Academic productivity of young people with allergic rhinitis: A MASK-air® study

Short title: Allergen immunotherapy improves school performance

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Abstract

Background: Several studies have suggested an impact of allergic rhinitis on academic productivity. However, large studies with real-world data (RWD) are not available.

Objective: To use RWD to assess the impact of allergic rhinitis on academic performance (measured through a visual analog scale – VAS education – and the WPAI+CIQ:AS questionnaire), and to identify factors associated with the impact of allergic rhinitis on academic performance.

Methods: We assessed data from the MASK-air® mHealth app of users aged 13-29 years with allergic rhinitis. We assessed the correlation between variables measuring the impact of allergies on academic performance (VAS education, WPAI+CIQ:AS impact of allergy symptoms on academic performance, and WPAI+CIQ:AS percentage of education hours lost due to allergies), and other variables. Additionally, we identified factors associated with the impact of allergic symptoms on academic productivity through multivariable mixed models.

Results: 13,454 days (from 1,970 patients) were studied. VAS education was strongly correlated with the WPAI+CIQ:AS impact of allergy symptoms on academic productivity (Spearman correlation coefficient=0.71 [95%CI=0.58;0.80]), VAS global allergy symptoms (0.70 [95%CI=0.68;0.71]), and VAS nose (0.66 [95%CI=0.65;0.68]). In multivariable regression models, immunotherapy showed a strong negative association with VAS education (regression coefficient=-2.32 [95%CI=-4.04;-0.59]). Poor rhinitis control, measured by the combined symptom-medication score, was associated with worse VAS education (regression coefficient=0.88 [95%CI=0.88;0.92]), higher impact on academic productivity (regression coefficient=0.69 [95%CI=0.49;0.90]), and higher percentage of missed education hours due to allergy (regression coefficient=0.44 [95%CI=0.25;0.63]).

Conclusion: Allergy symptoms and worse rhinitis control are associated with worse academic productivity, while immunotherapy is associated with higher productivity.

Highlights box

- **What is already known about this topic?** Children with poorly controlled rhinitis may have diminished academic performance, although studies relying on real-world data and assessing factors modifying the impact of rhinitis on academic productivity are lacking.
- **What does the article add to our knowledge?** Results of this mHealth-based study suggest that (i) worse rhinitis control is associated with worse academic productivity, and that (ii) immunotherapy (but not medication use) is associated with improved academic productivity.
- **How does this study impact current management guidelines?** This study points to the importance of achieving a good rhinitis control among students, as well as to the need to better inform patients of effective available rhinitis treatments.

Keywords

Allergic rhinitis, MASK, real-world data, mobile health, academic productivity.

Abbreviations

AR: Allergic rhinitis

CI: Confidence interval

CSMS: Combined Symptom-Medication Score

IQR: Interquartile range

RWD: Real-world data

SCIT: Subcutaneous immunotherapy

SD: Standard deviation

SLIT: Sublingual immunotherapy

VAS: Visual Analog Scale

WPAI+CIQ:AS: Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific

Introduction

Allergic rhinitis (AR) is a highly prevalent disease, affecting more than 400 million people worldwide[1]. Its prevalence in children and adolescents shows great variability throughout the world, but AR may affect up to one-third of the population in the 13-14 years age interval[2]. Its bothersome symptoms may not only affect the quality of life[3,4], but also impair work and academic performance[5-9]. Several observational studies have shown that children with poorly controlled AR may have diminished examination performance[9], cognitive function and learning[10,11], and that their academic performance may thereby be affected [9-14]. However, studies on factors modifying the impact of allergic rhinitis on academic productivity are lacking.

These studies can be complemented with real-world data (RWD) obtained from mobile apps. MASK-air® is one of such mobile apps. It is a Good Practice of DG Santé for digitally-enabled patient-centered care in rhinitis and asthma multimorbidity[15,16]. In MASK-air®, users fill in a daily questionnaire assessing the impact of AR and asthma by means of visual analog scales (VASs)[16-21]. One of these VASs assesses the degree to which the users' symptoms impact their academic activities ("VAS education"). Moreover, in MASK-air®, academic activities are assessed at baseline when users start to use the app, and by an optional questionnaire, the Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI+CIQ:AS)[22-25]. Although several studies based on RWD from MASK-air® have been published, including studies on the impact of AR symptoms on work productivity[26,27], these have been mostly restricted to the adult population[28-32], and academic productivity has not been assessed.

In this study, we aimed to assess the impact of AR on academic performance, assessed by means of VAS education and the WPAI+CIQ:AS[22]. In addition, we aimed to assess the effect of treatment and to identify factors associated with the impact of allergic symptoms on academic performance.

Methods

Study design

We performed a cross-sectional study using MASK-air® data. We assessed the correlation between variables measuring the impact of allergies on academic performance (VAS education, impact of allergy symptoms on academic performance, and the percentage of education hours lost due to allergies; the latter two variables being obtained with WPAI+CIQ:AS), and other MASK-air® variables. In addition, we performed multivariable regression analyses identifying factors associated with increased impact of allergic symptoms on academic productivity, in which the observations were clustered by user, country, and month of the year.

Setting and participants

MASK-air®, a mobile app launched in 2015, is currently available to be downloaded freely from the Google Play and Apple App Stores in 28 countries (www.mask-air.com). We included the daily monitoring data of education days from MASK-air® users with a self-reported diagnosis of AR from May 21, 2015 to January 9, 2022. Users ranged in age from the age of digital consent (13 to 16 years depending on the country[33]) to 29 years (upper age limit definition of youth according to the Eurostat[34]).

Ethics

MASK-air® is European Conformity (CE1) registered (meeting European Union safety, health and environmental requirements) and complies with the General Data Protection Regulation. All data are anonymously introduced by users, and geolocation-related data are subsequently "blurred" using k-anonymity. Users consented to having their data analyzed for scientific purposes in the terms and conditions. The use of MASK-air® secondary data for research purposes (including on academic productivity) has been approved by an independent review board (Köln-Bonn, Germany). As a result, an independent review board approval was not required for this specific study.

Data sources and variables

MASK-air® currently comprises a daily monitoring questionnaire assessing the impact of allergy symptoms through four mandatory VASs on a 0 to 100 scale (with higher values indicating worse symptoms; Table E1). In addition, if users report that they are attending school or classes on that day, they are asked how much their allergic symptoms affected their academic performance on

that day by means of a 0-100 VAS ("VAS education"), with higher values indicating higher impact of allergic symptoms.

When reporting daily VAS, MASK-air® users are also asked to provide their daily medication use by means of a scroll list customized for each country. Based on reported medication, we were able to quantify days with no medication, days under monotherapy, and days under co-medication, for both AR and asthma. In order to more closely follow patient perspectives, monotherapy was defined as days with only one single medication being reported (use of a single drug formulation even if with more than one active compound[35-37]; for example, because nasal azelastine-fluticasone is a fixed combination, it is considered as monotherapy). Co-medication was defined as days with two or more medications/drug formulations.

In addition to the daily monitoring of symptoms and medication, MASK-air® users provide clinical and demographic information when setting up their profile. Given such baseline information, we were able to compute the number of reported allergy symptoms ("baseline symptoms"), and the number of different ways in which allergy symptoms affect the users ("baseline impact").

Users may also opt to respond to other questionnaires (i.e., non-mandatory questionnaires not included in the daily monitoring questionnaire), including the WPAI+CIQ:AS[22-25]. This is a 9-item patient-reported questionnaire assessing the weekly impact of allergies on work and academic productivity (Table E2). One question relates to the perceived impact of allergy symptoms on academic productivity (scored from 0 to 100, with higher values indicating higher perceived impact of allergic symptoms). The questionnaire also includes a question on the weekly number of hours spent attending school or classes, as well as one on the number of hours of school or classes missed in the past seven days due to allergies. We used the data provided by the users in these two questions to compute the outcome variable "Percentage of missed education hours".

Sample size

We analyzed all data from users meeting the eligibility criteria and with valid data. No sample size calculation was performed.

Biases

We addressed potential variability associated with age, by excluding patients aged over 29 years. There are potential information biases related to the self-reported nature of data collection. Potential selection bias may exist because app users are not representative of all patients with AR.

Statistical analysis

When responding to the MASK-air® daily monitoring questionnaire, it is not possible to skip any of the questions, and data are saved to the dataset only after the final answer. This precludes any missing data within each questionnaire.

Categorical variables were described using absolute and relative frequencies, while continuous variables were described using medians and interquartile ranges (IQRs). To account for the COVID-19 pandemic,[38,39] we calculated median VAS education before and after March 1, 2020.

Correlations between continuous variables (in particular, between education-related variables – VAS education, the percentage of missed education hours, and the perceived impact of allergy symptoms on academic productivity – and the remaining VASs and the cluster-based Combined Symptom-Medication Score [CSMS][30]) were assessed by computing Spearman correlation coefficients between these variables, as well as the repeated measures correlation coefficient, to account for repeated observations provided by the same users[40].

We subsequently identified the variables associated with VAS education by means of multilevel mixed-effects models[41], considering the clustering of observations by users, by country, and by month of the year (i.e., we adjusted our comparisons according to the clustering of multiple observations by users, of the users' country, and the month of the year in which the observation occurred). We selected the following independent variables for our regression model on VAS education: baseline impact of allergic rhinitis, baseline symptoms of allergic rhinitis, gender, age, self-reported diagnosis of asthma, VAS nose, VAS eyes, VAS asthma, use of immunotherapy, and use of medications. Given the existence of some variables highly correlated with those independent variables included in our model, we performed three additional regression analyses (sensitivity analyses), by (1) specifying types of immunotherapy and drug usage patterns (i.e., monotherapy *vs*. co-medication); (2) including VAS global while excluding VAS eyes and VAS nose; and (3) replacing all VASs and medication-related independent variables by the CSMS.

Finally, we identified variables potentially associated with the percentage of missed education hours and the impact of allergy symptoms on academic productivity by multilevel mixed-effects models, accounting for the clustering of observations by users and by countries. Given the smaller number of users reporting data on the WPAI:AS+CIQ questionnaire, independent variables in the model were selected by a backward stepwise approach, with the final models including the variables with p-value<0.10.

316 *P*-values <0.05 were considered statistically significant. A Holm-Bonferroni correction was
317 applied to account for multiple analyses. All statistical analyses were performed using R (version
318 4.0.3).

Results

Demographic characteristics of the patients

We analyzed 13,454 days from 1,970 patients aged 13 to 29 years (mean ± SD = 20.1 ± 4.1 years) (Figure E1), 60.3% of the observations being from female users (Table 1; Table E3 for distribution per each of the 27 countries). The median VAS education was 17 (IQR=28), with VAS education≥50/100 being observed in 1,757 days (13.1%). The median VAS education for patients with a self-reported diagnosis of asthma was 16 (IQR=27), while for those without asthma, it was 17 (IQR=27). Comparing patients by age group, the median VAS education level was higher for those aged 25-29 years (22) than for those aged 20-24 years (17) or 13-19 years (15) (Table E4). The median VAS education was 18 (IQR=28) before March 1, 2020, and 14 (IQR=24) afterwards. Figure 1 shows the seasonal trends of VAS education.

The WPAI+CIQ:AS was filled in for 125 weeks (by 107 different users; Table E5), with 44 (35.2%; 95%CI=26.2-44.2%) indicating the loss of at least some education hours due to allergies, and the median score of allergy impact on academic productivity being of 37.0 (IQR=48.0). In the pre-pandemic period, 32.4% (24/74) of the users indicated the loss of at least some education hours due to allergy, compared to 46.9% (15/32) in the post-pandemic period.

Correlations

VAS education was correlated with all variables (Table 2). It showed the strongest correlations with the WPAI+CIQ:AS impact of allergy symptoms on education productivity (Spearman rank correlation [95%CI]: ρ=0.71 [0.58;0.80]), the CSMS (ρ=0.70 [0.69;0.71]), VAS global (ρ=0.70 [0.68;0.71]), and VAS nose (ρ=0.66 [0.65;0.68]) (Table 2 and Figure 2). Similar results were obtained when correlations were assessed using repeated measures correlation coefficients for all variables except VAS asthma. The Spearman correlation coefficients between VAS asthma and education-related variables (VAS education and WPAI+CIQ:AS impact of allergy symptoms on academic productivity and percentage of hours missed) were consistently higher for patients with a self-reported diagnosis of asthma compared to those without a diagnosis of asthma (Table E6). Similar results were obtained in the repeated measures correlation between VAS asthma and VAS education (Table E6).

The WPAI+CIQ:AS impact on education was correlated with all other variables, from 0.71 (VAS education) to 0.37 (VAS asthma) (Table 2). However, no correlation was found for VAS asthma using repeated measures correlation coefficients (Table 2).

Multivariable regression analyses

In the main regression model, a baseline AR impact and VASs for ocular, nasal, and asthma symptoms were associated with VAS education, with VAS nose showing the strongest positive association (regression coefficient=0.38 [95%CI=0.37;0.39]); that is, on average, VAS education increased by 0.38 units (95%CI=0.37;0.39) per each unit increase in VAS nose on a scale of 0-100.

Medications increased VAS education by 0.23 units (95%CI=-0.92;0.47) for single medication, and by 1.70 units (95%CI=0.72;2.68) for co-medication. This means that days on medication increase VAS education by 0.23 to 1.70 units on a scale of 0-100, when adjusted for other independent variables. By contrast, negative associations were observed with the use of immunotherapy (-2.32 [95%CI=-4.04;-0.59]), meaning that, on average, days on immunotherapy reduce VAS education (in a scale of 0-100) by 2.32 units, when adjusted for other independent variables. A negative association was also found for having a self-reported diagnosis of asthma (regression coefficient=-2.81 [95%CI=-4.22;-1.39]) (Table 3).

The percentage of missed education hours was positively associated with the CSMS (regression coefficient=0.44 [95%CI=0.25;0.63]; $p<0.001$), with no further variables having a p-value<0.001. We found that the WPAI+CIQ:AS impact on academic productivity was associated with the baseline impact of AR (regression coefficient=5.79 [95%CI=2.17;9.41) and with CSMS (regression coefficient=0.69 [95%CI=0.49;0.90]). We also found that it was negatively associated with the use of immunotherapy (regression coefficient=-10.83 [95%CI=-22.28;0.62]) (Table 4).

Finally, we performed additional sensitivity analyses using different sets of independent variables, and found similar results (Table 5). Importantly, when replacing all VASs and daily reported medications by the CSMS as an independent variable, the CSMS was also strongly associated with VAS education (regression coefficient=0.88 [95%CI=0.88;0.92]).

Discussion

In this study, we observed that (i) daily VAS education is highly correlated with WPAI+CIQ:AS impact on academic productivity (ii) allergic rhinitis has a relevant impact on academic performance, (iii) nasal symptoms (assessed by VAS nose) are the main set of symptoms associated with impaired academic performance; (iv) immunotherapy (but no other medications) can be associated with a decreased VAS education; and (v) the CSMS is correlated with both VAS education, percentage of missed education hours, and WPAI+CIQ:AS impact on academic productivity.

Strengths and limitations

This study has limitations related to the use of mHealth apps. Firstly, there is a possibility of selection biases in mHealth studies due to an overrepresentation of patients who are more concerned about their health and of those suffering from more severe disease[32,37]. In addition, patients under AIT are usually accompanied by specialists and, therefore, are likely to have more severe disease than those in the general population. On the other hand, the participants of the present study are similar to those of the entire database in terms of baseline symptoms[37] and VAS levels[36,37]. There were, however, fewer users reporting asthma, and an overrepresentation of users from Mexico (although main model results are similar when excluding data from Mexico – Table E7). Our multilevel mixed-effects models did, however, take into account the country of the user.

Since most patients use the app for short periods of time and intermittently[42], we designed a cross-sectional study with days as the unit of analysis (although patients were used to cluster the reporting days). This approach has been applied in many MASK-air® studies[26,32,35,37,43]. However, given the cross-sectional nature of this study, we cannot establish a temporal relationship or causality between different variables, which would be particularly relevant for assessing the effect of medications.

In this analysis, we did not exclude data reported on weekends or during holidays, as it is only possible to fill in VAS education when the user reports having attended school or classes on that day, and WPAI:AS+CIQ concerns the entire 7 days prior to the user filling in the questionnaire (the day of submission is therefore not relevant).

Additionally, while VASs are obtained daily and concern solely the day on which they are filled in, the WPAI+CIQ:AS questionnaire concerns the 7 days before. Furthermore, the number of observations of users having filled in the WPAI+CIQ:AS was small, given that this is not a mandatory questionnaire in MASK-air®.

Finally, we do not have access to patient-independent measures of academic performance (e.g., marks in examinations), and the latter could not therefore have been used as an outcome variable. However, this limitation is shared by all mHealth studies. In fact, it would hardly be feasible to collect objective measures of academic performance, as (i) there is a large volume of patients in many different countries, and (ii) the installing and use of MASK-air® occurs on a voluntary basis (i.e., patients are not enrolled by physicians).

This study also has important strengths. We assessed RWD from a large set of young users from 27 different countries, with the structure of MASK-air® precluding the existence of missing data within each daily questionnaire response. MASK-air® VASs, the WPAI:AS+CIQ questionnaire, and the CSMS are allergy-specific and have been previously assessed and validated[25,29,30]. We built multivariable mixed-effects models in which we clustered observations by patients, and adjusted the analyses considering relevant clinical and demographic variables to reduce confounding. We found similar results in different models in sensitivity analyses, pointing to the robustness of the results.

Interpretation of the data

This is the first MASK-air® study to assess the association between AR and academic impact. The results are comparable with previous studies on the impact of AR on work productivity, concerning the association between the control of the disease and VAS education or work levels.[26]

We found that 45% of days had a VAS education>20/100, with 13% of days showing a VAS education>50/100. This indicates that AR has an important impact on academic productivity. Importantly, we found not only differences in VAS education levels, but also dissimilar patterns in VAS education seasonality before and after the COVID-19 pandemic. The latter was associated with a decrease in median VAS education in March and April, and an increase in June and July. The reasons for this difference are unclear, but may be attributed to the more generalized adoption of online learning (e.g., with school closure), which was particularly relevant during the first months of the pandemic. This may have rendered some students less exposed to seasonal allergens. In fact, there are relevant differences in variables associated with VAS education when considering the periods before and during the pandemic (Table E8). Further studies on the impact of the COVID-19 pandemic on allergies are warranted.

We also found an association between AR control (assessed by means of VAS nose, VAS eye, and the CSMS) and academic productivity. Previous classic observational studies had shown the impact of AR on academic productivity[9-11,13,14]. Our study is based on multivariable mixed models, which does not allow the comparison of our study with previous ones. Nevertheless, our

study adds that nasal symptoms (assessed by means of VAS nose) display a stronger association with worse academic performance than eye and asthma symptoms in patients from 27 countries. Furthermore, our study considers asthma as a comorbidity in allergic rhinitis patients, unlike previous studies, which focus mostly on asthma or rhinitis in isolation[9-11,13,14].

The results for asthma, indeed, are less evident. On the one hand, having a self-reported diagnosis of asthma was negatively correlated with VAS education. On the other hand, VAS asthma was not associated with VAS education in multivariable regression. A previous study in a Korean population of adolescents had found allergic rhinitis to be associated with improved academic performance, and asthma with poorer academic performance[12]. As expected, we found stronger positive correlations between VAS asthma and VAS education in asthmatic patients than in those without a self-reported diagnosis of asthma. This points to the complexity of the interaction between asthma and rhinitis which should be explored in further studies specifically addressed for assessing patients with asthma.

The effect of pharmacologic treatment may be surprising since our models showed an association with higher VAS education levels. However, this finding needs to be carefully considered, integrating both disease control and medication usage. In previous MASK-air® studies, patients increase their medications when they are not well-controlled, and the overall control is significantly lower when co-medication is used.[36] In line with these considerations, in the present study, comedication was found to be associated with a significant reduction in academic productivity. Thus, to understand the role of medications in academic performance and quality of life, a longitudinal study will be needed[44,45].

By contrast, immunotherapy has already been shown to be associated with a higher academic performance in AR patients[8]. In this study, we also found a large reduction of VAS education in patients under immunotherapy. These data are in line with a previous MASK-air® study[28], but extend its results, as immunotherapy brings a new component adds to the therapeutic options in allergic rhinitis. In MASK-air®, medications are most likely to be used as symptomatic treatment[46], whereas immunotherapy acts on the global allergic inflammation. These considerations may help to understand the differences between the two treatments.

Importantly, these results further validate the CSMS proposed based on MASK-air observations[30]. It is the only variable that can consistently be associated with VAS education, the percentage of missed education hours, and the perceived impact of allergy symptoms on academic productivity.

Generalizability

This study includes users aged 13 to 29 years from 27 different countries. Our results may be extended to adolescents and young adults from high- and upper-middle-income countries. However, it does not necessarily apply to school-attending AR patients of a younger age that cannot be studied using MASK-air® due to the age requirement for children to use digital tools.

Conclusion

In patients with AR, allergy symptoms, especially nasal symptoms, were found to be associated with worse academic productivity (higher VAS education), while immunotherapy was associated with higher productivity. The CSMS is consistently associated with academic productivity, as assessed by both VAS education and WPAI+CIQ:AS. These findings underline previous research on (i) the impact of the undertreatment of allergies on the impairment of cognitive functions, and (ii) the importance of public awareness, in order to better inform patients of effective available treatments, and to consider the need to accommodate academic curricula to individual health conditions.

References

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
2. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. Allergol Immunopathol (Madr) 2013;41:73-85.
3. Canonica GW, Mullol J, Pradalier A, Didier A. Patient perceptions of allergic rhinitis and quality of life: findings from a survey conducted in europe and the United States. World Allergy Organ J 2008;1:138-44.
4. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. Int Arch Allergy Immunol 2013;160:393-400.
5. Vandenplas O, Vinnikov D, Blanc PD, Agache I, Bachert C, Bewick M, et al. Impact of Rhinitis on Work Productivity: A Systematic Review. J Allergy Clin Immunol Pract 2018;6:1274-86.e9.
6. de la Hoz Caballer B, Rodríguez M, Fraj J, Cerecedo I, Antolín-Amérigo D, Colás C. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the Cross-sectional study to evAluate work Productivity in allergic Rhinitis compared with other common dIseases (CAPRI) study. Am J Rhinol Allergy 2012;26:390-4.
7. Jauregui I, Mullol J, Davila I, Ferrer M, Bartra J, del Cuvillo A, et al. Allergic rhinitis and school performance. J Investig Allergol Clin Immunol 2009;19 Suppl 1:32-9.
8. Roger A, Arcalá Campillo E, Torres MC, Millan C, Jauregui I, Mohedano E, et al. Reduced work/academic performance and quality of life in patients with allergic rhinitis and impact of allergen immunotherapy. Allergy Asthma Clin Immunol 2016;12:40.
9. Walker S, Khan-Wasti S, Fletcher M, Cullinan P, Harris J, Sheikh A. Seasonal allergic rhinitis is associated with a detrimental effect on examination performance in United Kingdom teenagers: Case-control study. Journal of Allergy and Clinical Immunology 2007;120:381-7.
10. Kremer B, den Hartog HM, Jolles J. Relationship between allergic rhinitis, disturbed cognitive functions and psychological well-being. Clin Exp Allergy 2002;32:1310-5.
11. Wilken JA, Berkowitz R, Kane R. Decrements in vigilance and cognitive functioning associated with ragweed-induced allergic rhinitis. Ann Allergy Asthma Immunol 2002;89:372-80.
12. Kim SY, Kim MS, Park B, Kim JH, Choi HG. Allergic rhinitis, atopic dermatitis, and asthma are associated with differences in school performance among Korean adolescents. PLoS One 2017;12:e0171394.
13. Spaeth J, Klimek L, Mösges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. Allergy 1996;51:893-906.
14. Karande S, Kulkarni M. Poor school performance. Indian J Pediatr 2005;72:961-7.
15. Bousquet J, Anto JM, Bachert C, Bosnic-Anticevich S, Erhola M, Haahtela T, et al. From ARIA guidelines to the digital transformation of health in rhinitis and asthma multimorbidity. Eur Resp J 2019;54:1901023.
16. Bousquet J, Bedbrook A, Czarlewski W, Onorato GL, Arnavielhe S, Laune D, et al. Guidance to 2018 good practice: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma. Clin Transl Allergy 2019;9:16.
17. Bousquet J, Arnavielhe S, Bedbrook A, Bewick M, Laude D, Mathieu-Dupas E, et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. Clin Transl Allergy 2018;8:45.
18. Bousquet J, Anto JM, Bachert C, Haahtela T, Zuberbier T, Czarlewski W, et al. ARIA digital anamorphosis: Digital transformation of health and care in airway diseases from research to practice. Allergy 2021;76:168-90.

19. Bousquet JJ, Schünemann HJ, Togias A, Erhola M, Hellings PW, Zuberbier T, et al. Next-generation ARIA care pathways for rhinitis and asthma: a model for multimorbid chronic diseases. Clin Transl Allergy 2019;9:44.
20. Bousquet J, Anto JM, Haahtela T, Jousilahti P, Erhola M, Basagana X, et al. Digital transformation of health and care to sustain Planetary Health: The MASK proof-of-concept for airway diseases-POLLAR symposium under the auspices of Finland's Presidency of the EU, 2019 and MACVIA-France, Global Alliance against Chronic Respiratory Diseases (GARD, WH0) demonstration project, Reference Site Collaborative Network of the European Innovation Partnership on Active and Healthy Ageing. Clin Transl Allergy 2020;10:24.
21. Klimek L, Bergmann KC, Biedermann T, Bousquet J, Hellings P, Jung K, et al. Visual analogue scales (VAS): Measuring instruments for the documentation of symptoms and therapy monitoring in cases of allergic rhinitis in everyday health care: Position Paper of the German Society of Allergology (AeDA) and the German Society of Allergy and Clinical Immunology (DGAKI), ENT Section, in collaboration with the working group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Otorhinolaryngology, Head and Neck Surgery (DGHNOKHC). Allergo J Int 2017;26:16-24.
22. Reilly MC, Tanner A, Meltzer EO. Work, Classroom and Activity Impairment Instruments. Clinical Drug Investigation 1996;11:278-88.
23. Devillier P, Bousquet J, Salvator H, Naline E, Grassin-Delyle S, de Beaumont O. In allergic rhinitis, work, classroom and activity impairments are weakly related to other outcome measures. Clin Exp Allergy 2016;46:1456-64.
24. Reilly MC, Tanner A, Meltzer EO. Allergy impairment questionnaires: validation studies. J Allergy Clin Immunol 1996;97.
25. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353-65.
26. Bédard A, Antó JM, Fonseca JA, Arnavielhe S, Bachert C, Bedbrook A, et al. Correlation between work impairment, scores of rhinitis severity and asthma using the MASK-air(®) App. Allergy 2020;75:1672-88.
27. Bousquet J, Bewick M, Arnavielhe S, Mathieu-Dupas E, Murray R, Bedbrook A, et al. Work productivity in rhinitis using cell phones: The MASK pilot study. Allergy 2017;72:1475-84.
28. Pfaar O, Sousa-Pinto B, Devillier P, Canonica GW, Klimek L, Zuberbier T, et al. Effects of allergen immunotherapy in the MASK-air study: a proof-of-concept analysis. Allergy 2021;76:3212-4.
29. Sousa-Pinto B, Eklund P, Pfaar O, Klimek L, Zuberbier T, Czarlewski W, et al. Validity, reliability, and responsiveness of daily monitoring visual analog scales in MASK-air®. Clin Transl Allergy 2021;11:e12062.
30. Sousa-Pinto B, Azevedo LF, Jutel M, Agache I, Canonica GW, Czarlewski W, et al. Development and validation of combined symptom-medication scores for allergic rhinitis. Allergy 2022;77(7):2147-2162.
31. Sousa-Pinto B, Sá-Sousa A, Amaral R, Czarlewski W, Bedbrook A, Anto JM, et al. Assessment of the Control of Allergic Rhinitis and Asthma Test (CARAT) using MASK-air. J Allergy Clin Immunol Pract 2022;10(1):343-345.e2.
32. Bédard A, Sofiev M, Arnavielhe S, Anto JM, Garcia-Aymerich J, Thibaudon M, et al. Interactions between air pollution and pollen season for rhinitis using mobile technology: a MASK-POLLAR study. J Allergy Clin Immunol Pract 2020;8:1063-73. e4.
33. Digital consent around the world - Taylor Wessing's Global Data Hub. (Accessed 18/01/2022, 2022, at https://globaldatahub.taylorwessing.com/article/digital-consent-around-the-world.)
34. Overview Youth Eurostat. (Accessed 2021-01-10, 2021, at https://ec.europa.eu/eurostat/web/youth.)
35. Bousquet J, Devillier, P, Arnavielhe S, Bedbrook A, Alexis-Alexandre G, van Eeerd M. Treatment of allergic rhinitis using mobile technology with real world data: The MASK observational pilot study. Allergy 2018;73(9):1763-1774.
36. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. J Allergy Clin Immunol 2019;144:135-43 e6.

590 37. Bedard A, Basagana X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al.
591 Treatment of allergic rhinitis during and outside the pollen season using mobile technology.
592 A MASK study. Clin Transl Allergy 2020;10:62.
593 38. Sousa-Pinto B, Anto JM, Sheikh A, de Lusignan S, Haahtela T, Fonseca JA et al. Comparison
594 of epidemiologic surveillance and Google Trends data on asthma and allergic rhinitis in
595 England. Allergy 2022;77:675-8.
596 39. Sousa-Pinto B, Heffler E, Anto A, Czarlewski W, Bedbrook A, Gemicioglu B, et al.
597 Anomalous asthma and chronic obstructive pulmonary disease Google Trends patterns during
598 the COVID-19 pandemic. Clin Transl Allergy 2020;10:47.
599 40. Bakdash JZ, Marusich LR. Repeated Measures Correlation. Frontiers in Psychology 2017;8.
600 41. Tabachnick BG, Fidell LS. Using Multivariate Statistics: Pearson Education; 2013.
601 42. Menditto E, Costa E, Midao L, Bosnic-Anticevich S, Novellino E, Bialek S, et al. Adherence
602 to treatment in allergic rhinitis using mobile technology. The MASK Study. Clin Exp Allergy
603 2019;49:442-60.
604 43. Bousquet J, Devillier P, Anto JM, Bewick M, Haahtela T, Arnavielhe S, et al. Daily allergic
605 multimorbidity in rhinitis using mobile technology: A novel concept of the MASK study.
606 Allergy 2018;73:1622-31.
607 44. Price D, Klimek L, Galffy G, Emmeluth M, Koltun A, Kopietz F, et al. Allergic rhinitis and
608 asthma symptoms in a real-life study of MP-AzeFlu to treat multimorbid allergic rhinitis and
609 asthma. Clin Mol Allergy 2020;18:15.
610 45. van Weissenbruch R, Klimek L, Galffy G, Emmeluth M, Koltun A, Kopietz F, et al. MP-
611 AzeFlu Improves the Quality-of-Life of Patients with Allergic Rhinitis. J Asthma Allergy
612 2020;13:633-45.
613 46. Sousa-Pinto B, Sá-Sousa A, Vieira RJ, Amaral R, Klimek L, Czarlewski W, et al. Behavioural
614 patterns in allergic rhinitis medication in Europe: A study using MASK-air® real-world data.
615 Allergy. 2022.

Table 1. Demographic and clinical characteristics associated with included MASK-air® observations/days and respective users.

Variable	Summary
Observations/days – *N* [*N* users]	13,454 [1970]
Females – *N* (%)	8119 (60.3)
Age – mean (SD)	20.1 (4.1)
European country — *N* (%)	7572 (56.3)
Self-reported asthma – *N* (%)	3908 (29.0)[a]
Baseline impact of AR [b] – median (IQR)	1.0 (3.0)
Symptoms affect sleep – *N* (%)	3821 (29.2)
Symptoms restrict daily activities – *N* (%)	4231 (32.3)
Symptoms restrict work/education activities – *N* (%)	3412 (26.1)
Symptoms are troublesome – *N* (%)	8130 (62.2)
Baseline symptoms [c] – median (IQR)	5.0 (3.0)
Rhinorrhea – *N* (%)	10,416 (78.6)
Nasal pruritus – *N* (%)	9292 (70.4)
Sneezing – *N* (%)	10,885 (82.2)
Nasal congestion – *N* (%)	10,959 (83.0)
Red eyes – *N* (%)	5739 (43.5)
Ocular pruritus – *N* (%)	7723 (58.6)
Watery eyes – *N* (%)	6109 (46.6)
Medication for AR	
No medication – *N* (%)	7834 (58.2)
Single medication– *N* (%)	3727 (27.7)
Co-medication – *N* (%)	1893 (14.1)
Medication for asthma	
No medication – *N* (%)	11539 (85.8)
Single medication– *N* (%)	1439 (10.7)
Co-medication – *N* (%)	476 (3.5)
Medication class	
Oral antihistamines – *N* (%)	3674 (27.3)
Topical antihistamines – *N* (%)	521 (3.9)
Intranasal steroids – *N* (%)	2401 (17.8)
Azelastine+Fluticasone – *N* (%)	740 (5.5)
Asthma drugs – *N* (%)	1915 (14.2)
Other drugs – *N* (%)	373 (2.8)
Immunotherapy (Days of patients under immunotherapy) – *N* (%)	3949 (30.2) [d]
SCIT – *N* (%)	2647 (19.7)
SLIT – *N* (%)	1298 (9.6)
CSMS – median (IQR)[e]	14.5 (20.4)
VAS	
VAS global – median (IQR)	21 (34)
VAS eyes – median (IQR)	7 (24)
VAS nose – median (IQR)	22 (36)
VAS asthma – median (IQR)	0 (8)
VAS asthma in users with a self-reported diagnosis of asthma – median (IQR)	7 (22)
VAS asthma in users without a self-reported diagnosis of asthma – median (IQR)	0 (3)
VAS education – median (IQR)[f]	17 (28)
VAS education <20 – *N* (%)	7402 (55.0)
VAS education 20-49 – *N* (%)	4295 (31.9)
VAS education ≥50 – *N* (%) [g]	1757 (13.1)
VAS education in users with a self-reported diagnosis of asthma – median (IQR)	16 (27)

VAS education in users without a self-reported diagnosis of asthma – median (IQR)	17 (27)
VAS education in the pre-pandemic period (before March 2020) – median (IQR)	18 (28)
VAS education in the post-pandemic period (after March 2020) – median (IQR)	14 (24)
WPAI+CIQ:AS[h]	
Percentage of missed education hours in a week due to allergies – median (IQR)	0 (10.45) [i]
Weeks of loss of at least some education hours due to allergies – *N* (%)	44 (35.2)
Impact of allergy symptoms on academic productivity – median (IQR)	27.0 (48.0)

AR = Allergic Rhinitis; CSMS = Combined symptom-medication score IQR = Interquartile Range; SCIT = Subcutaneous immunotherapy; SD = Standard deviation; SLIT = Sublingual immunotherapy; VAS = Visual Analog Scale; WPAI+CIQ:AS = Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific.

[a] *N* distinct users = 612; [b] Computed based on the number of reported allergy symptoms at baseline. [c] Computed based on the number of different ways in which allergy symptoms affect the users at baseline. [d] *N* distinct users = 294 (SCIT=162; SLIT=82); [e] < 18 years (Median (IQR)) = 12.1 (18.1), ≥ 18 years (Median (IQR)) = 15.2 (21.0); [f] < 18 years (Median (IQR)) = 14.0 (15.3), ≥ 18 years (Median (IQR)) = 18.0 (16.6); [g] *N* distinct users = 746; [h] *N* observations = 137; [i] Mean (Standard Deviation) = 13.4 (26.4).

Table 2. Spearman and repeated measures correlation coefficients for outcome variables and relevant independent variables.

	VAS education	VAS eyes	VAS nose	VAS asthma	VAS global	CSMS	Percentage of hours missed
Spearman correlation - correlation coefficient (95% CI)							
VAS education		0.39 (0.38;0.40)	0.66 (0.65;0.68)	0.15 (0.13;0.17)[a]	0.70 (0.68;0.71)	0.70 (0.69;0.71)	
Impact of allergy symptoms on academic productivity	0.71 (0.58;0.80)	0.40 (0.26;0.54)	0.43 (0.27;0.58)	0.37 (0.21;0.52)	0.51 (0.35;0.64)	0.56 (0.39;0.68)	0.50 (0.34;0.63)
Education hours missed	0.38 (0.23;0.52)	0.43 (0.26;0.56)	0.22 (0.05;0.38)	0.39 (0.21;0.55)	0.27 (0.11;0.42)	0.41 (0.24;0.55)	
Repeated measures correlation – correlation coefficient (95% CI)							
VAS education		0.41 (0.40 ;0.43)	0.58 (0.57;0.59)	0.27 (0.26;0.29)[b]	0.63 (0.62;0.64)	0.65 (0.64;0.66)	
Impact of allergy symptoms on academic productivity	0.86 (0.65;0.95)	0.71 (0.34;0.89)	0.70 (0.32;0.88)	0.01 (-0.47;0.49)	0.62 (0.20;0.85)	0.74 (0.34;0.91)	0.30 (-0.21;0.68)
Education hours missed	0.04 (-0.44;0.51)	0.09 (-0.41;0.54)	0.03 (-0.46;0.50)	-0.11 (-0.56;0.39)	-0.17 (-0.60;0.34)	-0.10 (-0.60;0.46)	

CI = Confidence Interval; CSMS = Combined Symptom-Medication Score; VAS = Visual Analog Scale

[a] With self-reported asthma: 0.363 (95%CI=0.334;0.394) Without self-reported asthma: 0.079 (95%CI=0.060;0.100);

[b] With self-reported asthma: 0.371 (95%CI=0.341;0.400) Without self-reported asthma: 0.233 (95%CI=0.211;0.254)

Table 3. Association between VAS education and other individual characteristics.

	Association with VAS education		
	Regression coefficient	**95% CI**	***p*-value**
Baseline symptoms [a]	-0.30	-0.62;0.02	0.065
Baseline impact [b]	1.10	0.60;1.59	<0.001
Male gender	0.55	-0.77;1.87	0.417
Age	-0.06	-0.21;0.10	0.474
Immunotherapy	-2.32	-4.04;-0.59	0.009
Any medication	0.65	0.00;1.29	0.050
Self-reported asthma	-2.81	-4.22;-1.39	<0.001
VAS eyes	0.18	0.17;0.19	<0.001
VAS nose	0.38	0.37;0.39	<0.001
VAS asthma	0.19	0.17;0.21	<0.001

This model was obtained by multilevel mixed effects linear regression. Coefficients and their 95% confidence intervals take into account the clustering of observations by users, by countries, and by time of the year.
CI = Confidence Interval; VAS = Visual Analog Scale.
[a] Computed based on the number of reported allergy symptoms at baseline. [b] Computed based on the number of different ways in which allergy symptoms affect the users at baseline.

Table 4. Association between WPAI+CIQ:AS impact of allergy symptoms on academic productivity and other explanatory variables.

	Regression coefficient	95% CI	*p*-value
Baseline symptoms	-2.40	-4.95;0.16	0.070
Baseline impact	5.79	2.17;9.41	0.002
Immunotherapy	-10.83	-22.28;0.62	0.067
CSMS	0.69	0.48;0.90	< 0.001

Models were obtained by multilevel mixed effects linear regression. Coefficients and their 95% confidence intervals consider the clustering of observations by users, and by countries.
CI = Confidence Interval; CSMS = Combined Symptom-Medication Score.
[a] Computed based on the number of reported allergy symptoms at baseline. [b] Computed based on the number of different ways in which allergy symptoms affect the users at baseline.

Table 5. Sensitivity analyses of the association between VAS education and other independent variables.

	Specifying immunotherapy types and medication patterns – Coefficient (95%CI) [*p*-value]	Including VAS global and excluding VAS eyes and VAS nose – Coefficient (95%CI) [*p*-value]	Replacing VASs and medication variables by the CSMS – Coefficient (95%CI) [*p*-value]
Baseline symptoms [a]	1.05 (0.55;1.54) [<0.001]	1.16 (0.67;1.66) [<0.001]	0.58 (0.58;1.61) [<0.001]
Baseline impact [b]	-0.30 (-0.61;0.02) [<0.001]	-0.15 (-0.47;0.16) [0.339]	-0.65 (-0.65;0.01) [0.056]
Male gender	0.49 (-0.83;1.81) [0.068]	0.63 (-0.68;1.94) [0.346]	-0.22 (-0.22;2.49) [0.101]
Age	-0.05 (-0.07;-0.04) [0.464]	-0.14 (-0.29;0.02) [0.078]	-0.31 (-0.31;0.01) [0.071]
Immunotherapy		-2.58 (-4.29;-0.87) [0.003]	-4.42 (-4.42;-0.9) [0.003]
SCIT	-2.06 (-4.24;0.13) [0.492]		
SLIT	-2.72 (-5.56;0.13) [0.066]		
Medication		0.39 (-0.25;0.82) [0.234]	
Single medication for AR	0.23 (-0.47;0.92) [0.525]		
Co-medication for AR	1.70 (0.72;2.68) [<0.001]		
Single medication for asthma	0.89 (-0.41;2.19) [0.179]		
Co-medication for asthma	-0.64 (-2.88;1.60) [0.575]		
Self-reported asthma	-2.95 (-4.40;-1.49) [<0.001]	-2.81 (-4.21;-1.41) [<0.001]	-4.88 (-4.88;-2.02) [<0.001]
VAS eyes	0.18 (0.17;0.19) [<0.001]		
VAS nose	0.38 (0.37;0.39) [<0.001]		
VAS asthma	0.19 (0.17;0.21) [<0.001]	0.17 (0.15;0.19) [<0.001]	
VAS global		0.52 (0.51;0.53) [<0.001]	
CSMS			0.88 (0.88;0.92) [<0.001]

These models were obtained by multilevel mixed effects linear regression, by varying the set independent variables selected. Coefficients and their 95% confidence intervals consider the clustering of observations by users, by countries, and by month of the year.

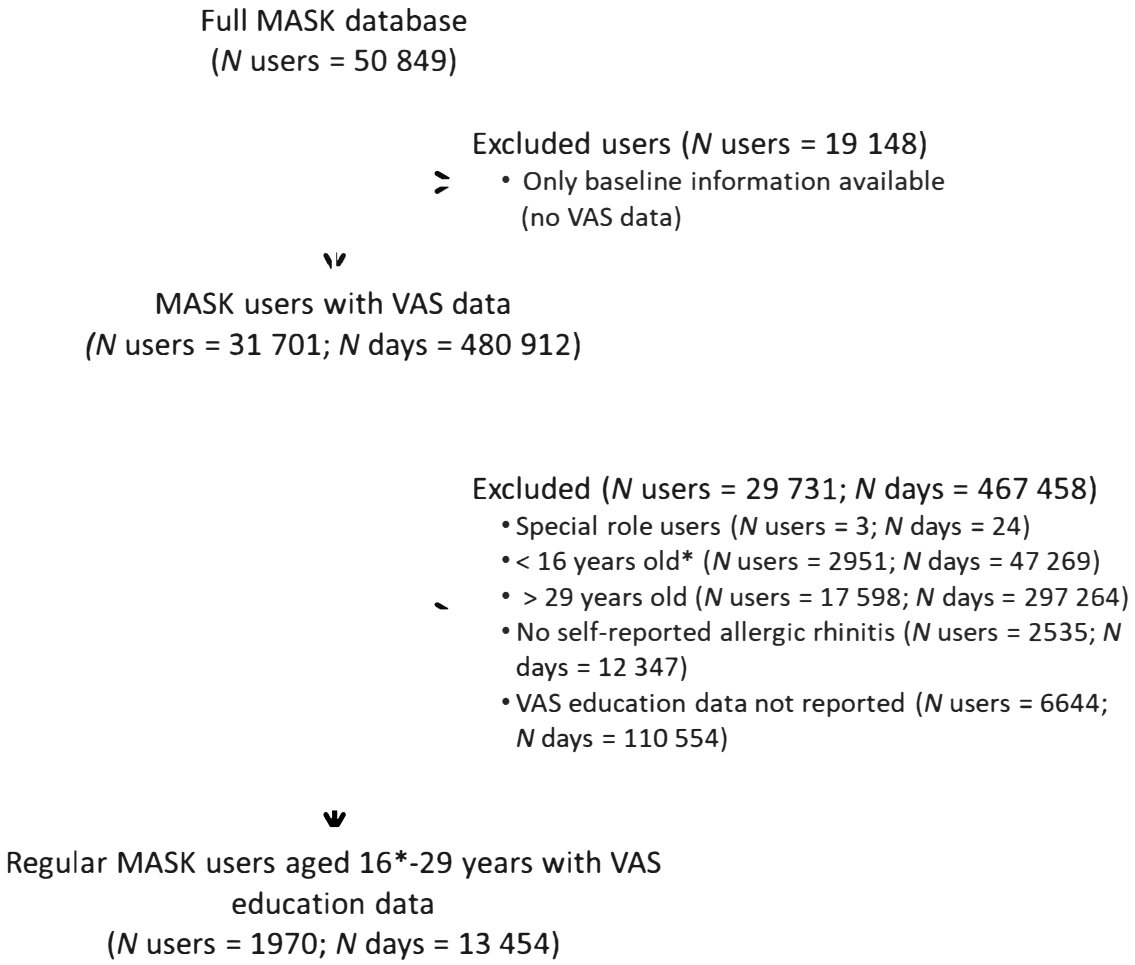
CI = Confidence Interval; CSMS = Combined Symptom-Medication Score; SCIT = Subcutaneous immunotherapy; SLIT = Sublingual immunotherapy; VAS = Visual Analog Scale.

[a] Computed based on the number of reported allergy symptoms at baseline. [b] Computed based on the number of different ways in which allergy symptoms affect the users at baseline.

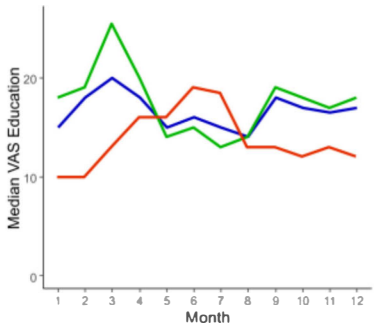
Figure captions

Figure 1. Monthly median VAS education.

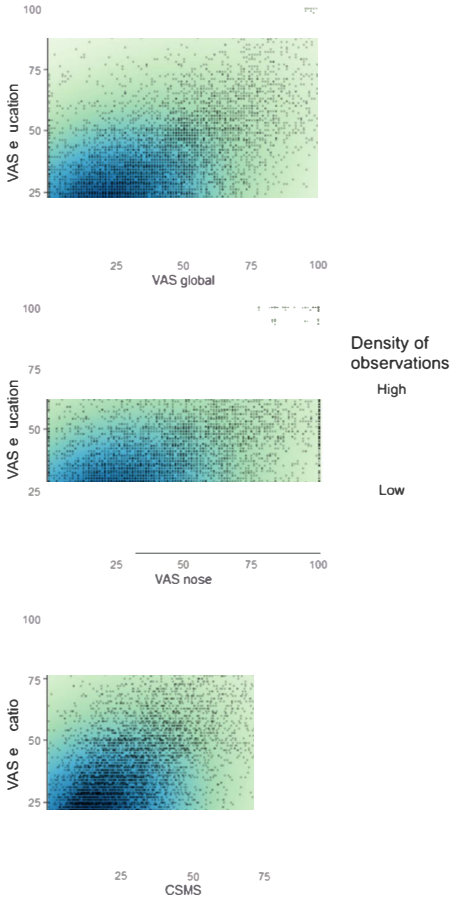
Figure 2. Scatter dots and density of observations considering visual analog scale (VAS) on the impact of allergy symptoms on academic productivity compared to VAS global allergy symptoms, VAS on nose symptoms, and combined symptom-medication score (CSMS)



*Or lower (not below 13 years old) for countries where the digital age of consent is lower



Total assessed period (2015-2022)
Pre-pandemic period (before March 2020)
Post-pandemic period (after March 2020)


100
75
50
25
VAS e ucation
25
50
75
100
VAS global
100
75
50
25
VAS e ucation
25
50
75
100
VAS nose
100
75
50
25
VAS e catio
25
50
75
CSMS
Density of observations
High
Low