Pediatric RESEARCH

POPULATION STUDY ARTICLE

Bidirectional association between GERD and asthma in children: two longitudinal follow-up studies using a national sample cohort

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BACKGROUND: The causal relationship between asthma and gastroesophageal reflux disease (GERD) is unknown in children.
METHODS: The Korean Health Insurance Review and Assessment Service-National Sample Cohort 2002–2013 was used. The population age <15 years was selected. In study I, 86,096 asthmatic children were 1:1 matched with 86,096 control I participants. In study II, 532 GERD children were 1:2 matched with 1064 control II participants. The stratified Cox proportional hazard ratios for GERD in patients with asthma (study I) and asthma in patients with GERD (study II) were analyzed.
RESULTS: In total, 0.7% (583/86,096) of the asthma group and 0.5% (430/86,096) of the control I group had GERD ($P < 0.001$). The asthma group demonstrated a 1.36 times higher HR for GERD than the control I group (95% CI = 1.20–1.54, $P < 0.001$). Subgroup analyses according to age and sex showed consistent results. In total, 15.0% (80/532) of the GERD group and 10.0% (106/1,064) of the control II group had asthma ($P < 0.001$). The GERD group showed a 1.62-fold higher HR for asthma than the control II group (95% CI = 1.21–2.18, $P < 0.001$).
CONCLUSION: GERD and asthma demonstrated a bidirectional relationship in children.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is defined as a reflux of the gastric contents into the esophagus, which is accompanied by troublesome symptoms or complications.[1] Although it is prevalent in children, the prevalence of GERD in children has only been reported in a small number of studies.[2] Among children with gastrointestinal or extraesophageal symptoms that are attributable to gastroesophageal reflux, as much as 57.4% of them were diagnosed with GERD in Europe.[2] In Korea, approximately 39.8% of children with abdominal pain had GERD.[3] GERD in children presents differently from that in adults, with frequent esophageal manifestations, including regurgitation and dysphagia, and extraesophageal symptoms.[4,5] These distinct features of GERD in children are explained by the immaturity of the gastroesophageal junction, a liquid milk-based diet, and a recumbent position in infants.[5] These factors may also contribute to pulmonary aspiration. Thus many previous studies reported respiratory symptoms, such as chronic cough and laryngitis, related to GERD in children.[6–8]

Only a few studies have suggested a cross-sectional relationship between GERD and asthma in children, although many studies have suggested a similar relationship in adults.[9,10] However, no longitudinal follow-up cohort study has investigated the temporal relationship between GERD and asthma in children. Most previous studies in children had cross-sectional designs, preventing conclusions regarding causality.[9,10] Recurrent mechanical reflux might attenuate the airway epithelial barriers and evoke the vagal reflex, which could contribute to the occurrence of asthma.[11] On the other hand, the comorbidities of asthma could induce systemic inflammation and subsequent airway inflammation, resulting in GERD.[9] In addition, a considerable number of pediatric patients suffer from both asthma and GERD.[9,10] Thus it can be speculated that there is a bidirectional association between asthma and GERD. We hypothesized that GERD could be a risk factor for asthma and that asthma could also be a risk factor for GERD in children. To test this hypothesis, two longitudinal follow-up studies were conducted. In study I, asthma patients were followed with regard to the occurrence of GERD compared to the control group. On the other hand, GERD patients were followed with regard to the occurrence of asthma in study II. To minimize the possible selection bias between study and control groups, age, sex, income, and region of residence were matched between the study and control groups. This is the first study to investigate the bidirectional relationship between GERD and asthma.

METHODS

Study population and data collection

The ethics committee of Hallym University (2017-I102) approved the use of these data. The need for written informed consent was exempted by the Institutional Review Board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service-National Sample Cohort (NSC). The detailed description of these data can be found in our previous studies.[12,13]

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Participant selection

Of the 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were treated for GERD. GERD was defined using the International Classification of Diseases (ICD)-10 code K21 from 2002 through 2013. We selected participants treated for GERD ≥2 times and prescribed a proton pump inhibitor for ≥2 weeks ($n = 137,807$).

We included participants who were diagnosed with asthma (ICD-10: J45) or status asthmaticus (J46) from 2002 through 2013. Among them, we selected participants who were diagnosed with asthma by a physician >2 times and who were treated with asthma-related medications, including inhaled corticosteroids (ICSs), ICSs combined with long-acting β2-agonists (LABAs), oral leukotriene antagonists, short-acting β2-agonists, systemic LABAs, xanthine derivatives, and systemic corticosteroids ($n = 230,764$). This method was modified from that in a previous study.[14] The participants were followed for up to 12 years.

Study I. Asthma patients were matched 1:1 with participants in this cohort (control I) who were not diagnosed with asthma from 2002 through 2013. The control group was selected from the total population ($n = 894,927$). Matching was performed for age group, sex, income group, and region of residence. To prevent selection bias when selecting the matched participants, the control I participants were sorted using another random number order and then selected from top to bottom. We set the index date as the date of the diagnosis of asthma. It was assumed that the matched control I participants were involved at the same time as each matched asthma participant (index date). Therefore, participants in the control group who died before the index date were excluded. Participants who had histories of GERD before the index date were excluded from both the asthma and control groups. In the asthma group, 14,634 participants were excluded. Asthma patients for whom we could not identify sufficient matching participants were excluded ($n = 21,531$). We excluded participants who were aged >14 years ($n = 108,503$). The mean follow-up times from the index date to the last date (December 31, 2013) or the date of death were similar in both the asthma (93.9 months, standard deviation [SD] = 44.1) and control I groups (93.8 months, SD = 44.2). Finally, 1:1 matching resulted in the inclusion of 86,096 asthma patients and 86,096 control I participants (Fig. 1a).

Study II. The GERD patients were matched 1:2 with participants in this cohort (control II) who were not diagnosed with GERD from 2002 through 2013. The control group was selected from the total population ($n = 987,884$). Matching was performed for age, group, sex, income group, and region of residence. To prevent selection bias when selecting the matched participants, the control II participants were first sorted using a random number order and then selected from top to bottom. We set the index date as the date of the diagnosis of GERD. It was assumed that the matched control II participants were involved at the same time of each matched GERD participant (index date). Therefore, participants in the control group who died before the index date were excluded. Participants who had histories of asthma before the index date were excluded from both the GERD and control groups. In the GERD group, 18,291 participants were excluded. GERD patients for whom we could not identify sufficient matching participants were excluded ($n = 519$). We excluded participants who were aged > 15 years ($n = 118,465$). The mean follow-up times from the index date to the last date (December 31, 2013) or the date of death were similar in both the GERD (83.9 months, SD = 40.0) and control II groups (83.9 months, SD = 40.0). Finally, 1:2 matching resulted in the inclusion of 532 GERD patients and 1064 control II participants (Fig. 1b).

Variables

The age groups were classified using 5-year intervals: 0–4, 5–9, and 10–14 years.[15] In total, three age groups were designated. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes).[15] These groups were recategorized into 5 classes (class 1 [lowest income]–5 [highest income]). The regions of residence were divided into 16 areas according to administrative districts. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Statistical analyses

A chi-square test was used to compare the rates of the general characteristics between the asthma and control groups (study I) and between the GERD and control groups (study II).

In study I, a stratified Cox proportional hazards model was used to analyze the hazard ratio (HR) for GERD (dependent variable) in patients with asthma (independent variable). In study II, another

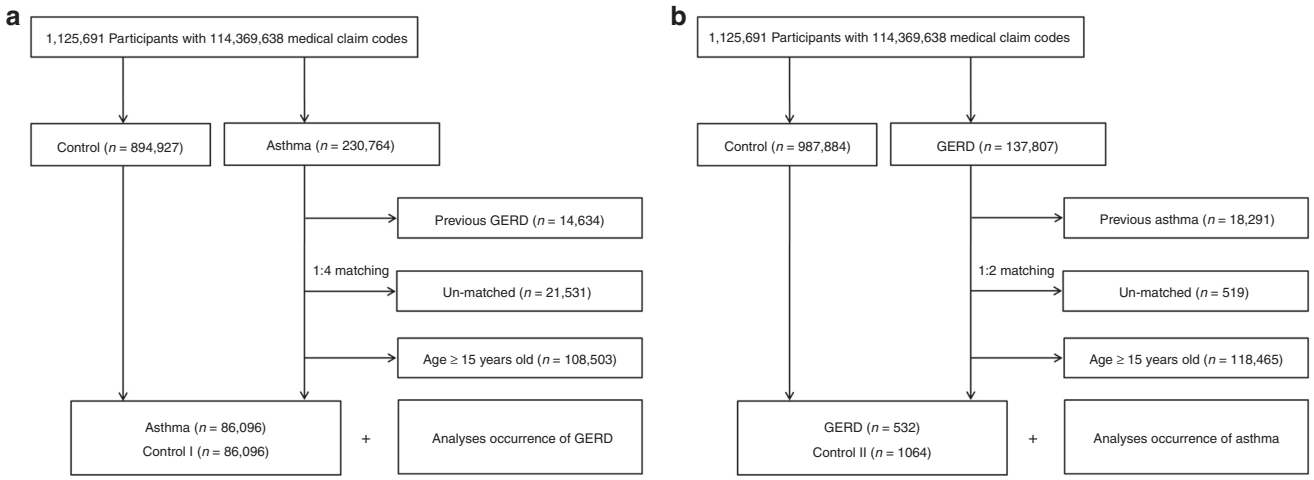

Fig. 1 Schematic illustration of the participant selection process that was used in the present study. a Of a total of 1,125,691 participants, 86,096 asthma patients were matched with 86,096 control I participants for age, group, sex, income group, and region of residence. **b** Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 116,502 GERD patients were matched with 233,004 control II participants for age, group, sex, income group, and region of residence.

Table 1. General characteristics of participants.

Characteristics	Study I			Study II		
	Asthma (*n*, %)	Control I (*n*, %)	*P* value	GERD (*n*, %)	Control II (*n*, %)	*P* value
Age (years)			1.000			1.000
0–4	60,859 (70.7)	60,859 (70.7)		58 (10.9)	116 (10.9)	
5–9	17,603 (20.4)	17,603 (20.4)		91 (17.1)	182 (17.1)	
10–14	7634 (8.9)	7634 (8.9)		383 (72.0)	766 (72.0)	
Sex			1.000			1.000
Male	44,384 (51.6)	44,384 (51.6)		217 (40.8)	434 (40.8)	
Female	41,712 (48.4)	41,712 (48.4)		315 (59.2)	630 (59.2)	
Income			1.000			1.000
1 (lowest)	6833 (7.9)	6833 (7.9)		59 (11.1)	118 (11.1)	
2	10,685 (12.4)	10,685 (12.4)		62 (11.7)	124 (11.7)	
3	19,618 (22.8)	19,618 (22.8)		97 (18.2)	194 (18.2)	
4	27,705 (32.2)	27,705 (32.2)		133 (25.0)	266 (25.0)	
5 (highest)	21,255 (24.7)	21,255 (24.7)		181 (34.0)	362 (34.0)	
Region of residence			1.000			
Urban	38,561 (44.8)	38,561 (44.8)		276 (51.9)	552 (51.9)	
Rural	47,535 (55.2)	47,535 (55.2)		256 (48.1)	512 (48.1)	
Asthma						0.003[a]
Yes	N/A	N/A		80 (15.0)	106 (10.0)	
No	N/A	N/A		452 (85.0)	958 (90.0)	
GERD			<0.001[a]			
Yes	583 (0.7)	430 (0.5)		N/A	N/A	
No	85,513 (99.3)	85,666 (99.5)		N/A	N/A	

GERD gastroesophageal reflux disease
[a]Chi-square test, significance at $P < 0.05$

stratified Cox proportional hazards model was used to analyze the HR for asthma (dependent variable) in patients with GERD (independent variable). Kaplan–Meier method and log-rank test were used. In these analyses, the participants were stratified by age, sex, income, and region of residence, and the 95% confidence intervals (CIs) were calculated.

In the subgroup analysis, we divided the participants by age and sex (<5, 5–9, and 10–14 years; male and female) because we thought that these variables might affect the relationship between GERD and asthma.

Two-tailed analyses were conducted, and *P* values <0.05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY, USA).

RESULTS

Study I

The mean time from the index date to GERD was 76.9 months (SD = 34.7) in the asthma group and 77.4 months (SD = 36.9) in the control I group. The rate of developing GERD was higher in the asthma group (0.7% [583/86,096]) than in the control I group (0.5% [430/86,096], $P < 0.001$, Table 1). The general characteristics (age, sex, income, and region of residence) of participants were exactly the same due to matching ($P = 1.000$).

The HR for GERD was 1.36 (95% CI = 1.20–1.54) in the asthma group ($P < 0.001$, Table 2 and Fig. 2a). In the subgroup analyses, all HRs for GERD were higher in the asthma group (each $P < 0.05$, Table 3). The adjusted HRs were 1.47 (95% CI = 1.14–1.90) in the group <5 years; 1.30 (95% CI = 1.06–1.58) in the group 5–9 years; 1.36 (95% CI = 1.11–1.67) in the group 10–14 years; 1.36 (95% CI = 1.13–1.65) in males; and 1.36 (95% CI = 1.15–1.60) in females.

Table 2. Crude and adjusted hazard ratios (95% confidence interval) of GERD in asthma (study I) and asthma in GERD (study II).

Characteristics	HR[a]	*P* value
Study I		
Asthma	1.36 (1.20–1.54)	<0.001[b]
Control	1.00	
Study II		
GERD	1.62 (1.21–2.18)	0.001[b]
Control	1.00	

[a]Stratified model for age, sex, income, and region of residence
[b]Cox proportional hazard regression model, significance at $P < 0.05$

Study II

The mean time from the index date to asthma was 28.3 months (SD = 27.5) in the GERD group and 22.3 months (SD = 24.7) in the control II group. The rate of developing asthma was higher in the GERD group (15.0% [80/532]) than in the control II group (10.0% [106/1064], $P < 0.001$, Table 1). The general characteristics (age, sex, income, and region of residence) of participants were exactly the same due to matching ($P = 1.000$).

The HR for asthma was 1.62 (95% CI = 1.21–2.18) in the GERD group ($P = 0.001$, Table 2 and Fig. 2b). In the subgroup analyses, the HRs for asthma were higher in all GERD groups except for the group 5–9 years and males (each $P < 0.05$, Table 4). The adjusted HRs were 1.78 (95% CI = 1.12–2.84) in the group <5 years, 1.69 (95% CI = 1.07–2.67) in the group 10–14 years, and 1.93 (95% CI = 1.30–2.93) in females.

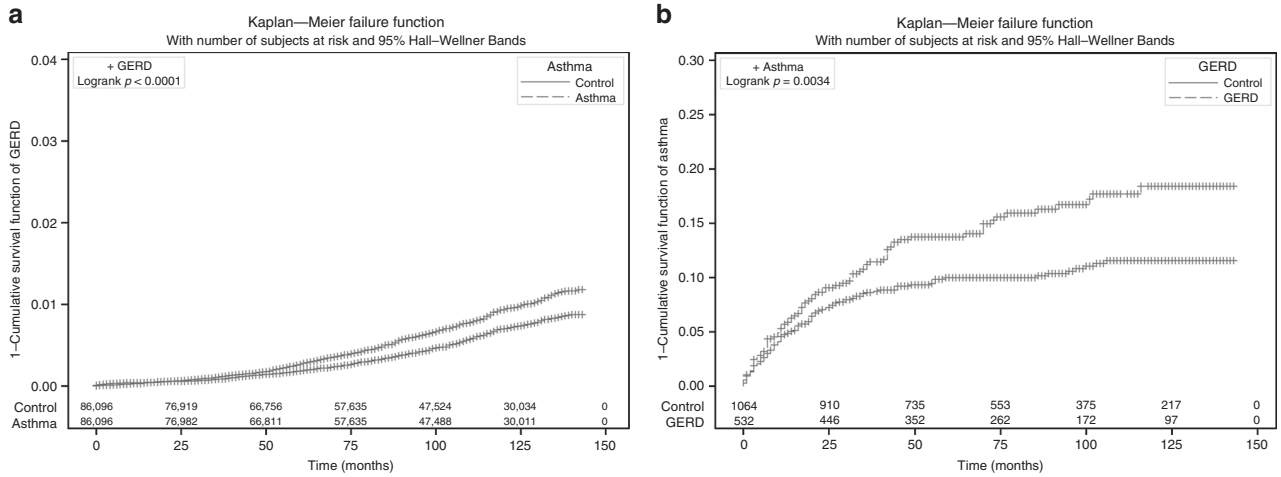

Fig. 2 Kaplan–Meier survival analysis. a The group with asthma demonstrated a higher cumulative rate of GERD than the control I group. **b** The group with GERD demonstrated a higher cumulative rate of asthma than the control II group.

Table 3. Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of GERD in asthma according to age and sex (study II).

Characteristics	HR[a]	*P* value
Age <5 years (*n* = 121,718)		
Asthma	1.47 (1.14–1.90)	0.003[b]
Control	1.00	
Age 5–9 years (*n* = 35,206)		
Asthma	1.30 (1.06–1.58)	0.010[b]
Control	1.00	
Age 10–14 years (*n* = 15,268)		
Asthma	1.36 (1.11–1.67)	0.004[b]
Control	1.00	
Men (*n* = 88,768)		
Asthma	1.36 (1.13–1.65)	0.001[b]
Control	1.00	
Women (*n* = 83,424)		
Asthma	1.36 (1.15–1.60)	<0.001[b]
Control	1.00	

[a]Stratified model for age, sex, income, and region of residence
[b]Cox proportional hazard regression model, significance at $P < 0.05$

Table 4. Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of asthma in GERD according to age and sex (study II).

Characteristics	HR[a]	*P* value
Age <5 years (n = 174)		
GERD	1.78 (1.12–2.84)	0.015[b]
Control	1.00	
Age 5–9 years (*n* = 273)		
GERD	1.21 (0.61–2.43)	0.586
Control	1.00	
Age 10–14 years (*n* = 1,149)		
GERD	1.69 (1.07–2.67)	0.024[b]
Control	1.00	
Men (n = 651)		
GERD	1.33 (0.87–2.04)	0.194
Control	1.00	
Women (*n* = 945)		
GERD	1.95 (1.30–2.93)	0.001[b]
Control	1.00	

[a]Stratified model for age, sex, income, and region of residence
[b]Cox proportional hazard regression model, significance at $P < 0.05$

DISCUSSION

Asthma elevated the risk of GERD, and GERD increased the risk of asthma in children. Asthmatic children demonstrated a 1.36 times higher risk of GERD than the control group (95% CI = 1.20–1.54, $P < 0.001$). The increased risk of GERD in asthmatic children was consistent in all age and sex subgroups. Likewise, children with GERD had a 1.62 times higher risk of asthma compared to the control group (95% CI = 1.21–2.18, $P = 0.001$). Younger (<5 years) and older (10–14 years) age subgroups and the female subgroup had elevated risks of asthma among children with GERD. The present results improved the previous findings on the association between GERD and asthma by delineating the reciprocal relationship between GERD and asthma.

GERD could increase the risk of asthma via reflux-induced airway damage and inflammation. A few prior studies reported elevated airway inflammation or damage in children with GERD.[16,17] In particular, neutrophilic airway inflammation was suggested as a mechanism in children with GERD. A retrospective study reported that the epithelial cell proportions and amount of substance P, which is related to neutrophilic inflammation, were increased in the bronchoalveolar lavage (BAL) of children with GERD.[16] Likewise, children suffering from GERD had a higher neutrophil proportion, lipid-laden macrophage index, and interleukin-8 level in BAL than the control group.[17] Neutrophilic inflammation is supposed to be related to steroid-refractory asthma in children.[18] In addition, children with allergic asthma could also have neutrophilic airway inflammation via viral-related responses in both aggravation and steady-state asthma.[19] Moreover, chronic anti-acid medication may weaken the cough and swallowing reflexes by lowering the acidity of the refluxate.[20] This inefficient cleansing of the refluxate by cough or swallowing might increase the susceptibility to inflammation and airway damage, thereby resulting in asthma. Indeed, non-acidic reflux as well as acidic reflux induces neutrophilic inflammation and promotes epithelial shedding in the airway in children.[16,21]

Furthermore, asthma might increase the risk of GERD via systemic inflammation or the vagal reflex. The shared vagal innervation between the esophagus and airway could link the cough or bronchoconstrictive stimuli to the esophago-gastric reflex, similar to the esophagus to airway reflex. The vagal reflex of the upper airway could induce neurogenic inflammation through the secretion of tachykinins and other neurotransmitters by nociceptive airway afferent nerves.[22] Vagal afferents from the esophagus converge with those from the airway, which suggests neural "crosstalk" between the distal esophagus reflex and cough or bronchoconstriction.[23] In addition, several studies have proposed the role of systemic inflammation in asthma patients. In particular, obesity-related asthma and GERD in children were reported to be associated with systemic inflammation, which can induce T-helper cell type 1-dominant non-atopic inflammation, insulin resistance, and other metabolic dysregulation.[24,25] This extrarespiratory inflammation in asthmatic patients could contribute to the occurrence of GERD.

In the subgroup analysis, among children with GERD, females but not males had an increased risk of asthma in this study. This could be partially due to the small number of GERD patients in the male subgroup in this study. The number of GERD patients was 1.5 times higher in the female subgroup than in the male subgroup in the present study cohort. Thus the statistical power could be insufficient in the male subgroup.

This was one of the largest cohort studies on the relationship between asthma and GERD in children. This large study population provided adequate controls matched for age, sex, income, and region of residence. Because this study used health claim data, unbiased medical availability was crucial for the fidelity of results. Thus the socioeconomic factors, which largely determine medical accessibility, were matched between the study and control groups in this study. In addition, both GERD and asthma were classified using both the diagnosis by a physician and medication histories instead of a self-reported survey. These objective and multiple selection criteria enhanced the validity of the current results. The classification methods for asthma were verified in a previous study.[14] Because this study considered asthma or GERD patients who were diagnosed and treated by physicians, it ensured sufficiently symptomatic disease states. However, because this study could not count the subclinical cases, underdiagnosed or untreated asthma or GERD was missed and the detection bias could not be excluded in the analyses. Moreover, the severity and management of asthma or GERD were heterogeneous among the study populations. The types of asthma could not be differentiated. Last, possible comorbidities, such as smoking, obesity, and other metabolic disorders, can induce both asthma and GERD. The information of body weight was not available in the National Health Insurance Service-NSC. Future investigations on the causality of the relationship between asthma and GERD are warranted with consideration of these potential confounders.

CONCLUSION

GERD was associated with the high risk of asthma and asthma was associated with the high risk of GERD in children.

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AUTHOR CONTRIBUTIONS

S.Y.K. and H.-R.K. conceived the study. H.G.C., D.J.O. and B.P. designed and directed the study. S.Y.K. and H.G.C. drafted the manuscript. H.-R.K. and C.M. analyzed the data. All authors have read and approved the final version of the manuscript for publication.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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