Gastroenteritis during infancy is a novel risk factor for allergic disease

Hui-Hsien Pan, MD[a,b], Ko-Huang Lue, PhD[a,c], Hai-Lun Sun, PhD[a,b], Min-Sho Ku, PhD[a,b,*]

Abstract

Antibiotics during infancy, delivery, and breastfeeding affect the intestinal microbiota in early life and is associated with allergic disease. Gastroenteritis (GE) during infancy also affects intestinal microbiota in early life, however, its relationship to allergic disease has not been investigated.

Data of 45,499 males and 49,430 females, from birth to 5 years of age, were collected from a national database in Taiwan. Subjects were categorized into early GE (GE within 0–6 months) and non-early GE group (no GE within 0–6 months). The rates of asthma (AS), allergic rhinitis (AR), and atopic dermatitis (AD) over 5 years were evaluated and compared between the groups. In patients with AS, AR, and AD, the number of clinical visits and drug prescriptions for the allergic disease was also evaluated to assess the effect of early GE on allergic disease.

After adjusting for the effect of GE in later life and other factors, the rates of AS [OR (odds ratio) 1.54, 95% confidence interval (CI) 1.48–1.60], AR [OR 1.49, 95% CI 1.45–1.54], and AD [OR 1.40, 95% CI 1.33–1.47] were higher in the early GE group than in the non-early GE group. The magnitude of the increase was higher in females than in males. In those with AS, AR, and AD, the number of clinical visits and drug prescriptions was not different between the early GE and non-early GE groups. In children with early GE, good control of GE in the following years lowered the rate of allergic disease.

Early-life GE was associated with increased rates of AS, AR, and AD in later life and this was trend more prominent in females.

Abbreviations: AD = atopic dermatitis, AR = allergic rhinitis, AS = asthma, ATC = anatomical therapeutic chemical, CI = confidence interval, GE = gastroenteritis, ICD9 = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, OR = odds ratio.

Keywords: allergic disease, allergic rhinitis, asthma, atopic dermatitis, gastroenteritis, infant

1. Introduction

Asthma (AS), allergic rhinitis (AR), and atopic dermatitis (AD) are common chronic diseases, which have a negative impact on the quality of life and school performance.[1] These diseases can be controlled but they are not curable. Therefore, understanding the risk factors and preventing the development of allergic diseases is crucial. However, the causes and risk factors for allergic diseases are not fully understood.

Early-life events or diseases, such as perinatal circumstances or early allergen exposure are reported to increase the prevalence of allergic diseases.[2] Additionally, changes in the intestinal microbiota in early life have been reported to affect the development of allergic diseases in later life.[3,4] Early-life environmental factors, such as caesarian section delivery, infant feeding mode, early microbial exposure, and the use of antibiotics in infancy can alter the gut microflora and lead to allergic diseases in later life.[3,4] Moreover, acute gastroenteritis (GE) and intestinal infection have been reported to result in significant changes in the gut microbiota.[5] We speculate that early-life GE might change the gut microbiota in infants and could be associated with allergic diseases. However, evidence to support this hypothesis is scarce.

Using the National Health Insurance Research Database (NHIRD) in Taiwan, we performed a large, longitudinal, population-based research study to establish the relationship between early-life GE and allergic diseases. The effect of early-life GE on the development of allergic disease and subsequent frequencies of clinical visit and medical drug prescription for the allergic disease were evaluated.

2. Methods

2.1. Database

The NHIRD was created by the National Health Research Institute (NHRI) in Taiwan.[6,7] The NHRI randomly sampled a representative database of 1 million subjects in 2010 through systematic sampling and this served as our data source. The database provides information on patient identification, birth
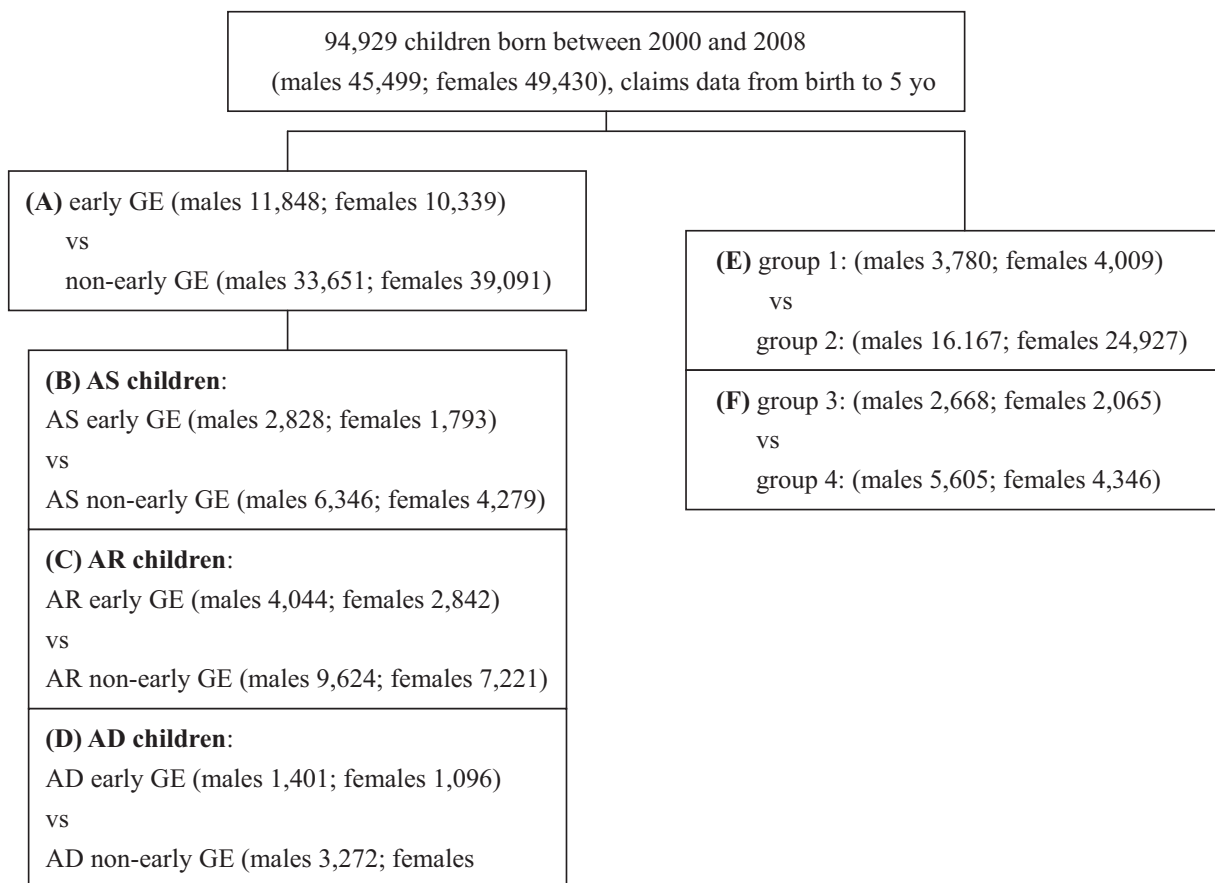
date, sex, diagnostic codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9), prescription drugs, medical care facilities, and other items. The institutional review board of Chung Shan Medical University Hospital, Taichung, Taiwan, approved this study (ethics approval number: CS13006).

2.2. Data collection and study flowchart

The study flowchart is presented in Figure 1. Subjects born between 2000 and 2008 were randomly selected from the NHIRD. Their claims data from birth to 5 years old (yo) were

analyzed. We excluded children with malignant neoplasm, congenital anomalies of the digestive system, and anyone who had undergone surgery of the gastrointestinal system. The subjects were divided into the following groups: early-life GE (early GE) and non-early life GE (non-early GE). GE was diagnosed according to the ICD9 code including infectious or noninfectious etiology as follows: the diagnosis of noninfectious GE and colitis (ICD9 558.9), intestinal infectious diseases (ICD9 001–009), other intestinal helminthiases (ICD9 127), and unspecified intestinal parasitism (ICD9 129) before 6 months old (mo). Those with GE before 6 mo were included in the early-GE group, and those without were in the non-early GE group.

94,929 children born between 2000 and 2008
(males 45,499; females 49,430), claims data from birth to 5 yo

(A) early GE (males 11,848; females 10,339)
vs
non-early GE (males 33,651; females 39,091)

(B) AS children:
AS early GE (males 2,828; females 1,793)
vs
AS non-early GE (males 6,346; females 4,279)

(C) AR children:
AR early GE (males 4,044; females 2,842)
vs
AR non-early GE (males 9,624; females 7,221)

(D) AD children:
AD early GE (males 1,401; females 1,096)
vs
AD non-early GE (males 3,272; females

(E) group 1: (males 3,780; females 4,009)
vs
group 2: (males 16.167; females 24,927)

(F) group 3: (males 2,668; females 2,065)
vs
group 4: (males 5,605; females 4,346)

(A). AS, AR, AD rates between early GE group and non-early GE

(B). AS clinical visits and rate of inhaled steroid; AS early GE vs. AS non-early GE

(C). AR clinical visits and rate of nasal steroid prescription; AR early GE vs. AR non-early GE

(D). AD clinical visits and rate of tacrolimus/pimecrolimus prescription; AD early GE vs. AD non-early
    GE

(E) (F) AS, AR, AD rates between group 1 vs. group 2; group 3 vs. group 4.
    group 1: GE before 6 mo with good GE control during 6 mo to 5 yo.
    group 2: no GE before 6 mo with good GE control during 6 mo to 5 yo.
    group 3: GE before 6 mo with poor GE control during 6 mo to 5 yo.
    group 4: no GE before 6 mo with poor GE control during 6 mo to 5 yo.

Figure 1. Study flowchart.

2.3. Rate of allergic disease between early GE and non-early GE group

Rates of AS, AR, and AD between early GE and non-early GE groups were compared. The criteria for AS, AR, and AD were as follows: at least 2 diagnoses of AR (ICD9 477), AS (ICD9 493), or AD (ICD9 691.8) within 5 yo. Because AS, AR, and AD are chronic diseases, those with disease duration of <180 days were excluded. The mean number of clinical visits for GE from 6 mo to 5 yo were compared between the groups to investigate if early-life GE would increase the frequency of GE in later life or not.

2.4. Clinical visits and drug prescription for allergic disease

Children with AS were divided into the following groups: AS early GE (AS patients with early-life GE) and AS non-early GE (AS patients without early-life GE). Children with AR and AD were also divided into similar groups. Throughout 5 years, the mean number of clinical visits for AS, AR, and AD were compared between the respective groups. Based on whether given prescription during the 5 years, the prescription rate for inhaled and nasal steroid as well as topical drugs tacrolimus/pimecrolimus in AS, AR, and AD subjects were compared between the various groups. These drugs are expensive in Taiwan and are only prescribed if patients have severe symptoms. Anatomical Therapeutic Chemical (ATC) code J R03AK and R03BA were used for inhaled steroids, R01AD was used for nasal steroids, and D11AX14 and D11AX15 were used for tacrolimus and pimecrolimus, respectively.

2.5. Selective groups

In early GE and non-early GE groups, if GE was well-controlled in later life (during 6 mo–5 yo), the subjects were further divided into group 1, early GE with good control, and group 2, non-early GE with good control. In the early GE and non-early GE groups, if there was poor GE control in later life (during 6 mo–5 yo), the subjects were further divided into group 3, early GE with poor control, and group 4, non-early GE with poor control. The criteria for good GE control was: 5 or fewer clinical visits for GE, without emergency room (ER) visit and admission related to GE between 6 mo and 5 yo. The criterion for poor GE control was 5 to 15 clinical visits for GE with at least 2 ER visits or 1 admission for GE between 6 mo and 5 yo. AS, AR, and AD rate was compared between these groups. We compared the rates between group 1 and group 2, to assess whether good control of GE in later years decreases the rates of allergic disease in those with early GE.

2.6. Determining confounding factors

The following factors that affect allergic and gastrointestinal diseases were included in our analysis: preterm, low/high birth weight (ICD9 764–766), perinatal infection (infections specific to the perinatal period, ICD9 771), obesity (ICD9 278), and nutritional deficiencies (ICD9). Antibiotic use in infancy[8] and early-life infection[9] or respiratory disease[10] are often accompanied by gastrointestinal disease and are associated with the development of allergic diseases. We included the following diagnoses as possible confounders in our analysis: prescribed antibiotics for systemic use, infectious disease (infections other than intestinal infection, ICD9 010-136 or urinary tract infection, ICD9 599.0), and respiratory disease (ICD9 460–488) before 6 mo. ATC codes J01, J02, J04, and J05 were used for "antibiotics for systemic use". Despite GE in early life, GE in later life might also affect the development of allergic diseases. The number of GE visits during 6 mo and 5 yo was used as a surrogate for GE conditions in later life.

The socioeconomic status was defined according to the parent's occupation which includes

(1) teacher or public official,
(2) company employee,
(3) other jobs,
(4) peasant or fisherman, and
(5) low-/non-fixed income earner.

Based on Liu's report,[11] the urbanization levels were grouped into seven levels. Level 1 is the most urbanized and level 7 is the least urbanized. Due to low frequency, levels 5 to 7 were grouped together as level 5. All the factors mentioned above were considered as risk factors and were adjusted for.

2.7. Statistical analysis

All analyses were performed using SAS version 9.1 for Windows (SAS Inc., Cary, NC) and PASW Statistics 18 (IBM, Armonk, NY). The Chi-square test was used to compare the rate of AS, AR, and AD between groups. The t test was used to assess differences in the frequency of oral disease and the number of clinical visits between groups. Multivariate logistic regression and multivariate regression analyses were used to adjust for confounding factors (socioeconomic status, urbanization, perinatal infection, preterm, low/high birth weight, obesity, nutritional deficiencies, infections or respiratory disease before 6 mo, use antibiotics before 6 mo, and number of GE visits during 6 mo and 5 yo). A 2-sided P value of <.05 was defined as statistically significant.

3. Results

3.1. Study flowchart and demographic data

The study flowchart and demographic data are presented in Figure 1 and Table 1, respectively. In total, 94,929 subjects were enrolled. Of all subjects, 22,187 (23.4%) met the criteria for early GE. Of all subjects, 15,246 (16.1%) met the AS criteria, 23,731 (25.0%) met the AR criteria, and 8537 (9.0%) met the AD criteria. We found a significant difference in socioeconomic status, urbanization, perinatal infection, nutritional deficiencies, infections or respiratory disease before 6 mo, and use of antibiotics before 6 mo between early GE and non-early GE groups, for both sexes. High respiratory disease rate was noted due to low payment and convenient clinical visits in Taiwan.

3.2. Rate of allergic diseases between early GE and non-early GE group

In total, the rate of AS was 20.8% in early GE and 14.6% in the non-early group, (OR 1.54, 95% CI 1.48–1.60, adjusted P value <.001). The rate of AR was 31.0% in early GE and 23.2% in non-early GE group (OR 1.49, 95% CI 1.45–1.54, adjust P value <.001). The rate of AD was 11.3% in early GE and 8.3% in non-early GE group (OR 1.40, 95% CI 1.33–1.47, adjust P value <.001). The results according to sex are presented in Table 2. The

Table 1

Comparison of demographic data and characteristics between early-GE and non-early-GE group, in males and in females, respectively.

	Male			Female		
	Early-GE (n = 11,848)	Non-early-GE (n = 10,339)	P value	Early-GE (n = 33,651)	Non-early-GE (n = 39,091)	P value
Socioeconomic status			<.001			<.001
Teacher or public official	6.3%	7.3%		6.2%	6.3%	
Company employee	52.1%	53.9%		52.7%	53.5%	
Other jobs	24.1%	22.7%		23.4%	24.1%	
Peasant or fisherman	11.5%	10.0%		11.6%	10.0%	
Low-/non-fixed income	6.0%	6.1%		6.0%	6.1%	
Urbanization			<.001			<.001
1 (highest)	26.4%	29.7%		26.3%	29.3%	
2	28.3%	29.0%		29.2%	29.4%	
3	20.7%	19.1%		19.7%	18.5%	
4	14.5%	13.1%		14.8%	13.6%	
5 (lowest)	10.1%	9.1%		9.9%	9.2%	
Preterm, low/high birth weight	2.2%	2.0%	.265	2.1%	2.1%	.688
Perinatal infection	2.6%	1.5%	<.001	2.0%	1.6%	.004
Infectious disease before 6 mo	24.5%	14.7%	<.001	21.0%	10.8%	<.001
Respiratory disease before 6 mo	93.0%	73.4%	<.001	88.6%	59.5%	<.001
Nutritional deficiencies	1.5%	1.2%	.036	1.8%	1.0%	<.001
Antibiotics before 6 mo	43.8%	27.8%	<.001	39.1%	20.3%	<.001

Chi-Square test was used for the analysis.

rates of AS, AR, and AD were all higher in the early GE group for both sexes. These results were all statistically significant, after adjusting the number of GE visits during 6 mo and 5 yo and other confounders. Compared to early GE males, females with early GE had higher rates of AS (OR: male 1.35; female 1.71), AR (OR: male 1.29; female 1.67), and AD (OR: male 1.25; female 1.56).

3.3. Frequencies of clinical visits and prescribed medication for each allergic disease

Next, we investigated the effect of early-life GE on the subsequent frequencies of clinical visit and medical drug prescription in the 5 years. The results are presented in Table 3. In AR females with early GE, there was a slight increase in clinic visits for AR

compared to females with non-early GE (9.51 AR visit times in AR early GE group and 8.48 AR visit times in AR non-early GE group, P value .049). No difference in the number of drug prescriptions (inhaled, nasal steroid, and tacrolimus/pimecrolimus) and other visit times between groups.

3.4. Rate of allergic diseases between selective groups

The results are presented in Table 4. Those subjects with poor GE control in later life (group 3 and 4) had dramatically higher rates of allergic disease compared to those with good control in later life (group 1 and 2), regardless of early or non-early GE. A difference was noted in both sexes. In those with good control in later life, children with early GE (group 1) still had higher rates of

Table 2

Comparison of the rate of AS, AR, and AD between early GE group vs non-early GE group, in males and females, respectively.

Rate of asthma (AS)

	Male			Female		
	Number (%)	OR (95%CI)	P value	Number (%)	OR (95%CI)	P value
Early GE	2828 (23.9%)			1793 (17.9%)		
Non-early GE	6346 (18.9%)	1.35 (1.28–1.42)	.021	4279 (10.9%)	1.71 (1.61–1.81)	<.001

Rate of allergic rhinitis (AR)

	Male			Female		
	Number (%)	OR (95%CI)	P value	Number (%)	OR (95%CI)	P value
Early GE	4044 (34.1%)			2842 (27.5%)		
Non-early GE	9624 (28.6%)	1.29 (1.24–1.35)	.003	221 (18.5%)	1.67 (1.59–1.76)	<.001

Rate of atopic dermatitis (AD)

	Male			Female		
	Number (%)	OR (95%CI)	P value	Number (%)	OR (95%CI)	P value
Early GE	1401 (11.8%)			1096 (10.6%)		
Non-early GE	3272 (9.7%)	1.25 (1.17–1.33)	<.001	2768 (7.1%)	1.56 (1.45–1.68)	<.001

P value: multivariate logistic regression was used to adjust the concounders: socioeconomic status, urbanization, perinatal infection, preterm, low/high birth weight, obesity, nutritional deficiencies, infectious, or respiratory disease before 6 mo, ever use antibiotics before 6 mo and gastroenteritis (GE) visit times (6 mo–5 yo).

Table 3

Comparison of the mean clinical visits (over 5 years) for AS, AR, and AD; drugs prescription rates (inhaled steroid for AS, nasal steroid for AR and tacrolimus/pimecrolimus for AD) between early GE vs non-early GE, in males and females, respectively.

AS children, mean clinical AS visit times (5 yr) and inhaled steroid prescription rate (5 yr)

	Male				Female			
	Visit times	*P* value	Inhaled steroid	*P* value	Clinical visit	*P* value	Inhaled steroid	*P* value
AS early GE	11.71		35.2%		10.63		29.8%	
AS non-early GE	10.93	.857	34.8%	.709	9.81	.790	30.1%	.868

AR children, mean clinical AR visit times (5 year) and anasal steroid prescription rate (5 year)

	Male				Female			
	Visit times *t*	*P* value	Nasal steroid	*P* value	Clinical visit	*P* value	Nasal steroid	*P* value
AR early GE	9.70		47.0%		9.51		38.7%	
AR non-early GE	9.39	.417	45.1%	.602	8.48	.049	38.4%	.939

AD children, mean clinical AD visit times (5 yr) and tacrolimus/pimecrolimus prescription rate (5 yr)

	Male				Female			
	visit times	*P* value	tacrolimus/pimecrolimus	*P* value	clinical visit	*P* value	tacrolimus/pimecrolimus	*P* value
AD early GE	5.51		4.9%		5.28		3.7%	
AD non-early GE	5.58	.499	5.0%	.675	5.18	.996	5.1%	.117

P value: multivariate regression analyses was used to adjust the concounders: socioeconomic status, urbanization, perinatal infection, preterm, low/high birth weight, obesity, nutritional deficiencies, infectious, or respiratory disease before 6 mo, ever use antibiotics before 6 mo and gastroenteritis (GE) visit times (6 mo–5 yo).

AS, AR, and AD compared to children without early GE (group 2). The magnitude of the increased rate was higher in females for the 3 allergic diseases (females had higher OR). In those with poor control in later life, children with early GE (group 3) had higher rates of AR and AD as compared to children without early GE (group 4).

4. Discussion

Our population-based longitudinal cohort study elucidated the association between early-life GE and increased rates of AS, AR, and AD in later life (5 yo). The magnitude of the increased rate was higher in females for the 3 allergic diseases. However, the association between early-life GE and the number of clinical visits and drug prescriptions for the allergic diseases was weak or absent. The results indicated that early-life GE is associated with the development of allergic disease but not with the subsequent frequencies of clinical visits and medical drug prescription.

Over the past decades, there has been growing evidence supporting the crucial role of intestinal microbiota in the maturation of the immune system in early life and its association with allergic diseases.[3] Diversity[12] and composition[13] of neonate intestinal microbiota were reported to be associated with allergy sensitization, eczema, and AS. From exposure to the mother's vaginal, fecal, or even *in utero* microbiota, intestinal microbial colonization begins at birth.[14] Early-life environmental factors, such as caesarian section delivery,[15] infant feeding mode,[16] early microbial exposure,[9] and antibiotic use in infancy,[8] have been reported to induce dysbiosis of the intestinal microbial. These environmental factors have also been reported to be associated with allergic disease.[8,9,17,18]

Bacterial,[5] viral,[19] and parasitic[20] gastrointestinal infections may result in significant differences in intestinal microbiota diversity. Hand et al reported that during gastrointestinal infection, tolerance to commensal microbiota is lost and the immunological profile changes as well.[21] Moreover, the non-infectious gastrointestinal disease may also influence the

composition of intestinal bacteria.[22] These studies suggest that GE in early life may induce changes in the intestinal microbiota that can contribute to early-life environmental risk factors for the development of the allergic disease. However, there is little evidence supporting the association between early GE and allergic disease. In our present study, we report an association between early-life GE and allergic disease.

We speculated that those with early-life GE may have poor control of GE in later life. Our study found that during later life (6 mo–5 yo), mean clinical visits for GE was higher in the early GE group (10.38 visits) than that of the non-early GE group (4.79 visits). The gastrointestinal disease has been reported to be associated with higher rates of allergic disease in both children and adults.[23,24] Thus, the question posed is whether the increased rate of allergic disease is due to the early effects of GE or poor control of GE in later life. After adjusting the number of GE visits during 6 mo to 5 yo, we could exclude the interference of "later life GE" in allergic disease formation. In selective groups, both group 1 and group 2 had good GE control during 6 mo to 5 yo. Consequently, the effect of increased GE related-suffering in later life could be excluded. We compared the rate of allergic disease between group 1 (early GE) and group 2 (non-early GE). We found the rates of AS, AR, and AD were higher in group 1. Therefore, we concluded that early-life GE could affect the rate of allergic disease in later life, despite the condition of GE in later years.

To the best of our knowledge, only Ahn et al have observed a weak association between acute GE during the first year of life and childhood AS,[25] but the possibility of recall bias limits the conclusion in this cross-sectional study. On the other hand, the condition of GE in later life and its role in the development of AS were not discussed in the study.[25]

Our study has several strengths. First, our study was a retrospective cohort including large sample size and follow-up for 5 years. This large national survey is also representative of the general population in Taiwan. Second, previous studies focused on the prevalence of allergic diseases in relation to different

Table 4

Comparison of the rate of AS, AR, and AD between group 1 vs group 2 and group 3 vs group 4, in males and females, respectively.

Rate of asthma (AS)

	Male			Female		
	Number (%)	OR (95%CI)	P value	Number (%)	OR (95%CI)	P value
Group1	627 (16.6%)			431 (10.8%)		
Group2	2157 (13.3%)	1.29 (1.17–1.42)	.023	1702 (6.8%)	1.64 (1.47–1.84)	<.001
Group3	823 (30/8%)			526 (25.5%)		
Group4	1602 (28.6%)	1.11 (1.01–1.23)	.388	921 (21.2%)	1.27 (1.12–1.44)	.072

Rate of allergic rhinitis (AR)

	Male			Female		
	Number (%)	OR (95%CI)	P value	Number (%)	OR (95%CI)	P value
Group1	948 (25.1%)			767 (19.1%)		
Group2	3436 (21.3%)	1.24 (1.14–1.35)	.001	3021 (12.1%)	1.72 (1.57–1.87)	<.001
Group3	1177 (44.1%)			825 (40.4%)		
Group4	2294 (40.9%)	1.14 (1.04–1.25)	.015	1509 (34.7%)	1.25 (1.12–1.39)	.023

Rate of atopic dermatitis (AD)

	Male			Female		
	Number (%)	OR (95%CI)	P value	Number (%)	OR (95%CI)	P value
Group1	347 (9.2%)			331 (8.3%)		
Group2	1232 (7.6%)	1.23 (1.08–1.39)	.001	1227 (4.9%)	1.74 (1.53–1.97)	<.001
Group3	401 (15.0%)			292 (14.1%)		
Group4	688 (12.3%)	1.26 (1.11–1.44)	<001	520 (12.0%)	1.21 (1.04–1.41)	.036

P value: multivariate logistic regression was used to adjust the concounders: socioeconomic status, urbanization, perinatal infection, preterm, low/high birth weight, obesity, nutritional deficiencies, infectious, or respiratory disease before 6 mo, ever use antibiotics before 6 mo.

environmental factors. We, additionally, evaluate the influence of the subsequent frequencies of clinical visit and medical drug prescription for allergic disease. Third, antibiotic use in infancy,[8] early-life infectious disease,[9] or early-life respiratory disease[10] is often accompanied by gastrointestinal disease and is associated with allergic disease. These important confounding factors were adjusted in our study, but are seldom adjusted in other studies. Lastly, by the control of GE in later life (comparing the rate of allergic disease between group 1 and group 2), or by adjusting GE visit times in later life, we exclude the effect of late GE on the development of allergic diseases. Thus, we could focus on the effect of early-life GE on the development of allergic diseases.

Our study has some limitations. First, family history, birth history, breastfeeding, and other environmental factors, which are associated with the allergic disease were not evaluated in this study. Second, there was no clinical evaluation or investigation of biological samples, such as intestinal microbiota, to support our hypotheses. Third, the percentages of infectious or non-infectious subjects in early-GE groups cannot be counted accurately in the database study. A case-control study in the future is necessary to find the association between early-infectious-GE, early-noninfectious-GE, and allergic disease.

5. Conclusions

Our results demonstrate that GE in early-life was associated with increased risk of subsequent development of AS, AR, and AD. This increased rate was higher in females, compared to males. In children with early-life GE, good control of GE in later life is associated with decreased development of AS, AR, and AD, compared to those with poor control. However, the development of allergic disease was still higher than those without early-life GE and good control of GE in later life.

Preventing the development of allergic disease before their development is essential. These results suggest that preventing GE in infancy might be a novel method to prevent the development of allergic diseases. Prevention of antibiotic abuse when a pediatrician treats GE would be a detailed plan to reduce the development of allergic diseases. However, further biological research, clinical data, and case-control studies are necessary to fully understand the association.

Author contributions

Conceptualization: Min-Sho Ku, Hai-Lun Sun.
Data curation: Min-Sho Ku, Hui-Hsien Pan.
Investigation: Min-Sho Ku, Hui-Hsien Pan.
Methodology: Min-Sho Ku, Hui-Hsien Pan, Hai-Lun Sun.
Software: Min-Sho Ku, Hui-Hsien Pan, Hai-Lun Sun.
Supervision: Min-Sho Ku, Ko-Huang Lue.
Validation: Ko-Huang Lue.
Visualization: Ko-Huang Lue.
Writing – original draft: Hui-Hsien Pan.
Writing – review & editing: Min-Sho Ku, Ko-Huang Lue.

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