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

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Abstract

Atopic dermatitis (AD) is the chronic relapsing inflammatory skin disorder that affects both in childhood and adulthood. Mounting evidence indicates that gut dysbiosis contributes to AD via the gut-skin axis. Constipation could 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 longitudinal nationwide population-based cohort study. We collected 87015 people with constipation and 87015 patients without constipation between 1999 and 2013 from the Longitudinal Health Insurance Database, which is the subset of 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. 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, people with constipation 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). In subgroup analyses, people aged 12-19 years had a 2.34-fold higher risk of AD in the constipation cohort (aHR; 95% CI, 1.84-2.98). Moreover, people with constipation had a higher likelihood of AD, regardless of gender, and with or without comorbidities, as well as the usage of corticosteroids, and antihistamines. Constipation is connected with a significantly risk factor of AD. Clinicians should be careful of the possibility of AD in people with constipation. Further study is warranted to investigate the possible pathological mechanisms of underlying this relationship.

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Running Head: Constipation and atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is the chronic relapsing inflammatory skin disorder that affects both in childhood and adulthood. Mounting evidence indicates that gut dysbiosis contributes to AD via the gut-skin axis. Constipation could 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 longitudinal nationwide population-based cohort study. We collected 87015 people with constipation and 87015 patients without constipation between 1999 and 2013 from the Longitudinal Health Insurance Database, which is the subset of 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. 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, people with constipation 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). In subgroup analyses, people aged 12-19 years had a 2.34-fold higher risk of AD in the constipation cohort (aHR; 95% CI, 1.84-2.98). Moreover, people with constipation had a higher likelihood of AD, regardless of gender, and with or without comorbidities, as well as the usage of corticosteroids, and antihistamines. Constipation is connected with a significantly risk factor of AD. Clinicians should be careful of the possibility of AD in people with constipation. Further study is warranted to investigate the possible pathological mechanisms of underlying this relationship.

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

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 by data obtained from the large national longitudinal database. We hypothesized that constipation could impact the risk of AD and evaluated this hypothesis by analyzing the population-based retrospective cohort from Taiwanese National Health Insurance Research Database (NHIRD).

METHODS

Data source

This study analyzed the NHIRD, which includes the healthcare data of almost 99% of Taiwanese 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 the 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 this research was permitted 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 outpatient visits at least three times or one hospitalization were selected for inclusion in the final analysis. The index date of this cohort was started 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 had been followed up until the occurrence of atopic dermatitis, 31 December 2013, or withdrawal from the NHI system, whichever happened first.

Covariates and matching

The baseline characteristics were age, gender, hypertension (ICD-9-CM=401-405), chronic liver disease (ICD-9-CM=571), hyperlipidemia (ICD-9-CM=272.0-272.4), diabetes (ICD-9-CM=250), chronic kidney disease (ICD-9-CM=585), chronic obstructive pulmonary disease (COPD) (ICD-9-CM =491, 492, 496), cardiovascular disease (ICD-9-CM=410-414), stroke (ICD-9-CM=430-438), cancer (ICD-9-CM=140-208), 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 outpatient visits at least three times or once hospitalization. In addition, corticosteroids and antihistamines during the study period were contained 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, 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 considered a probability that was estimated through logistic regression. The binary variable was the constipation group and non-constipation group.

Statistical analysis

Comparisons between the constipation group and non-constipation group were demonstrated by 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 performed to evaluate the cumulative incidence of atopic dermatitis and log-rank test was utilized to test the significance. Cox proportional hazard model was applied to estimate the hazard ratio of atopic dermatitis between the constipation group and non-constipation group. Analyses were performed using statistical software SPSS version 18.0.

RESULTS

The research flowchart is shown in Fig. 1. We identified 87015 people with constipation and 87015 matched controls between 1999 and 2013 from the LHID. 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 revealed 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, people 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 revealed 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 applied 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 disclosed a lower risk of AD compared with non-users.

The Kaplan–Meier curves are shown in Fig. 2. The cumulative incidence of AD showed significantly higher in constipated people than in non-constipated patients, and the log-rank test for the comparison of cumulative incidence curves resulted in the 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. Best of our knowledge, this is the first and largest epidemiological research to utilize the nationwide 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 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 disclosed significantly higher in patients with hypertension, chronic liver disease, COPD, or diabetes,. 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 connected 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 indicated that alterations in the gut microbiota might 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 metabolic products, specifically SCFAs, functioned as important drivers of T-cell subset proliferation and activity.[28,29] Morevoer, it has been shown that production of intestinal microbial SCFAs might down-regulate proinflammatory reactions at the allergen-insult site.[13,30,31] In contrast, immune homeostasis might be destroyed by typical "Westernized" dietary intake, which can be characterized as being high proportion in fat and less proportion in fiber, altering the gut microflora, and resulting in reduced production of SCFAs.[10,13,32–34] Furthermore, SCFAs might affect bowel motility via stimulating the contraction of colonic muscles, thereby helping to relieve or prevent constipation.[35,36] Therefore, low fiber intake in constipated subjects might also have a key role in the development of atopy. Taken together the currently available evidence indicates 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 intestinal microbiome and how relevant this is to AD. Further comprehensive metagenomic and metabolomic analyses of the intestinal microbiota in constipated people 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 NHI administration monitors the accuracy of the claims data to prevent violations. Second, the NHIRD does not contain data on covariates, such as social adversity, personal lifestyle, family history, laboratory data and environmental factors. Although we adjusted for various comorbidities and matched propensity scores, these unmeasured confounding factors could have affected our results. Third, it remains unclear as to whether the findings of our study may 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 alert to the elevated risk of developing AD. Furthermore, clinicians should determine the condition of the bowels, including the intestinal microbiota, in patients with AD. The precise pathophysiological relationship between constipation and atopic dermatitis still requires further research.

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None.

CONFLICT OF INTEREST:

There is no conflict of interest in this research.

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Figure Captions

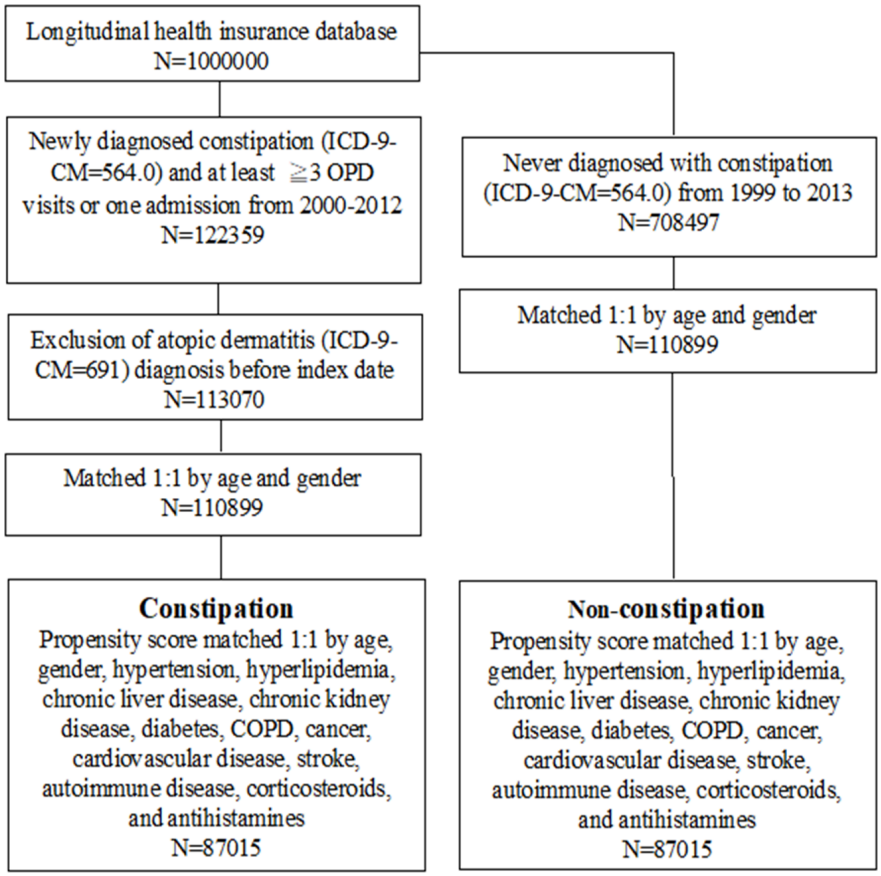

Figure 1. Flowchart of enrolment of constipation and non-constipation groups.

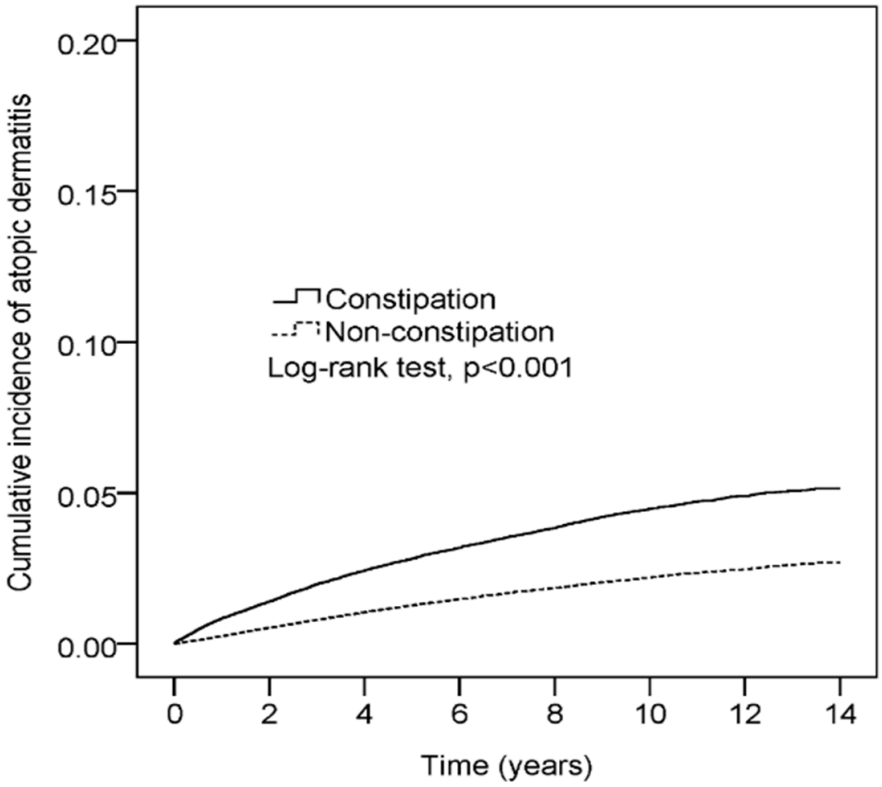

Figure 2. Kaplan–Meier curve of cumulative incidence proportion of atopic demattits in constipation group and non-constipation group

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