

Effectiveness of sublingual immunotherapy in pediatric cedar pollinosis: A real-world database study

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Abstract

Background: Pediatric allergic rhinitis (AR), including cedar pollinosis (CP), is increasing in Japan. We investigated the effects of sublingual immunotherapy (SLIT), which has limited studies of its effectiveness in real-world settings, on children with CP.

Methods: This retrospective cohort study used a claim database in 2018–2021. Children aged ≤ 15 years with CP records in 2019 were eligible and were followed up through 2021. We included 2,962 CP children undergoing SLIT and 547 who were not. The medication score was used to evaluate SLIT effectiveness in the cedar pollen dispersal season each year. Adverse events and the occurrence of allergic diseases were also evaluated.

Results: Medication score was higher in the SLIT group during the index period but lower in 2021 compared to the non-SLIT group (mean $\pm$ standard deviation: 5.17 ± 2.39 and 4.74 ± 2.38 in 2019, 3.13 ± 2.30 and 3.55 ± 2.48 in 2021, respectively). The adjusted mean difference between groups from 2019 to 2021 was -0.62 (95% confidence interval: -0.86 to -0.39 , $p < 0.0001$), and the medication score was reduced in the SLIT group (risk ratio: 1.2: 1.1–1.3). The occurrence of adverse events involving

abdominal disorders (adjusted odds ratio [aOR]: 0.64: 0.51–0.81), asthma exacerbation (aOR: 0.37: 0.24–0.57), and allergic diseases involving hay fever unrelated to CP (aOR: 0.60: 0.45–0.80) or asthma (aOR: 0.71: 0.58–0.86) was lower in the SLIT group.

Conclusion: In children with CP, SLIT is effective, well tolerated, and could decrease the occurrence of other allergic diseases.

Keywords: Adverse events, Cedar pollinosis, Children, Effectiveness, Sublingual Immunotherapy

1 Introduction

Allergic rhinitis (AR) incidence is increasing, affecting more than one in 5–10 people worldwide.¹ It forces patients to use allergy medicine that may have considerable side effects and impact their lives.² In Japan, AR prevalence is increasing annually. In 2019, it was 49.2%, and that of pollinosis was 42.5%, with Japanese cedar pollen-induced seasonal AR (hereafter referred to as Japanese cedar pollinosis [CP]) accounting for 38.8% of pollinosis cases—an increase from previous years.³ Furthermore, the prevalence of CP is rapidly increasing at younger ages, with prevalence rates of 3.8%, 30.1%, and 49.5% among 0–4, 5–9, and 10–19-year-old individuals, respectively.³

Sublingual immunotherapy (SLIT) is an effective desensitization therapy developed over the last 20 years and recommended at Grade A for AR in adults.⁴ For CP, CedarCure™ (Torii pharmaceutical co., Ltd, Tokyo, Japan) using Japanese cedar pollen extract (JCPE) was launched in Japan on June 29, 2018, with no age restriction for use, and SLIT is now available for children with cedar pollen allergies. Although SLIT with cedar pollen extract is highly effective,^{5,6} and studies including children have shown its efficacy,⁷ whether SLIT is effective in real-world settings and on other allergic diseases and its adverse events needs to be clarified. Moreover, there is limited evidence of childhood SLIT use. Therefore, this study evaluated the effectiveness of SLIT using a

medication score (MS)¹ in children with CP based on a large nationwide claim database and evaluated adverse effect occurrences and effects on other allergic diseases, including hay fever other than cedar pollinosis, asthma, and atopic dermatitis.

2 Methods

2.1 Study design

This retrospective cohort study used an insurance claim database provided by JMDC Inc. (Tokyo, Japan),⁸ a commercial healthcare data vendor. The JMDC database contains data from over 200 social health insurance plans covering approximately 13.2 million employees and their dependents, including children, with cumulative enrollment since 2005. The study period was from January 1, 2018, to July 31, 2021.

2.2 Data source

The JMDC database includes inpatient and outpatient data, patient-level demographic information, prescriptions, procedures, hospitalizations, and medical examination dates. Insurance claim data were collected from clinics, hospitals, and pharmacies and linked by a personal identifier, allowing enrollees to be tracked across different medical facilities. Diagnoses are represented by codes based on both the International

Classification of Diseases, 10th Edition (ICD-10), and standard domestic diagnosis codes for claims. All prescriptions were coded using the Anatomical Therapeutic Chemical Classification System and Japan-specific drug codes. Procedures were coded using Japan-specific procedure codes.

2.3 Patients

From all patient records, we included children with a CP disease code (Japanese diagnosis code, 8848069) between January 1, 2018, and December 31, 2019, aged ≤ 15 years. Patients were defined as having CP if they had been prescribed any of the medications listed in Supplement 1 for seasonal AR (based on the revised Japanese AR guidelines³) in the 2019 CP exposure season. Those whose observation period is only until April 30, 2021, were excluded.

2.4 Exposure

Patients with CP who started SLIT from June 1, 2019, to December 31, 2019, were classified under the exposure group, whereas those who did not undergo SLIT were classified under the control group. JCPE has two formulations—CidartrenTM (Torii Pharmaceutical co., Ltd) and CidarCureTM. However, CidartrenTM was withdrawn soon

after CedarCureTM was launched, and the study period was after the first season of cedar pollen allergy following the launching of CedarCureTM. Subcutaneous immunotherapy has been rarely used for cases of CP after the launch of CedarCureTM. Hence, only patients treated with CedarCureTM were included in the exposure group for JCPE. CedarCureTM is available in 2,000-Japanese-allergy-unit (JAU) tablets administered during the 1st week and 5,000 JAU tablets consumed daily from the 2nd week to maintain SLIT. In this study, those prescribed 5,000-JAU CedarCureTM between June 1, 2019, and December 31, 2019, were included in the SLIT group.

2.5 Outcomes

The primary outcome was MS of the SLIT and non-SLIT groups during the cedar pollen dispersal season^{9,10} (January 1 to May 31 of 2019, 2020, and 2021, respectively; January 1 to May 31 of 2019 was set as the index period). MS was calculated by categorizing and scoring the drugs into the same groups as those used in the patient-selection criteria.^{3,11,12} MS was recorded according to the sum of MS scores corresponding to the use of a drug in that medication efficacy group (see Supplementary Table 1) based on the World Allergy Organization taskforce recommendation¹¹, and some of the drug groups were assigned MS scores based on the Japanese Guidelines for

Allergic Rhinitis 2020³. MS was assigned with or without using the drug in the medication efficacy group. Only MS was studied because there were no data on symptoms. Generally, allergy severity was analyzed by combining MS with a symptom score for a “combined symptom and medication score.” MS and symptom scores were weighted equally in the combined symptom and MS^{11,12}. Symptoms cannot be assessed in claim database studies, and more severe symptoms increase medications used and medications with higher MS, including steroids; the outcome was evaluated as a continuous value for MS alone.

Secondary outcomes were the occurrences of the insurance-named diseases related to each adverse effect listed on the CedarCureTM package insert. Disease names were checked by the Japanese disease codes, and those that differed (e.g., ticks as the cause, pregnancy, etc.) were excluded and used from the final extract (Supplement 2) from June 1, 2019, to July 31, 2021, in each group (Supplement 3). Asthma was divided into two categories: asthma related disease excluding exacerbation, and asthma exacerbation disease.

The insurance-named allergic disease occurrence (pollinosis, asthma, including asthma and asthma exacerbation; and atopic dermatitis (Supplement 2) from June 1, 2019, to July 31, 2021 in each group was also studied. To assess allergic disease occurrence, a

washout period was established 180 days before the comparison period. Cases that developed a related insurance-named disease during the 180 days before the comparison period were excluded (Supplement 3).

Patients with asthma were defined as those using any inhaled corticosteroids or inhaled corticosteroids+long-acting β -agonists at least one time in the outcome period to ensure validity.

2.6 Ethics

Anonymized claim data were used in this study; hence, personalized information or informed consent was not required. This study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (approval number: R3336) on February 3, 2022, and was conducted in accordance with the Declaration of Helsinki.

2.7 Statistical methods

Baseline characteristics from January 2019 to May 2019 were reported as means (standard deviations) or medians (interquartile ranges) for continuous variables and numbers with percentages for categorical data. For the primary analysis, we conducted a

linear regression analysis and estimated the adjusted mean difference (aMD) in MS between the SLIT and non-SLIT groups. Furthermore, the difference in MS from the index period to the last observation period was reviewed using percentage reduction (%), risk difference, and risk ratio by the degree of MS reduction. For secondary analysis, logistic regression analyses were conducted; the adjusted odds ratio (aOR) for adverse events in the SLIT group, similar events in the non-SLIT group, and allergic diseases were estimated. Each outcome was adjusted for age, sex, severity based on MS, history of hay fever other than CP, asthma, atopic dermatitis, and history of anaphylaxis. These adjusted variables were decided by a directed acyclic graph with our knowledge of childhood AR, a literature review, and data source availability. Statistical significance was set at $p < 0.05$. All analyses were performed using SAS statistical environment version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

Overall, 3,509 patients with CP aged ≤ 15 years who were prescribed one or more pollen allergy medications in the index period and were available for follow-up were included in this study. The selection process for patients is described in the study flow diagram (Figure 1). The patients' background data (sex, age, MS, and percentage of patients with

pollinosis diseases other than CP and asthma) were comparable between the non-SLIT and SLIT groups. However, the SLIT group had a slightly higher MS and age and a slightly lower atopic dermatitis prevalence and history of anaphylactic diseases than the non-SLIT group (Table 1).

3.1 Effectiveness of SLIT

The primary endpoints were MS in each year from 2019 to 2021 and aMD in each group. From the index period in 2019 to the evaluation period in 2021, the decrease in MS score in the SLIT group (5.17 to 3.13) versus non-SLIT (4.74 to 3.5) and aMD was -0.62 (95% CI: -0.86- -0.19, $p < 0.0001$).

In the index period, MS was higher in the SLIT than in the non-SLIT group (5.17 ± 2.39 vs 4.74 ± 2.38 , respectively; aMD 0.22 [95% CI: 0.05–0.39]; $p = 0.01$). In 2020, the first season following the start of SLIT, both groups showed a decrease in MS, with a slightly higher MS in the SLIT group (aMD: 0.12; 95% CI: -0.08 to 0.33; $p = 0.23$). In 2021, the second season following SLIT initiation, MS in the non-SLIT group slightly increased from 3.35 ± 2.50 in 2020 to 3.55 ± 2.48 in 2021. However, in the SLIT group, MS decreased from 3.50 ± 2.25 in 2020 to 3.13 ± 2.30 in 2021 (aMD: -0.40; 95% CI: -0.61 to -0.19; $p < 0.001$).

Therefore, MS was significantly lower in the SLIT than in the non-SLIT group (Table 2). MS in 2021 decreased compared with the index period by 59.4% in the non-SLIT group and 70.9% in the SLIT group, with a risk difference of 11.5 (95% CI: 7.0 to 15.9)% and a risk ratio of 1.2 (95% CI: 1.1 to 1.3) (Figure 2).

3.2 Adverse events

During CP from June 1, 2019 to July 31, 2021, the occurrence of insurance-named diseases listed on the CedarCure™ attachment as side effects, including abdominal disorder (aOR: 0.64; 95% CI: 0.51–0.81; p=0.0002), asthma (aOR: 0.76; 95% CI: 0.63–0.93; p=0.007), and asthma exacerbations (aOR: 0.37; 95% CI: 0.24–0.57; p<0.0001), were significantly lower in the SLIT than in the non-SLIT group. The two groups did not differ in skin rash, laryngeal edema, perioral symptoms, and anaphylaxis (Table 3).

3.3 Newly added allergy-related insurance-named disease during CP

The occurrence of insurance-named allergic diseases inducing hay fever other than CP was significantly lower in the SLIT group (aOR: 0.60; 95% CI: 0.45–0.80; p=0.0005) (breakdown shown in Supplement 4), as was the occurrence of the insurance-named allergic diseases asthma (aOR: 0.71; 95% CI: 0.58–0.86; p=0.0005). There was no

significant difference in the occurrence with atopic dermatitis between both groups (Table 4).

4 Discussion

In children with CP, according to the data recorded in the database, SLIT is effective. The effect was observed despite occurring during the coronavirus pandemic. In the SLIT group, rather high MS and severe pollinosis were estimated in the index period but decreased after SLIT during the second season. SLIT was well tolerated, with few adverse events. As for the newly added allergy-related insurance-named diseases, there were fewer cases of hay fever other than CP and asthma in the SLIT group than in the non-SLIT group.

In this study, the aMD of MS from 2019 to 2021 was -0.62. This effect may be less significant than that reported in previous randomized control trials that included young adults^{5, 13} and children.¹⁴ There are four possible reasons for this. First, SLIT itself may not be highly effective for children with CP in various real-world clinical settings. Referring to the effects of SLIT in real-world settings on birch pollen allergies, 35% of adult and child patients reduced their medications compared with the control group¹⁵, while the risk difference in MS reduction in this study was 11.5%. Moreover, a study of

grass pollen reported no difference in effectiveness in children in a primary care setting.¹⁶ Second, both groups had fewer opportunities for cedar pollen exposure. Many people stayed at home due to the coronavirus pandemic restrictions in 2020. The average number of cedar pollen dispersals nationwide was very low in 2020 and low in 2021 compared with 2019.¹⁰ Third, patients refrained from visiting hospitals during the pandemic. Since patients, even those with cancer did not visit a doctor.¹⁷ It was estimated that visits for prescriptions of pollen medication decreased, regardless of severity. Finally, there is the possibility of medication noncompliance in the real world. Adolescents have a greater tendency for SLIT medication noncompliance.¹⁸ Sublingual immunotherapy is more effective in those who adhere to its dosing regimen^{7, 19} and have better compliance.^{20, 21}

Listed on the CedarCure™ attachment as side effects were asthma-like symptoms, asthma exacerbations, and abdominal symptoms, which were significantly reduced in the SLIT group compared with the non-SLIT group. There were no real world signals of anaphylactic risk or other adverse events, despite being mentioned in the labeling. This study suggests a significant decrease in asthma occurrence in the SLIT group, unlike previous systematic reviews.²² Conversely, several real-world studies have shown favorable effects of SLIT on asthma similar to this study.^{15, 23, 24} This study was based on

insurance claim data, the actual symptoms were unknown, and the diagnosis may have included an asthma-like chronic cough caused by stimulation of the post-nasal drip due to AR.²⁵ Patients with hay fever often develop asthma with rhinitis.²⁶

It is unclear what causes the decrease in abdominal symptoms with SLIT; SLIT did not increase abdominal pain or diarrhea.²⁷ There are no previous reports of SLIT reducing abdominal symptoms. Thus, the decrease in abdominal symptoms is not likely a direct result of the patient being a child or JCPE adverse effect. Possible causes may include fewer hospital visits by children whose AR symptoms are relieved by SLIT, fewer opportunities for the common cold, fewer oral medications, and fewer gastrointestinal symptoms as side effects.

In this study, SLIT suggested the possibility of reducing new occurrences of hay fever and asthma in patients with CP. Because the results include both new and relapsed cases, there is a limitation due to the study's methodology, which indicates that SLIT may have prevented the atopic march. In contrast, there was no clear reduction in atopic dermatitis occurrence. This may be attributed to patients with CP being mostly in their teens following atopic dermatitis onset.²⁸

The limitations of the study are mainly related to the design (retrospective) and data source. We could not determine the severity of symptoms; thus, owing to a strong

correlation between symptoms and MS,²⁹ we believe that the results regarding SLIT effectiveness in children are reliable. Second, in insurance claim databases, disease names that differ from actual conditions are often provided to patients for billing purposes.³⁰ To increase validity, the study was limited to patients with CP taking medication during the cedar pollen dispersal season. CedarCure™ is prescribed only for patients with test-proven CP in Japan.

In pediatric patients with Japanese cedar pollen-induced seasonal AR, sublingual immunotherapy effectively decreased medications, was well-tolerated with few adverse events, decreased new asthma-like syndrome, and other pollinosis, and may have a positive effect on new allergic diseases like asthma and other pollinosis.

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296 and editing. Koji Kawakami: project administration, resources, validation, writing,
297 review, and editing.

298

299 **Key message**

300 CP is rapidly increasing among children living in Japan, and children's social life was
301 affected by CP. As this real-world study showed, SLIT with JCPE, which was issued in
302 2018, is effective for children with CP, and adverse events do not increase, possibly
303 leading to a more positive application of SLIT to children and, consequently, improving
304 their healthy social life.

References

1. Meltzer EO, Blaiss MS, Naclerio RM, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy Asthma Proc* 2012;33:S113-S141.
2. Nathan RA. The burden of allergic rhinitis. *Allergy Asthma Proc* 2007;28:3-9.
3. Okubo K, Fujieda S, Gotoh M, et al. Executive summary: Japanese guidelines for allergic rhinitis 2020. *Allergol Int* 2023;72:41-53.
4. Roberts G, Pfaar O, Akdis CA, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy* 2018;73:765-798.
5. Yang Y, Zhou W, Chen A. Efficacy of sublingual immunotherapy for cedar pollinosis: a systematic review and meta-analysis. *Ann Allergy Asthma Immunol* 2016;117:348-353.
6. Yamanaka K, Shah SA, Sakaida H, et al. Immunological parameters in prophylactic sublingual immunotherapy in asymptomatic subjects sensitized to Japanese cedar pollen. *Allergol Int* 2015;64:54-59.
7. Yonekura S, Gotoh M, Kaneko S, Maekawa Y, Okubo K, Okamoto Y. Disease-modifying effect of Japanese cedar pollen sublingual immunotherapy tablets. *J Allergy Clin Immunol Pract* 2021;9:4103-4116.e14.

- 323 8. Nagai K, Tanaka T, Kodaira N, Kimura S, Takahashi Y, Nakayama T. Data resource
324 profile: JMDC claims database sourced from health insurance societies. *J Gen Fam Med*
325 2021;22:118-127.
- 326 9. Sasaki K, Ohshiro T, Sakio R, et al. Efficacy of seasonal allergic rhinitis using an 810
327 nm diode laser system. *Laser Ther* 2019;28:11-18.
- 328 10. Ministry of the Environment. Pollen Information Website.
329 <https://www.env.go.jp/chemi/anzen/kafun/>. Accessed February 23, 2023.
- 330 11. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for
331 standardization of clinical trials with allergen specific immunotherapy for respiratory
332 allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy*
333 2007;62:317-324.
- 334 12. Pfaar O, Demoly P, Gerth van Wijk R, et al. Recommendations for the
335 standardization of clinical outcomes used in allergen immunotherapy trials for allergic
336 rhinoconjunctivitis: an EAACI Position Paper. *Allergy* 2014;69:854-867.
- 337 13. Feng B, Wu J, Chen B, et al. Efficacy and safety of sublingual immunotherapy for
338 allergic rhinitis in pediatric patients: a meta-analysis of randomized controlled trials.
339 *Am J Rhinol Allergy* 2017;31:27-35.
- 340 14. Chen L, Lei L, Cai Y, Li T. Specific sublingual immunotherapy in children with

341 perennial rhinitis: a systemic review and meta-analysis. *Int Forum Allergy Rhinol*
342 2020;10:1226-1235.

343 15. Wahn U, Bachert C, Heinrich J, Richter H, Zielen S. Real-world benefits of allergen
344 immunotherapy for birch pollen-associated allergic rhinitis and asthma. *Allergy*
345 2019;74:594-604

346 16. Röder E, Berge MY, Hop WC, et al. Sublingual immunotherapy with grass pollen is
347 not effective in symptomatic youngsters in primary care. *J Allergy Clin Immunol*
348 2007;119:892-898.

349 17. Kuzuu K, Misawa N, Ashikari K, et al. Gastrointestinal cancer stage at diagnosis
350 before and during the COVID-19 pandemic in Japan. *JAMA Netw Open*
351 2021;4:e2126334.

352 18. Imanaka T, Sato I, Kawasaki Y, Kanazawa Y, Kawakami K. An analysis of factors
353 associated with compliance and dropout of sublingual immunotherapy on Japanese
354 cedar pollinosis patients. *Int Forum Allergy Rhinol* 2019;9:615-623.

355 19. Gotoh M, Yonekura S, Imai T, et al. Long-term efficacy and dose-finding trial of
356 Japanese cedar pollen sublingual immunotherapy tablet. *J Allergy Clin Immunol Pract*
357 2019;7:1287-1297.e8.

358 20. Sieber J, Köberlein J, Mösges R. Sublingual immunotherapy in daily medical

359 practice: effectiveness of different treatment schedules - IPD meta-analysis. *Curr Med*
360 *Res Opin* 2010;26:925-932.

361 21. Liu W, Zeng Q, He C, et al. Compliance, efficacy, and safety of subcutaneous and
362 sublingual immunotherapy in children with allergic rhinitis. *Pediatr Allergy Immunol*
363 2021;32:86-91.

364 22. Fortescue R, Kew KM, Leung MST. Sublingual immunotherapy for asthma.
365 *Cochrane Database Syst Rev* 2020;9:CD011293.

366 23. Fritzsche B, Contolo M, Porsbjerg C, et al. Long-term real-world effectiveness of
367 allergy immunotherapy in patients with allergic rhinitis and asthma: Results from the
368 REACT study, a retrospective cohort study. *Lancet Reg Health Eur* 2022;13:100275

369 24. Zielen S, Deviller P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy
370 provides long-term relief in allergic rhinitis and reduces the risk of asthma: A
371 retrospective, real-world database analysis. *Allergy* 2018;73:165-177.

372 25. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough.
373 *Lancet* 2008;371:1364-1374.

374 26. Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma
375 (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN
376 and Allergen). *Allergy* 2008;63:8-160.

- 377 27. Agostinis F, Foglia C, Landi M, et al. The safety of sublingual immunotherapy with
378 one or multiple pollen allergens in children. *Allergy* 2008;63:1637-1639.
- 379 28. Khan SJ, Dharmage SC, Matheson MC, Gurrin LC. Is the atopic march related to
380 confounding by genetics and early-life environment? A systematic review of sibship and
381 twin data. *Allergy* 2018;73:17-28.
- 382 29. Calderon MA, Bernstein DI, Blaiss M, Andersen JS, Nolte H. A comparative
383 analysis of symptom and medication scoring methods used in clinical trials of
384 sublingual immunotherapy for seasonal allergic rhinitis. *Clin Exp Allergy*
385 2014;44:1228-1239.
- 386 30. Rudmik L, Xu Y, Kukec E, Liu M, Dean S, Quan H. A validated case definition for
387 chronic rhinosinusitis in administrative data: a Canadian perspective. *Int Forum Allergy*
388 *Rhinol* 2016;6:1167-1172.

Figure legends

Figure 1. Flowchart of study participant selection process.

Figure 2. Medication score reduction due to SLIT from the index (2019) to the evaluation periods (2020, 2021)

The graph shows the difference in medication score (MS) between the sublingual immunotherapy (SLIT) and non-SLIT groups from the index period to 2020 and 2021. In each evaluation period, the left graph shows all patients who reduced MS from the index period to the evaluation season regardless of the number of points of decrease. In each evaluation period, the right graph shows all patients with an MS reduction greater than 3 points. MS for oral steroids is 3 points. For every comparison, the risk difference (RD) and risk ratio (RR) with 95% confidence interval are also shown.

Table 1. Backgrounds of pediatric patients with cedar pollinosis in the non-SLIT and SLIT groups

	Non-SLIT group		SLIT group	
	n=547		n=2,962	
Sex/male, n (%)	326	(59.6)	1,866	(63.0)
Age (years), median (IQR)	10.1	(7.8, 12.3)	10.7	(8.8, 12.5)
Medication Score, mean (SD)	4.74	(2.38)	5.18	(2.39)
Hay fever other than cedar pollinosis, n (%)	547	(100)	2,962	(100)
Asthma, n (%)	70	(12.8)	370	(12.5)
Atopic dermatitis, n (%)	177	(32.4)	804	(27.1)
History of anaphylaxis, n (%)	18	(3.3)	76	(2.6)

During the baseline period of January 1, 2019 to May 31, 2019.

IQR, interquartile range; SLIT, sublingual immunotherapy; and SD, standard deviation.

1 Table 2. Trends and comparisons of medication scores by year

Year	Cedar pollen number ¶ (n/cm ²)	Non-SLIT group, n=547 (SD)	SLIT group, n=2,962 (SD)	Adjusted MD	95%CI	p- value
2019 [†]	4,512	4.74 (2.38)	5.17 (2.39)	0.22	(0.05- 0.39)	0.01
2020 [‡]	1,289	3.35 (2.50)	3.50 (2.25)	0.12	(-0.08- 0.33)	0.23
2021 [§]	2,780	3.55 (2.48)	3.13 (2.30)	-0.40	(-0.61- -0.19)	0.0001
2019 to 2020		-1.39 (2.80)	-1.68 (2.64)	-0.10	(-0.33- 0.13)	0.39
2019 to 2021		-1.19 (2.7)	-2.05 (2.77)	-0.62	(-0.86 - -0.39)	<0.0001

2 [†] 2019 period: January 1, 2019 to May 31, 2019.

3 [‡] 2020 period: January 1, 2020 to May 31, 2020.

4 [§] 2021 period: January 1, 2021, to May 31, 2021.

5 ¶ The average number of cedar pollen dispersals nationwide

6 MD adjusted by age, sex, severity of pollinosis, asthma, atopic dermatitis, and anaphylaxis.

7 CI, confidence interval; MD, mean difference; and SLIT, sublingual immunotherapy.

8

1 Table 3. Occurrence of events listed as adverse effects during cedar pollinosis in the JCPE-SLIT
2 attachment

Insurance disease names	Non-SLIT group, n (n=547)	n (%)	SLIT group, n (n=2,962)	n (%)	Adjusted OR	95%CI	p-value
Abdominal disorder (pain, diarrhea)	115	(21.0)	428	(14.4)	0.64	(0.51–0.81)	0.0002
Asthma	230	(42.0)	1000	(33.8)	0.76	(0.63–0.93)	0.007
Asthma exacerbation	36	(6.6)	69	(2.3)	0.37	(0.24–0.57)	<0.0001
Skin rash (hives, etc.)	100	(18.3)	422	(14.2)	0.83	(0.65–1.06)	0.14
Laryngeal edema	3	(0.5)	18	(0.6)	1.09	(0.32–3.72)	0.90
Perioral symptom	2	(0.4)	1	(0.03)	0.09	(0.01–1.00)	0.05
Anaphylaxis	20	(3.7)	68	(2.3)	0.57	(0.28–1.18)	0.13

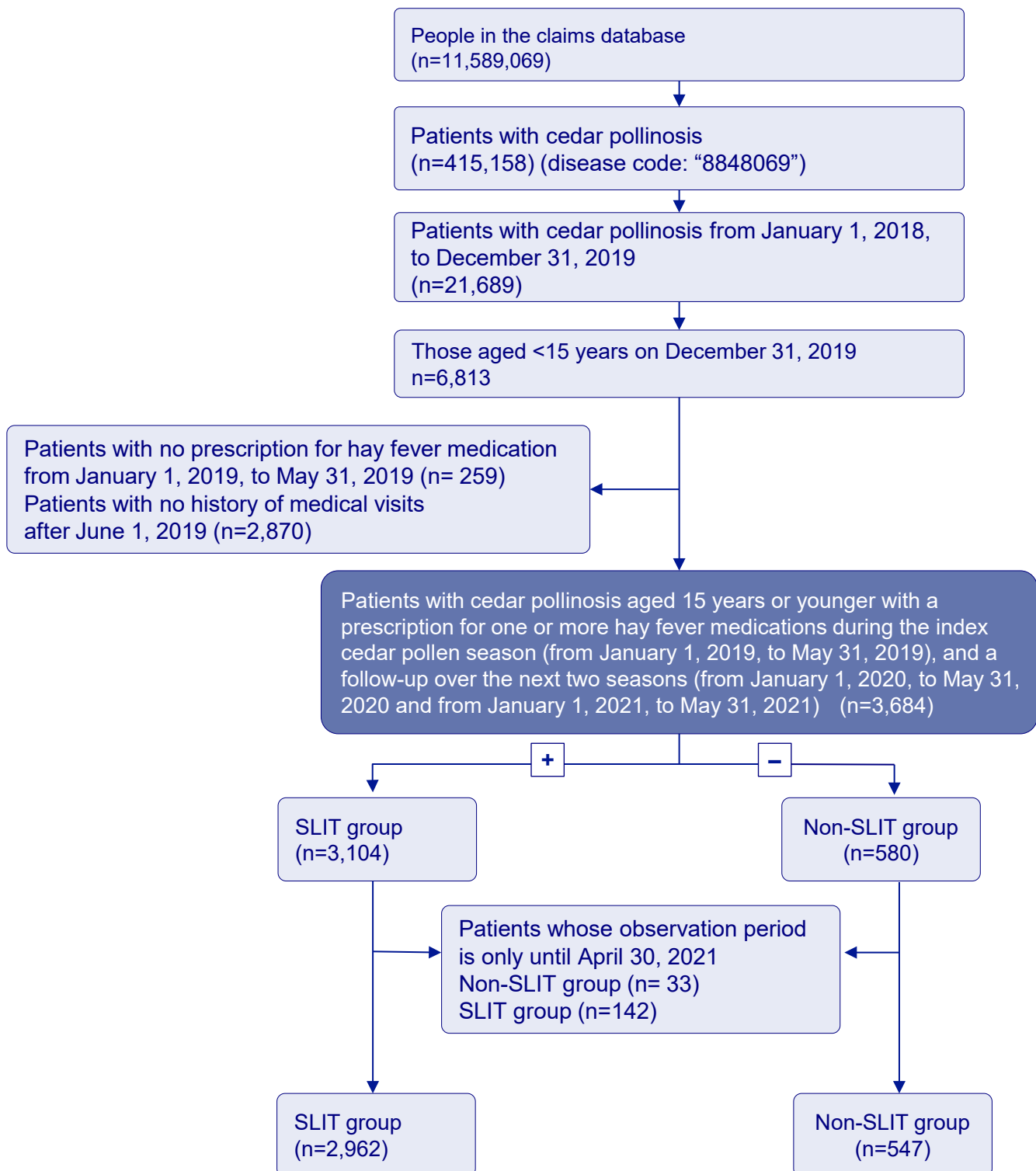
3 Adjusted for age, sex, severity, asthma, atopic dermatitis, and anaphylaxis. The observation
4 period was from June 1, 2019 to July 31, 2021.
5 CI, confidence interval; JCPE, Japanese cedar pollen extract; OR, odds ratio; and SLIT,
6 sublingual immunotherapy.

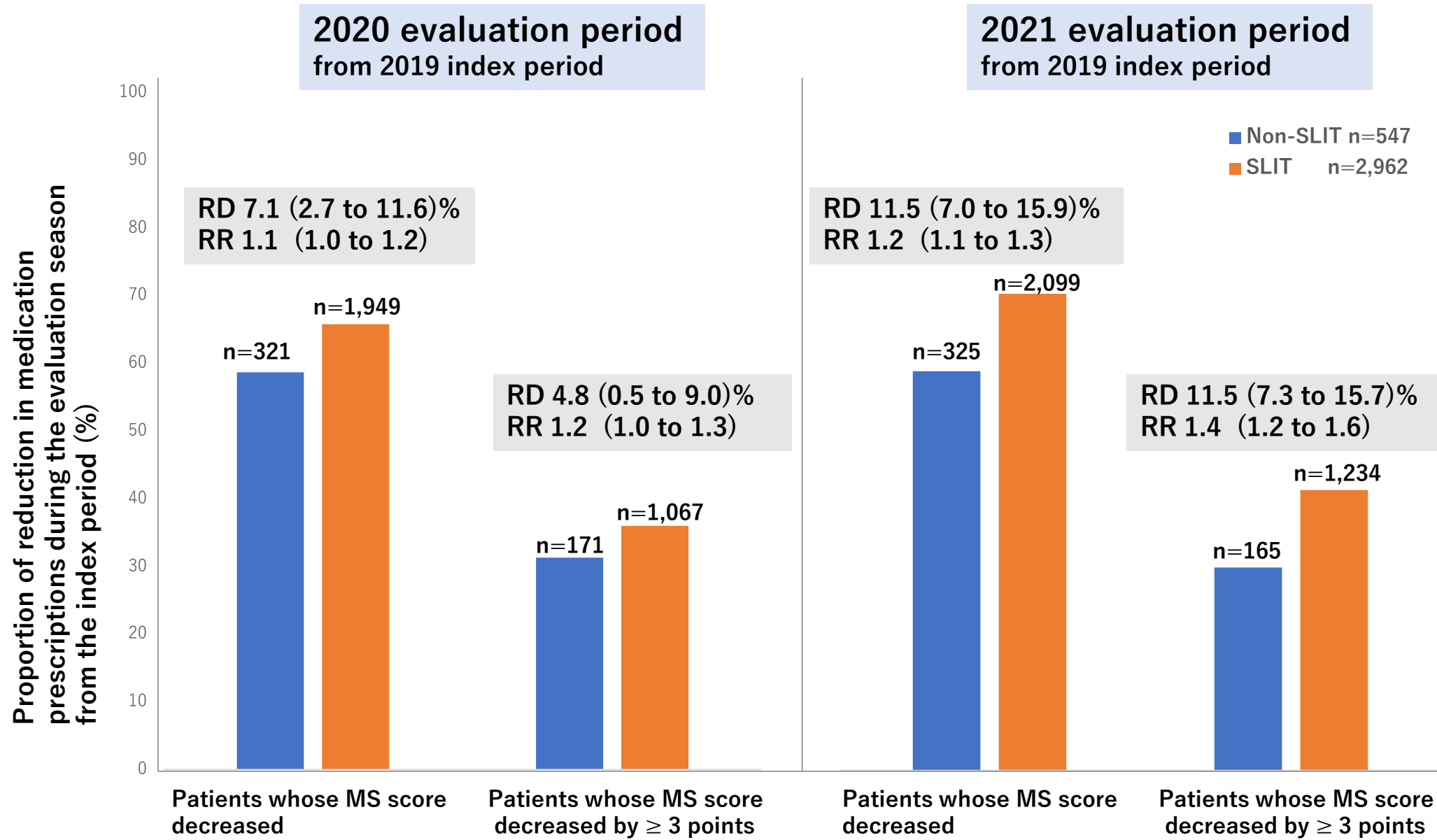
1 Table 4. Newly added allergy-related insurance-named diseases during the course of cedar
2 pollinosis

Insurance disease names	Non-SLIT group, n (%) (n=547)		SLIT group, n (%) (n=2,962)		Adjusted OR	95%CI	p-value
Hay fever, other than cedar pollinosis	488	(89.2)	2,447	(82.6)	0.60	(0.45– 0.80)	0.0005
Asthma	240	(43.9)	1,021	(34.5)	0.71	(0.58– 0.86)	0.0005
Atopic dermatitis	133	(24.3)	736	(24.9)	1.24	(0.97– 1.59)	0.09

3 Adjusted for age, sex, severity, asthma, atopic dermatitis, and anaphylaxis. The observation
4 period was from June 1, 2019 to July 31, 2021.

5 CI, confidence interval; OR, odds ratio; and SLIT, sublingual immunotherapy.





Supplement 1. Medication group and the code extracted from the database

Medication	WHO-ATC code				
First-generation antihistamines	R06AA02	R06AA04	R06AA52	R06AB04	R06AD01
	R06AD02	R06AE	R06AX	R06AX02	R06AX24
Second-generation antihistamines	R06AA07	R01AC	R01AC08	R06AD07	R06AE06
	R06AE07	R06AE09	R06AX07	R06AX13	R06AX17
	R06AX22	R06AX26	R06AX27	R06AX28	R06AX29
Chemical mediator release inhibitors	R03BC01	R03DX	A07EB01		
Th2 cytokine inhibitors	R03DX				
Antileukotrienes	R03DC01	R03DC02	R03DC03		
Prostaglandin D2-thromboxane A2 receptor antagonist	R01AC	R03DX	R03DX06		
Corticosteroids(oral)	H02AA02	H02AB01	H02AB02	H02AB04	H02AB05
	H02AB06	H02AB08	H02AB09	H02AB10	H02BX
corticosteroids(intranasal)	R01AD01	R01AD03	R01AD04	R01AD08	R01AD09
	R01AD12	R01AD52			
Corticosteroids(conjunctival)	S03BA01	S01BA02	S03BA03	S01BA04	S01BA05
	S01BA06	S01BA07	S01CA03	S03CA06	S01CA08
Second-generation antihistamine/vasoconstrictor combination drugs	R01BA52				
Vasoconstrictors (intranasal)	R01AA05	R01AA06	R01AA08	R01AA09	
Chemical mediator release inhibitors (intranasal)	R01AC	R01AC01			
Antihistamine (intranasal)	R01AC02	S01GX08			
Chemical mediator release inhibitors (conjunctival)	S01GX	S01GX01			
Antihistamine (conjunctival)	S01GX02	S01GX08	S01GX09	S01GX10	
Anti-IgE mAb	R03DX05				
Herbal medicines, others	S01B	S01GA51	S01GX	S01XA	S01XA01
	V03AX				

Supplement 2. Insurance disease name and the code extracted from the database

Group of insurance disease name	Standard domestic diagnosis codes for claims	Standard domestic diagnosis	ICD10 code
Cedar pollinosis	8848069	Cedar pollinosis	J301
Hay fever other than cedar pollinosis	8847603	Seasonal allergic conjunctivitis	H101
	3721002	Allergic conjunctivitis	H101
	8847665	Perennial allergic conjunctivitis	H101
	8833084	Vasomotor rhinitis	J300
	8850428	Quercus serrata allergic rhinitis	J301
	8850457	Japanese white birch pollen allergy	J301
	8848099	Ragweed pollinosis	J301
	8848097	Japanese cypress pollinosis	J301
	8850596	Mugwort allergy	J301
	8848025	Poaceous pollinosis	J301
	8850567	Pollen allergy caused by East Asian alder	J301
	8850388	Timothy grass pollen allergy	J301
	8850566	Allergy caused by sweet vernal grass	J301
	8848033	Orchard grass pollinosis	J301
	4770002	Pollinosis	J301
	8845847	Allergic rhinoconjunctivitis	J301,H101
	4779016	Seasonal allergic rhinitis	J302
	8837835	Perennial allergic rhinitis	J303
	4779015	Allergic sinusitis	J304
	8830398	Allergic nasopharyngitis	J304
	4779004	Allergic rhinitis	J304
Asthma	4939003	Allergic asthma	J450
*Background and allergic disease use	4930001	Atopic asthma	J450
All asthma disease codes.	4930005	Childhood asthma	J450
*Adverse effects use,	4930002	Extrinsic asthma	J450

Asthma: Asthma disease code except	8834797	Pediatric asthmatic bronchitis	J450
asthma exacerbation	8847408	Infantile asthma	J450
asthma exacerbation: only use asthma	4939016	Psychogenic asthma	J451
exacerbation disease code	4939039	Nonatopic asthma	J451
	8831609	Infectious asthma	J451
	8833884	Mixed asthma	J458
	8841641	Exercise-induced asthma	J459
	4939022	Asthmatic bronchitis	J459
	8844994	Steroid-dependent asthma	J459
	4939008	Bronchial asthma	J459
	8846176	Cough variant asthma	J459
	4939038	Nocturnal asthma	J459
	4939037	Intractable asthma	J459
asthma exacerbation	4939010	Status asthmaticus	J46-
	4939012	Asthmatic attack	J46-
Atopic dermatitis	8840031	Prurigo of Besnier	L200
	8830277	Atopic neurodermatitis	L208
	6918009	Childhood eczema on limbs	L208
	8832415	Acute infantile eczema	L208
	8840380	Chronic infantile eczema	L208
	8838291	Endogenic eczema	L208
	8834787	Pediatric eczema	L208
	6918023	Infantile dermatitis	L208
	8832800	Flexural eczema	L208
	6918011	Pediatric atopic dermatitis	L208
	6918013	Dry form infantile eczema	L208
	8839542	Diffuse neurodermatitis	L208
	6918002	Atopic dermatitis	L209
	8845116	Atopic skin	L988
Anaphylaxis	9950009	Drug-induced shock	T886
	8830280	Anaphylactic shock	T782
	8830279	Anaphylaxis	T782
Abdominal disorder	8838431	Infantile winter diarrhea	A080
	93012	Intractable infantile diarrhea	A099

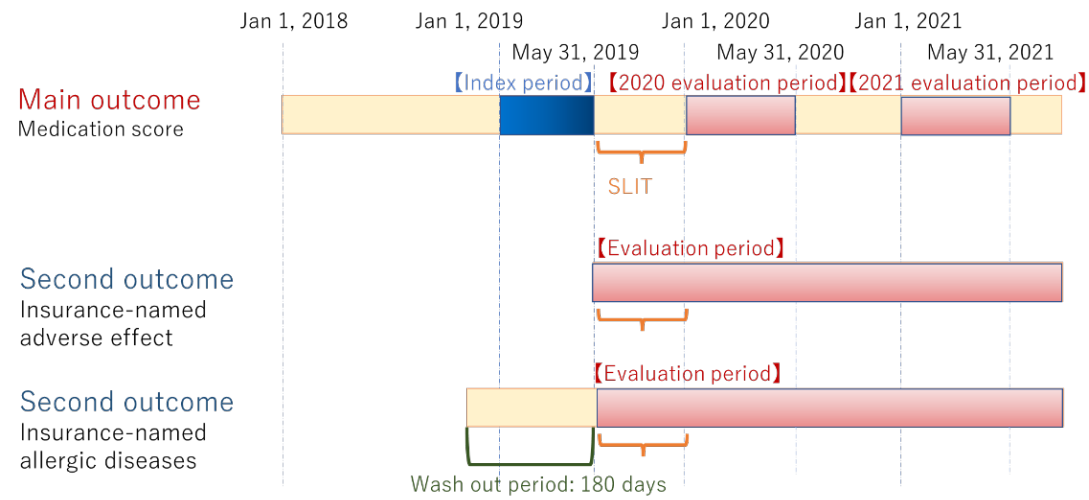
93021	Infantile diarrhea	A099
8833267	Diarrhea	A099
3064017	Psychogenic diarrhea	F453
3078008	Psychogenic abdominal pain	F454
5580005	Dietetic diarrhea	K522
8830392	Allergic diarrhea	K522
8840341	Chronic diarrhea	K529
8838959	Fermentative diarrhea	K529
8839193	Noninfectious colitis	K529
5580021	Habitual diarrhea	K529
8833268	Irritable bowel syndrome with diarrhea	K580
8847702	Mixed irritable bowel syndrome	K580
5645001	Functional diarrhea	K591
8840836	Loin pain	M545
7890005	Acute abdomen	R100
8834689	Indigestion	R101
8834690	Dyspeptic diarrhea	R101
8830562	Stomachache	R101
8832373	Acute dyspepsia	R101
7865013	Epigastric pain	R101
8842811	Dyspepsia	R101
8834690	Dyspeptic diarrhea	R101
7890008	Upper abdominal pain	R101
8850275	Pubic region pain	R102
7339033	Pelvic pain	R102
8837750	Intestinal colic	R103
7890003	Ileocecal pain	R103
8839039	Recurrent umbilical colic	R103
8836793	Groin pain	R103
7890012	Iliac fossa pain	R103
8844725	Lower abdominal cramp	R103
7890022	Periumbilical pain	R103
8831434	Lower abdominal pain	R103
7890021	Subumbilical pain	R103
5439008	Appendicular colic	R103
8835218	Persistent umbilical colic	R103

	8834796	Pediatric colicky pain	R104
	8835224	Persistent abdominal pain	R104
	7890020	Abdominal wall pain	R104
	7890014	Recurrent abdominal pain	R104
	7890027	Cyclic abdominal pain	R104
	7890029	Colic	R104
	8838495	Infantile colic	R104
	7890017	Abdominal tenderness	R104
	7890011	Flank pain	R104
	8839710	Abdominal pain	R104
Skin rash	8849747	Acquired angioedema	D841
	8841367	Psychogenic urticaria	F54-
	8841357	Papular urticaria	L282
	8841311	Allergic urticaria	L500
	8841381	Idiopathic urticaria	L501
	8841351	Febrile urticaria	L502
	8841355	Cold urticaria	L502
	8841356	Mechanical urticaria	L503
	8841370	Vibratory urticaria	L504
	8841323	Cholinergic urticaria	L505
	8842601	Contact urticaria	L506
	8847200	Autoimmune urticaria	L508
	8841366	Cyclic recurrent urticaria	L508
	8841393	Chronic urticaria	L508
	7573086	Hemorrhagic urticaria	L508
	8841394	Drug-induced urticaria	L508
	8841304	Urticaria	L509
	8839286	Nonbullous erythema multiforme	L510
	8835719	Bullous eythema multiforme	L511
	6951003	Stevens-Johnson syndrome	L511
	8840867	Lyell's syndrome type drug eruption	L512
	8845586	Toxic epidermal necrolysis	L512
	6951008	Erythema multiforme exudativum	L518
	8845563	Severe multiform exudative erythema- acute stage	L518
	8836978	Erythema multiforme arthropathy	L519

	6951007	Erythema multiforme	L519
	6952002	Erythema nodosum	L52-
	8833124	Erythema nodosum arthropathy	L52-
	8837641	Toxic erythema	L530
	8834995	Exudative toxic erythema	L530
	8830919	Centrifugal annular erythema	L531
	6950014	Erythema annulare	L532
	8830920	Erythema papulatum centrifugum	L538
	6959008	Palmar erythema	L538
	8832266	Papular erythema	L538
	8847003	Papule erythroderma	L538
	6958022	Measly erythema	L539
	6950012	Erythema dyschromicum perstans	L539
	8847023	Eczema secondary erythroderma	L539
	8846989	Atopic erythroderma	L539
	6900028	Erythroderma	L539
	8833656	Erythema	L539
	8841382	Solar urticaria	L563
	8832703	Giant urticaria	T783
	9951007	Angioneurotic edema	T783
	8832329	Acute local edema	T783
	8832703	Giant urticaria	T783
	7823039	Cyclic edema	T783
	8832450	Acute essential edema	T783
Laryngeal edema	8832441	Acute edematous laryngitis	J040
	4785016	Edematous chorditis	J382
	4786005	Glottis edema	J384
	8835964	Supraglottic edema	J384
	8835960	Subglottic edema	J384
	4786002	Laryngeal edema	J384
	8839446	Nasopharyngeal edema	J392
	4782018	Throat edema	J392
	7823010	Facial edema	R600
Perioral symptom	7820014	Oral abnormal sensation	R198
	5289025	Mouth pain	R198
	8833409	Oral paresthesia	R198

4782032	Pharynx burning sensation	R448
4782031	Tightness of pharynx	R448
8846274	Burning mouth syndrome	R51-

Supplement 3. Evaluation period of main outcome and second outcome.



Supplement 4. The breakdown of hay fever illnesses other than cedar pollen in Table 4

	Slit		total
	—	+	
Allergic conjunctivitis	181	1044	1225
Pollinosis	9	31	40
Allergic rhinitis	280	1309	1589
Allergic sinusitis	0	1	1
Seasonal allergic rhinitis	7	21	28
Allergic nasopharyngitis	0	2	2
Vasomotor rhinitis	1	1	2
Perennial allergic rhinitis	0	21	21
Allergic rhinoconjunctivitis	1	4	5
Seasonal allergic conjunctivitis	1	11	12
Perennial allergic conjunctivitis	0	1	1
Poaceous pollinosis	1	0	1
Orchard grass pollinosis	1	0	1
Japanese cypress pollinosis	2	0	2
Ragweed pollinosis	3	1	4
Pollen allergy caused by East Asian alder	1	0	1
	488	2447	2935