58–1.14	0.75–1.15		0.97–1.43	0.90–1.58
Respiratory allergy	0–5						
	OR	1.52	1.34	1.03	1.00 (Ref)	0.96	1.29
	95% CI	1.01–2.29	0.98–1.83	0.82–1.28		0.79–1.17	0.99–1.69
	6–12						
	OR	1.15	1.22	0.99	1.00 (Ref)	1.14	1.16
	95% CI	0.83–1.59	0.91–1.64	0.83–1.18		0.98–1.32	0.92–1.47
	13–17						
	OR	1.10	1.06	1.03	1.00 (Ref)	1.18	1.31
	95% CI	0.74–1.62	0.77–1.44	0.84–1.27		0.99–1.42	1.01–1.70
Eczema/skin allergy	0–5						
	OR	1.18	1.07	1.13	1.00 (Ref)	1.00	1.05
	95% CI	0.81–1.72	0.83–1.37	0.94–1.36		0.84–1.18	0.81–1.38
	6–12						
	OR	1.03	1.09	0.97	1.00 (Ref)	1.05	1.07
	95% CI	0.69–1.54	0.81–1.48	0.81–1.16		0.88–1.25	0.83–1.40
	13–17						
	OR	1.19	1.14	1.21	1.00 (Ref)	1.27	1.01
	95% CI	0.79–1.81	0.75–1.74	0.92–1.57		1.01–1.58	0.75–1.37

Discussion

Results from this national sample of US children aged 0–17 years provided marginal evidence for increased prevalence of food allergy among very low birthweight children (weighing 500–1,499 g at birth) aged 6–12 years at the time of survey. However, based on the observed estimates across the different birthweight categories in all age groups, there was no clear and consistent pattern of a positive or inverse association between birthweight and food allergy. In general, estimates were stronger in male children as compared to estimates in females. In addition, marginally significant odds ratios indicating greater risk for respiratory allergy and hay fever were observed among LBW children weighing less than 1,500 g aged 0–5 years, when compared to those in the referent category. Based on these findings, it appears that associations indicating increased risk of food or respiratory allergy in the very low birthweight category of 500–1,499 g could be predominantly due to an effect of being born preterm rather than low

birthweight. This conclusion is further substantiated by the lack of a clear trend of an association between birthweight and food allergy with increasing or decreasing birthweight among all age groups.

Similar to our study findings, the only other study (conducted in Canada) that specifically investigated the association between birthweight and risk of food allergies in children using a birth cohort found no association between food allergy and LBW children [5]. This non-significant association also held in small-for-gestational-age children. In our study significant increased odds of food allergy among very low birthweight children were only noted in 6–12 year old children. Since most food allergies present shortly after the introduction of the food into regular diet [18], it is possible that exposure to a wider variety of foods that is limited in very young children may expand after beginning school.

The present study also supported prior findings [3, 5] indicating greater risk of food allergies among male compared to female children. A biopsychosocial mechanism involving sex-specific genetic and hormonal factors has been suggested to explain this association [19, 23]. Since the prevalence of other allergies in the child have shown to be generally coexisting with food allergy prevalence in children [5, 24, 25], we conducted additional analyses to examine trends in birthweight and other allergy outcomes. Associations between respiratory allergy, hay fever, and skin allergy and birthweight were limited.

Certain limitations of this study should be noted. Data collected on birthweight and food allergy relied on parental or proxy reports, which have potential misclassification bias as compared to obtaining confirmatory information through medical records and tests to detect allergic (IgE) antibodies to food allergens. However, adult reports of child's food allergy in NHIS are comparable to other surveys where parental reports about food allergy have been based on if the allergy was diagnosed by a health care professional [26]. Clinically diagnosed food allergy prevalence was estimated to be 4.2% in children 1–5 years of age and 3.8% in children 6–19 years of age based on NHANES 2005–2006 data [27]. Furthermore, the National Institute of Allergy and Infectious Diseases (the lead NIH Institute on food allergy research) reports a current food allergy prevalence of 5% in children [28] while other reports have reported prevalence to be between 4–6% [29] and 3–6% [7], consistent with NHIS estimates. Similarly, previous studies have also demonstrated that parental recall of child's birthweight can be a good proxy for recorded birthweight [30, 31].

We were not able to adjust for prenatal exposure to smoking and gestational diabetes in the NHIS database. Similarly, NHIS does not allow us to distinguish between small for gestational age (SGA) infants and preterm infants. However, in the absence of a distinct trend for an association between birthweight and allergy, our findings for food allergy, respiratory allergy, and hay fever found in children weighing less than 1,500 g at birth more likely reflects an effect for preterm births rather than low birthweight. Hence, adjustment for gestational age will probably not affect findings in this birthweight category. Information on allergies to specific foods or age at onset of allergic reactions was not available in NHIS. Lastly, to adjust for SES, the child files were merged with the adult and family files. However, NHIS is not well-suited for analyses across adult and child files and thus final confidence interval estimates for this measure

may be imprecise. To determine the extent of this potential bias, analyses were repeated without adjusting for SES as a covariate. The associations remained unchanged [data not shown].

Despite these potential limitations, the main strength of this study is the use of nationally representative data to investigate the association between food allergy and birthweight, permitting more generalizable results. Further, as a nationally representative sample, the study includes information on children from varying racial/ethnic, age and socioeconomic backgrounds, thereby allowing tests of heterogeneity of effect by several important domains (e.g., age and sex).

There are two main potential mechanisms for the impact of birthweight on food allergy. One body of evidence suggests that low birthweight babies have an immature intestine that allows higher gut permeability, resulting in increased absorption of antigens that are presented to the resident immune cells within the wall of the gut [11, 32, 33, 34, 35]. Another line of research suggests that early exposure to antigens could lead to tolerance instead of sensitization in LBW infants if the immune system is too immature to mount a response [14]. Hence by the time maturity develops, the immune system that would have been inundated with the antigen may not recognize it as foreign. For instance, Siltanen et al. [36] showed low levels of antibodies for cow's milk in LBW children as compared to term children and decreased long-term risk of atopic sensitization for preterm children than for those born at term [13].

Conclusions

Current preventive measures for food allergy include allergen avoidance and better management of allergic reactions. Since development of food allergies appears to be another potential impact of being born preterm or with very low birthweight, any public health effort to minimize preterm births in general could also possibly influence food allergy prevalence among children. Furthermore, practice implications could include additional care and vigilance for food allergy symptoms among infants born preterm or very low birthweight in the US.

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