Influence of constipation on atopic dermatitis: A nationwide population-based cohort study in Taiwan

Yen Chu Huang[1], Meng Che Wu[1], Yu-Hsun Wang[2], and James Cheng-Chung Wei[3]

[1]Taichung Veterans General Hospital
[2]Chung Shan Medical University Hospital
[3]Chung Shan Medical University

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Abstract

Background Atopic dermatitis (AD) is the chronic inflammatory disorder that affects both in childhood and adulthood. Mounting evidence indicates that gut dysbiosis contributes to AD via the gut-skin axis. Constipation can result in alteration of the gut microflora. The clinical impact of constipation on AD has not been researched. Therefore, we aim to assess the risk of AD in constipated patients by the population-based cohort study. Methods We collected 87015 constipated people and 87015 people without constipation between 1999 and 2013 from the Taiwanese National Health Insurance Research Database. Propensity score analysis was administrated to match age, gender, comorbidities, and medications at a ratio of 1:1. Multiple Cox regression analysis was utilized to evaluate the adjusted hazard ratio of AD. In addition, sensitivity tests and a stratified analysis were conducted. Results The incidence of AD was 4.7 per 1,000 person-years in the constipation group, which was higher than the rate of 2.2 per 1,000 person-years observed in the non-constipation group. After adjustment for age, gender, comorbidities, corticosteroids, and antihistamine, constipated people had a 2.11-fold greater risk of AD compared to those without constipation (adjusted hazard ratio [aHR]: 2.11 (95% C.I. 1.98-2.24). Moreover, constipated people had a higher likelihood of AD, regardless of gender, comorbidities, as well as the usage of corticosteroids, and antihistamines. Conclusion Constipation is associated with a significantly risk factor of AD. Clinicians should be careful of the possibility of AD in constipated people. Further study is warranted to investigate the possible pathological mechanisms of this relationship.

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Yen-Chu HUANG,[1,] [++]Meng-Che WU,[1,] [++], Yu-Hsun WANG,[2] James Cheng-Chung WEI[3,4,5,6]

[1]*Division of Pediatric Gastroenterology, Children's Medical Center, Taichung Veterans General Hospital,*[2]*Department of Medical Research, Chung Shan Medical University Hospital* ,

[3]*Department of Rheumatology, BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University,*

[4]*Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University,*

[5]*Division of Allergy, Immunology and Rheumatology, Chung Shan Medical University Hospital; Institute of Medicine, College of Medicine, Chung Shan Medical University,*[6]*Graduate Institute of Integrated Medicine, China Medical University*

Short running title: Constipation and atopic dermatitis

Correspondence: James Cheng-Chung Wei, Institute of Medicine, Chung Shan Medical University, No. 110, Sec 1, Jianguo N. Road, Taichung City, 40201, Taiwan. Email: wei3228@gmail.com

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++ These authors are co-first authors

ABSTRACT

Background

Atopic dermatitis (AD) is the chronic inflammatory disorder that affects both in childhood and adulthood. Mounting evidence indicates that gut dysbiosis contributes to AD via the gut-skin axis. Constipation can result in alteration of the gut microflora. The clinical impact of constipation on AD has not been researched. Therefore, we aim to assess the risk of AD in constipated patients by the population-based cohort study.

Methods

We collected 87015 constipated people and 87015 people without constipation between 1999 and 2013 from the Taiwanese National Health Insurance Research Database. Propensity score analysis was administrated to match age, gender, comorbidities, and medications at a ratio of 1:1. Multiple Cox regression analysis was utilized to evaluate the adjusted hazard ratio of AD. In addition, sensitivity tests and a stratified analysis were conducted.

Results

The incidence of AD was 4.7 per 1,000 person-years in the constipation group, which was higher than the rate of 2.2 per 1,000 person-years observed in the non-constipation group. After adjustment for age, gender, comorbidities, corticosteroids, and antihistamine, constipated people had a 2.11-fold greater risk of AD compared to those without constipation (adjusted hazard ratio [aHR]: 2.11 (95% C.I. 1.98-2.24). Moreover, constipated people had a higher likelihood of AD, regardless of gender, comorbidities, as well as the usage of corticosteroids, and antihistamines.

Conclusion

Constipation is associated with a significantly risk factor of AD. Clinicians should be careful of the possibility of AD in constipated people. Further study is warranted to investigate the possible pathological mechanisms of this relationship.

Key words: constipation, atopic dermatitis, national health insurance research database, gut microbiota, gut dysbiosis.

What's Known?

1. Recent researches revealed that gut dysbiosis contributes to atopic dermatitis via the gut-skin axis.
2. Constipation can result in alteration of the gut microflora.

What's New?

1. Constipated people had a 2.11-fold greater risk of atopic dermatitis compared to those without constipation. Moreover, constipated people had a higher likelihood of atopic dermatitis, regardless of gender, comorbidities, as well as the usage of corticosteroids, and antihistamines.
2. Constipation is associated with a significantly risk factor of atopic dermatitis. Clinicians should be careful of the possibility of atopic dermatitis in constipated people.

INTRODUCTION

Atopic dermatitis (AD) is a long-lasting, relapsing pruritic inflammatory skin disorder that occurs in both childhood and adulthood. It leads to a defective skin barrier and strengthened T-cell responses to allergens and microbes from surroundings, resulting in chronic inflammatory reaction.[1] In the past few years, the

prevalence of atopic dermatitis has increased rapidly in developed countries such as the United States[2] and in Taiwan.[3] AD not only increases social, financial, and psychological burdens[4], but also makes a deleterious effect on quality of life, [5] and is associated with comorbidities.[6]

Interestingly, there is growing evidence showing an association between AD and constipation, a common condition affecting children and adults worldwide and a frequent reason for visits to gastroenterologists. The mean global prevalence of constipation in adults is 16% and that in children is 12%.[7] Although constipation has few life-threatening complications, it can affect physical and emotional distress for patients and their family members, eventually impairing quality of life. Complications of constipation included hemorrhoids, fecal incontinence, and rectal prolapse, which often increases the frequency of outpatient department visits or hospitalizations, resulting in increased cost of health insurance.

Constipation is now considered to be a causative factor in gut dysbiosis[8] and therapeutic approaches are increasingly incorporating probiotics, prebiotics, or synbiotics with a view to manipulating the intestinal microbiota.[9] In addition, recent study has demonstrated that the gut microbiota might exert important regulatory effects via the gut-skin axis.[10]For example, intestinal dysbiosis and lower concentration of short-chain fatty acids (SCFAs) in the bowel are found in patients with AD.[11–14] In a Korean study, which investigated the gut microbiome and relevant metabolites in patients with AD, dysbiosis of Faecalibacterium prausnitzii was observed in stool samples of patients with AD. This condition decreases the production of propionate and butyrate, resulting in the dysregulation of intestinal inflammation and the defect of the epithelial barrier (leaky gut), thereby allowing penetration of toxin and microbes into systemic circulation, which activates Th2 immune responses, eventually culminating in skin damage.[12] Some researches have suggested that allergic disease might be connected with constipation.[15,16]Furthermore, previous research has indicated that prolonged stool stasis may change the intestinal environment and microbiota, resulting in deleterious effects on gut motility and mucosal immunity.[17,18] Whether constipation predisposes susceptible individuals to AD is unknown. Currently, there are scanty data on the association between constipation and AD in the literature. Moreover, this relationship has never been investigated using data obtained from a large national longitudinal database. We hypothesized that constipation could impact the risk of AD and evaluated this hypothesis by analyzing a nationwide population-based retrospective cohort from Taiwan's National Health Insurance Research Database (NHIRD).

METHODS

Data source

This retrospective cohort study analyzed the National Health Insurance Research Database (NHIRD) which contains the healthcare data of almost 99% of Taiwan's entire population, i.e., 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.[19,20] The patients' data were de-identified prior to release to the authors, in accordance with privacy protocols, and the study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (IRB no. CS15134).

Study group and outcome measurement

The study population was composed of patients with newly diagnosed constipation (ICD-9-CM codes=564.0) from 2000 to 2012. To ensure accuracy of diagnoses, 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, in order to ensure that all subjects had new-onset atopic dermatitis, we excluded any diagnosis of atopic dermatitis (ICD-9-CM=691) occurring before the index date. The non-constipation group constituted individuals who had never been diagnosed with constipation (ICD-9-CM=564.0) for the period 1999 to 2013.

The outcome variable was defined as a diagnosis of atopic dermatitis (ICD-9-CM=691) 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 liver disease (ICD-9-CM=571), chronic kidney disease (ICD-9-CM=585), diabetes (ICD-9-CM=250), chronic obstructive pulmonary disease (ICD-9-CM =491, 492, 496), cancer (ICD-9-CM=140-208), 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. In addition, corticosteroids and antihistamines during the study period were included and defined as usage for at least [?]30 days.

Then, propensity score matching based on age, gender, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, chronic obstructive pulmonary disease (COPD), cancer, cardiovascular disease, stroke, autoimmune disease, corticosteroids, and antihistamines was performed in order 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 performed using absolute standardized differences (ASD). When the absolute standardized differences were less than 0.1, the characteristics of the two groups were deemed to be similar.[21] Kaplan-Meier analysis was used to calculate the cumulative incidence of atopic dermatitis and log-rank test was used to test the significance. Cox proportional hazard model was used to estimate the hazard ratio of atopic dermatitis between the constipation and non-constipation groups. Analyses were performed using statistical software SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The study flowchart is shown in Fig. 1. We identified 87015 patients with constipation and 87015 matched controls between 1999 and 2013 from the LHID, a subset of Taiwan's National Health Insurance Research Database. Table 1 shows the demographic characteristics of the study participants. The constipated patients and non-constipation cohort were similar in age and gender distribution. There were no statistically significant differences between the constipation and non-constipation groups after propensity score matching. The median follow-up duration in constipated group is 7.9 years and 8.5 years in non-constipated groups, respectively.

As shown in Table 2, the incidence of AD was 4.7 per 1,000 person-years in the constipation group, which was higher than the rate of 2.2 per 1,000 person-years observed in the non-constipation group. After adjustment, patients with constipation had a significantly higher risk of AD than those without constipation (aHR: 2.11, 95% C.I. 1.98-2.24, p<0.001) In addition, the age groups < 6 years and [?]65 years showed a relatively higher risk of AD. (aHR of < 6 years old group: 2.94, 95% C.I. 2.64-3.28, p<0.001; [?]65 years old group: 1.60, 95% C.I. 1.47-1.75, p<0.001). Compared with women, men had a non-significantly lower risk of AD (aHR, 0.96; 95% CI, 0.9-1.02; p=0.16). In term of comorbidities, we observed that people with hypertension, chronic liver disease, diabetes, or COPD had a relatively higher risk of AD. (hypertension:1.21, 95% C.I. 1.1-1.33, p<0.001; chronic liver disease:1.34, 95% C.I. 1.13-1.59, p=0.001; diabetes:1.20, 95% C.I. 1.07-1.35, p=0.002; COPD: 1.44, 95% C.I. 1.21-1.7, p<0.001). By contrast, patients using corticosteroids or antihistamines during the study for period at least 30 days had a lower risk of AD. (corticosteroids: 0.76, 95% C.I. 0.70-0.82, p<0.001; antihistamines: 0.53, 95% C.I. 0.50-0.57, p<0.001)

Subgroup analyses were performed to assess the association between constipation and AD based on demographic characteristics, as shown in Table 3. Patients in the constipation group aged 12-19 years, had a 2.34-fold greater risk of AD compared with the same age group in the non-constipation group (aHR; 95%

CI,1.84-2.98, P < 0.001). Patients aged 20-39, 40-64, and [?]65 years in the constipation group had a 2.23, 2.19, and 2.08-fold greater risk of AD.(aHR; 95% CI, 1.98-2.50, 1.93-2.48 and 1.85-2.34; P < 0.001), respectively. Among females, compared with those without constipation, there was a 2.16-fold higher risk of AD in patients with constipation (aHR; 95% CI, 2.01-2.33; P < 0.001). Among males, there was 1.95-fold higher risk of AD in patients with constipation (aHR; 95% CI, 1.75-2.16; P < 0.001). Furthermore, constipated patients had a higher likelihood of AD, regardless of comorbidities. However, constipated patients with using corticosteroids or antihistamines had a lower risk of AD compared with non-users.

The Kaplan–Meier curves are shown in Fig. 2. The cumulative incidence of AD 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, constipated patients had a 2.11-fold higher risk for AD than non-constipated patients, regardless of age, gender, or comorbidities. To the best of our knowledge, this is the first and largest epidemiological study to use a nationwide longitudinal population-based dataset to clarify the relationship between constipation and AD. This association could be of clinical and pathophysiological importance. Our findings highlight the considerably higher risk of AD in people with constipation. Constipation thus seems to be influential in the development of AD. Clinicians should be alert to the possibility of AD in patients with constipation. Similarly, constipated patients should be informed of the possible risk of AD and be provided with appropriate management for AD as required. Our findings further underline the importance of maintaining good bowel habits so as to avoid constipation, which would in turn mitigate risk of AD.

Our findings are in line with an epidemiological study conducted in Japan, which analyzed the risk factors for allergic disease in 21802 senior high school students, aged 15-18 years old, living in the same prefecture between 2012 and 2013.[22] The results of the study indicated that constipated students had a 1.17-fold risk for developing AD, which was comparable to the 2.34-fold elevated risk found among teenagers in our study (95% C.I. 1.84-2.98 p<0.001). Moreover, we observed a significantly higher risk of AD not in only childhood, but also in adulthood.

We also noticed that the risk of AD was significantly higher in patients with hypertension, chronic liver disease, diabetes, or chronic obstructive pulmonary disease. Most of these comorbidities, such as diabetes and COPD, were associated with chronic inflammatory status, which might lead to release of serum cytokines and T-cell activation. We also speculate that constipation might worsen pre-existing dysbiosis in vulnerable patients with diabetics who may therefore have an increased risk of AD. Intriguingly, a general population study conducted in Copenhagen, suggested that null mutations in the filaggrin gene in patients with diabetes were associated with a higher prevalence of atopic dermatitis. This result implies that poor protection of skin barrier in diabetes patients may lead greater to exposure allergens and increased epidermal water loss.[23]

The pathophysiological mechanisms underlying the relationship between constipation and atopic dermatitis remain unclear. In recent years, there has been considerable research conducted on the gut microbiota and a number of investigations have suggested that alterations in the microbiota could contribute to constipation and constipation-related symptoms.[9,18] Compare to the healthy people, constipated individuals had relatively lower amount of obligate bacteria (e.g. Bifidobacterium, Lactobacillus, and Bacteroides spp.) and relatively higher amount of potentially pathogenic microbes, such as Pseudomonas aeruginosa. These changes in the intestinal environment could influence bowel motility by the active substances.[24]. Similar changes in gut microbiota were reported in patients with AD. For instance, a study in Japan indicated that lower Bifidobacterium counts were found in patients with AD compared with those of healthy people in the fecal microflora.[25] In addition, other studies observed that there were low numbers of Bifidobacterium and Bacteroides spp. as well as a lack of intestinal microbiota variation in AD patients.[26,27] Some studies demonstrated that microbial-derived metabolites, especially short-chain fatty acids (SCFAs), functioned as key drivers of T-cell subset proliferation and activity.[28,29] In addition, it has been shown that production of intestinal microbial SCFAs might down-regulate proinflammatory responses at the site of allergen

insult.[13,30,31] In contrast, immune homeostasis might be destroyed by typical "Westernized" dietary intake, which can be characterized as being high in fat and low in fiber, altering the gut microflora, and resulting in reduced production of SCFAs.[10,13,32–34] Furthermore, SCFAs might affect bowel motility by stimulating the contraction of colonic smooth muscles, thereby helping to relieve or prevent constipation.[35,36] Therefore, low fiber intake in constipated subjects might also play a role in the development of atopy. Taken together the currently available evidence suggests that the gut microbiota might play a pivotal mechanistic role linking constipation and atopic dermatitis. It is not known how constipation changes the composition of the gut microbiome and how relevant this is to AD. Further comprehensive metagenomic and metabolomic analyses of the gut microbiota in constipated patients are warranted to elucidate the mechanisms underlying these associations.

The major advantages of this study were the relatively long follow-up period and large sample size. A complete past history of utilized medical services was available for all cases. Thus, there was minimal selection, information, and recall bias. As such, it was possible to properly test our hypothesis. There were some potential limitations in our study. First, the diagnoses of constipation and AD were entirely dependent on the ICD-9 codes in the administrative dataset. We did not perform a review of the patients' medical records so it was not possible to verify the accuracy of diagnoses, and therefore there may have been some misclassification. It is worth noting, however, that any misclassifications were more likely to be random, and associations are often underestimated rather than overestimated. In addition, clinical judgment might have varied among clinicians, and so diagnoses may not have been consistent, which might have influenced their validity. However, Taiwan's National Health Insurance administration monitors the accuracy of the claims data to prevent violations. Second, the NHIRD does not include data on covariates, such as personal lifestyle, family history, social adversity, laboratory data and environmental factors. Although we adjusted for various comorbidities and matched propensity scores, these unmeasured confounding factors might have affected our results. Finally, it remains unclear as to whether the findings of our study can be extrapolated to other ethnic groups, as the majority of our patients were Taiwanese. Further clinical studies should include other ethnicities and nationalities to determine the generalizability of the associations observed herein.

CONCLUSION

In conclusion, individuals with constipation had a 2.11-fold greater risk for atopic dermatitis compared with those without constipation. Constipated patients should be aware of the elevated risk of developing AD. Furthermore, clinicians should determine the condition of the bowels, including the gut microbiota, in patients with AD. The precise pathophysiological relationship between constipation and atopic dermatitis still requires further research.

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CONFLICT OF INTEREST:

There is no conflict of interest in this research.

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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 use 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 matching	Before propensity score matching	Before propensity score m
	Constipation (N =110899) n	Constipation (N =110899) %	Non-constipation (N =110 n
Age			
<6	4651	4.2	4651
6-11	3359	3.0	3359
12-19	8292	7.5	8292
20-39	32037	28.9	32037
40-64	33344	30.1	33344
65	29216	26.3	29216
Mean ± SD	45.4 ± 23	45.4 ± 23	45.4 ± 23
Gender			
Female	73301	66.1	73301

	Before propensity score matching	Before propensity score matching	Before propensity score m
Male	37598	33.9	37598
Hypertension	21935	19.8	15523
Hyperlipidemia	6468	5.8	4461
Chronic liver disease	4425	4.0	2340
Chronic kidney disease	1231	1.1	763
Diabetes	10830	9.8	6466
COPD	4812	4.3	2509
Cancer	4152	3.7	2025
Cardiovascular disease	7005	6.3	4398
Stroke	6550	5.9	3021
Autoimmune disease	618	0.6	415
Corticosteroids	32270	29.1	18997
Antihistamines	79368	71.6	57770

ASD: Absolute standardized differences; COPD: Chronic obstructive pulmonary disease.

Table 2. Cox proportional hazard model

	No. of atopic dermatitis	Observed Person-Years	Incidence Density (Per 1000 Person-Years)
Group			
Non-constipation	1573	705410	2.2
Constipation	3152	667788	4.7
Age			
40-64	1106	409739	2.7
<6	554	98762	5.6
6-11	194	56789	3.4
12-19	311	113750	2.7
20-39	1273	414951	3.1
65	1287	279207	4.6
Gender			
Female	3173	957928	3.3
Male	1552	415270	3.7
Hypertension	826	179183	4.6
Hyperlipidemia	192	50805	3.8
Chronic liver disease	143	30295	4.7
Chronic kidney disease	31	5825	5.3
Diabetes	364	73319	5.0
COPD	148	26095	5.7
Cancer	70	18836	3.7
Cardiovascular disease	200	50361	4.0
Stroke	172	31796	5.4
Autoimmune disease	22	5546	4.0
Corticosteroids	827	318060	2.6
Antihistamines	2873	1017398	2.8

COPD: Chronic obstructive pulmonary disease; ID: Incidence density (per 1000 person-years); +Adjusted for age, gender, hypertension, hyperlipidemia, chronic liver disease, chronic kidney disease, diabetes, COPD, cancer, cardiovascular disease, stroke, autoimmune disease, corticosteroids, and antihistamines.

Table 3. Subgroup analysis of Cox proportional hazard model

	Constipation	Constipation
	N	No. of atopic dermatitis
Age		
<6	25784	743
6-11	4208	349
12-19	2814	110
20-39	6682	214
40-64	25261	865
65	22266	871
p for interaction=	p for interaction=	p for interaction=
Gender		
Female	58813	2139
Male	28202	1013
p for interaction=	p for interaction=	p for interaction=
Hypertension	Hypertension	
No	72637	2596
Yes	14378	556
p for interaction=	p for interaction=	p for interaction=
Hyperlipidemia	Hyperlipidemia	
No	82925	3025
Yes	4090	127
p for interaction=	p for interaction=	p for interaction=
Chronic liver disease	Chronic liver disease	Chronic liver disease
No	84705	3059
Yes	2310	93
p for interaction=	p for interaction=	p for interaction=
Chronic kidney disease	Chronic kidney disease	Chronic kidney disease
No	86386	3129
Yes	629	23
p for interaction=	p for interaction=	p for interaction=
Diabetes		
No	80723	2901
Yes	6292	251
p for interaction=	p for interaction=	p for interaction=
Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease
No	84636	3061
Yes	2379	91
p for interaction=	p for interaction=	p for interaction=
Cancer		
No	84942	3103
Yes	2073	49
p for interaction=	p for interaction=	p for interaction=
Cardiovascular disease	Cardiovascular disease	Cardiovascular disease
No	82972	3016
Yes	4043	136
p for interaction=	p for interaction=	p for interaction=
Stroke		
No	83922	3020
Yes	3093	132

	Constipation	Constipation
p for interaction=	p for interaction=	p for interaction=
Autoimmune disease	Autoimmune disease	Autoimmune disease
No	86629	3137
Yes	386	15
p for interaction=	p for interaction=	p for interaction=
Corticosteroids	Corticosteroids	
No	68401	2632
Yes	18614	520
p for interaction=	p for interaction=	p for interaction=
Antihistamines	Antihistamines	
No	30192	1336
Yes	56823	1816
p for interaction=	p for interaction=	p for interaction=

Figure Captions

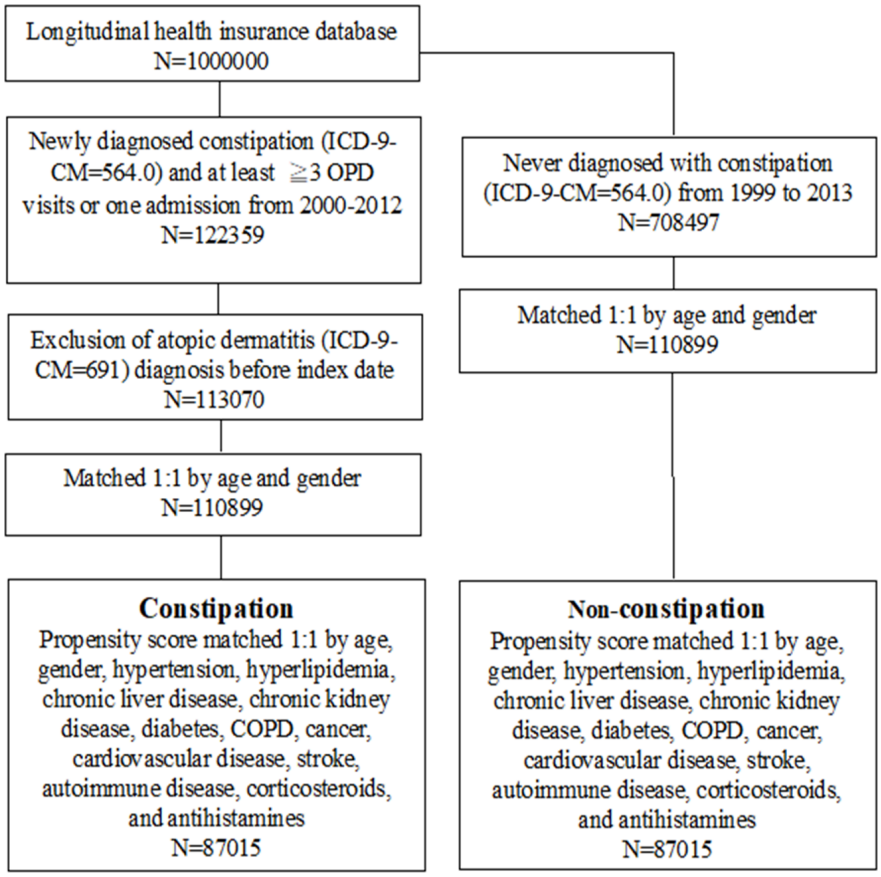


Figure 1. Flowchart of enrolment of constipation and non-constipation groups.

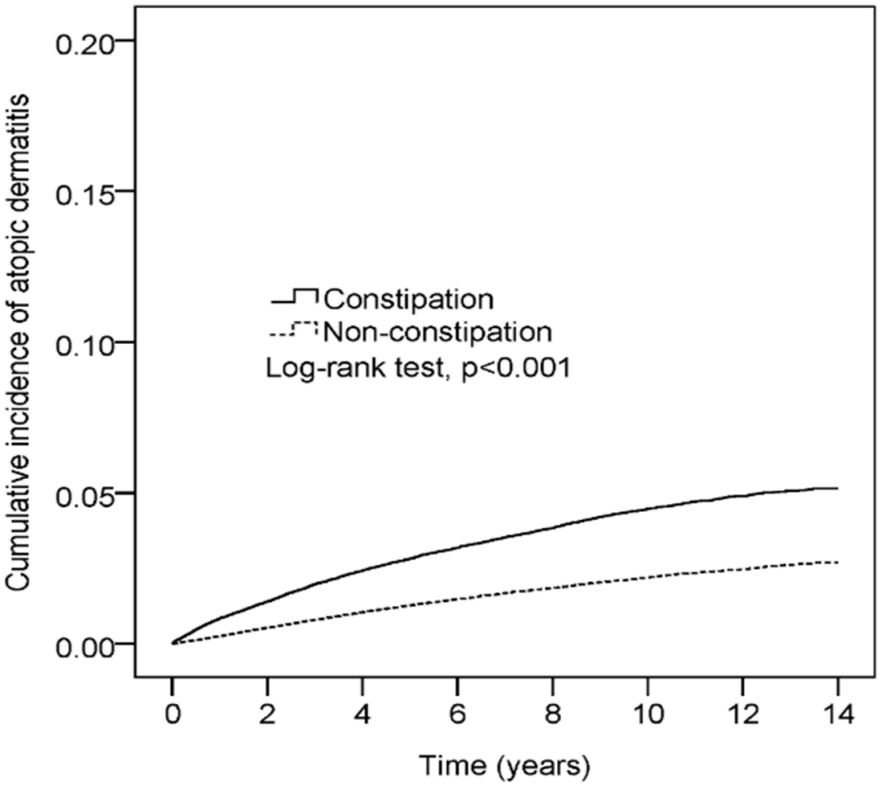
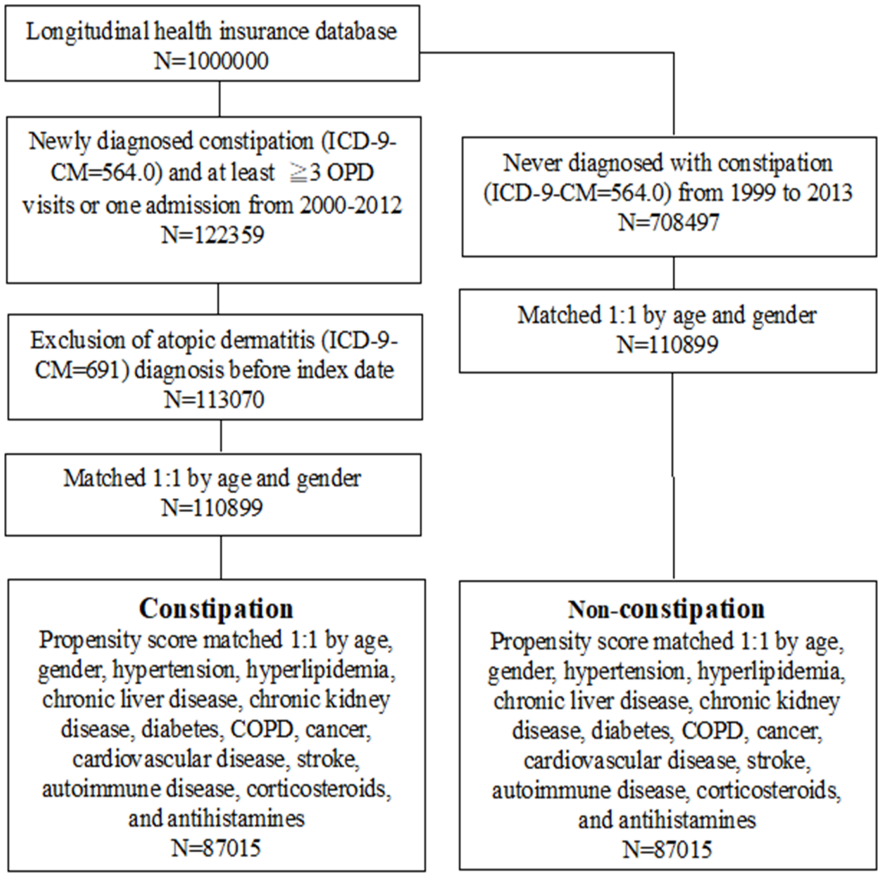
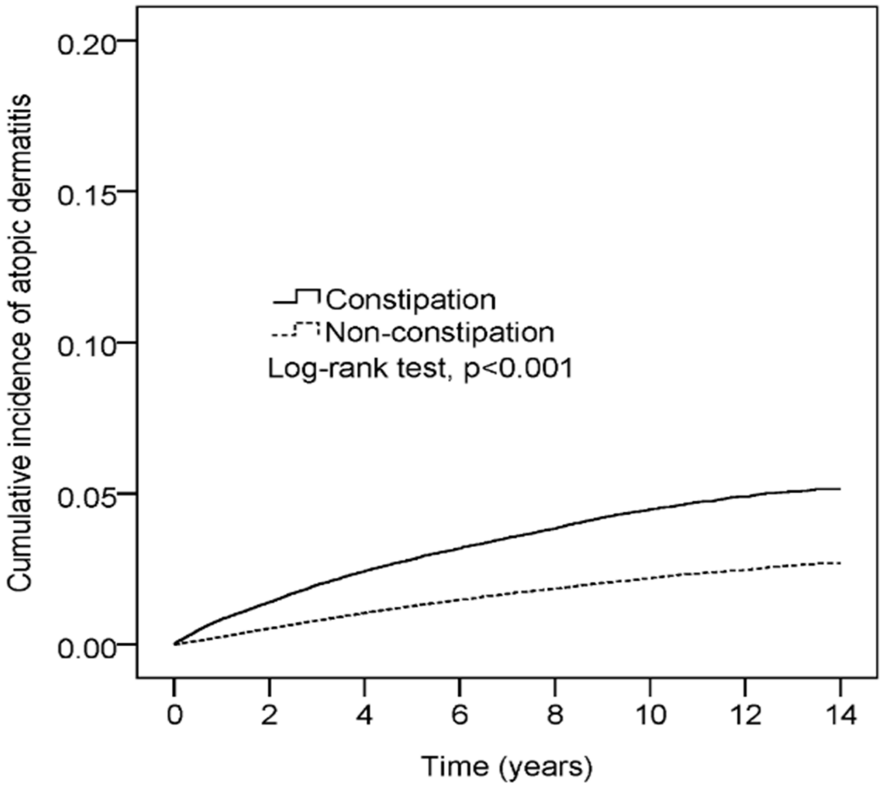


Figure 2. Kaplan–Meier curve of cumulative incidence proportion of atopic demattits in constipation group and non-constipation group





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