

# 1 Academic productivity of young people with allergic 2 rhinitis: A MASK-air<sup>®</sup> study

## 3 Short title: Allergen immunotherapy improves school performance

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148 **Abstract**

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

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

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

161 Results: 13,454 days (from 1,970 patients) were studied. VAS education was strongly correlated  
162 with the WPAI+CIQ:AS impact of allergy symptoms on academic productivity (Spearman  
163 correlation coefficient=0.71 [95%CI=0.58;0.80]), VAS global allergy symptoms (0.70  
164 [95%CI=0.68;0.71]), and VAS nose (0.66 [95%CI=0.65;0.68]). In multivariable regression  
165 models, immunotherapy showed a strong negative association with VAS education (regression  
166 coefficient=-2.32 [95%CI=-4.04;-0.59]). Poor rhinitis control, measured by the combined  
167 symptom-medication score, was associated with worse VAS education (regression  
168 coefficient=0.88 [95%CI=0.88;0.92]), higher impact on academic productivity (regression  
169 coefficient=0.69 [95%CI=0.49;0.90]), and higher percentage of missed education hours due to  
170 allergy (regression coefficient=0.44 [95%CI=0.25;0.63]).

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

## 173 **Highlights box**

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

## 184 **Keywords**

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

## 186 **Abbreviations**

187 AR: Allergic rhinitis

188 CI: Confidence interval

189 CSMS: Combined Symptom-Medication Score

190 IQR: Interquartile range

191 RWD: Real-world data

192 SCIT: Subcutaneous immunotherapy

193 SD: Standard deviation

194 SLIT: Sublingual immunotherapy

195 VAS: Visual Analog Scale

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

## 198 Introduction

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

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

219  
220 In this study, we aimed to assess the impact of AR on academic performance, assessed by means  
221 of VAS education and the WPAI+CIQ:AS<sup>22</sup>. In addition, we aimed to assess the effect of  
222 treatment and to identify factors associated with the impact of allergic symptoms on academic  
223 performance.



## 224 **Methods**

### 225 **Study design**

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

### 233 **Setting and participants**

234 MASK-air<sup>®</sup>, a mobile app launched in 2015, is currently available to be downloaded freely from  
235 the Google Play and Apple App Stores in 28 countries ([www.mask-air.com](http://www.mask-air.com)). We included the  
236 daily monitoring data of education days from MASK-air<sup>®</sup> users with a self-reported diagnosis of  
237 AR from May 21, 2015 to January 9, 2022. Users ranged in age from the age of digital consent  
238 (13 to 16 years depending on the country<sup>33</sup>) to 29 years (upper age limit definition of youth  
239 according to the Eurostat<sup>34</sup>).

### 240 **Ethics**

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

### 249 **Data sources and variables**

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

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

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

264 In addition to the daily monitoring of symptoms and medication, MASK-air<sup>®</sup> users provide  
265 clinical and demographic information when setting up their profile. Given such baseline  
266 information, we were able to compute the number of reported allergy symptoms (“baseline  
267 symptoms”), and the number of different ways in which allergy symptoms affect the users  
268 (“baseline impact”).

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

## 278 **Sample size**

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

## 281 **Biases**

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

## 285 **Statistical analysis**

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

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

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

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

310 Finally, we identified variables potentially associated with the percentage of missed education  
311 hours and the impact of allergy symptoms on academic productivity by multilevel mixed-effects  
312 models, accounting for the clustering of observations by users and by countries. Given the smaller  
313 number of users reporting data on the WPAI:AS+CIQ questionnaire, independent variables in the  
314 model were selected by a backward stepwise approach, with the final models including the  
315 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).

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## 319 **Results**

### 320 **Demographic characteristics of the patients**

321 We analyzed 13,454 days from 1,970 patients aged 13 to 29 years (mean  $\pm$  SD = 20.1  $\pm$  4.1 years)  
322 (Figure E1), 60.3% of the observations being from female users (Table 1; Table E3 for distribution  
323 per each of the 27 countries). The median VAS education was 17 (IQR=28), with VAS  
324 education  $\geq$ 50/100 being observed in 1,757 days (13.1%). The median VAS education for patients  
325 with a self-reported diagnosis of asthma was 16 (IQR=27), while for those without asthma, it was  
326 17 (IQR=27). Comparing patients by age group, the median VAS education level was higher for  
327 those aged 25-29 years (22) than for those aged 20-24 years (17) or 13-19 years (15) (Table E4).  
328 The median VAS education was 18 (IQR=28) before March 1, 2020, and 14 (IQR=24) afterwards.  
329 Figure 1 shows the seasonal trends of VAS education.

330 The WPAI+CIQ:AS was filled in for 125 weeks (by 107 different users; Table E5), with 44  
331 (35.2%; 95%CI=26.2-44.2%) indicating the loss of at least some education hours due to allergies,  
332 and the median score of allergy impact on academic productivity being of 37.0 (IQR=48.0). In  
333 the pre-pandemic period, 32.4% (24/74) of the users indicated the loss of at least some education  
334 hours due to allergy, compared to 46.9% (15/32) in the post-pandemic period.

### 335 **Correlations**

336 VAS education was correlated with all variables (Table 2). It showed the strongest correlations  
337 with the WPAI+CIQ:AS impact of allergy symptoms on education productivity (Spearman rank  
338 correlation [95%CI]:  $\rho=0.71$  [0.58;0.80]), the CSMS ( $\rho=0.70$  [0.69;0.71]), VAS global ( $\rho=0.70$   
339 [0.68;0.71]), and VAS nose ( $\rho=0.66$  [0.65;0.68]) (Table 2 and Figure 2). Similar results were  
340 obtained when correlations were assessed using repeated measures correlation coefficients for all  
341 variables except VAS asthma. The Spearman correlation coefficients between VAS asthma and  
342 education-related variables (VAS education and WPAI+CIQ:AS impact of allergy symptoms on  
343 academic productivity and percentage of hours missed) were consistently higher for patients with  
344 a self-reported diagnosis of asthma compared to those without a diagnosis of asthma (Table E6).  
345 Similar results were obtained in the repeated measures correlation between VAS asthma and VAS  
346 education (Table E6).

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

### 350 **Multivariable regression analyses**

351 In the main regression model, a baseline AR impact and VASs for ocular, nasal, and asthma  
352 symptoms were associated with VAS education, with VAS nose showing the strongest positive  
353 association (regression coefficient=0.38 [95%CI=0.37;0.39]); that is, on average, VAS education  
354 increased by 0.38 units (95%CI=0.37;0.39) per each unit increase in VAS nose on a scale of 0-  
355 100.

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

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

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



## 374 Discussion

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

## 382 Strengths and limitations

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

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

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

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

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

412 This study also has important strengths. We assessed RWD from a large set of young users from  
413 27 different countries, with the structure of MASK-air<sup>®</sup> precluding the existence of missing data  
414 within each daily questionnaire response. MASK-air<sup>®</sup> VASs, the WPAI:AS+CIQ questionnaire,  
415 and the CSMS are allergy-specific and have been previously assessed and validated<sup>25,29,30</sup>. We  
416 built multivariable mixed-effects models in which we clustered observations by patients, and  
417 adjusted the analyses considering relevant clinical and demographic variables to reduce  
418 confounding. We found similar results in different models in sensitivity analyses, pointing to the  
419 robustness of the results.

#### 420 **Interpretation of the data**

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

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

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



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

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

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

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

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

## 470 **Generalizability**



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

## 475 **Conclusion**

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

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616 **Table 1. Demographic and clinical characteristics associated with included MASK-**  
 617 **air<sup>®</sup> observations/days and respective users.**

Variable	Summary
Observations/days – <i>N</i> [ <i>N</i> users]	13,454 [1970]
Females – <i>N</i> (%)	8119 (60.3)
Age – mean (SD)	20.1 (4.1)
European country — <i>N</i> (%)	7572 (56.3)
Self-reported asthma – <i>N</i> (%)	3908 (29.0) <sup>a</sup>
Baseline impact of AR <sup>b</sup> – median (IQR)	1.0 (3.0)
Symptoms affect sleep – <i>N</i> (%)	3821 (29.2)
Symptoms restrict daily activities – <i>N</i> (%)	4231 (32.3)
Symptoms restrict work/education activities – <i>N</i> (%)	3412 (26.1)
Symptoms are troublesome – <i>N</i> (%)	8130 (62.2)
Baseline symptoms <sup>c</sup> – median (IQR)	5.0 (3.0)
Rhinorrhea – <i>N</i> (%)	10,416 (78.6)
Nasal pruritus – <i>N</i> (%)	9292 (70.4)
Sneezing – <i>N</i> (%)	10,885 (82.2)
Nasal congestion – <i>N</i> (%)	10,959 (83.0)
Red eyes – <i>N</i> (%)	5739 (43.5)
Ocular pruritus – <i>N</i> (%)	7723 (58.6)
Watery eyes – <i>N</i> (%)	6109 (46.6)
Medication for AR	
No medication – <i>N</i> (%)	7834 (58.2)
Single medication – <i>N</i> (%)	3727 (27.7)
Co-medication – <i>N</i> (%)	1893 (14.1)
Medication for asthma	
No medication – <i>N</i> (%)	11539 (85.8)
Single medication – <i>N</i> (%)	1439 (10.7)
Co-medication – <i>N</i> (%)	476 (3.5)
Medication class	
Oral antihistamines – <i>N</i> (%)	3674 (27.3)
Topical antihistamines – <i>N</i> (%)	521 (3.9)
Intranasal steroids – <i>N</i> (%)	2401 (17.8)
Azelastine+Fluticasone – <i>N</i> (%)	740 (5.5)
Asthma drugs – <i>N</i> (%)	1915 (14.2)
Other drugs – <i>N</i> (%)	373 (2.8)
Immunotherapy (Days of patients under immunotherapy) – <i>N</i> (%)	3949 (30.2) <sup>d</sup>
SCIT – <i>N</i> (%)	2647 (19.7)
SLIT – <i>N</i> (%)	1298 (9.6)
CSMS – median (IQR) <sup>e</sup>	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) <sup>f</sup>	17 (28)
VAS education <20 – <i>N</i> (%)	7402 (55.0)
VAS education 20-49 – <i>N</i> (%)	4295 (31.9)
VAS education ≥50 – <i>N</i> (%) <sup>g</sup>	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 <sup>h</sup>	
Percentage of missed education hours in a week due to allergies – median (IQR)	0 (10.45) <sup>i</sup>
Weeks of loss of at least some education hours due to allergies – <i>N</i> (%)	44 (35.2)
Impact of allergy symptoms on academic productivity – median (IQR)	27.0 (48.0)

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

622 <sup>a</sup> *N* distinct users = 612; <sup>b</sup> Computed based on the number of reported allergy symptoms at baseline. <sup>c</sup> Computed based  
623 on the number of different ways in which allergy symptoms affect the users at baseline. <sup>d</sup> *N* distinct users = 294  
624 (SCIT=162; SLIT=82); <sup>e</sup> < 18 years (Median (IQR)) = 12.1 (18.1), ≥ 18 years (Median (IQR)) = 15.2 (21.0); <sup>f</sup> < 18  
625 years (Median (IQR)) = 14.0 (15.3), ≥ 18 years (Median (IQR)) = 18.0 (16.6); <sup>g</sup> *N* distinct users = 746; <sup>h</sup> *N* observations  
626 = 137; <sup>i</sup> Mean (Standard Deviation) = 13.4 (26.4).  
627



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

	VAS education	VAS eyes	VAS nose	VAS asthma	VAS global	CSMS	Percentage of hours missed
<b>Spearman correlation - correlation coefficient (95% CI)</b>							
VAS education	—	0.39 (0.38;0.40)	0.66 (0.65;0.68)	0.15 (0.13;0.17) <sup>a</sup>	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)	—
<b>Repeated measures correlation – correlation coefficient (95% CI)</b>							
VAS education	—	0.41 (0.40;0.43)	0.58 (0.57;0.59)	0.27 (0.26;0.29) <sup>b</sup>	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)	—
630	CI = Confidence Interval; CSMS = Combined Symptom-Medication Score; VAS = Visual Analog Scale						
631	<sup>a</sup> With self-reported asthma: 0.363 (95%CI=0.334;0.394) Without self-reported asthma: 0.079 (95%CI=0.060;0.100);						
632	<sup>b</sup> With self-reported asthma: 0.371 (95%CI=0.341;0.400) Without self-reported asthma: 0.233 (95%CI=0.211;0.254)						

633 **Table 3. Association between VAS education and other individual characteristics.**  
 634

	Association with VAS education		
	Regression coefficient	95% CI	<i>p</i> -value
Baseline symptoms <sup>a</sup>	-0.30	-0.62;0.02	0.065
Baseline impact <sup>b</sup>	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

635 This model was obtained by multilevel mixed effects linear regression. Coefficients and their 95% confidence  
 636 intervals take into account the clustering of observations by users, by countries, and by time of the year.

637 CI = Confidence Interval; VAS = Visual Analog Scale.

638 <sup>a</sup> Computed based on the number of reported allergy symptoms at baseline. <sup>b</sup> Computed based on the number of different  
 639 ways in which allergy symptoms affect the users at baseline.

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

	<b>Regression coefficient</b>	<b>95% CI</b>	<b>p-value</b>
643 Baseline symptoms	-2.40	-4.95;0.16	0.070
644 Baseline impact	5.79	2.17;9.41	0.002
645 Immunotherapy	-10.83	-22.28;0.62	0.067
646 CSMS	0.69	0.48;0.90	< 0.001

648 Models were obtained by multilevel mixed effects linear regression. Coefficients and their 95% confidence intervals  
 649 consider the clustering of observations by users, and by countries.

650 CI = Confidence Interval; CSMS = Combined Symptom-Medication Score.

651 <sup>a</sup> Computed based on the number of reported allergy symptoms at baseline. <sup>b</sup> Computed based on the number of  
 652 different ways in which allergy symptoms affect the users at baseline.



653 **Table 5. Sensitivity analyses of the association between VAS education and other**  
 654 **independent variables.**  
 655

	<b>Specifying immunotherapy types and medication patterns – Coefficient (95%CI) [p-value]</b>	<b>Including VAS global and excluding VAS eyes and VAS nose – Coefficient (95%CI) [p-value]</b>	<b>Replacing VASs and medication variables by the CSMS – Coefficient (95%CI) [p-value]</b>
Baseline symptoms <sup>a</sup>	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 <sup>b</sup>	-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) [ $<0.001$ ]

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

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

661 <sup>a</sup> Computed based on the number of reported allergy symptoms at baseline. <sup>b</sup> Computed based on the number of  
 662 different ways in which allergy symptoms affect the users at baseline.

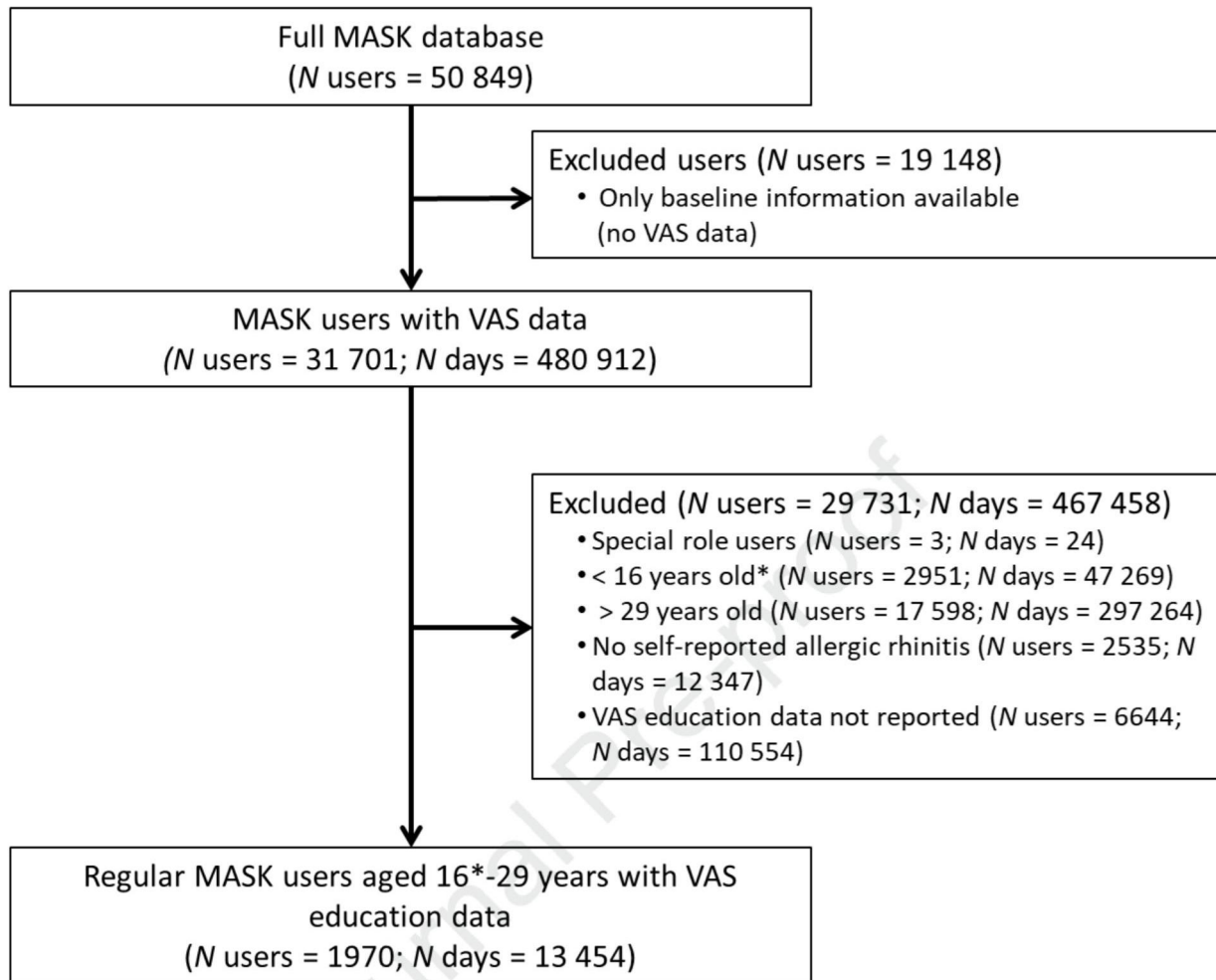
663

664 **Figure captions**

665 **Figure 1. Monthly median VAS education.**

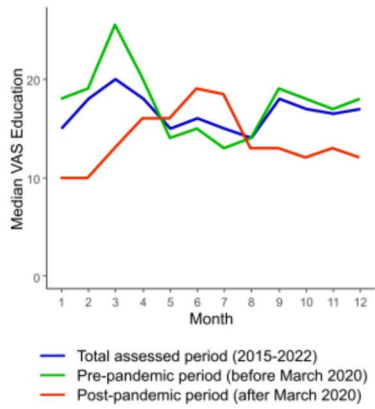
666 **Figure 2. Scatter dots and density of observations considering visual analog scale**  
667 **(VAS) on the impact of allergy symptoms on academic productivity compared to**  
668 **VAS global allergy symptoms, VAS on nose symptoms, and combined symptom-**  
669 **medication score (CSMS)**

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





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