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Original Article

Individual characteristics and associated factors of hay fever: A large-scale mHealth study using AllerSearch

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CI, confidence interval;

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consent; IQR, interquartile range;

mHealth, mobile health; NSS, nasal

symptom score; NSS, non-nasal symptom

score; ORs, odds ratios; P4

medicine, predictive, preventive,

personalized, and participatory medicine;

PPI, Patient and Public Involvement;

TSS, total symptoms score

ABSTRACT

Background: The prevalence of hay fever, a multifactorial allergic disease, is increasing. Identifying individual characteristics and associated factors of hay fever is essential for predictive, preventive, personalized, and participatory (P4) medicine. This study aimed to identify individual characteristics and associated factors of hay fever using an iPhone application AllerSearch.

Methods: This large-scale mobile health-based cross-sectional study was conducted between February 2018 and May 2020. Individuals who downloaded AllerSearch in Japan and provided a comprehensive self-assessment (general characteristics, medical history, lifestyle habits, and hay fever symptoms [score range 0–36]) were included. Associated factors of hay fever (vs. non-hay fever) and severe hay fever symptoms were identified using multivariate logistic and linear regression analyses, respectively.

Results: Of the included 11,284 individuals, 9041 had hay fever. Factors associated with hay fever (odds ratio) included age (0.98), female sex (1.33), atopic dermatitis (1.40), history of dry eye diagnosis (1.36), discontinuation of contact lens use during hay fever season (3.34), frequent bowel movements (1.03), and less sleep duration (0.91). The factors associated with severe hay fever symptoms among individuals with hay fever (coefficient) included age (−0.104), female sex (1.329), history of respiratory disease (1.539), history of dry eye diagnosis (0.824), tomato allergy (1.346), discontinuation of contact lens use during hay fever season (1.479), smoking habit (0.614), and having a pet (0.303).

Conclusions: Our large-scale mobile health-based study using AllerSearch elucidated distinct hay fever presentation patterns, characteristics, and factors associated with hay fever. Our study establishes the groundwork for effective individualized interventions for P4 medicine.

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Introduction

Hay fever is a common allergy that affects approximately 30 million people in Japan, and its prevalence is expected to increase.¹ Lifelong symptoms and comorbidities of hay fever, such as allergic conjunctivitis and allergic rhinitis, can impair a patient's quality of life and affect their learning ability, sleeping habits, and work productivity.¹ Therefore, the development of individualized, predictive, and preventive measures against the onset and aggravation of hay fever is imperative.^{2,3}

Hay fever is a multifactorial disease caused by environmental factors such as exposure to pollen and air pollutants (particulate matter 2.5); lifestyle habits, such as diet, use of contact lens, smoking habit, and exercise; and epidemiological factors, such as younger age, female sex, and genetics.^{4–8} However, the multifactorial nature of hay fever, which encompasses a myriad of variables closely related to an individual's ever-changing living conditions, presents difficulty in collecting meaningful data through traditional epidemiological research.^{2,9} Additionally, the disease presentation varies with the age at onset, possibly because of the physiological changes that occur from youth to adulthood.¹⁰ The propensity of hay fever to remain chronic, and its associated comorbidities—allergic rhinitis, allergic conjunctivitis, and allergic dermatitis, increase the complexity of its presentation and pathogenesis. Considering that the contributory factors are highly individualized, a longitudinal personalized treatment approach would be better than a single, standardized treatment.

Mobile health (mHealth) refers to remote diagnostic and medical services provided through mobile devices.¹¹ It enables self-management of diseases and is an accessible source of evidence-based medical information. mHealth has become a source of personalized user health data for researchers and healthcare providers who seek to prescribe treatments based on individualized factors, based on a user's daily living environment.¹² mHealth is convenient for collecting big medical data owing to its penetrance and the ever-increasing capabilities of commonplace mobile devices.^{13,14} The ability to collect user data widely and longitudinally without interfering with their daily living patterns allows to accurately and holistically present data that depict both population- and individual-based symptom patterns.^{15–17}

Additionally, the real-time aspect of mHealth incentivizes participants as they can access the collected data, along with appropriate and updated medical advice. These advantages make mHealth an ideal option for the generation and collection of robust, cross-sectional medical big data to enable effective deployment of predictive, preventive, personalized, and participatory (P4) medicine for managing hay fever.^{2,9,18}

The present study utilized the unique characteristics of mHealth-based data collection to identify individualized characteristics and associated factors for hay fever and elucidate mechanisms of its pathogenesis and actualize P4 medicine.

Methods

AllerSearch smartphone application

AllerSearch smartphone application was developed using Apple Inc.'s (Cupertino, CA, USA) open-source framework, ResearchKit.² In Japan, AllerSearch was released on Apple's App Store on February 1, 2018, under consignment contract with Juntendo University Graduate School of Medicine, Tokyo, Japan, and Innojin, Inc., Tokyo, Japan.² It is freely available on Apple's App Store. Figure 1a shows a screenshot of AllerSearch's user interface.

Included survey questionnaires in AllerSearch were to produce a consensus version by a scientific committee including allergy specialists, ophthalmologists, otolaryngologists, epidemiologists, and the Patient and Public Involvement (PPI) members.^{2,3}

Study enrollment and participants

This large-scale, crowdsourced, cross-sectional observational study with prospective data collection was conducted between February 1, 2018, and May 1, 2020. Potential participants were recruited via the Apple's App Store, and this study was announced on online media (<https://allergy-search.com>) and social networking service platforms (Twitter; <https://twitter.com/allersearch>, and Facebook; <https://www.facebook.com/allersearchapp/>). After being informed about the nature of the study and possible consequences, all Apple product users electronically provided informed consent (eConsent). This study was approved by the Independent Ethics Committee of Juntendo University Graduate School of Medicine

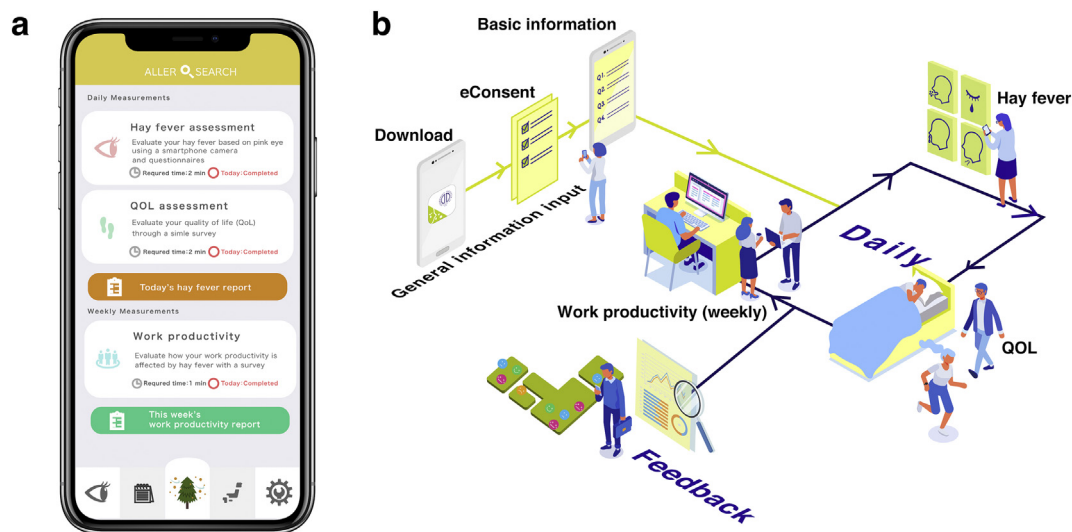


Fig. 1. Screenshot and the description of user experience of AllerSearch. (a) Screenshot of the AllerSearch user interface; (b) Workflow of user data collection (user journey map) for AllerSearch. QOL, quality of life.

(approval number, 17–061) and was conducted in accordance with the principles of the Declaration of Helsinki.¹⁹ The methodology and results of this survey are reported according to the checklist for reporting results of internet e-surveys.²⁰

Study participants downloaded AllerSearch using their own App Store credentials. Among those who provided eConsent were users who provided their basic information and completed the daily hay fever monitoring survey. Figure 1b provides a schematic diagram of user experience. After providing eConsent, participants provided basic information, including that on demographics, medical history, lifestyle, hay fever status, and preventive behavior for hay fever. Supplementary Table 1 lists the specific questions and parameters used for data collection. Subsequently, participants used the “daily tasks” function to receive daily assessments of the conjunctiva and provide answers to questionnaires on hay fever, including the nasal symptom score (NSS), non-nasal symptom score (NNSS),²¹ daily subjective symptoms, and work productivity. Finally, participants were provided their assessment results and a hay fever forecast map.²

Data collection

The impression count (number of times the app has been displayed on the App Store) and number of downloads, installs, and sessions (number of times the app has been used for >2 s) were collected as key performance indicators using App Analytics provided through App Store Connect. The data of participants, such as demographics, general characteristics, medical history, and lifestyle information, with reference to previous studies on hay fever and associated factors, were provided by users through AllerSearch. Furthermore, we examined the preventive and treatment behavior of the participants, including the use of air purifier, eye drops, eye wash, glasses and goggles, masks, oral medication, nasal drops, and sublingual and subcutaneous desensitization therapies.

Ascertainment of hay fever symptoms

Individuals were classified into three groups (non-hay fever, hay fever, and unknown) according to their response to the following

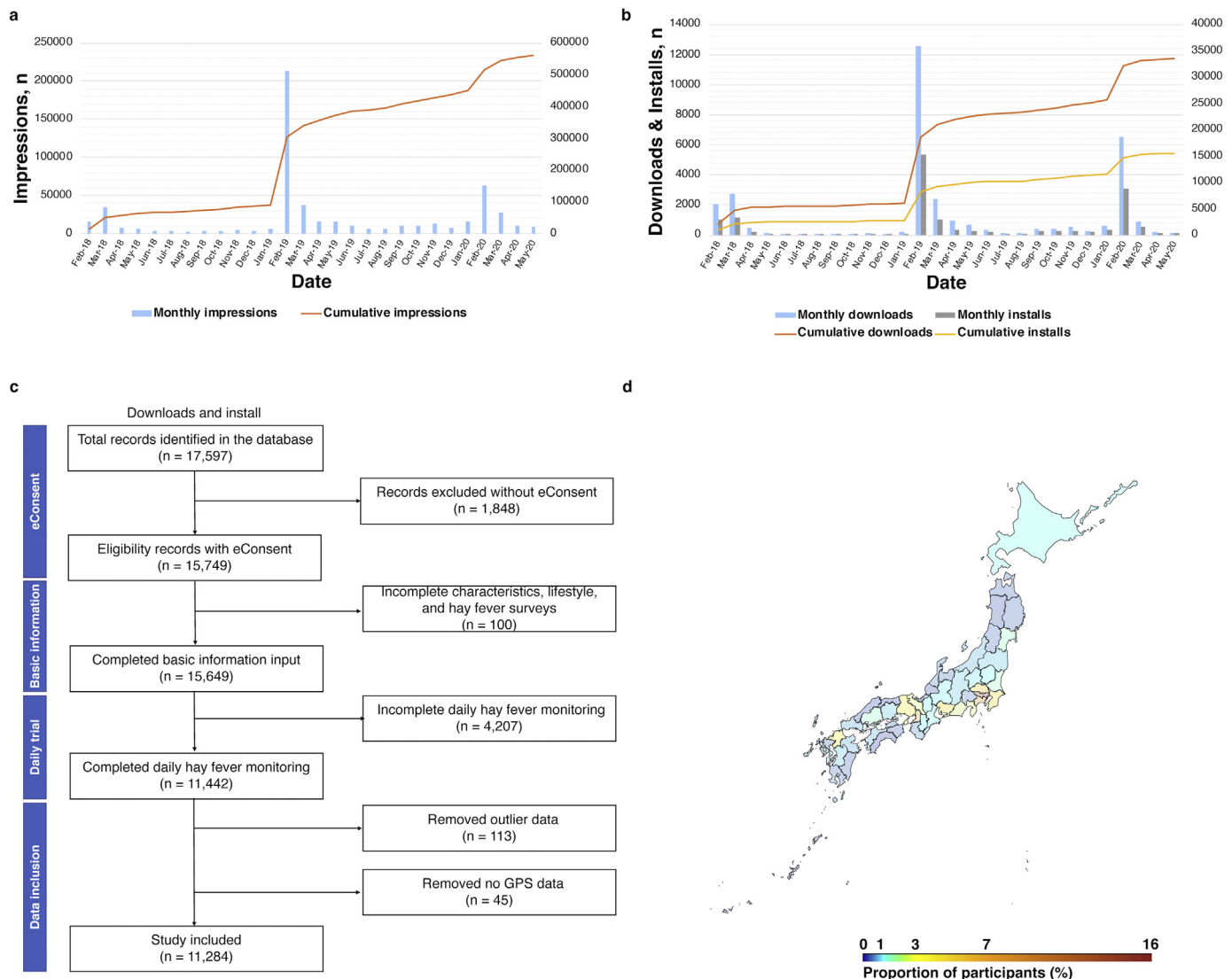


Fig. 2. Study cohort description. Specific key performance indicators for AllerSearch are presented as follows: (a) impression count and (b) download and install counts. (c) Schematic representation for enrollment, exclusion, and inclusion of the participants in this study. (d) Map illustrating the geographical distribution of the users. eConsent, electronically provided informed consent, GPS, global positioning system.

question “Do you have hay fever?” (Supplementary Table 1). Hay fever symptoms were evaluated based on a composite score, including the NSS and NNSS (Supplementary Table 2). The NSS consisted of items pertaining to rhinorrhea, nasal congestion, nasal itching, sneezing, and interference with daily life. The NNSS consisted of items pertaining to itchy eyes, watery eyes, eye redness, and itchy ears and mouth. Each item of the NSS and NNSS was scored on a 4-point scale as follows: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms.²¹ The sum of the individual scores for NSS and NNSS was the total symptoms score (TSS, range 0–36).

Statistical analysis

Characteristics of participants were compared among the non-hay fever, hay fever, and unknown groups. Continuous variables are presented as medians and interquartile ranges for non-normally distributed variables based on the Shapiro–Wilk test, and categorical variables are presented as percentages. We performed the Mann–Whitney *U* test for non-normally distributed continuous variables and the chi-square test for categorical variables. Differences with *P*-values < 0.05 were considered statistically significant.

Multivariable logistic regression analyses were performed to identify factors associated with hay fever (versus non-hay fever). In addition, multivariable linear regression analyses were performed to identify factors associated with severe hay fever symptoms in individuals with hay fever.

All data were analyzed using STATA, version 15.1 (Stata Corp, College Station, TX, USA). Additionally, a heatmap for the geographic distribution of the participants in Japan was constructed using the heatmap function of the matplotlib module (ver. 0.9.0, Python 3).

Patient and public involvement

During the initial planning, execution, and analysis of this project, the PPI approach was not implemented.

Results

Application downloads and clinical study enrollment

Figures 2a and b shows the key performance indicators of AllerSearch collected through App Analytics between February 1, 2018, and May 1, 2020. The total impression count was 553,553 (Fig. 2a). AllerSearch was downloaded to completion 33,308 times and was installed 15,464 times during this period (Fig. 2b). Figure 2c shows the flow diagram for participant enrollment in the study. In our database, 17,597 individual data were identified via unique identifier extraction. Of those, 15,749 individuals provided eConsent (agreement rate, 89.5%) and 1848 did not respond. Among those who consented to participate, 15,649 individuals provided basic information and 11,442 completed the daily hay fever monitoring survey. After excluding 4207 individuals with incomplete data records, 113 with outlier data, and 45 without geographic data, 11,284 of the 17,597 initial users (64.1%) were included in this study. A comparison of the included and excluded individuals (Supplementary Table 3) shows that the included participants had a higher female to male ratio and proportion of hay fever than those excluded. The geographic distribution of the participants in Japan was as follows (Fig. 2d): Tokyo (22.2%), 2510 users; Kanagawa (9.5%), 1070 users; and Osaka (8.5%), 957 users (more details are presented in Supplementary Table 4).

Participants' characteristics

Table 1 summarizes the demographics, medical history, lifestyle habits, and residential environment of the 11,284 included participants. The median age of the participants was 34 years (range, 23–46 years); 56.4% of the participants were women; and 80.1% of the participants presented with hay fever, 13.5% with an unknown diagnosis, and 6.4% with non-hay fever. A younger age, higher female to male ratio, lower frequency of diabetes, and higher frequency of atopic dermatitis and history of dry eye diagnosis were observed in the hay fever group than in the non-hay fever group. The hay fever group had a higher frequency of contact lens use. Bowel movements (times per week) were significantly higher in the hay fever group than in the non-hay fever group. Moreover, the percentage of participants with smoking habits was less in the hay fever group than in the non-hay fever group. Across the three age groups classified based on the presence of hay fever, the highest proportion of hay fever was observed in the 20–30-year and 30–40-year age groups (Fig. 3a). The highest frequency of hay fever onset was observed in the 10–20-year age group, followed by the 20–30-year and <10-year age groups (Fig. 3b). The onset of hay fever was significantly earlier in women than in men (men, 20 years [12–30] vs. women, 16 years [10–25], *P* < 0.001) (butterfly plot in Fig. 3c). The highest frequency of both onset and symptom aggravation was observed in March, followed by April every year (Fig. 3d). The two peaks of onset and aggravation coincided with the beginning of the spring and autumn seasons, both of which have a higher level of pollen release than the other months in Japan. In addition, this study revealed that there were more severe hay fever symptoms in individuals with hay fever in both seasons (spring and fall) compared to individuals with hay fever only in the spring season (Supplementary Table 5).

Table 2 summarizes the symptom characteristics of included participants. Participants in the hay fever group had a variety of symptoms, including nasal and non-nasal symptoms. The score of each nasal and non-nasal symptom in the hay fever group was significantly higher than that in the non-hay fever group. The TSS in the hay fever group was approximately five times that in the non-hay fever group (TSS: hay fever group, 5 [2–10]; non-hay fever, 1 [0–4]; *P* < 0.001).

Factors associated with hay fever

Table 3 shows the crude and fully-adjusted odds ratios (ORs) of each factor for the hay fever group (vs. non-hay fever group). A younger age, female sex, no history of diabetes, history of atopic dermatitis, history of dry eye diagnosis, discontinuation of contact lens use during hay fever season, more frequent bowel movements per week, and less sleep duration per day were independently associated with hay fever.

Next, Table 4 shows the factors associated with severe hay fever symptoms among individuals with hay fever in the multivariable linear regression analysis. Younger age, female sex, medicated hypertension, unknown for history of diabetes, history of heart disease, liver disease, malignant tumor, respiratory disease, and none for systemic disease, history of dry eye diagnosis, unknown for dry eye diagnosis, tomato allergy, discontinued contact lens during hay fever season, smoking habit, and having a pet were positively associated with severe hay fever symptoms.

Preventive and treatment behavior

Table 5 shows the preventive and treatment behaviors among the groups. Mask usage was the most frequent preventive behavior, followed by the use of oral medications and eye drops.

Table 1
Demographics and characteristics of participants included in the study.

		Non-hay fever	Hay fever		Unknown	P value	Overall
		N (%) = 720 (6.4)	N (%) = 9041 (80.1)	P value	N (%) = 1523 (13.5)		N (%) = 11,284 (100)
Demographic characteristics							
Age (years), median (IQR)		39 (28–51)	34 (23–46)	<.001	31 (23–44)	<.001	34 (23–46)
Women, N (%)		310 (43.1)	5085 (56.2)	<.001	963 (63.2)	<.001	6358 (56.4)
Height (cm), median (IQR)		166 (159–172)	163 (157–170)	<.001	162 (156–170)	<.001	163 (157–170)
Weight (kg), median (IQR)		61 (54–72)	58 (51–68)	<.001	57 (50–67)	<.001	59 (51–68)
Medical history							
Medicated hypertension, N (%)	No	578 (80.3)	7330 (81.1)	<.001	1161 (76.2)	<.001	9069 (80.4)
	Medicated	65 (9.0)	493 (5.5)		73 (4.8)		631 (5.6)
	Unmedicated	35 (4.9)	311 (3.4)		46 (3.0)		392 (3.5)
	Unknown	42 (5.8)	907 (10.0)		243 (16.0)		1192 (10.6)
Diabetes, N (%)	No	633 (87.9)	8085 (89.4)	<.001	1301 (85.4)	<.001	10,019 (88.8)
	Yes	38 (5.3)	201 (2.2)		38 (2.5)		277 (2.5)
	Unknown	49 (6.8)	755 (8.4)		184 (12.1)		988 (8.8)
Systemic diseases, N (%)	Blood disease	16 (2.2)	135 (1.5)	.127	14 (0.9)	.012	165 (1.5)
	Brain disease	12 (1.7)	98 (1.1)	.154	19 (1.2)	.351	128 (1.1)
	Collagen disease	4 (0.6)	47 (0.5)	.898	11 (0.7)	.651	62 (0.6)
	Heart disease	24 (3.3)	181 (2.0)	.016	38 (2.5)	.258	243 (2.2)
	Kidney disease	13 (1.8)	162 (1.8)	.979	22 (1.4)	.520	197 (1.8)
	Liver disease	8 (1.1)	156 (1.7)	.217	16 (1.1)	.896	180 (1.6)
	Malignant tumor	13 (1.8)	129 (1.4)	.414	23 (1.5)	.603	165 (1.5)
	Respiratory disease	64 (8.9)	851 (9.4)	.643	112 (7.4)	.207	1027 (9.1)
	N/A	586 (81.4)	7489 (82.8)	.324	1308 (85.9)	.006	9383 (83.2)
	Atopic dermatitis, N (%)	89 (12.4)	1616 (17.9)	<.001	223 (14.6)	.145	1928 (17.1)
	Tomato allergy, N (%)	13 (1.81)	246 (2.72)	.141	28 (1.8)	.957	287 (2.54)
	Mental illness, N (%)	No	654 (90.8)	.123	1332 (87.5)	.053	9988 (88.5)
History of dry eye diagnosis, N (%)	Yes	35 (4.9)	495 (5.5)		92 (6.0)		622 (5.5)
	Previously had	31 (4.3)	544 (6.0)		99 (6.5)		674 (6.0)
	No	458 (63.6)	4669 (51.6)	<.001	727 (47.7)	<.001	5854 (51.9)
	Yes	133 (18.5)	2090 (23.1)		284 (18.7)		2507 (22.2)
	Unknown	129 (17.9)	2282 (25.2)		512 (33.6)		2923 (25.9)
Residential environment							
Living room, N (%)	Hardwood	521 (72.4)	6546 (72.4)	.058	1014 (66.6)	.016	8081 (71.2)
	Carpet	144 (20.0)	1747 (19.3)		362 (23.8)		2253 (20.0)
	Tatami (Japanese straw-based floor)	30 (4.2)	474 (5.2)		74 (4.9)		578 (5.1)
	Vinyl	9 (1.3)	169 (1.9)		45 (3.0)		223 (2.0)
Bedroom, N (%)	Other	16 (2.2)	105 (1.2)		28 (1.8)		149 (1.3)
	Hardwood	446 (61.9)	5670 (62.7)	.041	925 (60.7)	.221	7041 (62.4)
	Carpet	120 (16.7)	1554 (17.2)		272 (17.9)		1946 (17.3)
	Tatami (Japanese straw-based floor)	126 (17.5)	1584 (17.5)		255 (16.7)		1965 (17.4)
	Vinyl	9 (1.3)	121 (1.3)		40 (2.6)		170 (1.5)
Pet, N (%)	Other	19 (2.6)	112 (1.2)		31 (2.0)		162 (1.4)
		222 (30.8)	2974 (32.9)	.257	544 (35.7)	.023	3740 (33.1)
Lifestyle habits							
Coffee intake (cups per day), median (IQR)		2 (1–3)	1 (0–2)	<.001	1 (0–2)	<.001	1 (0–2)
Contact lens use, N (%)	No	363 (50.4)	4125 (45.6)	<.001	683 (44.9)	<.001	5171 (45.8)
	Discontinued during hay fever season	139 (19.3)	1600 (17.7)		238 (15.6)		1977 (17.5)
	Past use	6 (0.8)	279 (3.1)		10 (0.7)		295 (2.6)
	Current use	212 (29.4)	3037 (33.6)		592 (38.9)		3841 (34.0)
Exercise (hours per week), median (IQR)		1 (0–2)	1 (0–2)	.393	1 (0–3)	.755	1 (0–2)
Exercise (times per week), median (IQR)		1 (1–4)	1 (0–3)	.190	1 (0–4)	.809	1 (0–4)
Bowel movements (times per week), median (IQR)		5 (3–7)	6 (3–7)	.011	5 (3–7)	.943	6 (3–7)
Sleep duration (hours per day), median (IQR)		6 (6–7)	6 (6–7)	.642	6 (6–7)	.693	6 (6–7)
Smoking habit, N (%)	No	473 (65.7)	6360 (70.4)	.010	1023 (67.2)	.758	7856 (69.6)
	Yes	133 (18.5)	1313 (14.5)		264 (17.3)		1710 (15.2)
	Previously had	114 (15.8)	1368 (15.1)		236 (15.5)		1718 (15.2)
	Rarely	294 (40.8)	3815	.836	725 (47.6)	.025	1,019 (45.4)
Yogurt intake, N (%)	Once a week	143 (19.9)	1643 (18.2)		296 (19.4)		439 (19.6)
	Twice or thrice a week	117 (16.3)	1448 (16.0)		195 (12.8)		312 (13.9)
	Four or five times a week	57 (7.9)	736 (8.1)		109 (7.2)		166 (7.4)
	Everyday	109 (15.1)	1399 (15.5)		198 (13.0)		307 (13.7)

IQR, interquartile range; N/A, not applicable.

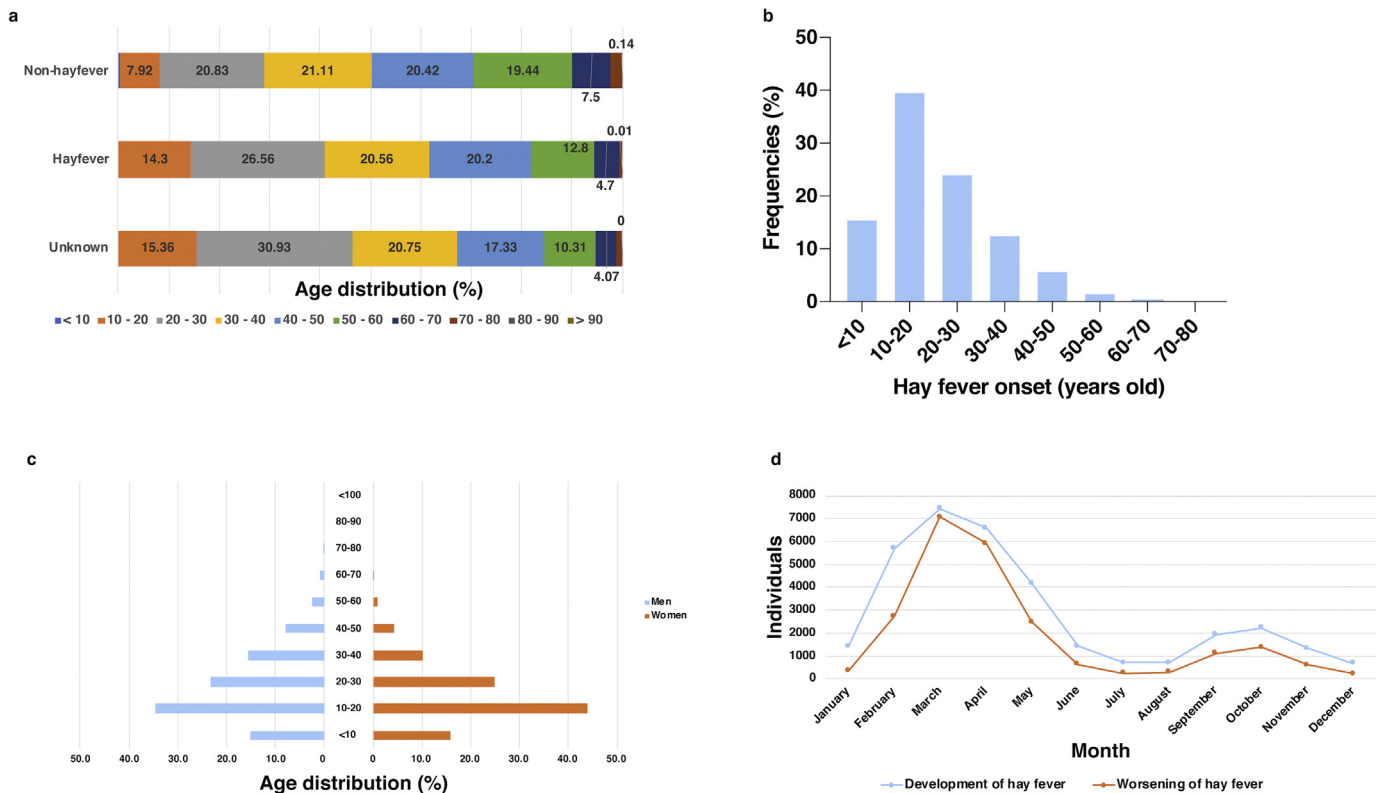


Fig. 3. Age distribution and seasonal variation of hay fever of the included participants. (a) Age distribution within each group comprising the included individuals. (b) Age distribution at hay fever onset. (c) Butterfly plot for sex-specific age distribution of individuals with hay fever. (d) The month of onset and aggravation of hay fever in individuals with hay fever.

Discussion

Hay fever is a highly multifactorial disease with heterogeneous phenotypes that vary widely in terms of disease onset, symptoms, and severity. This study employed an mHealth-integrated smartphone application to successfully collect large data on hay fever and successfully identify the factors associated with hay fever and associated behaviors at an individual level. Our study establishes the groundwork for effective individualized behavioral and therapeutic interventions for P4 medicine.

Hay fever is typically chronic and has complex presentations influenced by environmental factors, host characteristics, and

lifestyle factors, all of which may continuously induce pathogenesis.¹ Additionally, hay fever may change its presentation and organ involvement throughout a patient's course of life ("allergic march"). In addition, younger age of onset of hay fever was significantly associated with severe hay fever symptoms (Supplementary Table 6), conversely the affected period of hay fever was negatively associated with severe hay fever symptoms (Supplementary Table 7). Therefore, seamless transition of care among pediatrics, adult medicine, and geriatric medicine and preventing the onset of hay fever at a younger age are crucial. The need for collaboration between multiple specialties (dermatology, otorhinolaryngology, and ophthalmology) for hay

Table 2
Symptoms of participants included in the study.

Symptoms	Non-hay fever N (%) = 720 (6.4)	Hay fever N (%) = 9041 (80.1)	P value	Unknown N (%) = 1523 (13.5)	P value
Nasal symptom score, 0–4, median (IQR)					
Rhinorrhea	0 (0–1)	1 (0–2)	<.001	1 (0–2)	<.001
Nasal congestion	0 (0–1)	1 (0–1)	<.001	1 (0–1)	<.001
Nasal itching	0 (0–0)	1 (0–1)	<.001	0 (0–1)	<.001
Sneezing	0 (0–1)	1 (0–1)	<.001	1 (0–1)	<.001
Effects on daily life	0 (0–0)	1 (0–2)	<.001	0 (0–1)	<.001
Total nasal symptom score, 0–20	1 (0–3)	4 (1–7)	<.001	3 (1–6)	<.001
Non-nasal symptom score, 0–4, median (IQR)					
Eye itching	0 (0–1)	1 (0–2)	<.001	0 (0–1)	<.001
Tearing	0 (0–0)	0 (0–1)	<.001	0 (0–1)	<.001
Eye redness	0 (0–0)	0 (0–1)	<.001	0 (0–1)	<.001
Ear and/or nose itching	0 (0–0)	0 (0–1)	<.001	0 (0–0)	<.001
Total non-nasal symptoms score, 0–16	0 (0–1)	1 (0–3)	<.001	1 (0–3)	<.001
Total nasal and non-nasal symptoms score, 0–36	1 (0–4)	5 (2–10)	<.001	4 (2–8)	<.001

IQR, interquartile range.

Table 3

Factors associated with hay fever in individuals with hay fever compared to those without hay fever.

Variables	Crude odds ratio (95% CI)	P value	Fully-adjusted odds ratio (95% CI)	P value
Age (every 1 year)	0.98 (0.97–0.98)	<.001	0.98 (0.98–0.99)	<.001
Female sex	1.70 (8.72–10.68)	<.001	1.33 (1.11–1.58)	.002
Body mass index	0.96 (0.94–0.98)	<.001	0.98 (0.96–1.00)	.102
Medicated hypertension	0.58 (0.44–0.76)	<.001	1.05 (0.78–1.43)	.749
Diabetes	No	1 (ref)	1 (ref)	
	Yes	0.41 (0.29–0.59)	0.63 (0.43–0.93)	.021
	Unknown	1.21 (0.89–1.63)	1.09 (0.80–1.48)	.588
Atopic dermatitis	1.54 (1.23–1.94)	<.001	1.40 (1.11–1.77)	.005
Systemic disease, yes	Blood disease	0.67 (0.39–1.13)	0.78 (0.42–1.45)	.431
	Brain disease	0.65 (0.35–1.18)	0.82 (0.40–1.68)	.593
	Collagen disease	0.94 (0.34–2.60)	0.97 (0.33–2.86)	.956
	Heart disease	0.59 (0.38–0.91)	0.66 (0.38–1.17)	.154
	Kidney disease	0.99 (0.56–1.75)	1.13 (0.58–2.20)	.713
	Liver disease	1.56 (0.76–3.19)	2.11 (0.97–4.56)	.059
	Malignant tumor	0.79 (0.44–1.40)	0.96 (0.48–1.93)	.914
	Respiratory disease	1.07 (0.82–1.39)	0.94 (0.57–1.55)	.802
	None	1.10 (0.91–1.34)	0.96 (0.58–1.59)	.884
Mental illness	No	1 (ref)	1 (ref)	
	Yes	1.16 (0.81–1.64)	1.01 (0.70–1.45)	.964
	Previously had	1.43 (0.99–2.08)	1.28 (0.88–1.87)	.192
History of dry eye diagnosis	No	1 (ref)	1 (ref)	
	Yes	1.54 (1.26–1.88)	1.36 (1.10–1.68)	.004
	Unknown	1.73 (1.42–2.12)	1.54 (1.25–1.89)	<.001
Tomato allergy	1.52 (0.87–2.67)	.144	1.44 (0.80–2.59)	.221
Coffee intake, cups per day	0.89 (0.86–0.93)	<.001	0.96 (0.91–1.01)	.107
Contact lens use	No	1 (ref)	1 (ref)	
	Past use	4.09 (1.81–9.25)	0.97 (0.79–1.20)	.796
	Discontinued during hay fever season	1.01 (0.83–1.24)	3.34 (1.47–7.60)	.004
	Current use	1.26 (1.06–1.50)	0.93 (0.77–1.13)	.478
Exercise, hours per week	1.00 (0.99–1.01)	.861	1.00 (0.99–1.01)	.728
Bowel movement, times per week	1.02 (1.00–1.04)	.051	1.03 (1.01–1.05)	.006
Smoking habit	No	1 (ref)	1 (ref)	
	Yes	0.73 (0.60–0.90)	0.83 (0.67–1.02)	.081
	Previously had	0.89 (0.72–1.10)	1.18 (0.95–1.48)	.139
Pet	1.10 (0.93–1.30)	.257	1.08 (0.91–1.27)	.394
Sleep duration, hours per day	0.96 (0.90–1.02)	.152	0.91 (0.85–0.97)	.003
Yogurt intake	Rarely	1 (ref)	1 (ref)	
	Once a week	0.89 (0.72–1.09)	0.88 (0.71–1.09)	.240
	Twice or thrice a week	0.95 (0.76–1.19)	0.96 (0.76–1.20)	.701
	Four or five times a week	1.00 (0.74–1.34)	1.04 (0.77–1.41)	.787
	Everyday	0.99 (0.79–1.24)	1.17 (0.92–1.48)	.209
Living room	Hardwood	1 (ref)	1 (ref)	
	Carpet	0.97 (0.80–1.17)	0.91 (0.73–1.13)	.376
	Tatami (Japanese straw-based floor)	1.26 (0.86–1.84)	1.32 (0.88–1.98)	.186
	Vinyl	1.49 (0.76–2.94)	1.69 (0.73–3.92)	.220
	Other	0.52 (0.31–0.89)	0.65 (0.33–1.29)	.220
Bedroom	Hardwood	1 (ref)	1 (ref)	
	Carpet	1.02 (0.83–1.26)	1.04 (0.82–1.32)	.751
	Tatami (Japanese straw-based floor)	0.99 (0.81–1.21)	1.05 (0.84–1.31)	.665
	Vinyl	1.06 (0.53–2.10)	0.74 (0.31–1.77)	.498
	Other	0.46 (0.28–0.76)	0.48 (0.25–0.91)	.024

CI, confidence interval; ref, reference.

fever management creates a barrier to forming an effective integrated system among healthcare providers.²² This study overcomes this obstacle and demonstrates an effective method to create individualized biological profiles based on symptoms, lifestyle factors, and preventive measures, all of which were collected with an mHealth application. Moreover, this study confirms previously reported factors associated with hay fever, including younger age, female sex, diabetes, contact lens use, increased frequency of bowel movement, and decreased sleep duration.^{8,13,14,23–27} Consistent with previous studies,²⁸ the highest percentage of hay fever was observed among those aged 10–30 years; therefore, a major proportion of the affected population may benefit from mHealth-based interventions owing to their active utilization of smartphone applications.² Since these comprehensive results were obtained from the present study, the effectiveness of a mHealth-based study is emphasized. The global

user count of smartphone applications is projected to surpass 6.3 billion by the end of 2022,²⁹ indicating the potential of digital phenotyping and digital interventions in routine healthcare. mHealth holds a great advantage for longitudinal, individualized large data collection on subjective symptoms, socio-behavioral factors, and lifestyle factors without hampering participants' daily life patterns; this may shift the paradigm from facility-based healthcare to patient-centered lifelong medical care during routine living.³⁰

This study identified relevant factors associated with hay fever and severe hay fever symptoms using an mHealth-based collection of real-world data. Recent studies have shown the association between hay fever and dry eye disease.^{13,14,31} Allergic conjunctivitis and dry eye disease are the most common inflammatory disorders affecting the anterior ocular surface; these disorders are synergistically exacerbated by the inflammatory

Table 4
Factors associated with severe hay fever symptoms in individuals with hay fever.

Variables		Univariate linear regression			Multivariable linear regression		
		Coefficient	95% CI	P value	Coefficient	95% CI	P value
Age (every 1 year)		-.112	-.120–.104	<.001	-.104	-.114–.094	<.001
Female sex		1.748	1.518–1.978	<.001	1.329	1.074–1.585	<.001
Body mass index		-.113	-.145–.081	<.001	.028	-.006–.061	.103
Medicated hypertension		-.1707	-.2215–.1199	<.001	.933	.393–1.472	.001
Diabetes	No	1 (reference)	—	—	1 (reference)	—	—
	Yes	-.1660	-.2443–.878	<.001	.149	-.0638–.936	.710
	Unknown	1.333	.916–1.750	<.001	.587	.177–.998	.005
Atopic dermatitis		.480	.179–.782	.002	.190	-.107–.486	.210
Systemic disease, yes	Blood disease	-.1374	-.2327–.422	.005	.608	-.454–1.670	.262
	Brain disease	-.884	-.2000–.232	.120	1.211	-.006–2.429	.051
	Collagen disease	-.183	-.1790–1.424	.823	.993	-.659–2.645	.239
	Heart disease	-.675	-.1500–.150	.109	1.029	.059–1.998	.038
	Kidney disease	-.913	-.1785–.042	.040	.700	-.312–1.711	.175
	Liver disease	-.316	-.1204–.572	.486	2023	1.011–3.035	<.001
	Malignant tumor	-.1501	-.2475–.527	.003	1.332	.183–2.481	.023
	Respiratory disease	.094	-.302–.490	.640	1.539	.733–2.345	<.001
	None	.651	.345–.957	<.001	1.649	.830–2.467	<.001
Mental illness	No	1 (reference)	—	—	1 (reference)	—	—
	Yes	.572	.063–1.081	.028	.0420	-.460–.544	.870
	Previously had	.183	-.304–.669	.462	-.0610	-.536–.414	.801
History of dry eye diagnosis	No	1 (reference)	—	—	1 (reference)	—	—
	Yes	.923	.636–1.211	<.001	.824	.530–1.117	<.001
	Unknown	1.405	1.126–1.684	<.001	.884	.607–1.161	<.001
Tomato allergy		1.446	.736–2.156	<.001	1.346	.653–2.039	<.001
Coffee intake, cups per day		-.440	-.516–.363	<.001	.005	-.079–.089	.907
Contact lens use	No	1 (reference)	—	—	—	—	—
	Past use	-.535	-.857–.213	.001	-.203	-.522–.115	.211
	Discontinued during hay fever season	2.109	1.432–2.785	<.001	1.479	.818–2.141	<.001
	Current use	.758	.496–1.019	<.001	-.212	-.481–.057	.122
Exercise, hours per week		.009	-.004–.022	.0191	.003	-.010–.016	.692
Bowel movement, times per week		-.029	-.057–.001	.040	-.011	-.039–.0165	.432
Smoking habit	No	1 (reference)	—	—	1 (reference)	—	—
	Yes	.105	-.227–.438	.0535	.614	.281–.947	<.001
	Previously had	-.1104	-.1431–.777	<.001	.270	-.063–.603	.112
Pet		.539	.293–.785	<.001	.303	.063–.543	.013
Sleep duration, hours per day		.237	.138–.336	<.001	-.018	-.116–.081	.726
Yogurt intake	Rarely	1 (reference)	—	—	1 (reference)	—	—
	Once a week	-.226	-.550–.097	.170	.005	-.310–.319	.977
	Twice or thrice a week	-.515	-.854–.177	.003	-.240	-.571–.090	.154
	Four or five times a week	-.992	-.1434–.551	<.001	-.204	-.636–.227	.353
	Everyday	-.1163	-.1506–.821	<.001	-.051	-.394–.292	.769
Living room	Hardwood	1 (reference)	—	—	1 (reference)	—	—
	Carpet	.695	.400–.991	<.001	.230	-.090–.550	.158
	Tatami (Japanese straw-based floor)	.471	-.051–.993	.077	.413	-.124–.951	.132
	Vinyl	-.423	-.1278–.431	.0332	-.725	-.182–.367	.193
	Other	1.933	.854–3.012	<.001	.683	-.535–1.902	.272
Bedroom	Hardwood	1 (reference)	—	—	1 (reference)	—	—
	Carpet	.578	.264–.892	<.001	.285	-.054–.623	.099
	Tatami (Japanese straw-based floor)	-.149	-.461–.163	.350	.231	-.094–.557	.163
	Vinyl	-.090	-.1099–.918	.860	.477	-.810–1.764	.467
	Other	2.000	.953–3.048	<.001	.721	-.461–1.904	.232

CI, confidence interval; ref, reference.

and immune mechanisms on the ocular surface and disruption of ocular homeostasis.³² Especially, the severity of both hay fever and dry eye disease increases during the spring season, which is characterized by low humidity and an increase in air-borne pollens, and occurs in the month of February in Japan.³¹ Therefore, since dry eye disease is considered a modifiable factor in individuals with hay fever, it is necessary to provide treatment of dry eye disease in addition to treatment for allergic conjunctivitis.

This study identified an association between hay fever and contact lens use, based on the association between allergic conjunctivitis and contact lens use.^{16,33} Our findings revealed that many individuals used contact lenses despite developing symptoms of hay fever (Table 1). Since contact lens use induces dry eye disease¹⁶ and allergic conjunctivitis, contact lens discontinuation

during hay fever season may be necessary for individuals with hay fever. Therefore, early identification of individual factors associated with hay fever using mHealth is necessary for a timely recommendation of appropriate interventions.

Although smoking habit is one of the most common modifiable risk factors for a variety of disease, previous studies have not clearly established an association between smoking habit and hay fever.³⁴ This study also showed that smoking habit had no association with hay fever (vs. non-hay fever) as shown in Table 3. However, smoking habit had a positive association with severe hay fever symptom as shown in Table 4. A previous study showed a minor preventive effect of smoking on hay fever using the Mendelian randomization approach.³⁵ Further investigation is needed to clarify the pathological mechanism of the association between smoking habit and hay fever.

Table 5

Preventive and treatment behaviors of the included participants.

	Non-hay fever N (%) = 720 (6.4)	Hay fever N (%) = 9041 (80.1)	P value	Unknown N (%) = 1523 (13.5)	P value	Overall N (%) = 11,284 (100)
Preventative and treatment behavior, yes, N (%)						
Air purifier	161 (22.4)	3707 (41.1)	<.001	328 (21.5)	.659	4196 (37.2)
Eye drops	158 (21.9)	5734 (63.4)	<.001	355 (23.3)	.472	6247 (55.4)
Eye wash	172 (23.9)	3683 (40.7)	<.001	408 (26.8)	.143	4263 (37.8)
Glasses and goggles	73 (10.1)	2162 (23.9)	<.001	132 (8.7)	.259	2367 (21.0)
Mask	347 (48.2)	7717 (85.4)	<.001	944 (62.0)	<.001	9008 (79.8)
Oral medication	125 (17.4)	5981 (66.2)	<.001	198 (13.0)	.006	6304 (55.9)
Nasal drops	76 (10.6)	3886 (43.0)	<.001	147 (9.7)	.504	4109 (36.4)
Sublingual and subcutaneous desensitization therapy	13 (1.8)	236 (2.6)	.187	8 (0.5)	.003	257 (2.3)
Others	11 (1.5)	605 (6.7)	<.001	48 (3.2)	.025	664 (5.9)
None	323 (44.9)	317 (3.5)	<.001	461 (30.3)	<.001	1101 (9.8)

Personalized behavioral interventions remain a challenge within the traditional facility-based framework. However, real-time behavioral interventions, such as lifestyle adjustments, preventive measures, and risk assessment, are possible with mHealth, owing to its advantages such as its longitudinal nature and capability for holistic individualized assessments. Such digital phenotyping and intervention through mHealth enable the delivery of various behavioral treatments as stand-alone or coached interventions.³⁶ For instance, for participants with factors associated with hay fever, including younger age and female sex, a personalized intervention for dry eye disease and contact lens usage could be initiated. Furthermore, customized recommendations of preventive measures (Table 5) may become accessible to those with barriers to healthcare. In the future, secure and efficient routes should be established to deliver the data collected using mHealth to the providers in the healthcare system.

Our study has some limitations associated with crowdsourced research using a smartphone application, similar to those reported in previous studies.^{13–17} First, this study may have been subjected to selection bias based on age, sex, socioeconomic factors, and other user characteristics (Supplementary Table 3). Participants who had more interest in hay fever and had experienced hay fever symptoms might have completed all surveys and were subsequently included. The elderly or people lacking access to smart devices or mobile-service providers might have been underrepresented, whereas younger people who utilize smart devices more often and people who can socioeconomically afford a smartphone might have been overrepresented. mHealth accrued a nationally representative participant pool; however, many participants resided in urban localities, leading to possible geographical bias (Supplementary Table 4). Furthermore, participants were limited to iPhone users in Japan who might exhibit distinct behavioral and consumer habits. Therefore, random sampling of controls from the general population might be ideal. Second, this study employed many self-administered surveys, leading to possible recall bias or over-reporting. However, despite possible bias, two distinct peaks of hay fever onset and disease severity were successfully identified (Fig. 3d), consistent with known hay fever seasons in Japan. The internal validity of the paper-based and smartphone-based questionnaires was demonstrated in our previous study.¹³ However, socioeconomic status, education level, cultural background, and some important unmeasured factors related to hay fever were not investigated. Third, this was a cross-sectional study; therefore, temporal relationships and causality between hay fever and the studied factors could not be inferred. Additionally, this smartphone-based study determined the presence of hay fever solely based on the administered questionnaires and might be prone to false-positives owing to the lack of a physician-confirmed diagnosis.

Despite these limitations, AllerSearch, our in-house smart-phone application, represents a novel digital tool for conducting research and collecting real-world data across diverse populations, and this integration of technology and medical research may eventually become mainstream. The role of mHealth technology in the field of allergic diseases has been endorsed by the “Be He@lthy Be Mobile” initiative of the World Health Organization and by position papers of the American College of Allergy, Asthma and Immunology and the European Academy of Allergy and Clinical Immunology.^{37–39} Such applications can be used to supplement traditional hospital-based research, thereby encompassing a broader population. To better serve this purpose and counteract the aforementioned limitations, AllerSearch was launched on the Android platform along with a software update on cross-specialty data integration, user interface, and PPI.² Furthermore, AllerSearch enables preventive care by identifying individuals at risk of hay fever earlier than that currently possible, which may help in providing P4 medicine.

In summary, this study identified a large proportion of individuals with hay fever with distinct biological profiles using AllerSearch. Seemingly heterogeneous patterns of hay fever symptoms were successfully identified based on comprehensive presentations. Identified hay fever symptoms were associated with various factors and preventive behaviors. mHealth demonstrated advantages in accumulating multidimensional and comprehensive population data that retain individualized elements through its wider outreach and digital phenotyping capabilities; it may also help in deciphering the pathophysiology underlying the heterogeneity of hay fever. mHealth implementation in medical research and practice may elucidate patterns in numerous heterogeneous pathologies beyond hay fever and lay a robust foundation for P4 medicine.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.12.004>.

Conflict of interest

AllerSearch was created using Apple's ResearchKit (Cupertino, CA, USA). Tin and YO are the owners of Innojin, Inc., Tokyo, Japan who developed AllerSearch. The rest of the authors have no conflict of interest.

Authors' contributions

Tin conceived the concept of this paper. All authors contributed to the development of the study protocol and collected the data. Tin, MN (d,e), and MI performed the data analysis and data visualization. Tin and YO performed funding acquisition. All authors reviewed the data analyses, advanced the concepts within the paper, and drafted the manuscript.

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Supplementary Data

SUPPLEMENTARY TABLES

Supplementary Table 1. Survey questions

Questions	Variables	Details of variables
User characteristics		
	Age	Integer input, years
	Sex	Choose one {'Man,' 'Woman'}
	Height	Integer input, cm
	Weight	Integer input, kg
Please provide information on your siblings. How many siblings do you have?	Sibling	Integer input, sibling count, sibling position

What is your position among your siblings (e.g., first-born, second-born)?		
Medical history		
Have you ever been diagnosed with hypertension?	Medicated hypertension	Choose one {'No,' 'I am being treated for hypertension,' 'I have untreated hypertension,' 'I do not know'}
Have you ever been diagnosed with diabetes?	Diabetes (HbA1c level)	Choose one {'Yes,' 'No,' 'I do not know'}. If 'Yes,' scale bar input of HbA1c level (5–15%)
Have you experienced any of the following illnesses?	Systemic diseases	Multiple choice among {'Heart disease,' 'Respiratory disease,' 'Brain disease,' 'Liver disease,' 'Kidney disease,' 'Blood disease,' 'Malignant tumor,' 'Collagen disease,' 'N/A'}
If you have eczema (atopic dermatitis), when	Atopic dermatitis	Choose one {'Infancy (before 1 year of age),' 'Early

did it start?		childhood (age 1–6 years),' 'Middle childhood (age 7–12 years),' Early adolescence (after the age of 13 years)'} }
Do you experience swollen lips after consuming products containing tomato?	Tomato allergy	Choose one {'Yes,' 'No'}
Do you have any mental illness?	Mental illness	Choose one {'No,' 'Yes', 'Previously had'}
Do you have any of the following mental illnesses?	Mental illness	If 'Yes' in the previous question, multiple choice among {'Depression,' 'Schizophrenia,' 'Other mental illness'}
Have you ever been diagnosed with dry eye disease?	Dry eye disease	Choose one {'No,' 'Yes', 'I do not know'}
Living environment		

What type of flooring do you have for your living room?	Living	Choose one {'Hardwood,' 'Carpet,' 'Tatami (Japanese straw-based floor),' 'Vinyl,' 'Other'}
What type of flooring do you have for your bedroom?	Bedroom	Choose one {'Hardwood,' 'Carpet,' 'Tatami (Japanese straw-based floor),' 'Vinyl,' 'Other'}
Do you currently own any pets?	Pet	Multiple choice among {'No,' 'Dog,' 'Cat,' 'Rabbit,' 'Rodents (such as hamsters, guinea pigs),' 'Birds,' 'Other'}
Lifestyle		
How many cups of coffee do you drink per day on average?	Coffee intake	Integer input, cups
Have you ever used contact lenses?	Contact lens use	Choose one {'I have been using contact lenses,' 'I have, but they were discontinued during hay fever season,' 'I

		have used contact lenses in the past,' 'I have never used contact lenses'}
What type of contact lenses do (or have) you use(d)?	Types of contact lenses	Choose one {'Soft/Daily disposable,' 'Soft/Bi-weekly disposable,' 'Soft/Monthly disposable,' 'Soft/Yearly disposable,' 'Hard,' 'Colored/Daily disposable,' 'Colored/Bi-weekly disposable,' 'Colored/Monthly disposable,' 'Colored/Yearly disposable'}
Please enter your exercise frequency and duration in the past week.	Exercise	Integer input, days and hours
Please select the major exercise type that you undertake.	Exercise category	Choose one {'Walking,' 'Light exercise,' 'Bowling' 'Swimming,' 'Equipment-based training,' 'Jogging,' 'Marathon,' 'Hiking,' 'Cycling,' 'Fishing,' 'Golfing

		(including indoor ranges),' 'Baseball (including catch ball),' 'Other'}
Are you using eye drops (artificial tears)?	Eye drops	Choose one {'Currently using (non-contact lens user),' 'Currently using without removing contact lens (contact lens user),' 'Currently using after removing contact lenses (contact lens user),' 'Not currently using'}
Do you use eye wash solutions? If yes, at what time of the day do you use them?	Eye wash	Multiple choice among {'Morning,' 'Afternoon,' 'Evening,' 'Before sleeping,' 'When symptoms worsen,' 'Do not use eye wash'}
Please enter the average frequency of bowel movements per week.	Bowel movements	Integer input, times
Please enter your average sleep duration per	Sleep duration	Integer input, hours

day.		
Do you currently smoke or have you smoked in the past?	Smoking	Choose one {'No,' 'Yes,' 'Have before'} If 'Yes' or 'Have before,' scale bar input of Number of cigarettes per day, Number of years smoked
How many times do you consume yogurt (or yogurt-containing products) per week?	Yogurt intake	Choose one {'Rarely,' 'Once a week,' 'Twice or thrice a week,' 'Four or five times a week,' 'Everyday'}
Hay fever		
Do you have hay fever?	Hay fever	Choose one {'Yes,' 'No,' 'Unknown'}
When did your hay fever start?	Hay fever onset	Integer input, years old
In which months of the year does your hay fever occur?	Months when hay fever develops	Multiple choice among {'January,' 'February,' 'March,' 'April,' 'May,' 'June,' 'July,' 'August,' 'September,' 'October,' 'November,' 'December'}

In which months of the year does your hay fever worsen?	Months when hay fever worsens	Multiple choice among {'January,' 'February,' 'March,' 'April,' 'May,' 'June,' 'July,' 'August,' 'September,' 'October,' 'November,' 'December'}
Have you ever received subcutaneous or sublingual allergen immunotherapy (desensitization/hyposensitization)?	Sublingual and subcutaneous desensitization therapy	Choose one {'Yes,' 'No'}
Please tell us which of the following hay fever prevention methods you have been using.	Preventive behavior	Multiple choice among {'Mask,' 'Eye drops,' 'Nasal spray/drops,' 'Medication,' 'Air purifier,' 'Glasses and goggles,' 'Other,' 'Not using any'}

Abbreviations: HbA1c, glycated hemoglobin; N/A, not applicable.

has been over the past 24 hours?	4	
How severely does hay fever affect your daily activities?	NSS item 5	
How much eye itching did you experience over the past 24 hours?	NNSS item 1	
How much eye-watering did you experience over the past 24 hours?	NNSS item 2	
How much eye redness did you experience over the past 24 hours?	NNSS item 3	

How much itching of the ear and nose did you experience over the past 24 hours?	NNSS item 4	
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Abbreviations: NSS, nasal symptom score; NNSS, non-nasal symptom score.

Supplementary Table 3. Results from the generalization analysis to compare the included and excluded individuals

		Included individuals		Excluded individuals			Overall	
		N (%) = 11,284 (71.6)	Number of responses	N (%) = 4,465 (28.4)	Number of responses	<i>P</i> value	N (%) = 15,749 (100)	Number of responses
Demographic characteristics								
Age (years), median (IQR)		34 (23–46)	11,284	34 (24–47)	4,463	0.015	34 (24–46)	15,747
Women, N (%)		6,358 (56.3)	11,284	2,220 (49.7)	4,465	<.001	8,578 (54.5)	15,749
Height (cm), median (IQR)		163 (157– 170)	11,284	165 (158– 171)	4,465	<.001	164 (157– 171)	15,749

Weight (kg), median (IQR)		59 (51–68)	11,284	60 (51–70)	4,465	<.001	59 (51–69)	15,749
Hay fever, N (%)	No	720 (6.4)	11,284	383 (8.6)	4,465	<.001	1,103 (7.0)	15,749
	Yes	9,041 (80.1)		3,524 (78.9)			12,565 (79.8)	
	Unknown	1,523 (13.5)		558 (12.5)			2,081 (13.2)	
Medical history								
Medicated hypertension, N (%)	No	9,069 (80.4)	11,284	3,478 (77.9)	4,465	0.002	12,547 (79.7)	15,749
	Medicated	631 (5.6)		309 (7.0)			940 (6.0)	

	Unmedicated	392 (3.5)		172 (3.9)			564 (3.6)	
	Unknown	1,192 (10.6)		506 (11.3)			1,698 (10.8)	
Diabetes, N (%)	No	10,019 (88.8)	11,284	3,873 (86.7)	4,465	<.001	13,892 (88.2)	15,749
	Yes	277 (2.5)		111 (2.5)			388 (2.5)	
	Unknown	988 (8.8)		481 (10.8)			1,469 (9.3)	
Systemic diseases, N (%)	Blood disease	165 (1.5)	11,284	62 (1.4)	4,465	.727	227 (1.4)	15,749
	Brain disease	128 (1.1)	11,284	58 (1.3)	4,465	.389	186 (1.2)	15,749

	Collagen disease	62 (0.6)	11,284	29 (0.7)	4,465	.455	91 (0.6)	15,749
	Heart disease	243 (2.2)	11,284	95 (2.1)	4,465	.920	338 (2.2)	15,749
	Kidney disease	197 (1.8)	11,284	99 (2.0)	4,465	.340	285 (1.1)	15,749
	Liver disease	180 (1.6)	11,284	62 (1.4)	4,465	.342	242 (1.5)	15,749
	Malignant tumor	165 (1.5)	11,284	59 (1.3)	4,465	.501	224 (1.4)	15,749
	Respirator y disease	1,027 (9.1)	11,284	378 (8.5)	4,465	.207	1,405 (8.9)	15,749

	N/A	9,383 (83.2)	11,284	3,754 (84.1)	4,465	.160	13,137 (83.4)	15,749
Atopic disease, N (%)		1,928 (17.1)	11,284	802 (18.0)	4,465	.191	2,730 (17.3)	15,749
Tomato allergy, N (%)		287 (2.5)	11,284	121 (2.7)	4,465	.553	408 (2.6)	15,749
Mental illness, N (%)	No	9,988 (88.5)	11,284	3,993 (89.4)	4,465	.176	13,981 (88.8)	15,749
	Yes	622 (5.5)		238 (5.3)			860 (5.5)	
	Previously had	674 (6.0)		234 (5.2)			908 (5.8)	
History of dry eye diagnosis,	No	5,854 (51.9)	11,284	2,367 (53.0)	4,465	.433	8,221 (52.2)	15,749

N (%)								
	Yes	2,507 (22.2)		973 (21.8)			3,480 (22.1)	
	Unknown	2,923 (25.9)		1,125 (25.2)			4,048 (25.7)	
Residential environment								
Living room, N (%)	Hardwood	8,081 (71.6)	11,284	3,255 (72.9)	4,465	.007	11,336 (72.0)	15,749
	Carpet	2,253 (20.0)		787 (17.6)			3,040 (19.3)	
	Tatami (Japanese straw-base d floor)	578 (5.1)		257 (5.8)			835 (5.3)	

	Vinyl	223 (2.0)		103 (2.3)			326 (2.1)	
	Other	149 (1.3)		63 (1.4)			212 (1.4)	
Bedroom, N (%)	Hardwood	7,041 (62.4)	11,284	2,781 (62.3)	4,465	.298	9,822 (62.4)	15,749
	Carpet	1,946 (17.3)		741 (16.6)			2,687 (17.1)	
	Tatami (Japanese straw-base d floor)	1,965 (17.4)		788 (17.7)			2,753 (17.5)	
	Vinyl	170 (1.5)		87 (2.0)			257 (1.6)	
	Other	162 (1.4)		68 (1.5)			230 (1.5)	
Pet, N (%)		3,740 (33.1)	11,284	1,380 (30.9)	4,465	.007	5,120 (32.5)	15,749

Lifestyle habits								
Coffee intake (cups per day), median (IQR)		1 (0–2)	11,284	1 (0–2)	4,457	.228	1 (0–2)	15,741
Contact lens use, N (%)	Current use	3841 (34.0)	11,284	1,374 (30.8)	4,465	<.001	5,215 (33.1)	15,749
	Discontin- ed during hay fever season	295 (2.6)		91 (2.0)			386 (2.5)	
	Past use	1,977 (17.5)		802 (18.0)			2,779 (17.7)	

	No	5,171 (45.8)		2,198 (49.2)			7,369 (46.8)	
Exercise (hours per week), median (IQR)		1 (0–2)	11,284	1 (0–2)	4,465	.610	1 (0–2)	15,749
Exercise (times per week), median (IQR)		1 (0–4)	11,283	1 (0–3)	4,465	.186	1 (0–3)	15,748
Eye drops, N (%)		5,621 (49.8)	11,284	2,076 (46.5)	4,465	<.001	7,697 (48.9)	15,749
Eye wash, N (%)		4,263 (37.8)	11,284	1,514 (33.9)	4,465	<.001	5,777 (36.7)	15,749
Bowel		6 (3–7)	11,284	5 (3–7)	4,465	.119	6 (3–7)	15,749

movements (times per week), median (IQR)								
Sleep duration (hours per day), median (IQR)		6 (6–7)	11,284	6 (6–7)	4,459	.349	6 (6–7)	15,749
Smoking habit, N (%)	No	7,856 (69.6)	11,284	3,054 (68.4)	4,465	.325	10,910 (69.3)	15,749
	Yes	1,710 (15.2)		705 (15.8)			2,415 (15.3)	
	Previously had	1,718 (15.2)		706 (15.8)			2,424 (15.4)	

Yogurt intake, N (%)	Rarely	4,834 (42.8)	11,284	1,920 (43.0)	4,465	.647	6,754 (42.9)	15,749
	Once a week	2,082 (18.5)		844 (18.9)			2,926 (18.6)	
	Twice or thrice a week	1,760 (15.6)		713 (16.0)			2,473 (15.7)	
	Four or five times a week	902 (8.0)		360 (8.1)			1,262 (8.0)	
	Everyday	1,706 (15.1)		628 (14.1)			2,334 (14.8)	

Abbreviation: IQR, interquartile range; N/A, not applicable.

Supplementary Table 4. Geographic distribution of the participants

Prefecture	Participants, number (%)
Hokkaido	154 (1.36)
Aomori	49 (0.43)
Iwate	49 (0.43)
Miyagi	196 (1.74)
Akita	33 (0.29)
Yamagata	53 (0.47)
Fukushima	106 (0.94)
Ibaraki	205 (1.82)
Tochigi	150 (1.33)

Gunma	126 (1.12)
Saitama	711 (6.30)
Chiba	600 (5.32)
Tokyo	2510 (22.24)
Kanagawa	1070 (9.48)
Niigata	92 (0.82)
Toyama	54 (0.48)
Ishikawa	70 (0.62)
Fukui	40 (0.35)
Yamanashi	62 (0.55)
Nagano	104 (0.92)
Gifu	133 (1.18)

Shizuoka	282 (2.50)
Aichi	626 (5.55)
Mie	151 (1.34)
Shiga	134 (1.19)
Kyoto	286 (2.53)
Osaka	957 (8.48)
Hyogo	512 (4.54)
Nara	135 (1.20)
Wakayama	73 (0.65)
Tottori	29 (0.26)
Shimane	36 (0.32)
Okayama	106 (0.94)

Hiroshima	189 (1.67)
Yamaguchi	88 (0.78)
Tokushima	45 (0.40)
Kagawa	57 (0.51)
Ehime	92 (0.82)
Kochi	27 (0.24)
Fukuoka	432 (3.83)
Saga	52 (0.46)
Nagasaki	92 (0.82)
Kumamoto	107 (0.95)
Oita	85 (0.75)
Miyazaki	50 (0.44)

Kagoshima	59 (0.52)
Okinawa	15 (0.13)
Total	11,284 (100)

Supplementary Table 5. Characteristics of individuals with hay fever in spring, autumn, and both seasons

		Hay fever				
	Season	Spring	Autumn		Spring and Autumn	
		N (%) = 4,622 (65.0)	N (%) = 316 (4.4)	<i>P</i> value	N (%) = 2,169 (30.5)	<i>P</i> value
Demographic characteristics						
Age (years), median (IQR)		32 (23–44)	36 (25–48.5)	.006	30 (22-43)	<.001
Women, N (%)		2,461 (53.3)	182 (57.6)	.134	1,469 (67.7)	<.001
Height (cm), median (IQR)		164 (158–171)	162 (156–170)	.014	161 (156-168)	< .001
Weight (kg),		59 (51–68)	58.5 (50–68)	.356	56 (50-67)	< .001

median (IQR)						
Medical history						
Medicated hypertension, N (%)	No	3,757 (81.3)	242 (76.6)	.120	1,801 (83.0)	.022
	Medicated	217 (4.7)	23 (7.3)		82 (3.8)	
	Unmedicated	159 (3.4)	13 (4.1)		50 (2.3)	
	Unknown	489 (10.6)	38 (12.0)		236 (10.9)	
Diabetes, N (%)	No	4,108 (88.9)	276 (87.3)	.457	1,942 (89.5)	.054
	Yes	99 (2.1)	10 (3.2)		28 (1.3)	
	Unknown	415 (6.8)	30 (9.5)		199 (9.2)	
Systemic diseases, N (%)	Blood disease	70 (1.5)	7 (2.2)	.331	30 (1.4)	.675

	Brain disease	42 (0.9)	9 (2.9)	.001	26 (1.2)	.263
	Collagen disease	18 (0.4)	3 (1.0)	.139	15 (0.7)	.095
	Heart disease	94 (2.0)	6 (1.9)	.869	40 (1.8)	.600
	Kidney disease	80 (1.7)	7 (2.2)	.527	44 (2.0)	.393
	Liver disease	82 (1.8)	7 (2.2)	.569	27 (1.2)	.106
	Malignant tumor	63 (1.4)	5 (1.6)	.746	25 (1.2)	.475
	Respiratory disease	343 (7.4)	41 (13.0)	< .001	328 (15.1)	< .001
	N/A	3,907 (84.5)	244 (77.2)	.001	1,705 (78.6)	< .001

Atopic dermatitis, N (%)		761 (16.5)	62 (19.6)	.145	512 (23.6)	< .001
Tomato allergy, N (%)		109 (2.4)	7 (2.2)	.871	94 (4.3)	< .001
Mental illness, N (%)	No	4,132 (89.4)	268 (84.8)	.040	1,846 (85.1)	< .001
	Yes	226 (4.9)	22 (7.0)		168 (7.8)	
	Previously had	264 (5.7)	26 (8.2)		155 (7.2)	
History of dry eye diagnosis, N (%)	No	2,467 (53.4)	150 (47.5)	.049	990 (45.6)	< .001
	Yes	977 (21.1)	84 (26.6)		602 (27.8)	

	Unknown	1.178 (25.5)	82 (26.0)		577 (26.6)	
Residential environment						
Living room, N (%)	Hardwood	3,345 (72.4)	217 (68.7)	.472	1,557 (71.8)	.308
	Carpet	920 (19.9)	74 (23.4)		418 (19.3)	
	Tatami (Japanese straw-based floor)	216 (4.7)	17 (5.4)		125 (5.8)	
	Vinyl	91 (2.0)	4 (1.3)		40 (1.8)	
	Other	50 (1.1)	4 (1.3)		29 (1.3)	
Bedroom, N (%)	Hardwood	2,888 (62.5)	200 (63.3)	.041	1,374 (63.4)	.572

	Carpet	841 (18.2)	48 (15.2)		364 (16.8)	
	Tatami (Japanese straw-based floor)	773 (16.7)	64 (20.3)		368 (17.0)	
	Vinyl	64 (1.4)	2 (0.6)		37 (1.7)	
	Other	56 (1.2)	2 (0.6)		26 (1.2)	
Pet, N (%)		1,446 (31.3)	112 (35.4)	.124	803 (37.0)	< .001
Lifestyle habits						
Coffee intake (cups per day), median (IQR)		1 (0–2)	1 (0–2)	.432	1 (0–2)	.019

Contact lens use, N (%)	No	2,083 (45.1)	155 (49.1)	.004	941 (43.4)	.035
	Discontinued during hay fever season	754 (16.3)	68 (21.5)		410 (18.9)	
	Past use	155 (3.4)	5 (1.6)		59 (2.7)	
	Current use	1,630 (35.3)	88 (27.9)		759 (35.0)	
Exercise (hours per week), median (IQR)		1 (0–2)	1 (0–3)	.346	1 (0–2)	.589
Exercise (times per week), median		1 (0–3)	1 (0–3)	.548	1 (0–4)	.929

(IQR)						
Bowel movements (times per week), median (IQR)		6 (3–7)	6 (3–7)	.323	6 (3–7)	.940
Sleep duration (hours per day), median (IQR)		6 (6–7)	6 (6–7)	.642	6 (6–7)	.870
Smoking habit, N (%)	No	3,265 (70.6)	229 (72.5)	.318	1,534 (70.7)	.879
	Yes	681 (14.7)	37 (11.7)		311 (14.3)	
	Previously had	676 (14.6)	50 (15.8)		324 (14.9)	

Yogurt intake, N (%)	Rarely	1,964 (42.5)	145 (45.9)	.683	926 (42.7)	.959
	Once a week	826 (17.9)	57 (18.0)		401 (18.5)	
	Twice or thrice a week	756 (16.4)	51 (16.1)		344 (15.9)	
	Four or five times a week	391 (8.5)	22 (7.0)		179 (8.3)	
	Everyday	685 (14.8)	41 (13.)		319 (14.7)	
Symptoms						
Nasal symptom score, 0–4, median (IQR)						

Rhinorrhea		1 (0-2)	1 (0-2)	< .001	1 (1-2)	< .001
Nasal congestion		1 (0-1)	1 (0-2)	.008	1 (0-2)	< .001
Nasal itching		0 (0-1)	1 (0-1)	.039	1 (0-2)	< .001
Sneezing		1 (0-1)	1 (0-2)	.125	1 (0-2)	< .001
Effects on daily life		1 (0-2)	1 (0-2)	.007	1 (0-2)	< .001
Total nasal symptom score, 0– 20		3 (1-6)	4 (2-7)	< .001	4 (2-7)	< .001
Non-nasal symptom score, 0– 4, median (IQR)						
Eye itching		1 (0-2)	1 (0-2)	.227	1 (0-2)	< .001

Tearing		0 (0-1)	0 (0-1)	.018	0 (0-1)	< .001
Eye redness		0 (0-1)	0 (0-1)	.017	0 (0-1)	.003
Ear and/or mouse itching		0 (0-1)	0 (0-1)	< .001	0 (0-1)	< .001
Total non-nasal symptoms score, 0– 16		1 (0-4)	2 (0.5-4)	< .001	2 (0-4)	< .001
Total nasal and non-nasal symptoms score, 0–36		5 (2-9)	6 (3-11)	< .001	6 (3-11)	< .001

Abbreviation: IQR, interquartile range.

Supplementary Table 6. Association between hay fever onset and severe hay fever symptoms in individuals with hay fever

		Univariate linear regression			Multivariable linear regression		
Variables		Coefficient	95% CI	<i>P</i> value	Coefficient	95% CI	<i>P</i> value
Hay fever onset, age (every 1 year)		-.091	-.102--.081	< .001	-.066	-.077--.056	< .001
Female sex		2.063	1.829–2.297	< .001	1.526	1.267–1.784	< .001
Body mass index		-.103	-.136--.071	< .001	-.003	-.036--.031	.869
Medicated hypertension		-1.700	-2.218--1.182	< .001	.158	-.380--.695	.566
Diabetes	No	1 (reference)	–	–	1 (reference)	–	–
	Yes	-1.639	-2.437--.841	< .001	-.209	-1.005--.587	.607
	Unknown	1.327	.902–1.752	< .001	.788	.372–1.203	< .001

Atopic dermatitis		.642	.334–.949	< .001	.189	-.113–.490	.220
Systemic disease, yes	Blood disease	-1.079	-2.050–.107	.030	.582	-.494–1.659	.289
	Brain disease	-.675	-1.813–.463	.245	1.479	.246–2.712	.019
	Collagen disease	-.282	-1.921–1.357	.736	1.076	-.599–2.751	.208
	Heart disease	-.733	-1.575–.108	.088	1.080	.097–2.062	.031
	Kidney disease	-1.032	-1.921–.145	.023	.759	-.266–1.784	.147
	Liver disease	-.165	-1.070–.740	.721	1.904	.879–2.929	< .001
	Malignant tumor	-1.473	-2.467–.480	.004	.944	-.220–2.108	.112
	Respiratory disease	.257	-.146–.661	.212	1.682	.866–2.499	< .001

	None	.570	.257–.882	< .001	2.022	1.194–2.851	< .001
Mental illness	No	1 (reference)	–	–	1 (reference)	–	–
	Yes	.781	.262–1.300	.003	.070	-.439–.579	.787
	Previously had	.373	-.124–.869	.141	-.0196	-.501–.461	.936
History of dry eye diagnosis	No	1 (reference)	–	–	1 (reference)	–	–
	Yes	1.097	.804–1.390	< .001	.724	.427–1.021	< .001
	Unknown	1.471	1.187–1.756	< .001	1.019	.739–1.300	< .001
Tomato allergy		1.979	1.255–2.702	< .001	1.273	.572–1.976	< .001
Coffee intake, cups per day		-.446	-.524–-.369	< .001	-.170	-.252–-.087	< .001
Contact lens use	No	1 (reference)	–	–	1 (reference)	–	–

	Past use	-.439	-.767--.111	.009	-.334	-.657--.012	.042
	Discontinued during hay fever season	2.202	1.512–2.891	< .001	1.705	1.035–2.375	< .001
	Current use	.784	.517–1.050	< .001	.010	-.261–.281	.941
Exercise, hours per week		.009	-.005–.022	.221	.002	-.011–.015	.756
Bowel movement, times per week		-.041	-.069--.012	.005	-.006	-.033–.022	.696
Smoking habit	No	1 (reference)	–	–	1 (reference)	–	–
	Yes	.121	-.218–.460	.483	.619	.281–.956	< .001
	Previously had	-1.106	-1.439--.772	< .001	-.072	-.407–.262	.673

Pet		.577	.327–.828	< .001	.304	.061–.548	.014
Sleep duration, hours per day		.205	.104–.306	< .001	.051	-.048–.150	.310
Yogurt intake	Rarely	1 (reference)	–	–	1 (reference)	–	–
	Once a week	-.130	-.460–.120	.440	-.095	-.413–.224	.561
	Twice or thrice a week	-.467	-.812–.122	.008	-.385	-.719–.051	.024
	Four or five times a week	-.804	-1.254–.354	< .001	-.533	-.969–.098	.016
	Everyday	-1.075	-1.425–.726	< .001	-.493	-.836–.150	.005
Living room	Hardwood	1 (reference)	–	–	1 (reference)	–	–
	Carpet	.700	.399–1.001	< .001	.368	.044–.691	.026

	Tatami (Japanese straw-based floor)	.624	.092–1.156	.021	.507	-.038–1.051	.068
	Vinyl	-.391	-1.262–.481	.380	-.736	-1.843–.371	.193
	Other	1.916	.816–3.017	.001	1.006	-.229–2.240	.110
Bedroom	Hardwood	1 (reference)	–	–	1 (reference)	–	–
	Carpet	.573	.252–.893	< .001	.252	-.0915–.595	.151
	Tatami (Japanese straw-based floor)	-.062	-.380–.256	.701	.043	-.285–.373	.794

	Vinyl	.077	-.952–1.105	.884	.431	-.873–1.735	.517
	Other	1.865	.797–2.933	.001	.764	-.434–1.963	.211

Abbreviation: CI, confidence interval.

Supplementary Table 7. Association between affected period from the onset and severe hay fever symptoms in individuals with hay fever

		Univariate linear regression			Multivariable linear regression		
Variables		Coefficient	95% CI	<i>P</i> value	Coefficient	95% CI	<i>P</i> value
Affected period, years		-.082	-.093--0.071	< .001	-.049	-.061--0.038	< .001
Female sex		2.063	1.829–2.297	< .001	1.424	1.163–1.684	1.684
Body mass index		-.103	-.136--0.071	< .001	-.010	-.043--0.024	.561
Medicated hypertension		-1.700	-2.218--1.182	< .001	-.179	-.714--0.355	.511
Diabetes	No	1 (reference)	—	—	1 (reference)	—	—
	Yes	-1.639	-2.437--0.841	< .001	-.435	-1.23--0.363	.285

	Unknown	1.327	.902–1.752	< .001	.802	.385–1.219	< .001
Atopic dermatitis		.642	.334–.949	< .001	.417	.115–.718	.007
Systemic disease, yes	Blood disease	-1.079	-2.050–.107	.030	.696	-.384–1.776	.207
	Brain disease	-.675	-1.813–.463	.245	1.474	.236–2.712	.020
	Collagen disease	-.282	-1.921–1.357	.736	1.172	-.509–2.853	.172
	Heart disease	-.733	-1.575–.108	.088	1.177	.191–2.163	.019
	Kidney disease	-1.032	-1.921–.145	.023	.851	-.177–1.880	.105
	Liver disease	-.165	-1.070–.740	.721	2.113	1.083–3.142	< .001
	Malignant tumor	-1.473	-2.467–.480	.004	1.009	-.160–2.177	.091
	Respiratory	.257	-.146–.661	.212	1.954	1.135–2.773	< .001

	disease						
	None	.570	.257–.882	< .001	2.192	1.362–3.023	< .001
Mental illness	No	1 (reference)	–	–	1 (reference)	–	–
	Yes	.781	.262–1.300	.003	.154	-.356–.665	.553
	Previously had	.373	-.124–.869	.141	.015	-.468–.497	.953
History of dry eye diagnosis	No	1 (reference)	–	–	1 (reference)	–	–
	Yes	1.097	.804–1.390	< .001	.688	.390–.986	< .001
	Unknown	1.471	1.187–1.756	< .001	.998	.717–1.280	< .001
Tomato allergy		1.979	1.255–2.702	< .001	1.451	.746–2.156	< .001
Coffee intake, cups per day		-.446	-.524–-.369	< .001	-.197	-.279–-.114	< .001

Contact lens use	No	1 (reference)	–	–	1 (reference)	–	–
	Past use	-.439	-.767–-.111	.009	-.398	-.721–-.074	.016
	Discontinued during hay fever season	2.202	1.512–2.891	< .001	1.737	1.065–2.410	< .001
	Current use	.784	.517–1.050	< .001	.029	-.244–.301	.837
Exercise, hours per week		.009	-.005–.022	.221	.005	-.009–.018	.486
Bowel movement, times per week		-.041	-.069–-.012	.005	-.001	-.029–.027	.940
Smoking habit	No	1 (reference)	–	–	1 (reference)	–	–
	Yes	.121	-.218–.460	.483	.542	.204–.881	.002

	Previously had	-1.106	-1.439—-.772	< .001	-.183	-.518—-.152	.284
Pet		.577	.327—.828	< .001	.318	.073—.562	.011
Sleep duration, hours per day		.205	.104—.306	< .001	.046	-.054—.145	.369
Yogurt intake	Rarely	1 (reference)	—	—	1 (reference)	—	—
	Once a week	-.130	-.460—.120	.440	-.071	-.390—.249	.666
	Twice or thrice a week	-.467	-.812—.122	.008	-.415	-.750—.080	.015
	Four or five times a week	-.804	-1.254—.354	< .001	-.534	-.972—.097	.017
	Everyday	-1.075	-1.425—.726	< .001	-.502	-.848—.157	.004
Living room	Hardwood	1 (reference)	—	—	1 (reference)	—	—

	Carpet	.700	.399–1.001	< .001	.366	.041–.691	.027
	Tatami (Japanese straw-based floor)	.624	.092–1.156	.021	.562	.016–1.108	.044
	Vinyl	-.391	-1.262–.481	.380	-.723	-1.834–.389	.203
	Other	1.916	.816–3.017	.001	.972	-.268–2.211	.124
Bedroom	Hardwood	1 (reference)	–	–	1 (reference)	–	–
	Carpet	.573	.252–.893	< .001	.233	-.112–.577	.185
	Tatami (Japanese straw-based	-.062	-.380–.256	.701	-.021	-.351–.308	.899

	floor)						
	Vinyl	.077	-.952–1.105	.884	.496	-.813–1.805	.458
	Other	1.865	.797–2.933	.001	.874	-.329–2.077	.155

Abbreviation: CI, confidence interval.