

*Original article***The risk of developing food allergy in premature or low-birth-weight children**

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Background: Premature or low-birth-weight children have increased gut permeability compared with term or normal-birth-weight children.

Objective: To determine whether premature or low-birth-weight children have an increased risk of developing food allergy compared with term or normal-birth-weight children.

Methods: The 1995 Manitoba Birth Cohort was studied using the Manitoba Health Services Insurance Plan (MHSIP) database. This database is a population-based, health care administrative and prescription database. It has records of every child born and subsequent utilization of the provincial health care system. The diagnosis of food allergy (ICD-9-CM code of 693 in hospital/medical claims or a prescription of injectable epinephrine excluding a sole diagnosis of venom allergy) was obtained up until the year 2002. The relative risks of food allergy in premature or low-birth-weight children compared with term or normal-birth-weight children were determined.

Results: A total of 13,980 children were born in 1995 and continue to live in the province of Manitoba. Of these, 592 children (4.23%) were found to have food allergy and epinephrine was prescribed in 316 (2.26%) children. No gestational age or birth weight group had a statistically significant increased risk for food allergy.

Conclusion: Prematurity and low birth weight are not associated with a change in risk for development of food allergy in childhood.

Clinical implications: Immaturity of the gastrointestinal tract or immune response does not seem to change the risk for development of food allergies. We ask whether early exposure to food antigens may protect premature children by increasing immune tolerance to those antigens. (*J Allergy Clin Immunol* 111:1111-1116, 2003.)

Key words: Epinephrine, food allergy, gestational age, low birth weight, prematurity

Early in life, immaturity of both immunologic and nonimmunologic components of the mucosal barrier in the gastrointestinal tract results in a marked increase in uptake of food antigens.^{1,2} However, despite the immune system of preterm infants being characterized as “immature compared to full term,”^{3,4} the infants can respond appropriately to antigenic stimuli, as demonstrated in vaccination programs.³⁻⁵ Very little is known of the immunologic response of preterm or low-birth-weight infants to dietary antigens.

Studies in preterm newborns have shown increased food antigen uptake caused by increased intestinal permeability, which is inversely related to gestational age.⁶⁻⁹ The amount of antigenically intact proteins that is absorbed may be up to 100-fold greater when compared with full-term children. Because of this increased permeability, it has been proposed that an increased risk of IgE-mediated food allergy exists in premature children.⁹⁻¹⁴ In fact, Lucas et al¹⁵ assessed “latent systemic anaphylactic sensitization” to cows’ milk in 61 preterm infants. They found that infants of low birth weight who receive cow’s milk formula develop systemic sensitization more rapidly than infants born at term.

Low birth weight is considered to be related to immaturity of digestive and absorptive function, which might cause increased macromolecular absorption,¹⁶ leading to food allergy. Also, insufficient secretory IgA resulting from an immature gut immune system in low-birth-weight infants¹⁰ may result in greater penetration of allergens in early life and in subsequent development of food allergy.

However, some studies have not found this relationship. For example, de Martino et al¹⁷ studied 80 preterm infants and compared them with 80 sex-matched and age-matched full-term infants at a mean age of 16 months. They found that the frequency of positive skin tests to foods and of atopic dermatitis were similar between the 2 groups. They suggested that increased intestinal permeability and antigen uptake have no role in triggering IgE sensitization to foods in these infants and that oral tolerance to food antigens may develop in preterm infants. Such tolerance might result from interaction of high antigen concentration with the immature immune system of the preterm infant.

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Abbreviations used

ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*

MHSIP: Manitoba Health Service Insurance Plan

NPV: Negative predictive value

PPV: Positive predictive value

SAGE: The Study of Asthma Genes and the Environment

Using a large population-based health care database, our aim was to determine whether premature or low-birth-weight children have an increased risk of developing food allergy when compared with term or normal-birth-weight children.

METHODS

The Study of Asthma Genes and the Environment (SAGE) is a study focusing on the 1995 Manitoba Birth Cohort. One of its platforms has been to analyze records from the Manitoba Health Services Insurance Plan (MHSIP) database (a population-based, linked health care administrative and prescription database). The complete healthcare records of the 1995 birth cohort, which includes physician visits, hospitalizations, and prescription drugs collected by MHSIP in the provision of universal health insurance to Manitoba residents, are available for analysis. Records of physician reimbursement for medical care provided are submitted under a fee-for-service arrangement and contain information on patient diagnosis at the 3-digit level of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) classification system. Discharge abstracts for hospital services include information on up to 16 ICD-9-CM diagnostic codes, of which the first diagnosis is the primary diagnosis responsible for the hospital stay. Prescription records are submitted by retail pharmacies for reimbursement by provincial drug insurance plans and for drug utilization review purposes, and they contain data on the date of prescription dispensing, drug name and identification number, dosage form, and quantity dispensed. The MHSIP databases are reliable, and valid data sources for describing health care contact for specific conditions and prescriptions dispensed.^{18,19} Record linkages among databases are achieved by the use of anonymized personal identifiers. A family registration number that is present in the MHSIP registry permits linkage of health care data of children with that of parents and siblings.

Children born in 1995 were divided into groups based on gestational age and birth weight (Table I). The diagnosis of food allergy was defined as an ICD-9-CM code of 693 in hospital/medical claims or a prescription of injectable epinephrine. Epinephrine dispensed for patients with a diagnosis of venom allergy (ICD-9-CM code = 989) was excluded. "Ever" having a food allergy was defined as a diagnosis of food allergy anytime during the first 7 years of life. "Current" food allergy was defined as a diagnosis of food allergy at the age of 6 or 7 years (from 2001 to 2002). Relative risks and odds ratios were calculated comparing various gestational ages or birth weights with term gestation (37-42 weeks) or normal birth weight (2500-4500 g)—the reference standard.

Factors potentially associated with food allergy were also derived from health care administrative records. These factors included gender, maternal history of asthma (physician visit or hospitalization for asthma [ICD-9-CM code = 493] current or up to 5 years before birth of child or prescription for asthma drug during birth year), maternal history of food allergy (physician visit or hospitalization for food

allergy [ICD-9-CM code = 693] in 1995 or a prescription for epinephrine in 1995/1996), cesarean section delivery, urban/rural location, and family income (neighborhood income quintiles derived from Statistics Canada Census public-use files).

Validation for our definition of IgE mediated food allergy can be found in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org.

The study was approved by the Health Research Ethics Board at the University of Manitoba and the Health Information Privacy Committee of Manitoba.

Statistical analysis

Relative risks (unadjusted) with 95% CIs were calculated to determine the likelihood of ever and current food allergy (diagnosis and prescription-based definition and prescription-based definition only) according to gestational age and birth weight. Logistic regression analysis was performed to select risk factors associated with food allergy from the following candidates identified in the literature: maternal history of asthma, maternal history of food allergy, gender, location of residence, cesarean section delivery, and household income. The likelihood (hazards ratio, 95% CI) of ever food allergy by gestational age and birth weight was determined from Cox proportional hazards regression, adjusting for the above risk factors. Similarly, the likelihood (odds ratio, 95% CI) of current food allergy was determined from logistic regression. All statistical analysis was performed with SAS software (SAS Institute, Inc, Cary, NC). Statistical significance was set at $P < .05$.

RESULTS

A total of 16,320 children were born in the province of Manitoba in 1995, of which 13,980 (85.7%) continued to live in the province in 2002. A description of these children based on birth weight and gestational age is shown in Table I. Of the 13,980 children, 881 (6.3%) were born prematurely (gestational age <37 weeks). Overall, 691 children (4.9%) were born with a birth weight less than 2500 g. From the total cohort, 592 children (4.23%) were found to have food allergy sometime in their life ("ever"). A prescription for epinephrine was dispensed for 316 (2.26%) children. Diagnosed food allergy prevalence at 6-7 years of age ("current") was 2.06%. A prescription for epinephrine was filled by 1.62% of these children (Table II). Frequency of food allergy according to gestational age and birth weight can be found in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org.

Eighteen children with a venom allergy and prescribed epinephrine were excluded from the analysis. All remaining children who were prescribed epinephrine were found to have food allergy (ICD-9-CM code = 693). The validation of our food allergy definition is found in this article's [Online Repository](http://www.jacionline.org) at www.jacionline.org.

Table III shows the unadjusted relative risks of ever and current food allergy for various gestational ages or birth weights compared with term gestation or normal birth weight. The risk for ever and current food allergy was not statistically significantly different among gestational ages or birth weights. The same results were obtained with the diagnosis and prescription-based definitions of food allergy and with the prescription-only definitions.

TABLE I. Distribution of babies born in 1995 by gestational age and birth weight

Birth weight (g)	Gestational age (wk)					Missing data	Total
	<28	28-31 (6/7)	32-36 (6/7)	Term (37-41) (6/7)	≥42		
<1000	28	*	*				33
1000-1499	9	45	15	*			70
1500-1999		31	85	16			132
2000-2499		*	255	199	*		456
Normal (2500-4499)			401	12,205	299	17	12,922
4500-4999			*	304	10		318
5000-5500				29	*		32
>5500				*	*		*
Missing data			2	5		5	12
Total	37	81	763	12,763	314	22	13,980

*Less than 5 children. Due to Health Privacy Information Act in the Province of Manitoba, we cannot put any identifiable data in manuscripts. Thus, we have hidden any box that may identify a child. Every child was used in the analysis.

TABLE II. Prevalence of food allergy and epinephrine prescribed

Time period	No. of children (N = 13,980)	Percent
Food allergy diagnosis		
Ever*	592	4.23%
Current†	288	2.06%
Epinephrine prescribed		
Ever*	316	2.26%
Current†	227	1.62%

*Ever = anytime during the first 7 years of life.

†Current = at the age of 6 or 7 years (2001-2002).

Before performing a multivariate analysis, we analyzed other factors that may be associated with food allergy (Table IV). A high income, maternal history of asthma, maternal history of food allergy, male gender, and urban location were found to be significant for increased risk of a food allergy diagnosis. Table V shows hazards ratios and odds ratios for gestational age and birth weight, correcting for these factors. The adjusted hazard ratios for ever food allergy and the adjusted odds ratios for current food allergy were similar to the unadjusted relative risks. No statistically significant increased risks were found for food allergy for either prematurity or low birth weight.

DISCUSSION

To the best of our knowledge, this population-based study is the first to examine prematurity or low birth weight and the risk of developing food allergy. Our data suggest that no association exists between gestational age and birth weight with the development of IgE-mediated food allergies. As a result, the theory that an immature gut mucosa results in increased permeability to large-molecular-weight proteins and predisposes the baby to early sensitization needs to be questioned.^{6-9,12}

Our results are consistent with several other studies.^{17,20-24} Lucas et al²⁰ compared the effects of banked

human breast milk versus cow's milk formula for use as the diet for 446 premature neonates. This group of infants had been considered at high risk for allergic sensitization to food antigens because of delayed gut maturity. In that study, no statistically significant difference was found between the children fed breast milk versus the specialized cow's milk formula. However, within the group of children with an atopic family history, the infants fed cow's milk formula had an increased likelihood of developing an allergy (including atopic dermatitis) (41% vs 16% of the breastfed infants). In that study, no confirmatory skin testing and immunologic data were presented. A possible conclusion from their study is that, with an atopic family history, premature children have an increased risk of developing IgE-mediated food allergy.

Siltanen et al²² have shown that preterm children (mean gestational age of 28.5 weeks) when compared with term children had significantly lower levels of antibodies of the IgG and IgA isotypes to whole cow's milk and alpha-casein at the age of 10 years. Measurable levels of IgE antibodies to egg were equally frequent in preterm and term groups. They found that those preterm children with atopic symptoms had the lowest quartile for IgG cow's milk antibodies. They inferred that the immaturity of the innate and specific defense mechanisms of the intestines of preterm infants with a birth weight <1500 g results in suppression of immune responses to oral antigens given early during life, and it makes these B cells more tolerant to these antigens. They demonstrated that prematurity is associated with the appearance of significantly less atopic sensitization by age 10 years than observed in an age-matched control group.

The American Academy of Pediatrics (AAP) recommends that, in children with a high risk of allergy, "solid foods should not be introduced until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts and fish until 3 years of age."^{25,26} These recommendations were instituted in an attempt to decrease the risk of developing atopic dermatitis.^{27,28} Fergusson et al²⁷ found that children exposed to 4 or more different types of solid food before 4 months had risks of recurrent

TABLE III. Unadjusted relative risks (95% CIs) of food allergy based on gestational age and birth weight

Factor	Ever	Ever, epinephrine	Current	Current, epinephrine
Gestational age				
<28 wk	1.9 (0.64-5.64)	2.35 (0.61-9.11)	*	*
28-31 wk	0.29 (0.04-2.03)	0.54 (0.08-3.78)	0.58 (0.08-4.09)	0.74 (0.1-5.19)
32-36 wk	0.98 (0.69-1.39)	0.74 (0.43-1.29)	0.68 (0.37-1.24)	0.63 (0.31-1.26)
Term	1.00	1.00	1.00	1.00
≥42 wks	0.82 (0.46-1.47)	0.97 (0.46-2.04)	0.75 (0.31-1.8)	0.76 (0.28-2.03)
Birth weight				
<1000 g	2.15 (0.73-6.35)	2.65 (0.69-10.22)	*	*
1000-1499 g	0.34 (0.05-2.37)	0.63 (0.09-4.39)	0.67 (0.09-4.68)	0.85 (0.12-5.95)
1500-1999 g	0.72 (0.27-1.89)	0.33 (0.05-2.35)	*	*
2000-2499 g	1.4 (0.96-2.04)	1.25 (0.72-2.16)	0.82 (0.41-1.64)	0.91 (0.43-1.92)
Normal	1.00	1.00	1.00	1.00
4500-4999 g	0.67 (0.35-1.28)	0.41 (0.13-1.28)	0.29 (0.07-1.17)	0.19 (0.03-1.32)
5000-5500 g	*	*	*	*
>5500 g	4.73 (0.82-27.37)	*	*	*

*No children in these categories.

TABLE IV. Unadjusted odds ratios of factors that may affect development/diagnosis of food allergy

Factor	Ever	Ever, epinephrine	Current	Current, epinephrine
Low income in 2001*	0.76 (0.64-0.91)	0.52 (0.41-0.67)	0.51 (0.39-0.66)	0.43 (0.32-0.59)
High income in 2001*	1.00	1.00	1.00	1.00
Maternal asthma†	1.55 (1.23-1.96)	1.54 (1.12-2.11)	1.59 (1.15-2.20)	1.66 (1.16-2.39)
No maternal asthma†	1.00	1.00	1.00	1.00
Maternal food allergy‡	4.04 (1.98-8.24)	3.11 (1.12-8.64)	5.37 (2.29-12.59)	3.22 (1.00-10.35)
No maternal food allergy‡	1.00	1.00	1.00	1.00
Urban location	1.92 (1.61-2.30)	1.80 (1.42-2.29)	2.0 (1.55-2.58)	1.88 (1.41-2.50)
Rural location	1.00	1.00	1.00	1.00
Male	1.34 (1.14-1.59)	1.50 (1.20-1.89)	1.40 (1.10-1.77)	1.50 (1.15-2.0)
Female	1.00	1.00	1.00	1.00
Cesarean section	1.16 (0.92-1.45)	1.25 (0.93-1.68)	1.30 (0.96-1.77)	1.34 (0.95-1.88)
No cesarean section	1.00	1.00	1.00	1.00

*Income based on postal codes in urban centers (Winnipeg and Brandon).

†Mothers with asthma defined by ICD-9-CM code 493 from 1990 to 1995 or at least 1 prescription of an asthma medication in 1995.

‡Mothers with food allergy defined by ICD-9-CM code 693 in 1995 or epinephrine prescription in 1995 or 1996.

||Urban centers were Winnipeg and Brandon.

or chronic eczema that were 2.9 times those of children who were not exposed to early solid feeding. However, individually, exposure to cow's milk, egg, cereals, vegetables, meat products, or fruit did not increase the risk for the development of atopic dermatitis. The AAP guidelines do not mention why they pick particular foods (dairy, eggs, peanuts, nuts, and fish), although these tend to be the most prevalent in causing IgE-mediated food allergy.²⁹ Many health care professionals have adopted these recommendations with the belief that this will reduce the risk of developing IgE-mediated food allergies. The theory is that at a young age (ie, <3 years), an immature and permeable gastrointestinal tract will result in increased antigen uptake. Thus, highly allergenic foods may be absorbed more easily, increasing the risk for sensitization. However, our large, population-based epidemiologic study does not support an increased risk for development of food allergy in premature or low-birth-weight infants from birth to 7 years of age. A possible mechanism preventing

sensitization might be the development of immunologic tolerance to orally ingested allergens in premature infants. Such tolerance might result from interaction of high antigen concentration with the immature immune system of the preterm infant.^{30,31}

These data prompt us to ask whether it may be possible that introducing highly allergenic proteins (such as peanut) early in life would tolerate (as opposed to sensitize) a child to that particular antigen? Rat and murine models have shown that high dose oral ovalbumin^{30,31} or peanut³¹ can lead to immune tolerance. It could be inferred that the current practice of attempting to avoid highly allergenic foods in an attempt to decrease antigen sensitization has, in fact, done the opposite, and it may have contributed to the increased prevalence of food allergy in North America. Complete avoidance of certain food antigens is nearly impossible, as children are almost certainly exposed to minute quantities of peanut antigen in our North American environment.³²⁻³⁶ In fact, low-dose,

TABLE V. Adjusted risks for ever food allergy (hazard ratio) and current food allergy (odds ratio) by gestational age and birth weight*

Predictor	Reference†	Hazard ratio for ever food allergy	Odds ratio for current food allergy
Gestational age‡			
<28 wk		1.10 (0.40-2.99)	‡
		0.85	
28-<32 wk		1.46 (0.75-2.82)	0.20 (0.01->999)
		0.26	
32-<37 wk		0.96 (0.78-1.18)	1.30 (0.65-2.62)
		0.68	
37-<42 wk	1.00		1.00
≥42 wk		0.90 (0.67-1.19)	1.18 (0.48-2.88)
		0.44	
Birth weight‡			
<1500 g		0.85 (0.40-1.82)	5.33 (0.01->999)
		0.68	
≥1500-<2500 g		0.93 (0.73-1.18)	1.25 (0.54-2.88)
		0.53	
≥2500-<4500 g	1.00		1.00
≥4500 g		0.92 (0.71-1.20)	3.57 (0.88-14.44)
		0.54	

‡No children in this category.

*Maternal asthma was defined by an ICD-9-CM code of 493 from 1990 to 1995 or at least 1 prescription of an asthma medication in 1995. Maternal food allergy was defined by an ICD-9-CM code of 693 in 1995 or at least 1 prescription of an epinephrine in 1995/1996. Income was determined by postal code regions and associated socioeconomic status. Location of residence was determined from postal code at birth. All covariates include the models as dummy variables. The adjusted models were adjusted for birth weight, maternal asthma, maternal food allergy, caesarean section, male gender, income and location of residence at birth.

†The reference category include those in the 37 to <42 weeks group or ≥2500 to <4500 g group.

‡Numbers in parenthesis are 95% CI. Number below is the *P* value.

intermittent exposure may be the trigger for developing IgE-mediated food allergies.

Our cohort cumulative lifetime prevalence of food allergy of 4.23% and period prevalence at the age of 6 or 7 years of 2.06% is consistent with the literature in which food allergy prevalence (depending on age) ranges from 2% to 8%.^{29,37,38} Also, cumulative lifetime prevalence of prescriptions of epinephrine was 2.26% of children and period prevalence at the age of 6 or 7 years was 1.62% of children. These rates are similar to the 1.44% prevalence described by Simons et al³⁹ for individuals younger than 17 years of age in the province of Manitoba.

In our study, food allergy was associated with a maternal history of asthma and food allergy, higher socioeconomic status (including income and location of residence), and male gender (Table IV). We used maternal history of asthma and food allergy as a proxy for an atopic family history. Data from our cohort are in agreement with other studies that have shown that male gender^{24,40-42} and a family history of atopy are risk factors for the development of food allergy.

One may argue that our definition of an IgE-mediated food allergy is somewhat suspect. Database definitions may have problems with respect to coding. We defined IgE-mediated food allergy for children using the ICD-9-CM code 693, which is “Dermatitis due to substances taken externally” and includes 693.0—due to drugs and medicines; 693.1—due to food; 693.8—due to other

specified substances taken internally; and 693.9—due to unspecified substance taken internally. We polled all allergists who worked in the province of Manitoba in the past 5 years (*n* = 12) and found that, when coding for a food allergy (based on history and skin prick test/radio-allergosorbent test), they use the ICD-9-CM code 693.1. Unfortunately, in our medical claims, our medical records only record the first 3 digits of an ICD-9-CM code. To validate our definition of food allergy (using an ICD-9-CM code of 693), we performed 2 additional analyses—comparing the ICD-9-CM code 693 and epinephrine prescriptions to gold standards—surveys to the SAGE cohort and physician assessments of a case control subgroup of the children. As shown in the results, using the physician diagnosis of IgE-mediated food allergies as gold standard resulted in the ICD-9-CM code having a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 67.86%, 98.20%, 79.17%, and 96.81%, respectively, to diagnose IgE-mediated food allergies. For an epinephrine prescription in 2001-2002, sensitivity, specificity, PPV, and NPV were 67.86%, 98.92%, 86.36%, and 96.84%, respectively, to diagnose IgE-mediated food allergies. The high specificities (>98%) confirm that an ICD-9-CM code of 693 is unlikely to have an important false-positive rate. The sensitivities were somewhat lower as they reflect children/families who were unaware that they had a serious allergy (ie, they may avoid the food they “didn’t like”). Thus, from these analyses, we are confident that an ICD-9-CM code is a

good reflection of an IgE-mediated food allergy in our cohort.

Besides using the ICD-9-CM code, we used a prescription of epinephrine (excluding a diagnosis of venom allergy) to represent a severe IgE-mediated food allergy where risk for anaphylaxis exists. Granted, some infrequent alternative reasons may exist for prescribing epinephrine (eg, severe asthma or systemic mastocytosis). However, these reasons are less likely in children less than or equal to 7 years. Furthermore, we polled the 12 allergists who worked in the province of Manitoba in the past 5 years. Epinephrine was prescribed for alternative reasons in only 6 children and included cold-induced urticaria ($n = 2$), severe asthma ($n = 1$), cat allergy ($n = 2$), and horse allergy ($n = 1$). Three of these children were not born in 1995, and for the other 3, the year of birth is unknown. These numbers are quite low and would be unlikely to affect our overall results. We are confident that epinephrine prescriptions are reflective of severe IgE-mediated food allergies, as all of our children who were dispensed epinephrine also had an ICD-9-CM diagnostic code of 693. As with the ICD-9-CM code food allergy definition, analysis using epinephrine prescriptions alone did not reveal any statistical significance between premature or low-birth-weight and term or normal-birth-weight groups.

A discrepancy remains between an ICD-9-CM code of 693 and an epinephrine prescription. Two reasons likely play a role. First, a child who has atopic dermatitis exacerbated by food allergy may not be prescribed epinephrine, which is a common practice among Canadian allergists. Second, our prescription database only records epinephrine if it has been prescribed and dispensed. If epinephrine was prescribed, but never purchased from a pharmacy, it would not be recorded in the database. As a result, under-reporting for epinephrine prescriptions may have occurred.

In summary, using a large population database, we have found that prematurity or low birth weight do not play a role in the likelihood of food allergy. Additional large population studies should be undertaken to confirm this observation. We hypothesize that oral intake of highly allergenic proteins in early life may tolerize rather than sensitize children. Carefully designed and monitored studies are also required to inform the health care community as to the best approach to the introduction of foods for infants and young children.

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APPENDIX A

Data were accessed from the Population Health Research Data Repository at the Manitoba Centre for Health Policy, Winnipeg, Manitoba, Canada. The results and conclusions are those of the authors, and no official endorsement by Manitoba Health was intended or should be inferred. We would like to acknowledge the computer analysis support of Matthew Dahl in creating the 1995 birth cohort and to give a special thanks to the SAGE (Study of Asthma, Genes and the Environment) team, including Rishma Chooniedass, Miriam Clement, Donna Everette, Brenda Gerwing, Marilyn Lilley, Tanya Lilley-Chan, Ingrid Loewen, Melissa Moyon, Rasheda Rabbani, Diane Stewart, Michelle Tillett, and John Weselake.

VALIDATION OF FOOD ALLERGY DEFINITION

Validation of the definition of IgE-mediated food allergy as an ICD-9-CM code of 693 was done via 3 methods.

1. A Poll of all allergists ($n = 12$) who practice or have practiced in the province of Manitoba in the past 5 years. They were asked what diagnostic code they used for IgE-mediated food allergies (based on history, skin prick testing, radioallergosorbent test, and oral food challenges). They were also queried as to whether they prescribed epinephrine for reasons other than food or venom allergy.
2. As part of the Study of Asthma Genes and the Environment (SAGE) study, a survey was sent to all children born in the province of Manitoba in 1995. On the survey, parents were asked whether their child had a food allergy. Using this survey as a gold standard, the sensitivity, specificity, positive predictive value (PPV) and negative value (NPV) of an ICD-9-CM code of 693 and a prescription of epinephrine to diagnose food allergies were calculated.
3. Using the case control cohort of the SAGE study, 613 children from across the province of Manitoba were assessed by a pediatric allergist (J.L. or A.B.) to diagnose food allergy. IgE-mediated food allergy was diagnosed by a thorough history and physical examination. With respect to history, questions regarding the food eaten, timeline of the reaction, symptoms of reaction (hives, wheeze, cough, shortness of breath, vomiting, diarrhea, etc) as well as treatment of reaction (given antihistamine, taken to emergency room and treatment with epinephrine, and assessed by an allergist in the community) were queried. Presence of other atopic conditions (asthma, atopic dermatitis, and allergic rhinitis) and family history of atopy was also obtained. Finally, findings were supplemented by detection of the presence/absence of allergen-specific IgE (*in vivo* and/or *in vitro*). Using this physician diagnosis as a gold standard, sensitivities, specificities,

PPVs, and NPVs were established for an ICD-9-CM code of 693 in 2001-2002 (current) and a prescription of epinephrine to diagnose IgE-mediated food allergies.

OUTCOME OF FOOD ALLERGY DEFINITION VALIDATION

1. A poll of all 12 allergists who practiced in the Province of Manitoba in the past 5 years confirmed that each of these allergists used an ICD-9-CM code of 693.1 for IgE-mediated food allergy as their diagnostic code. Also, in the past 5 years, the only times ($n = 6$) epinephrine was prescribed for alternative reasons in this age group included cold-induced urticaria ($n = 2$), severe asthma ($n = 1$), cat allergy ($n = 2$), and horse allergy ($n = 1$). Three of these children were not born in 1995. For the other 3 children, the year of birth is unknown.
2. Using the SAGE survey as the gold standard ($n = 3558$), we could determine that an ICD-9-CM code of 693 in 2001-2002 (current) had a sensitivity, specificity, PPV, and NPV of 39.90%, 98.96%, 68.75% and 96.63%, respectively, to diagnose food allergy. For an epinephrine prescription in 2001-2002, to diagnose food allergy, sensitivity, specificity, PPV, and NPV were 38.86%, 99.55%, 83.33%, and 96.60%, respectively.
3. By using the diagnosis of food allergy by a pediatric allergist (history $\pm$ skin prick tests/radioallergosorbent test) as the gold standard in our case control cohort ($n = 613$), we could determine that an ICD-9-CM code of 693 in 2001-2002 (current) had a sensitivity, specificity, PPV, and NPV of 67.86%, 98.20%, 79.17%, and 96.81%, respectively, to diagnose IgE-mediated food allergies. For an epinephrine prescription in 2001-2002, sensitivity, specificity, PPV, and NPV were 67.86%, 98.92%, 86.36%, and 96.84%, respectively, to diagnose IgE-mediated food allergies (Youden Index = 0.66 for both ICD-9-CM code of 693 and epinephrine prescription).

TABLE E1. Frequencies of food allergy by gestational age and birth weight

	Percent ever	Percent current
Gestational age		
<28 wk	8.1	0
28-31 6/7 wk	1.2	1.2
32-36 6/7 wk	4.2	1.4
Term	3.5	2.1
<42 wk	3.5	1.6
Birth weight		
<1000 g	9.1	0
1000-1499 g	1.4	1.4
1500-1999 g	3.0	0
2000-2499 g	5.9	1.8
Normal	4.2	2.1
4500-4999 g	2.8	0.6
5000-5500 g	0	0
>5500 g	20	0