The Influence of Constipation on Asthma: A Real-world, Population-based Cohort Study

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Abstract

Background Among respiratory diseases, asthma is one of the most burdensome disorder worldwide. Growing evidence disclose gut dysbiosis may contribute to asthma via the gut-lung axis. Constipation can lead to alteration of the gut microflora. The clinical impact of constipation on asthma has not been researched. Therefore, we aim to assess the risk of asthma in constipated patients by a nationwide population-based cohort study. Methods We analyzed 82421 constipated patients and 82421 individuals without constipation between 1999 and 2013 from the Taiwanese National Health Insurance Research Database. Analysis of propensity score was utilized to match age, gender, comorbidities, and medications at a ratio of 1:1. Besides, multiple Cox regression analysis was performed to evaluate the adjusted hazard ratio of asthma. Furthermore, sensitivity tests and a stratified analysis were conducted. Results The incidence of asthma was 10.8 per 1,000 person-years in the constipation group, which was higher than the rate of 5.6 per 1,000 person-years observed in the non-constipation group. After adjustment for age, gender, comorbidities, and medications, constipated patients had a 1.91-fold greater risk of asthma compared to those without constipation (adjusted hazard ratio [aHR]: 1.91 (95% C.I. 1.84-1.99). In subgroup analyses, patients aged 20-39 years had a 2.04-fold highest risk of asthma in the constipation cohort (aHR:2.04, 95% CI, 1.84-2.26). Besides, the severity of constipation is associated with an increased risk of asthma; the aHR was 1.76 (1.69-1.85), 2.15(2.03-2.27), and 2.29(2.10-2.49) for $<$ 3 times, 3-12 times, and [?]12 times of laxatives prescription within one year, respectively. ($p<0.001$) Moreover, constipated patients had a higher likelihood of asthma, regardless of gender, comorbidities, and medications. Conclusion Constipation relates to a significantly increased risk of asthma. Physicians should be aware of the possibility of asthma in constipated people. Further research is warranted to investigate the possible pathological mechanisms of this association.

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Short running title: Constipation and asthma

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ABSTRACT

Background

Among respiratory diseases, asthma is one of the most burdensome disorder worldwide. Growing evidence disclose gut dysbiosis may contribute to asthma via the gut-lung axis. Constipation can lead to alteration of the gut microflora. The clinical impact of constipation on asthma has not been researched. Therefore, we aim to assess the risk of asthma in constipated patients by a nationwide population-based cohort study.

Methods

We analyzed 82421 constipated patients and 82421 individuals without constipation between 1999 and 2013 from the Taiwanese National Health Insurance Research Database. Analysis of propensity score was utilized to match age, gender, comorbidities, and medications at a ratio of 1:1. Besides, multiple Cox regression analysis was performed to evaluate the adjusted hazard ratio of asthma. Furthermore, sensitivity tests and a stratified analysis were conducted.

Results

The incidence of asthma was 10.8 per 1,000 person-years in the constipation group, which was higher than the rate of 5.6 per 1,000 person-years observed in the non-constipation group. After adjustment for age, gender, comorbidities, and medications, constipated patients had a 1.91-fold greater risk of asthma compared to those without constipation (adjusted hazard ratio [aHR]: 1.91 (95% C.I. 1.84-1.99). In subgroup analyses, patients aged 20-39 years had a 2.04-fold highest risk of asthma in the constipation cohort (aHR:2.04, 95% CI, 1.84-2.26). Besides, the severity of constipation is associated with an increased risk of asthma; the aHR was 1.76 (1.69-1.85), 2.15(2.03-2.27), and 2.29(2.10-2.49) for $<$ 3 times, 3-12 times, and [?]12 times of laxatives prescription within one year, respectively. ($p<0.001$) Moreover, constipated patients had a higher likelihood of asthma, regardless of gender, comorbidities, and medications.

Conclusion

Constipation relates to a significantly increased risk of asthma. Physicians should be aware of the possibility of asthma in constipated people. Further research is warranted to investigate the possible pathological mechanisms of this association.

Key words: constipation, asthma, Longitudinal Health Insurance Database, gut microflora, dysbiosis

What's Known?

Recent studies showed that intestinal dysbiosis contributes to asthma via the gut-lung axis.

Constipation can lead to alteration of the gut microflora.

What's New?

Constipated people had a 1.91-fold greater risk for asthma compared with those without constipation. Furthermore, patients with constipation had a higher likelihood of asthma, regardless of gender, comorbidities, as well as the usage of corticosteroids and antihistamines.

Constipation relates to a significantly risk factor of asthma. Physician should take care of the possibility of developing asthma in constipated patients.

INTRODUCTION

Among respiratory diseases, asthma is one of the most burdensome disorder both affects in childhood and adulthood. The prevalence was estimated that there were more than 272 million people had asthma worldwide in 2017.[1] Asthma not only increases financial, social, and psychological burdens, but also makes a

harmful impact on quality of life, and is connected with comorbidities.[2] Interestingly, there is increasing evidence presenting an connection between asthma and constipation[3], a common condition affecting adults and children globally and a frequent reason for visits to physicians. The mean global prevalence of constipation in children is 12% and that in adult is 16%. [4] Even though constipation has few complications of life-threatening, it can make physical and mental distress for patients and their families, eventually impairing quality of life. Complications of constipation included hemorrhoids, rectal prolapse, and fecal or urine incontinence, which usually increases the frequency of hospitalizations or outpatient department visits, leading to increased burdens of health insurance.

Nowadays, constipation is seemed to be a causative factor in intestinal dysbiosis[5] and therapeutic managements are increasingly incorporating prebiotics, probiotics[6], or synbiotics with a view to regulating the intestinal microflora[7, 8]. Moreover, recent research has demonstrated that the gut microbiota would exert important regulatory effects via the gut-lung axis.[9-11] For instance, gut dysbiosis[12] and lower concentration of short-chain fatty acids (SCFAs) in the bowel are found in patients with asthma. This condition decreases the production of butyrate and propionate, leading to the dysregulation of gut inflammation and the defect of the intestinal epithelial barriers, resulting in leaky gut and allow penetration of microorganisms and toxins into systemic circulation, thereby activating Th2 immune responses, eventually contributing to airway inflammation. Some research have suggested that allergic diseases might be associated with constipation.[13, 14] Furthermore, previous study has demonstrated that stool stasis in the long time could influence the microbiota and environment of gut, resulting in deleterious effects on mucosal immunity and intestinal motility.[15] Whether if constipation predisposes susceptible people to asthma is unknown. At present, there are still scanty data on the connection between constipation and asthma in the literature. In addition, this association has never been investigated using a large-scale national longitudinal database. We hypothesized that constipation might influence the risk of asthma and assessed this hypothesis by analyzing a real-world, population-based retrospective cohort from National Health Insurance Research Database (NHIRD) in Taiwan.

METHODS

Data source

This study analyzed the National Health Insurance Research Database (NHIRD) that contains the healthcare data of almost 99% of Taiwan's entire population, approximately 23 million NHI beneficiaries. The database includes all insurance claims data, including outpatient visits, emergency visits, and hospitalizations. The Longitudinal Health Insurance Database, (LHID) is a subset of the NHIRD comprising one million individuals randomly sampled from the 23 million NHI beneficiaries for the period from 1999 to 2013.[16] The data of patients were de-identified prior to release to the users, in accordance with privacy protocols, and this study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (IRB no. CS15134).

Study group and outcome measurement

The population was composed of patients with newly diagnosed constipation (ICD-9-CM codes=564.0) from 2000 to 2012. To ensure accuracy of diagnoses, we excluded any diagnosis of constipation before 2000 and only patients with at least three outpatient visits or one hospitalization were selected for inclusion in the final analysis. The index date of this cohort was set as the first date of diagnosis of constipation. Furthermore, to ensure that all individuals had new-onset asthma, we ruled out any diagnosis of asthma (ICD-9-CM=493) happening before the index date. The non-constipation group constituted subjects who had never been diagnosed with constipation for the period 1999 to 2013.

The outcome variable was defined as a diagnosis of asthma with at least three outpatient visits or once hospitalization. The patients were followed up until the occurrence of atopic dermatitis, 31 December 2013, or withdrawal from the National Health Insurance system, whichever occurred first.

Covariates and matching

The baseline characteristics were age, gender, hypertension (ICD-9-CM=401-405), hyperlipidemia (ICD-9-CM=272.0-272.4), chronic kidney disease (ICD-9-CM=585), chronic liver disease (ICD-9-CM=571), chronic obstructive pulmonary disease (COPD) (ICD-9-CM =491, 492, 496), cancer (ICD-9-CM=140-208), diabetes (ICD-9-CM=250), cardiovascular disease (ICD-9-CM=410-414), stroke (ICD-9-CM=430-438), and autoimmune disease (ICD-9-CM=710.0, 720.0, 714.0). The comorbidities were defined as occurring within one year prior to the index date with at least three outpatient visits or once hospitalization. Besides, corticosteroids and antihistamines during the study period were included and defined as usage for at least [?]30 days. To assess the severity of constipation, we collected additional information on the total numbers of laxatives prescription (anatomical therapeutic chemical [ATC] classification system code A06A), which occurred within one year after the index date.

Moreover, propensity score matching based on age, gender, hypertension, hyperlipidemia, chronic kidney disease, chronic liver disease, COPD, cancer, diabetes, cardiovascular disease, stroke, autoimmune disease, corticosteroids, and antihistamines was applied to balance the heterogeneity of the two groups. The propensity score was a probability that was estimated through logistic regression. The binary variable was the constipation and non-constipation group.

Statistical analysis

Comparisons between the constipation group and non-constipation group were using absolute standardized differences (ASD). Whenever the ASD were less than 0.1, the characteristics of the two groups were deemed to be similar. On the other hand, Kaplan-Meier analysis was applied to calculate the cumulative incidence of asthma and then log-rank test was used to test the significance. Cox proportional hazard model was applied to estimate the hazard ratio of asthma between the constipation and non-constipation groups.

RESULTS

The flowchart is presented in Fig. 1. We identified 82421 patients with constipation and 82421 matched controls between 1999 and 2013 from the LHID. Demographic characteristics of this study participants are shown in Table 1. The constipated patients and non-constipation cohort were similar in age and gender distribution. After propensity score matching, there were no statistically significant differences between the constipation and non-constipation groups.

As shown in Table 2, the incidence of asthma was 10.8 per 1,000 person-years in the constipation group, which was higher than the rate of 5.6 per 1,000 person-years observed in the non-constipation group. After adjustment, patients with constipation had a significantly higher risk of asthma than those without constipation (aHR:1.91, 95% C.I. 1.84-1.99, p<0.001). Compared with women, men had a significantly higher risk of asthma (aHR:1.17; 95% CI, 1.12-1.22; p<0.001). In term of comorbidities, we observed that people with hypertension, COPD, or autoimmune disease had a relatively higher risk of asthma. (hypertension:1.22, 95% C.I. 1.15-1.29, p<0.001; COPD:3.21, 95% C.I. 2.94-3.50, p<0.001; autoimmune disease:1.42, 95% C.I. 1.17-1.73, p<0.001). By contrast, patients using corticosteroids or antihistamines during the study for period at least 30 days had a lower risk of asthma. (corticosteroids: 0.80, 95% C.I. 0.76-0.84, p<0.001; antihistamines: 0.61, 95% C.I. 0.59-0.64, p<0.001)

Table 3 showed that subgroup analyses were performed to assess the association between constipation and asthma based on demographic characteristics. Patients in the constipation group aged 20-39 years, had a 2.04-fold greater risk of asthma compared with the same age group in the non-constipation group (aHR; 95% CI,1.84-2.26, P < 0.001). Patients aged <20, 40-64, and [?]65 years in the constipation group had a 1.85, 1.70, and 2.02-fold greater risk of asthma.(aHR; 95% CI, 1.69-2.01, 1.57-1.83 and 1.89-2.16; P < 0.001), respectively. Among females, compared with those without constipation, there was a 1.86-fold higher risk of asthma in patients with constipation (aHR; 95% CI, 1.77-1.96; P < 0.001). Among males, there was 1.92-fold higher risk of asthma in patients with constipation (aHR; 95% CI, 1.80-2.04; P < 0.001). Furthermore, constipated patients had a higher likelihood of asthma, regardless of comorbidities and medications.

In addition, Table 4 presents that analysis for risk of asthma in constipated patients with laxatives prescrip-

tion. Compared to participants without constipation, the adjusted hazard ratio was 1.76 (95% CI, 1.69-1.85; P < 0.001), 2.15(95% CI, 2.03-2.27; P < 0.001), and 2.29(95% CI, 2.10-2.49; P < 0.001) for < 3 times, 3-12 times, and [?]12 times of laxatives prescription within one year, respectively. There appeared to be a dose-effect relationship between constipation severity and risk of asthma.The Kaplan–Meier curves are shown in Fig. 2. The cumulative incidence of asthma was significantly higher in constipated patients than in non-constipated patients, and the log-rank test for the comparison of cumulative incidence curves resulted in a P-value of <0.001

DISCUSSION

In this study, people with constipation had a 1.91-fold higher risk for developing asthma than non-constipated individuals, regardless of age, gender, comorbidities or medications. As far as we know, this is the largest epidemiological research by using a nationwide longitudinal population-based dataset to expound the association between constipation and asthma. This relationship might be of pathophysiological and clinical importance. Our findings emphasize the considerably higher risk of asthma in individuals with constipation. Constipation might be influential in the development of asthma. Physicians should take care about the possibility of asthma in patients with constipation. Correspondingly, constipated patients should be informed of the probable risk of asthma and be offered with applicable management for asthma as required. Our findings further highlight the importance of maintaining fair bowel habits in order to avoid constipation, which could in turn mitigate risk of asthma.

We also observed that the risk of developing asthma was significantly increased in patients with hypertension, chronic obstructive pulmonary disease (COPD), chronic liver disease, and autoimmune disease. Most of these comorbidities, such as COPD or autoimmune disease, were connected to chronic inflammation, which could contribute to release of serum cytokines and activate T-cell response. In addition, we further extended to suggest that constipation severity is associated with the risk of asthma. There seemed to be a dose-dependent relationship between constipation and subsequent risk of asthma, which strengthened our hypothesis.

The pathophysiological mechanisms underlying the association between constipation and asthma remain ambiguous. Currently, there has been considerable studies conducted between intestinal microbiota and asthma.[17-21] The extended "'hygiene hypothesis" discloses that the initial composition of the infant gut microflora plays a vital role in the development of atopic diseases.[22-24] Another research in United Kingdom, which analyzed the gut microbiome of the people with asthma, showed that there were abundant with Clostridiums spp. whereas Faecalibacterium prausnitzii and Bacteroides stercoris were depleted in individuals with asthma.[25] Similarly, some researches have suggested that alterations in the intestinal microflora would lead to constipation and constipation-related symptoms.[5, 7] In contrast to the healthy individuals, constipated patients had relatively higher amount of potentially pathogenic microbes, such as Clostridiums spp. and Pseudomonas aeruginosa, and relatively lower amount of Bacteroides spp., Bifidobacterium, and Lactobacillus.[26] These alternates in the intestinal surroundings could affect bowel motility by the active materials. Some studies exhibited that microbial-derived metabolites, mainly short-chain fatty acids (SCFAs), acted as pivotal drivers of T-cell subset activity and proliferation.[27] Furthermore, it has been disclosed that production of bowel microbial SCFAs could down-regulate proinflammatory reactions at the area of allergen insult.[28] Moreover, SCFAs might influence bowel motility via stimulating the contraction of colonic smooth muscles, thereby assisting to present or relieve constipation.[29, 30] By contrast, immune homeostasis would be devastated by proinflammatory dietary type, or "Westernized dietary style", which might be described as being low in fiber and high in fat, changing the intestinal microbiota, and leading to decrease SCFAs production. Hence, less fiber intake, such as fewer fresh fruits, in patients with constipation might be also pivotal role in developing atopy.[31, 32] Organizing the presently available corroboration suggests that the gut microbiota might be a key mechanistic part linking asthma and constipation. It is not known how constipation influence the configuration of the intestinal microflora and how applicable this condition is to asthma. Nevertheless, constipation appears to be the predisposing point for asthma. Further comprehensive metabolomic and metagenomic analyses of the gut microbiome in constipated individuals are warranted to clarify the potential mechanisms underlying these connections.

The major advantages of this study were the relatively large sample size and long follow-up period. An integrated past history of used medical services was accessible for all cases. Therefore, there was slightest selection, information, and recall bias. As such, it was feasible to properly examine our hypothesis. However, there some potential limitations existed in our study. First, the NHIRD does not include data on covariates, such as social adversity, personal lifestyle, family history, laboratory data and environmental factors. Although we adjusted for several comorbidities and matched propensity scores, these unmeasured confounding factors could have influenced our results. Second, the diagnoses of asthma and constipation were totally dependent on the ICD-9 codes in the administrative dataset. We did not undergo a review of the patients' medical documents so that it was not probable to check the accuracy of diagnoses, and thus there might have some misclassifications existed. It is worth noting, however, that any misclassifications were more probably to be random, and connections were often underestimated rather than overestimated. Besides, clinical judgment might be different among clinicians, and so diagnoses would not have been consistent, which might have affected the validity. However, Taiwan's National Health Insurance administration monitors the accuracy of the claims data to prevent violations. Finally, it keeps unclear as to if the findings of our study may be extrapolated to other ethnic groups, as the majority of our subjects were Taiwanese. Further clinical research should include other nationalities and ethnicities to define the generalizability of the relationship observed herein.

CONCLUSION

In conclusion, constipated people had a 1.91-fold greater risk for asthma compared with those without constipation. Individuals with constipation should be alert to the elevated risk of developing asthma. Moreover, physicians should define the intestinal condition, including the gut microbiome, in patients with asthma. The precise pathophysiological association between constipation and asthma still needs further research.

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CONFLICT OF INTEREST:

There is no conflict of interest in this study.

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AVAILABILITY OF DATA AND MATERIALS:

The LHID is a subset of the NHIRD, a database of all medical claims in Taiwan's NHI system. The usage of NHIRD is limited to research purposes only. Only Taiwanese citizens who fulfill the requirements for conducting research projects are eligible to apply for access to the National Health Insurance Research Database (NHIRD). Applicants must follow the Personal Data Protection Act (*https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=I0050021*) and related regulations of the National Health Insurance Administration and NHRI (National Health Research Institutes), and an agreement must be signed by the applicant and his/her supervisor upon application submission. The datasets generated and analyzed during the current study are available from the authors on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (Approval number CS15134) in Taiwan. The requirement for written consent from study subjects was waived by the Institutional Review Board, as the LHID consists of de-identified secondary data.

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Table 1. Demographic characteristics of constipation group and non-constipation group

	Before propensity score matched	Before propensity score matched		After propensity s
	Constipation (N =102467)	Non-constipation (N =102467)	ASD	Constipation (N =
Age			<0.001	
<20	15501 (15.1)	15501 (15.1)		13276 (16.1)
20-39	31798 (31.0)	31798 (31.0)		25192 (30.6)
40-64	30822 (30.1)	30822 (30.1)		24699 (30.0)
65	24346 (23.8)	24346 (23.8)		19254 (23.4)
Mean ± SD	44.1 ± 22.7	44.1 ± 22.7	<0.001	43.6 ± 22.8
Gender			<0.001	
Female	68983 (67.3)	68983 (67.3)		56360 (68.4)
Male	33484 (32.7)	33484 (32.7)		26061 (31.6)
Hypertension	18188 (17.8)	12651 (12.3)	0.152	12212 (14.8)
Hyperlipidemia	5500 (5.4)	3728 (3.6)	0.083	3684 (4.5)
Chronic liver disease	3829 (3.7)	2060 (2.0)	0.103	2109 (2.6)
Chronic kidney disease	1042 (1.0)	638 (0.6)	0.044	558 (0.7)
Diabetes	9368 (9.1)	5495 (5.4)	0.146	5556 (6.7)
COPD	2622 (2.6)	1337 (1.3)	0.091	1374 (1.7)
Autoimmune disease	966 (0.9)	584 (0.6)	0.043	571 (0.7)

	Before propensity score matched	Before propensity score matched		After propensity s
Corticosteroids	25401 (24.8)	14964 (14.6)	0.258	14855 (18.0)
Antihistamines	71110 (69.4)	51862 (50.6)	0.391	51741 (62.8)

ASD: Absolute standardized differences.

COPD: Chronic obstructive pulmonary disease.

Table 2. Cox proportional hazard model analysis for risk of asthma

	No. of asthma	PY	ID	Univariate		Multivariate	
				HR (95% C.I.)	p value	HR (95% C.I.)	p value
Group							
Non-constipation	3740	662847	5.6	1		1	
Constipation	6622	610672	10.8	1.88 (1.81-1.96)	<0.001	1.91 (1.84-1.99)	<0.001
Age							
<20	2250	249050	9.0	1		1	
20-39	1551	410253	3.8	0.40 (0.37-0.42)	<0.001	0.37 (0.35-0.40)	<0.001
40-64	2721	377274	7.2	0.75 (0.71-0.80)	<0.001	0.68 (0.64-0.72)	<0.001?¿?
65	3840	236941	16.2	1.60 (1.52-1.69)	<0.001	1.31 (1.23-1.39)	<0.001
Gender							
Female	6252	903955	6.9	1		1	
Male	4110	369563	11.1	1.57 (1.51-1.63)	<0.001	1.17 (1.12-1.22)	<0.001
Hypertension	2243	145764	15.4	1.98 (1.89-2.07)	<0.001	1.22 (1.15-1.29)	<0.001
Hyperlipidemia	517	43009	12.0	1.37 (1.25-1.50)	<0.001	0.91 (0.82-0.99)	0.037
Chronic liver disease	334	26518	12.6	1.50 (1.35-1.68)	<0.001	1.21 (1.09-1.36)	<0.001
Chronic kidney disease	79	5131	15.4	1.65 (1.32-2.06)	<0.001	1.06 (0.85-1.32)	0.624
Diabetes	836	61790	13.5	1.57 (1.46-1.69)	<0.001	0.96 (0.89-1.03)	0.273
COPD	568	12955	43.8	5.16 (4.74-5.61)	<0.001	3.21 (2.94-3.50)	<0.001
Autoimmune disease	104	7533	13.8	1.63 (1.35-1.98)	<0.001	1.42 (1.17-1.73)	<0.001
Corticosteroids	1876	250654	7.5	0.93 (0.89-0.98)	0.007	0.80 (0.76-0.84)	<0.001
Antihistamines	6212	915347	6.8	0.65 (0.62-0.68)	<0.001	0.61 (0.59-0.64)	<0.001

ID: Incidence density (per 1000 person-years).

PY: person-years.

COPD: Chronic obstructive pulmonary disease.

Table 3. Subgroup analysis of the association between constipation and asthma development

	Constipation	Constipation
	N	No. of asthma
Age		
<20	13276	1429
20-39	25192	1019
40-64	24699	1668
65	19254	2506
Gender		
Female	56360	3980

	Constipation	Constipation
Male	26061	2642
Hypertension		
No	70209	5193
Yes	12212	1429
Hyperlipidemia		
No	78737	6308
Yes	3684	314
Chronic liver disease	Chronic liver disease	
No	80312	6401
Yes	2109	221
Chronic kidney disease	Chronic kidney disease	
No	81863	6571
Yes	558	51
Diabetes		
No	76865	6084
Yes	5556	538
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease
No	81047	6261
Yes	1374	361
Autoimmune disease	Autoimmune disease	
No	81850	6554
Yes	571	68
Corticosteroids		
No	67566	5547
Yes	14855	1075
Antihistamines		
No	30680	2836
Yes	51741	3786

Table 4. Cox proportional hazard model analysis for risk of asthma in constipated patients with laxatives

	N	No. of asthma	Univariate		Multivariate
			HR (95% C.I.)	p value	HR (95% C.I.
Group					
Non-constipation	82421	3740	1		1
Constipation with Laxatives prescription <3 times	55070	3929	1.59 (1.52-1.66)	<0.001	1.76 (1.69-1.8
Constipation with Laxatives prescription =3-12 times	21332	2000	2.37 (2.24-2.50)	<0.001	2.15 (2.03-2.2
Constipation with Laxatives prescription [?]12 times	6019	693	3.39 (3.13-3.68)	<0.001	2.29 (2.10-2.4

+Adjusted for age, gender, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, COPD, autoimmune disease, corticosteroids, and antihistamines.

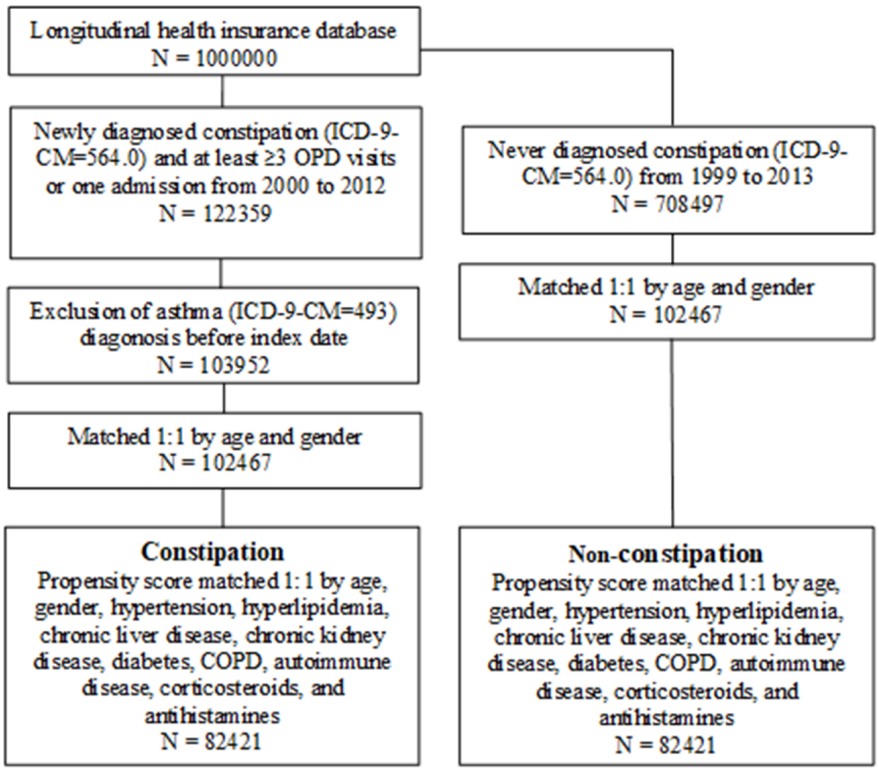


Figure 1. Flowchart of enrolment of constipation and non-constipation groups.

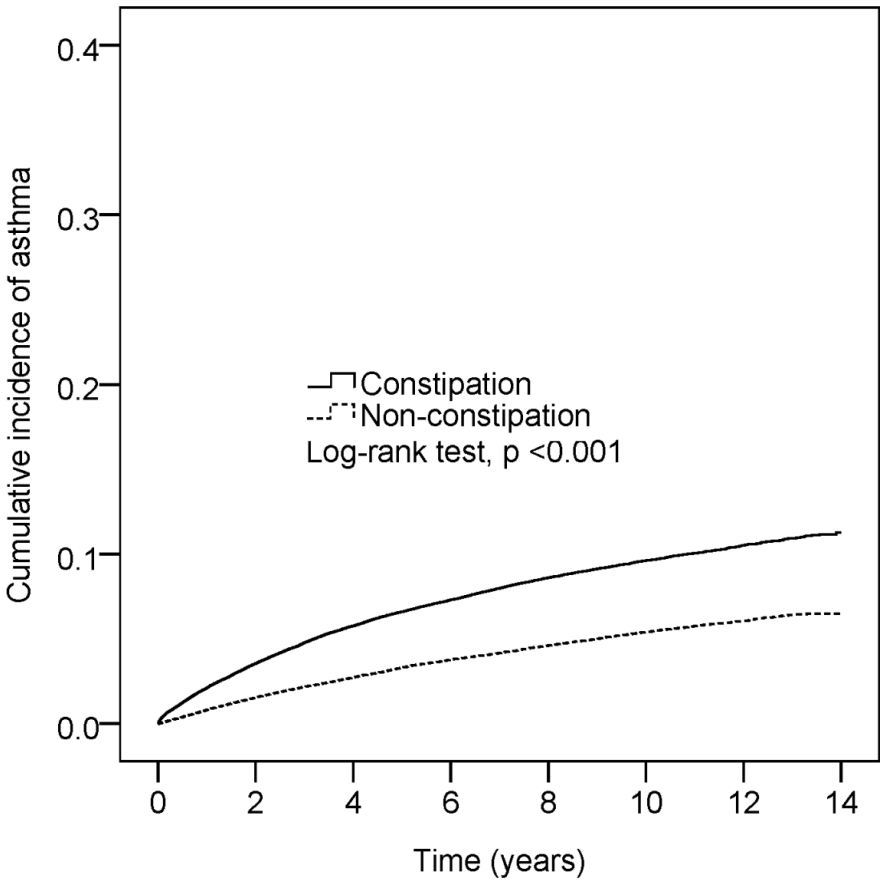
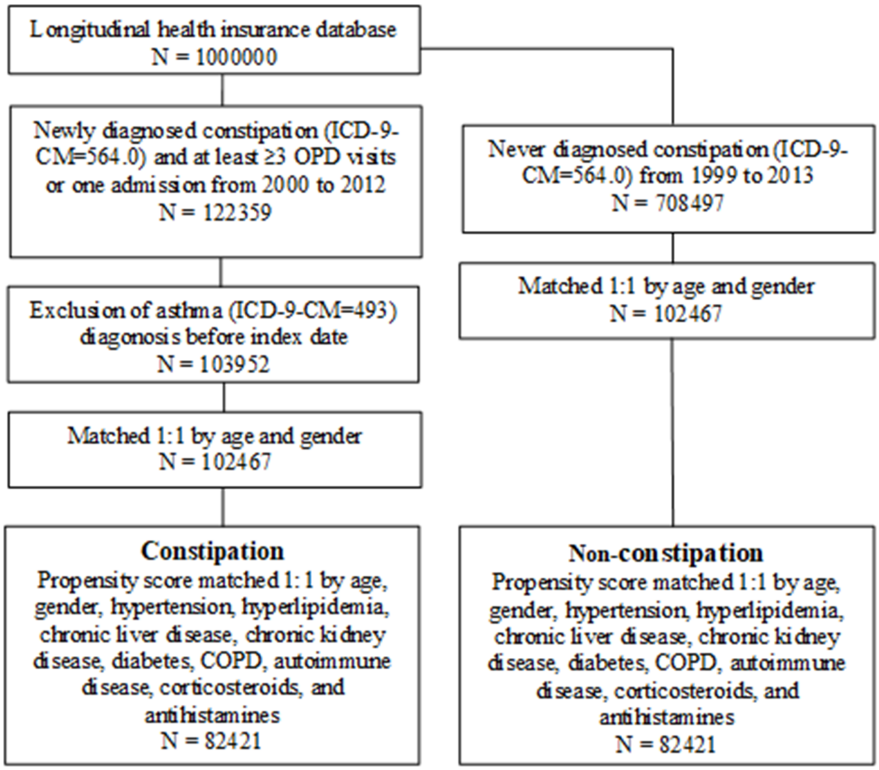
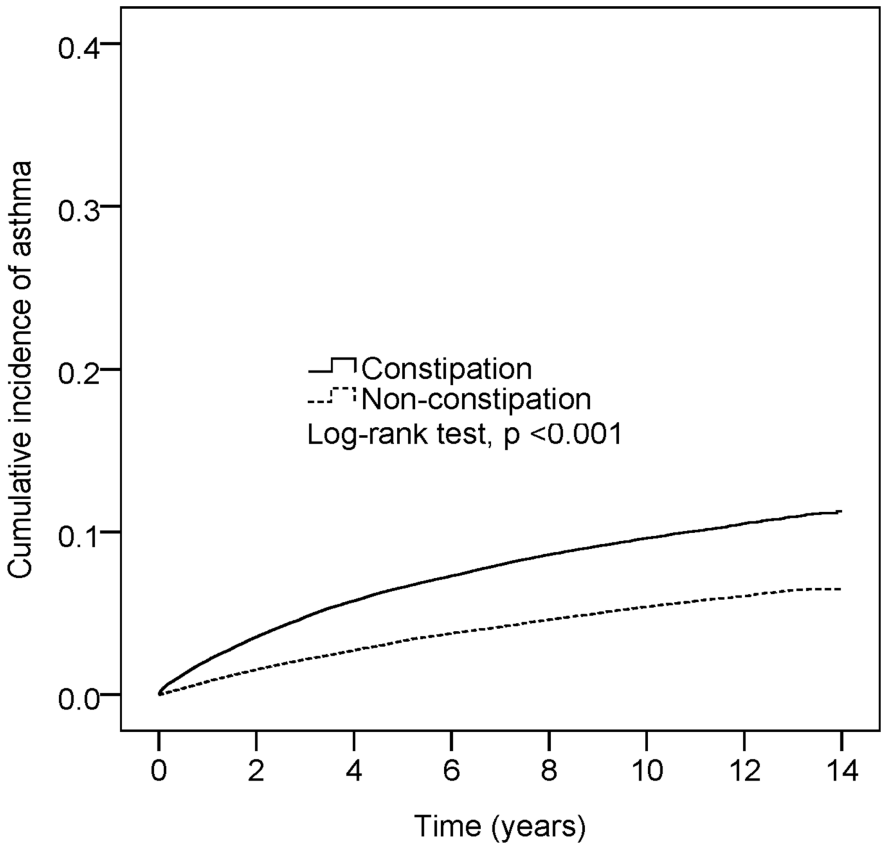


Figure 2. Kaplan–Meier curve of cumulative incidence proportion of asthma in constipation and non-constipation groups.





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