Journal of Microbiology, Immunology and Infection 55 (2022) 956–964

Available online at www.sciencedirect.com

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Original Article

Longitudinal changes in body mass index Z-scores during infancy and risk of childhood allergies

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Received 17 November 2020; received in revised form 16 September 2021; accepted 10 October 2021
Available online 25 October 2021

KEYWORDS
Allergic sensitization;
Asthma;
BMI Z-scores;
Breastfeeding;
IgE

Abstract *Background:* Few studies address the dynamic changes of body mass index (BMI) Z-scores during infancy with breastfeeding and their impact on childhood atopic diseases.
Methods: A total of 183 children from a birth cohort regularly followed-up for 4 years were enrolled in this study. Time series data of BMI Z-scores from 1 month to 2 years of age was clustered using *K*-means method in R software. Breastfeeding status during the first 6 months of life was recorded and classified. The total serum and specific immunoglobulin E (IgE) levels to food and inhalant allergens were measured at age 0.5, 1, 1.5, and 2 years.
Results: Using *K*-means clustering, the dynamic changes in BMI Z-scores were classified into three clusters (cluster A, increasing, n = 62; cluster B; decreasing, n = 62; cluster C, constant low, n = 59). Despite having no statistical association with atopic diseases, a decreasing trend in infantile BMI Z-scores was significantly associated with a higher prevalence of IgE

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https://doi.org/10.1016/j.jmii.2021.10.001

sensitization at age 1 which increased the risk of rhinitis development at age 4 ($P = 0.007$). No difference in BMI Z-scores was determined between different breastfeeding patterns. However, exclusive formula feeding ≥6 months was found to be significantly associated with mite sensitization at age 1.5 years which risks asthma development at age 4 ($P = 0.001$).
Conclusions: A decreasing trend of BMI Z-scores during infancy is determined to be inversely associated with IgE and allergen sensitization, which may potentially increase the risk of allergies in early childhood.

Introduction

Childhood obesity has been identified as a risk factor for the development of asthma in young adults.[1] A recent study reported that a high body mass index (BMI) after 2 years of age is an important predictor for being overweight at 8 years of age.[2] However, during infancy, growth is rapid, coupled with different feeding patterns and diets; furthermore, this is accompanied by a complex remodeling of the immune system.[3] Most importantly, sensitization to allergens in early life has consistently identified as being a risk toward the development of various childhood atopic diseases.[4] Few studies, however, have examined address the relationship between dynamic changes in BMI during infancy and allergen sensitization and atopic disease development in early childhood.

Breastfeeding is known to provide optimal nutrition, immune protection, and the regulation of growth and development for infants and young children.[5] Breastfeeding protects against common infections and further reduces the risk of children being overweight or obese.[6,7] Furthermore, because of its immune modulatory effects, breastfeeding potentially plays an essential role in the development of childhood allergic sensitization and atopic diseases.[8] However, the impact of breastfeeding on BMI changes during infancy remains uncertain, and there is no conclusive evidence confirming the association between infant feeding patterns and allergen sensitization relating to childhood atopic diseases.

This study aimed to determine the dynamic changes of weight, height, and BMI from 1 month to 2 years of age in children enrolled in a birth cohort in the Prediction of Allergies in Taiwanese Children (PATCH) study. The longitudinal changes in BMI Z-scores during infancy were clustered and assessed for different breastfeeding patterns. Their relevance to allergic sensitization and their impact on atopic disease in early childhood were also examined.

Methods

Study subjects and data collection

The subjects in this study were derived from a birth cohort of The Prediction of Allergies in Taiwanese Children (PATCH) initiated in 2007, which is a joint study set up to investigate environmental and genetic influences on asthma and allergies. We enrolled children who completed a 4-year follow-up period. Demographic characteristics such as sex, family history of atopy, exposure to passive smoking, household income, and history of breastfeeding were collected and analyzed. The childhood atopic diseases including eczema, allergic rhinitis, and asthma, were evaluated at different years of age by the same pediatric pulmonologist according to the criteria as described in our previous study.[9] Asthma was clinically diagnosed as having the symptoms with shortness of breath, coughing, and recurrent wheezing, based on the guidelines of the Global Initiative for Asthma.[10] However, episodes of wheezing induced by viral infections of the upper respiratory tract, few or no interval wheeze symptoms between viral illnesses, were excluded from atopic asthma.[11,12] Because the diagnosis of atopic diseases during early childhood was heavily relied on allergic symptoms which may be transient from time to time, childhood atopic diseases were confirmly diagnosed at age 4. This study was approved by the Ethics Committee of Clinical Research (No. 103-6236A3). All experiments in this study were performed in accordance with the relevant guidelines and regulations and written informed consent was obtained from a parent and/or legal guardian of all study subjects.

Measurement of BMI and clustering

The enrolled subjects were weighed and height measured at follow-up. To measure the true weight and height, precise measurements were done by well-trained registered professional nurse with strict adherence to the standard protocols including light indoor clothing and shoes removed.[13] BMI was defined as weight in kilograms divided by the square of height in meters according the World Health Organization (WHO). Overweight is defined as a BMI at or above the 85th percentile; obesity is a BMI at or above the 95th percentile.[14] Gender-specific Z-scores for weight-for-age, height-for-age, and BMI-for-age were calculated using the WHO international child growth standards as the reference.[15] A Z-score is calculated by subtracting the mean value, and divided by the standard deviation, representing the number of standard deviations above or below the mean.[15] For longitudinal clustering, because of the weight loss after birth and variance in time to return to birth weight,[16] time series data of BMI Z-scores from 1 month to 2 years of age were grouped into discrete and stable clusters by using *K*-means method in R software

(Lucent Technologies, NJ, USA, version 3.3.1). Longitudinal *K*-means (KML) is a non-parametric algorithm for clustering longitudinal data using the Calinski and Harabasz criterion $C(g)$.[17]

Breastfeeding history and patterns

Breastfeeding patterns were classified into three categories: exclusive breastfeeding, partial breastfeeding and exclusive formula feeding. Six-month duration of breastfeeding is recommended by WHO to achieve optimal growth, development and health.[18] Exclusive breastfeeding was defined as breastfeeding for at least 6 months without any supplementation including solid food or liquids, while exclusive formula feeding was defined as infant fed with only formula. Partial breastfeeding was defined as a combination of breastfeeding and formula feeding.[19]

Total serum and allergen-specific IgE levels

Total serum IgE levels and allergen-specific serum IgE levels were measured at 0.5, 1, 1.5 and 2 years of age. Total serum IgE levels were measured by ImmunoCAP (Phadia, Uppsala, Sweden), while allergen-specific serum IgE levels were measured by ImmunoCAP (ImmunoCAP Phadiatop Infant; Phadia). Food allergen including egg white and cow's milk as well as aeroallergens including *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* were measured.[20] Sensitization of total IgE levels and allergen-specific serum IgE levels were defined by using the cut-off levels of $\geq$100 kU/L and 0.35 kU/L respectively.[21]

Covariates

Potential confounders in relation to BMI, breastfeeding and atopic disease developments were collected. Confounding variables such as child's sex, gestational age, maternal age at delivery, parental history of atopy, passive smoke exposure from parents, any older siblings, and household income were included and analyzed.

Statistical analysis

All statistical analysis was conducted using the Statistical Package for the Social Sciences (version 20.0; SPSS Statistics for Windows, Armonk, NY, USA), while GraphPad Prism software (version 5.01; GraphPad Software Inc., San Diego, CA, USA) was used to plot data points for data organization and graphing. Univariate parametric and nonparametric tests such as ANOVA, chi-square test, Fisher's exact test, and Kruskal–Wallis rank sum test were applied for allergic sensitization categorized by BMI Z-score clusters. Logistic regression analysis was used to determine the relationship of BMI Z-scores and breastfeeding pattern with atopic diseases by adjusting for confounding factors. All statistical hypothesis tests mentioned above were two-tailed and a *P*-value of <0.05 was considered significant.

Results

Study population

Initially, a total of 258 newborns were recruited from 2007 to 2010 in Keelung Chang Gung Memorial Hospital; there were only 226 (87.6%), 210 (81.4%), 198 (76.7%), and 183 (70.9%) children completed a one-, two-, three-, and four-year follow-up period. The subject recruitment and the cohort profile were described in full detail in our previous study.[4,22] There were no significant differences in the demographic characteristics between these 183 and the 258 children recruited initially,[19] indicating that the 183 children enrolled could be a representative sample of the full cohort. At 4 years of age, atopic diseases including eczema, allergic rhinitis, and asthma were physician-diagnosed in 22, 80, and 32 children respectively.[22] A flow diagram of the study design is shown in Fig. 1A.

Clustering analysis of BMI Z-scores

Weight and height were measured at 1 and 6 months, and 1, 1.5, and 2 years of age. The dynamic changes in BMI Z-scores from 1 month to 2 years of age were stratified into three clusters (Fig. 1B). Cluster A (increasing, $n = 62$) comprised children with a gradual increase in BMI Z-scores from 0 to 1 at 6 months of age, followed by a constant BMI Z-score of 1. Cluster B (decreasing, $n = 62$) comprised children with a marked decrease in BMI Z-scores from 1 to 0 at 6 months of age, followed by a constant BMI Z-score of 0. Cluster C (constant low, $n = 59$) comprised children with a constantly low BMI Z-score of -1. The baseline characteristics of the enrolled children in relation to BMI Z-score clusters are summarized in Table 1. Having older siblings was significantly associated with decreased BMI Z-scores during infancy ($P = 0.026$). There was a significantly higher BMI related to overweight/obesity in cluster A at the age of 4 years ($P < 0.001$). However, no other significant differences were observed among the three clusters, including the pattern of breastfeeding and childhood atopic diseases.

Association of BMI Z-score clusters with IgE and allergic sensitization

The comparisons and differences among the three BMI Z-score clusters in terms of weight and height Z-scores at different ages are illustrated in Fig. 2A. The trend toward the increased BMI Z-scores in cluster A was significantly associated with an increase in weight Z-scores from the age of 1 month–2 years, whereas the trend toward reduced BMI Z-scores in cluster B was significantly associated with a decrease in weight Z-scores. However, there were no significant differences in the height Z-scores among these three clusters at different ages. Compared with children grouped in cluster A, a significantly higher prevalence of IgE sensitization was observed in children grouped in cluster B at the age of 1 and 1.5 years (Bonferroni-adjusted $P < 0.017$). Furthermore, a significantly higher prevalence of egg white and milk sensitization was found in children grouped in cluster B at age 1. Additionally, the occurrence of mite sensitization at 1.5 years of age was significantly

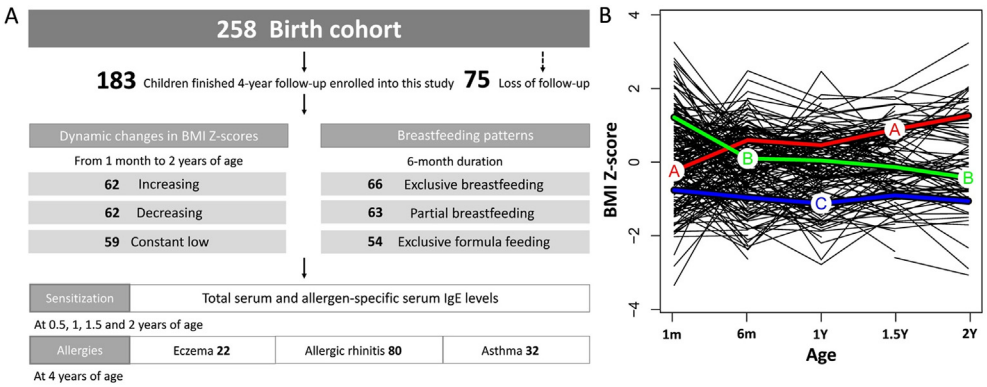

Fig. 1. A flow diagram of the study design (A) and clustering of BMI Z-scores during infancy (B). The pattern of BMI Z-scores from 1 month to 2 years of age clustering using *K*-means method in R software.

higher in children grouped in cluster B compared with those grouped in cluster C (Fig. 2B).

Association of breastfeeding patterns with IgE and allergic sensitization

Figure 3A shows the comparisons and differences among the different breastfeeding patterns with respect to Z-scores of BMI, weight, and height at different ages. No significant difference was observed in the BMI Z-scores between the three different breastfeeding patterns. However, compared to children who were exclusively breastfed, a significantly higher Z-score of weight and height was found at age 1.5 and 2 years in the formula-fed children. Moreover, there was also a significantly higher prevalence of milk and mite sensitization in formula-fed children at age 1.5 years (Fig. 3B, Bonferroni-adjusted $P < 0.017$). However, no significant difference was observed between

Table 1 Baseline characteristics of 183 children in relation to BMI Z-scores clustering from 1 month to the age of 2 years.

Characteristics	Cluster A (n = 62)	Cluster B (n = 62)	Cluster C (n = 59)	*P*-value
Family				
Maternal atopy	32 (51.6%)	26 (42.6%)	24 (40.7%)	0.432
Paternal atopy	31 (50.0%)	38 (62.3%)	32 (54.2%)	0.379
Parental smoking	36 (58.1%)	31 (50.0%)	28 (47.5%)	0.472
Older siblings	21 (33.9%)	36 (58.1%)	27 (45.8%)	0.026
Household income (NTD)				
Low, ≤500,000	29 (46.8%)	18 (29.5%)	20 (33.9%)	0.291
Medium, 500,000–1,000,000	21 (33.9%)	31 (50.8%)	28 (47.5%)	
High >1,000,000	12 (19.4%)	12 (19.7%)	11 (18.6)	
Infant				
Sex, male	34 (54.8%)	31 (50.0%)	36 (61.0%)	0.475
Maternal age (yr)	30 ± 4.1	31.5 ± 4.0	31.3 ± 4.8	0.101
Gestational age (wk)	38.5 ± 1.5	37.9 ± 2.2	38.0 ± 2.0	0.171
Birth BMI (kg/m^2)	12.4 ± 1.2	12.9 ± 2.7	12.3 ± 2.3	0.348
Breastfeeding ≥6 mo				
Exclusive	19 (30.6%)	21 (33.9%)	26 (44.1%)	0.519
Partial	25 (40.3%)	22 (35.5%)	16 (27.1%)	
Formula	18 (29.0%)	19 (30.6%)	17 (28.8%)	
Childhood at age 4				
BMI (kg/m^2)	17.9 ± 2.4	16.2 ± 1.7	15.0 ± 1.3	<0.001
Weight (kg)	18.9 ± 3.3	16.8 ± 2.1	15.5 ± 1.7	<0.001
Height (cm)	105.0 ± 4.8	103.4 ± 4.8	102.8 ± 4.6	0.128
Overweight/obesity	18 (50.0%)	5 (14.3%)	1 (2.6%)	<0.001
Atopic diseases				
Eczema	6 (12.2%)	9 (20.0%)	7 (17.5%)	0.584
Allergic rhinitis	26 (52.0%)	28 (62.2%)	26 (63.4%)	0.465
Asthma	10 (20.8%)	13 (28.9%)	9 (22.0%)	0.622

Data shown are mean ± SD or number (%) of patients as appropriate. BMI, body mass index; yr, year; NTD, new Taiwan dollar; wk, week; mo: month.

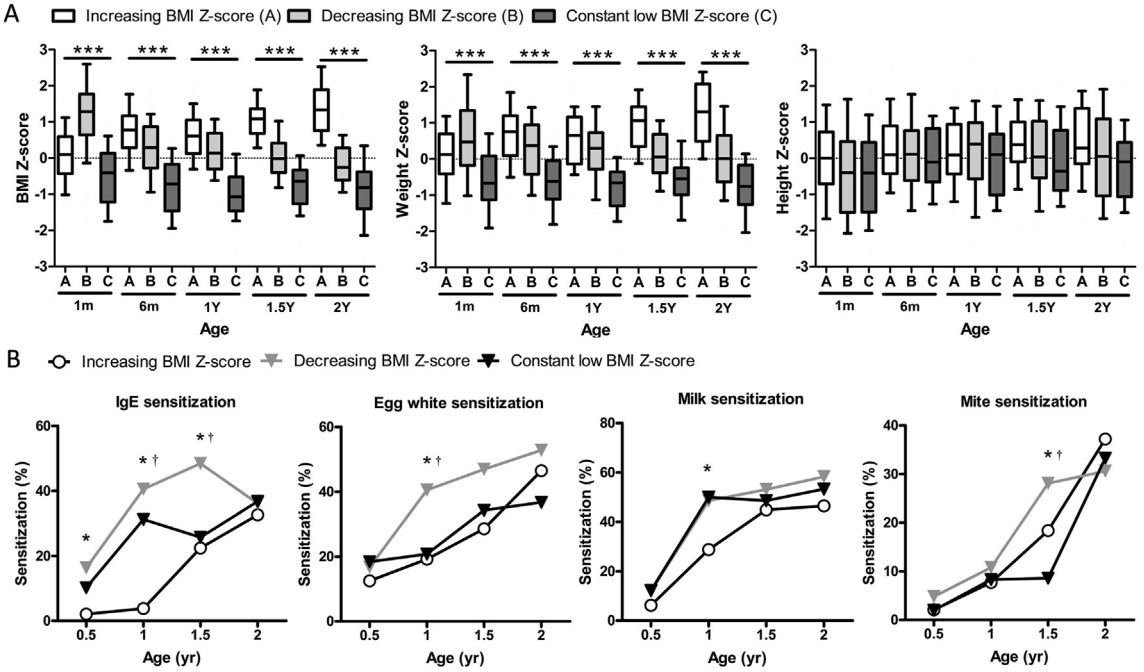

Fig. 2. BMI Z-score clusters with respect to weight and height Z-scores, and their relationships with allergic sensitization at different years of age. Comparisons and differences in BMI Z-scores clustering with weight Z-scores, and height Z-scores (A) and allergen sensitization to egg white, milk, mite, and IgE sensitization (≥100 kU/L) (B) at different years of age. The box-plot showing the median and the 10th, 25th, 75th, and 90th percentile. *P*-values referred to the comparisons of BMI Z-scores and weight Z-scores at different ages, IgE sensitization at age 0.5, 1, and 1.5 (cluster B vs. cluster A), egg white and milk sensitization at age 1 (cluster B vs. cluster A), and mite sensitization at age 1.5 (cluster B vs. cluster C) are indicated by the marker. $^{*}P < 0.05$; $^{***}P < 0.001$. † Significant by Bonferroni-adjusted *P* (*P* value $< 0.05/3$).

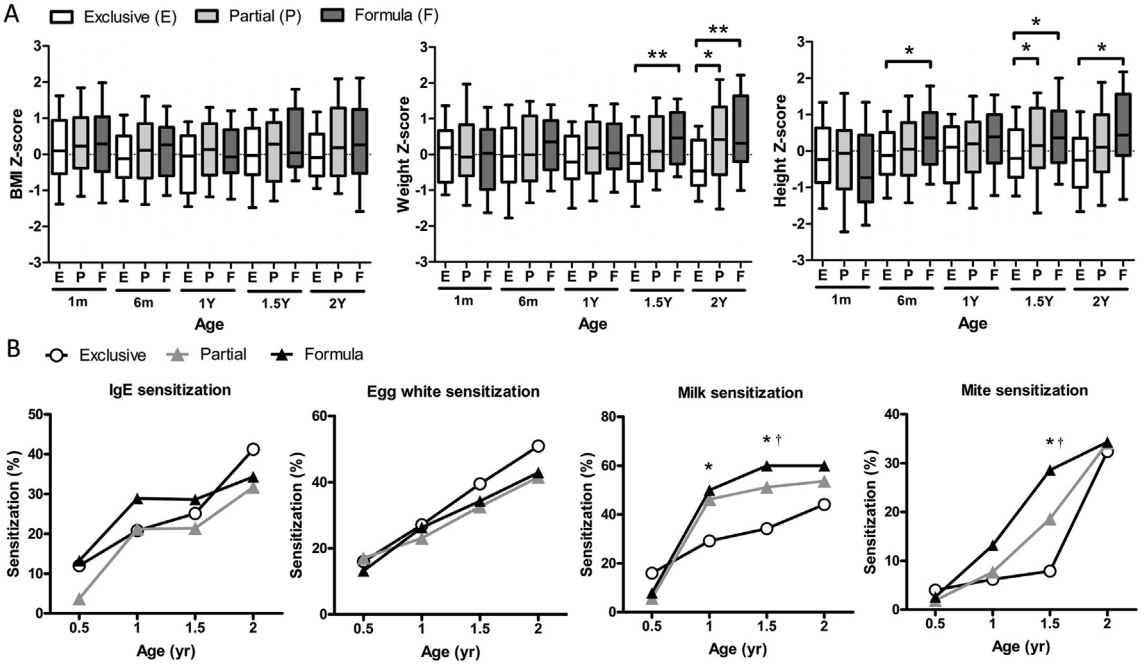

Fig. 3. Different breastfeeding patterns during infancy and their relationships with allergic sensitization at different years of age. Comparisons and differences of different breastfeeding patterns with BMI Z-scores, weight Z-scores, and height Z-scores (A), and allergen sensitization to egg white, milk, mite, and IgE sensitization (≥100 kU/L) (B) at different years of age. *P*-values referred to the comparisons of weight Z-scores and height Z-scores at the age 1.5 and 2, milk sensitization at age 1 and 1.5, and mite sensitization at age 1.5 (formula vs. exclusive breastfeeding) are indicated by the marker. $^{*}P < 0.05$; $^{**}P < 0.01$. † Significant by Bonferroni-adjusted *P* (*P* value $< 0.05/3$).

the different breastfeeding patterns in terms of the prevalence of IgE and egg white sensitization during infancy.

Association of BMI Z-scores and breastfeeding patterns with atopic diseases

Neither the BMI Z-score clusters nor the different breastfeeding patterns were associated with the risk of eczema, allergic rhinitis, or asthma throughout early childhood. However, compared with the increasing BMI Z-score in cluster A, the decreasing BMI Z-score in cluster B was associated with a higher risk of IgE sensitization at 1 and 1.5 years of age (Table 2, Bonferroni-adjusted $P < 0.017$). By contrast, as compared with exclusive breastfeeding $\geq$6 months, formula feeding was determined to be associated with a higher risk of sensitization to mites [odds ratio (OR), 5.88; 95% confidence interval (CI), 1.43–25; $P = 0.014$] at the age of 1.5 years (Table 2). Furthermore, the higher prevalence of IgE sensitization at age 1 and mite sensitization at age 1.5 were significantly associated with an increased risk of rhinitis (OR, 6.7; 95% CI, 1.7–26.6; $P = 0.007$) and asthma (OR, 8.1; 95% CI, 2.2–29.2; $P = 0.001$) at age 4 years respectively.

Discussion

A high BMI score and obesity have been identified to increase the risk of allergies in children. However, studies on the dynamic changes in BMI score during infancy and its relevance to atopic diseases later in childhood remain to be lacking. This study has demonstrated that a decrease in the infantile BMI Z-score is inversely associated with IgE sensitization which increases the risk of developing atopic diseases. Formula feeding is simultaneously associated with increased weight and height Z-scores without a change in BMI Z-scores. However, the high prevalence of allergic sensitization related to formula feeding is associated with an increased risk of allergies in early childhood.

The associations of birth order and sibship composition with overweight and obesity have been reported.[23] Children with no siblings are found to be more prone to became obese than children living with siblings.[24] In this study, changes of BMI Z-scores during infancy were characterized by weight Z-scores and negatively associated with children with older siblings, which is consistent with the reports from Western and Asian countries.[25,26] In Taiwan's traditional parenting style, parents dote on first-born infants and tend to provide them with excessive nutrition. After learning a few points from raising their first child, parents modify parenting practices to avoid excessive caloric intake and weight gain for younger siblings.[27]

Overweight infants are likely to remain overweight or obese as children, and a high BMI in infancy is strongly associated with early childhood obesity.[28,29] In addition, in this study, an increase in the BMI during infancy was not only highly associated with an increase in weight, but also with an increased risk of being overweight or obese in early childhood; this supports the report from the Danish cohort that rapid infant weight gain is a very strong predictor of childhood obesity.[30]

Several studies have demonstrated an association between obesity and allergic sensitization.[31] Despite not having exact script to explain this association, school-age children exhibiting a higher BMI are more likely to be allergic to allergens. In this study, the pattern of dynamic BMI Z-scores was observed to change significantly during the first year of life. In contrast to the trend observed in school-age children, a higher prevalence of food sensitization appeared to be associated with a decrease in BMI Z-scores during infancy. This contrary finding might be explained by the observation that, in some studies, food allergen sensitization tended to occur very early in life and often associated with negative effects on the growth and nutritional status of those infants.[32]

Many studies have already identified the relationship between increased childhood BMI and the later development of atopic diseases.[33,34] By contrast, both children with slow and fast weight gain in infancy have reported an increase in asthmatic symptoms later in life.[35,36] In this study, despite a lack of association between dynamic changes of infantile BMI Z-scores and atopic diseases, a decreasing trend during infancy appeared to be associated with a higher prevalence of IgE and allergen sensitization which risks the development of rhinitis and asthma in early childhood. Our results suggest that the underlying allergy and atopy should be considered in children that exhibit decreasing BMI Z-scores during the first 2 years of life.

Breastfeeding provides infants with a protective effect against later development of overweight and obesity in childhood.[37] In contrast, formula-fed infants are at greater risk for rapid weight gain leading to obesity in later childhood.[38] In this study, children who were formula-fed appeared to have both high weight and height Z-scores after age 1, resulting in no difference in the overall BMI Z-score change during infancy. It must be emphasized that although BMI can be used as a screening tool to identify possible weight problems, it is not used alone to assess nutritional status in growing children.

Breastfeeding has been reported to decrease the prevalence of allergen sensitization and subsequent allergies.[19,39] In this study, breastfeeding was not associated with the development of atopic diseases in children. By contrast, formula feeding related increased prevalence of allergic sensitization was strongly associated with risk of childhood allergic rhinitis and asthma. These findings support the notion that exclusively breastfeeding an infant potentially provides protection against allergic sensitization, reducing the risk of atopic disease development later in childhood.

The major limitation of this study is its small sample size, which may reduce the power of this cohort study and deem it less representative of the entire infant population of the community. Despite the fact that loss to follow-up is problematic in a cohort study, and often leads to bias, a follow-up rate as high as 70% minimized the potential for selection bias in this study. Most importantly, the strength of our study is its short-interval follow-up with long-term prospects as well as longitudinal analysis, yielding valid and important results.

In conclusion, a longitudinal analysis of the BMI Z-scores during infancy reveals a great dynamic change within the first year of life, characterized by weight Z-scores. A decreased

Table 2 Association of BMI Z-score cluster and breastfeeding pattern with the risk of IgE and allergen sensitization at different years of age.

	BMI Z-score cluster							Breastfeeding pattern						
Age	Cluster A	Cluster B			Cluster C			Formula feeding			Partial BF			Exclusive BF
	Reference	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value	Reference
6M														
IgE	Reference	16.67	1.37—100.0	**0.027**	7.37	0.67—81.6	0.103	1.82	0.29—1.12	0.524	1.35	0.39—4.63	0.635	Reference
Egg white	Reference	1.25	0.23—6.67	0.796	1.69	0.49—5.88	0.408	6.67	1.11—33.33	**0.037**	2.80	0.96—8.15	0.059	Reference
Milk	Reference	1.54	0.23—10.0	0.650	3.40	0.68—7.06	0.137	6.67	0.70—50.0	0.099	0.48	0.15—1.60	0.233	Reference
Mite	Reference	1.32	0.02—100.0	0.892	0.57	0.00—267.2	0.858	5.00	0.06—100.0	0.469	3.10	0.2—43.7	0.405	Reference
1Y														
IgE	Reference	16.67	2.86—100.0	**0.002**†	14.96	2.80—80.06	**0.002**†	1.64	0.47—5.88	0.440	1.50	0.60—3.73	0.383	Reference
Egg white	Reference	3.85	1.14—14.29	**0.030**	1.20	0.40—3.58	0.748	1.54	0.42—5.56	0.654	1.65	0.67—4.08	0.394	Reference
Milk	Reference	2.17	0.76—6.25	0.148	2.62	1.10—6.23	0.029	4.75	1.45—15.52	**0.010**†	0.48	0.22—1.03	0.059	Reference
Mite	Reference	2.08	0.35—12.50	0.420	1.03	0.20—5.32	1.026	1.23	0.24—6.37	0.803	1.10	0.30—4.07	0.882	Reference
1.5Y														
IgE	Reference	5.26	1.47—20.0	**0.011**†	1.41	0.44—4.46	0.562	5.88	1.43—25.0	**0.014**†	1.64	0.67—3.97	0.276	Reference
Egg white	Reference	4.55	1.25—16.67	**0.021**	1.68	0.56—5.09	0.358	2.70	0.79—9.09	0.112	1.52	0.65—3.57	0.337	Reference
Milk	Reference	0.94	0.33—2.70	0.916	1.00	0.38—2.65	0.999	1.83	0.65—5.13	0.253	1.03	0.46—2.35	0.930	Reference
Mite	Reference	2.78	0.73—11.11	0.133	0.62	0.12—3.26	0.572	3.39	0.86—13.39	0.082	1.25	0.46—3.45	0.662	Reference
2Y														
IgE	Reference	1.27	0.42—3.85	0.668	1.96	0.63—6.08	0.246	1.67	0.48—5.86	0.424	1.54	0.64—3.71	0.341	Reference
Egg white	Reference	1.35	0.46—4.00	0.739	0.86	0.29—2.57	0.789	0.81	0.22—3.02	0.757	1.23	0.53—2.87	0.632	Reference
Milk	Reference	1.27	0.44—3.57	0.664	1.01	0.36—2.83	0.978	2.05	0.59—7.05	0.147	0.93	0.41—2.11	0.868	Reference
Mite	Reference	0.56	0.17—1.82	0.335	0.71	0.22—2.30	0.569	2.33	0.33—8.59	0.204	0.88	0.41—2.41	0.980	Reference

BMI, body mass index; BF, breastfeeding; IgE, immunoglobulin E; M, month; Y, year; CI, confidence interval; OR, odds ratio. All *P*-values < 0.05, which is in bold, are significant. *P*-value was adjusted for child's sex, gestational age, maternal age at delivery, parental history of atopy, passive smoke exposure, any older siblings, and household income. † Significant by Bonferroni-adjusted *P* (*P* value $< 0.05/3$).

trend of BMI Z-scores during infancy appears to be associated with a high prevalence of IgE sensitization, risking the development of atopic diseases later in life. Formula feeding appears to promote a higher allergic sensitization, risking childhood allergies without association with BMI.

Funding

This study was financially supported by research grant of CMRPG3E1191-5 from the Chang Gung Medical foundation, Chang Gung University, Taiwan.

Declaration of competing interest

All the authors declare no conflicts of interest in relation to the present study.

Author contributions

W.-H.S. and K.-W.Y. drafted and revised the manuscript. J.-L.H. and K.-W.S. performed experimental work and interpretation. K.-F.C. and C.-C.W performed statistical analyses and presented the data. M.-H.T., M.-C.H., S.-L.L. and S.-H.L. were responsible for clinical evaluation of the children and data collection. C.-Y.C. design and supervised the study. All authors discussed the results and approved the final manuscript.

Acknowledgments

We would like to express our gratitude to the participants of our study, the pediatricians involved in the recruitment of these participants, as well as the entire PATCH team, including interviewers, nurses, technicians and research assistants.

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