Interactions Between Air Pollution and Pollen Season for Rhinitis Using Mobile Technology: A MASK-POLLAR Study

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Short title: Pollution and rhinitis with mHealth App

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41   **Abstract**

42   **Background:** Several studies have suggested an interaction between air pollution and pollen

43   exposure with an impact on allergy symptoms. However, large studies with real-life data are

44   not available.

45   **Objectives:** In the POLLAR (Impact of Air POLLution in Asthma and Rhinitis) project, we

46   investigated associations between major air pollutants (ozone and $PM_{2.5}$) and allergic rhinitis

47   control, during grass and birch pollen seasons as well as outside the pollen season.

48   **Methods:** The daily impact of allergic symptoms was recorded by the *Allergy Diary - MASK-*

49   *air -* App (a validated mHealth tool for rhinitis management), using visual analogue scales

50   (VASs) in Northern and Central Europe users in 2017 and 2018. Uncontrolled allergic rhinitis

51   was defined using symptoms and medications. Pollutant levels were assessed using SILAM

52   (System for integrated modelling of atmospheric composition). Pollen seasons were assessed

53   by regions using Google Trends. Generalized estimating equation models were used to

54   account for repeated measures per user, adjusting for gender, age, treatment and country.

55   Analyses were stratified by pollen seasons to investigate interactions between air pollutants

56   and pollen exposure.

57   **Results**: 3,323 geolocated individuals (36,440 VAS days) were studied. Associations between

58   uncontrolled rhinitis and pollutants were stronger during the grass pollen season. Days with

59   uncontrolled allergic rhinitis increased by 25% for an interquartile range increase in ozone

60   levels during the grass season: odds ratio (OR) of 1.25 [95% confidence interval (CI): 1.11-

61   1.41] in 2017 and of 1.14 [95% CI: 1.04-1.25] in 2018. A similar trend was found for PM2.5,

62   especially in 2017.

63   **Conclusions**: These results suggest that the relationship between uncontrolled allergic rhinitis

64   and air pollution is modified by the presence of grass pollens. This study confirms the impact

65   of pollutants in grass pollen season but not in birch pollen season.

66

67

Highlight box

1. **What is already known about this topic?** The impact of air pollutants on the severity of allergic rhinitis symptoms, and its modification by pollen exposure is still a matter of debate. Real-life studies have never been conducted using an mHealth App.

2. **What does this article add to our knowledge?** An association between air pollutants and rhinitis symptoms is observed during the grass but not the birch pollen season, suggesting an interaction between air pollutants and grass pollen.

3. **How does this study impact current management guidelines?** This paper is of primary importance in the development of next-generation GRADE guidelines that will embed real-world-evidence, aerobiology and air pollution.

Key words

Allergic rhinitis, MASK, mobile health, ozone, POLLAR pollen, pollution, PM2.5

4

112 **Abbreviations**

113 AR: Allergic rhinitis

114 GT: Google Trends

115 ICT: Information and Communication Technology

116 INN: International Nonproprietary Names

117 OTC: over the counter

118 MASK-rhinitis (Mobile Airways Sentinel NetworK for allergic rhinitis)

119 POLLAR: Impact of air POLLution on Asthma and Rhinitis

120 $PM_{2.5}$: Particulate matter 2.5

121 RCT: Randomized controlled trial

122 SILAM: System for integrated modelling of atmospheric composition

123 VAS: Visual Analogue Scale

124

125

Introduction

Allergic rhinitis (AR) impacts quality of life and affects sleep, work productivity, school performance and daily activities (1). Both pollen and outdoor air pollution exposure (2,3) are known to influence rhinitis symptoms. Several *in vitro* studies have suggested that traffic-related pollutants can disrupt pollen, a modification that causes more allergic symptoms (4,5). In particular, it has been suggested that particulate matter (PM) may interact with aeroallergens, promoting airway sensitization by modulating the allergenicity of airborne allergens (6), and that diesel exhaust carbon particles could interact with grass pollen allergens and trigger attacks of asthma (7). Several epidemiological studies have investigated the additive effects of air pollution and pollen exposure on rhinitis symptoms, with conflicting findings (8,9) but to our knowledge, no study has investigated the effect of the interaction between air pollution and pollen exposure on rhinitis symptoms (i.e. how the relationship between air pollution and allergy symptoms is modified by pollen exposure or vice versa). A few studies have investigated the effect of this interaction on *asthma* symptoms. One study conducted in two Spanish cities – one with high levels of air pollution and one with low levels of pollution - reported strong positive associations between air pollutants (ozone, SO_2 and PM_{10}) levels and seasonal allergic asthma symptoms, only in the city with high levels of pollution (10). One study has investigated associations between grass and birch pollen concentrations with hospital admissions for asthma, reporting stronger associations in the case of high PM_{10} and ozone concentrations (11). The two major pollutants reported in rhinitis are ozone and $PM_{2.5}$.

Mobile technology may help to better understand the links between pollution and allergic diseases. MASK-air (Mobile Airways Sentinel NetworK) is an information and communication technology (ICT) system centred around the patient (12-16) and operational in 23 countries. It uses a treatment scroll list which includes all medications customized for each country as well as visual analogue scales (VASs) to assess global allergy, rhinitis, eye and asthma control. Over 29,000 users and 200,000 VAS days have been recorded. MASK can be used to investigate the relationship between outdoor air pollutants and rhinitis.

In the frame of the POLLAR (Impact of Air POLLution in Asthma and Rhinitis) project, the objective of our study was to investigate the interaction between air pollution and allergens and its impact on allergy symptoms.

Methods

Design of the study

POLLAR (Impact of Air POLLution in Asthma and Rhinitis) is a project of the European Institute of Innovation and Technology (EIT Health) that embeds environmental data into the data of MASK-air

160   patients in order to deliver interconnected rhinitis management assistance during peak periods of air

161   pollution and promote measures that help people deal with health and societal consequences of the

162   condition (17). To achieve this, one of the objectives of POLLAR is to investigate the interaction

163   between air pollution and pollen exposure and its impact on AR control. A series of analyses were

164   carried out on the MASK-air data available for 2017 and 2018 in Northern and Central Europe. The

165   aim was to assess the impact of the two major pollutants associated with rhinitis (ozone and $PM_{2.5}$)

166   on the severity of rhinitis during and outside the estimated pollen seasons. To do so, we linked the

167   self-reported rhinitis symptoms obtained via an App with air pollution predictions obtained from the

168   SILAM (System for integrated modelling of atmospheric composition (18)) database. We then

169   conducted analyses separately by pollen seasons derived using Google Trends (GTs). We restricted

170   the study to Northern and Central Europe (Austria, Belgium, Czech Republic, Denmark, Finland,

171   France, Germany, Northern Italy, Lithuania, Netherlands, Poland, Sweden, Switzerland, United

172   Kingdom) since these pollen seasons are better identified than those in Southern Europe. The two

173   major pollen seasons included Betulaceae (i.e. birch) and grass (more details below).

174

175   ***Setting - study population and observations unit***

176   All days recorded by the users of the MASK-air app between February 2017 and October 2018 were

177   included with no exclusion criteria and according to methods previously described (16, 19, 20). The

178   unit of observations used in the present study is person-days (i.e. each day of app use by any user).

179   Some of the users used the app more than once a day to report symptoms. We carefully analyzed this

180   issue and found that the highest recording should be used and this approach was used to eliminate

181   duplicates/multiplicates (16,19).

182

183   Days where the App was used in Northern and Central Europe were included in the analyses.

184   Areas were defined as those above the latitude of Lyon (Figure E1). Table E1 summarizes the

185   number of days included in the study by country for each year.

186

187   <u>Ethics</u>

188   The Allergy Diary is CE1 registered. By using k-anonymity, the data were anonymized

189   including the data related to geolocation (21). An Independent Review Board approval was not

190   required since the study is observational and users agree to having their data analysed (terms

191   of use) (16,19,20).

m-health data

193 Geolocalized users assess their daily symptom control in a participatory way using the
194 touchscreen functionality on their smart phone to click on four consecutive VAS scores (i.e.
195 global, nasal and ocular symptoms and asthma, quantifying the degree of symptoms from 0 to
196 100). Only global VAS for rhinitis was used in the study. Concomitantly to the report of VAS
197 scores, users also input their daily medications using a scroll list which contains all country-
198 specific OTC and prescribed medications available for each country. The list has been
199 populated using IMS data. Days reported by users were thus either considered as days with or
200 without treatment. Information on gender, country of residence and year of birth was provided
201 for all users, through the creation of their profile upon registration to MASK-air.

202 The present study is another MASK study. Some of the raw data used in other papers (up to
203 December 2017) (16,20) were used in this study, but the analyses differed.

204 Outcomes

205 We considered two outcomes to assess the interaction between pollen seasons and pollutants:
206 "uncontrolled rhinitis" (as primary outcome) and VAS global (as secondary outcome).Uncontrolled
207 rhinitis was defined, based on the previous data already available for MASK (16, 20) as days with
208 "rhinitis high" according to the following criteria:

209   1. days with VAS global $\geq 50/100$
210   **or**
211   2. days with VAS global ≥ 35 and use of INCS-containing medication
212   **or**
213   3. days with VAS global ≥ 20 and use of at least 3 medications

214 Days were defined as controlled rhinitis otherwise.

215

216 ***Exposure data***

217 Health data from the mobile App was linked to environmental exposures (pollen and air pollution
218 data) by date and geolocation (when access to this information was allowed by the user of the app).

219 Air pollution data

220 Pollutants (ozone and $PM_{2.5}$ concentrations; spatial resolution: 12x12 km grid) for the whole of
221 Europe were obtained from the SILAM (System for integrated modelling of atmospheric

222 composition) database (18,22,23) of the Finnish Meteorological institute (http://silam.fmi.fi).
223 SILAM is a global-to-meso-scale dispersion model that uses anthropogenic emission datasets,
224 information on wild-land fires, meteorological data, as well as embedded emission computations for
225 sea salt, pollen, wind-blown dust, and natural volatile organic compounds to produce the forecasts of
226 several pollutants, including ozone and particulate matter with a diameter of less than 2.5 μm
227 ($PM_{2.5}$). We used forecasts for the same day at noon at a 0.1 degree resolution.

228 <u>Temperatures</u>

229 We used daily maximum temperature information from the dataset of NASA's Modern-Era
230 Retrospective Analysis for Research and Applications (MERRA). MERRA is a NASA reanalysis
231 dataset generated using version 5.2.0 of the Goddard Earth Observing System (GEOS-5). MERRA
232 uses observations (such as weather station data and satellite irradiance) from multiple platforms to
233 reanalyse these observations using numerical models based on physical rules of atmospheric motions
234 and to generate meteorological records (24).

235 <u>Urban *vs* rural area</u>

236 Information on urban *vs* rural area by geolocation was obtained using the Global Human Settlement
237 Layer data that classifies settlement typologies using data on population size, population and built-up
238 area (25). Classes 30–23–22–21 were aggregated to form the urban domain, while classes 13–12–
239 11–10 formed the rural domain.

240

241 <u>Pollen season</u>

242 The hypothesis of the study was that air pollution affects symptoms due to pollen exposure.
243 As explained above, we restricted the study to Northern and Central Europe since pollen seasons are
244 better identified there compared to Southern Europe. The two major pollen seasons included
245 Betulaceae (i.e. birch, alder, elm) and grass pollens. To identify the pollen seasons, we initially used
246 the visual inspection of GTs separately for 2017 and 2018. This is supported by previous results
247 showing that GTs could be used in France to identify the Betulaceae (birch) and grass pollen seasons
248 (26). We used three terms that we had previously validated (allergy, disease; allergic rhinitis, subject;
249 pollen, subject) (27). We did not use asthma as a term since it is not very sensitive except during
250 severe outbreaks (28).

251 Since there was an overlap between seasons in 2018, we used pollen counts – only available for a
252 subset of the study population - to refine the GTs analyses. These were provided by M Thibaudon
253 (RNSA) for France (29), KC Bergmann for Germany (30) and R Dubakiene for Lithuania.

254

255 *Statistical analysis*

256 Generalized Estimating Equations models (accounting for repeated daily measures per user) with a
257 binomial family and a logistic link were used to study the associations between pollutant
258 concentrations and uncontrolled rhinitis (with controlled rhinitis as a reference). We used the
259 interquartile range (IQR, i.e. 75th percentile (3rd quartile) minus 25th percentile (1st quartile)) as the
260 unit of exposure (i.e. ozone and $PM_{2.5}$) levels. The results of logistic regression models can therefore
261 be interpreted as the odds ratio of uncontrolled rhinitis risk obtained when comparing those exposed
262 to a pollutant at the third quartile (i.e. high exposure) to those exposed at the first quartile (i.e. low
263 exposure). This unit is commonly used in epidemiological studies on air pollution (31).

264 Models were adjusted for daily treatment (i.e. day with/without treatment), gender, age (derived from
265 the year of birth), and country of residence of the user. Analyses were stratified by pollen seasons
266 and formal tests for interaction between air pollutants and pollen season were conducted by
267 including the product term of pollution and pollen season in the same model. Separate analyses were
268 conducted for 2017 and 2018 (no pooled or meta-analysis was performed given the differences in the
269 assessment of pollen seasons between 2017 and 2018).

270 When evidence for an association was found between a pollutant and uncontrolled rhinitis, we
271 further adjusted for temperature in a sensitivity analysis, to investigate potential confounding. The
272 correlation between pollutant levels and temperature was calculated for each period/season, in order
273 to investigate potential collinearity. In order to investigate potential confounding, we conducted two-
274 pollutant models (i.e. models that include ozone and $PM_{2.5}$ simultaneously as exposures).

275 In order to investigate a potential lag-time in the effect of air pollution on allergic rhinitis control,
276 especially in a cross-sectional study, we repeated the analyses of the associations between air
277 pollution and uncontrolled rhinitis, using a 1-day lag (i.e. considering the air pollution levels of the
278 user's location on the previous day – assuming the geolocation on the previous day was the same as
279 the geolocation on the day the app was used). In order to investigate potential effect modification by
280 urbanization, associations were stratified by rural and urban areas. As a sensitivity analysis, we
281 repeated our main analyses by considering global VAS - which has been used in previous papers
282 (16,20) - as an outcome (instead of uncontrolled rhinitis), using mixed linear regression models (for
283 continuous outcome). In order to investigate potential non-linear effects, we repeated our analyses of

284 the associations between air pollutants and uncontrolled rhinitis, considering ozone and $PM_{2.5}$ in
285 quartiles, testing a linear trend.

286 Because pollen seasons were defined in 2018 only for a subset of the countries included in the 2017
287 analyses (Table E1), we checked as a sensitivity analysis whether associations observed in 2017
288 remain similar when we restrict our study sample to that subset.

289

290 **Results**

291 *Demographic characteristics of the users and usage of the app*

292 Both SILAM and GTs data were available for 36,440 days of VAS recorded by 3,323 *Allergy Diary*
293 App users in 2017 and 2018 in Northern and Central European countries (Figure 1).

294 Approximately 5% of the users did not report their age or reported an age below 10. Users
295 ranged in age from zero to 91 years (mean, SD: 34.7 ± 15.6 years). There were 54% of women
296 and 46% of men. There were 16,797 (46%) days without treatment and 19,699 (54%) days
297 with treatment. Uncontrolled rhinitis was observed in 20% of VAS days.

298 The number of days of VAS reported by user had a median [p25-p75] of 2 [1-7] and varied by
299 country of residence but not by gender or year of birth of the user. The daily global VAS score
300 had a median [p25-p75] of 13 [1-35] and varied by gender, country of residence, year of birth
301 of the user as well as daily treatment (Table E2).

302

303 *Estimation of the pollen season*

304 For 2017, three patterns of pollen seasons were determined corresponding to the three areas depicted
305 in Figure E1: 1) Continental and semi-continental climate (Germany, Austria, Belgium, Northern
306 France, Netherlands, Poland, Switzerland, Czech Republic, Northern Italy), 2) Northern countries
307 (Denmark, Finland, Lithuania, Sweden), and 3) the UK (Figure 2A). The Betulaeae and grass pollen
308 seasons could not be easily distinguished and the analysis was completed with pollen counts. For
309 most countries, two GT peaks were observed in 2017 (i.e. clear "birch" and "grass" peaks) with an in
310 between pollen seasons and no pollen season – see examples in Figure 3A.

311 For 2018, five patterns of pollen seasons were determined: 1) Germany, France and Switzerland, 2)
312 Belgium, Netherlands and Denmark, 3) the UK, 4) Austria and 5) Poland (Figure 2B). For most
313 countries, three GT peaks were observed in 2018 (i.e. in addition to the "birch" and "grass" peaks, an

314   intermediate peak was observed - see examples in Figure 3B). Since there was some uncertainty on
315   the intermediate birch-grass pollen season, pollen counts from Germany, France and Lithuania were
316   assessed and showed that grass pollens were retrieved during this intermediate season. Therefore, for
317   all countries, the grass pollen and the intermediate seasons were studied jointly.
318

319   *Associations between pollution and uncontrolled rhinitis*
320   Strong significant associations were observed between ozone concentrations and uncontrolled
321   rhinitis for both 2017 and 2018 overall (Table 1). These differences were not statistically significant
322   on formal testing for interaction when associations were stratified by seasons. No association was
323   observed during the birch season (odds ratios (ORs) per IQR increase in ozone levels: 1.10 (95%
324   confidence interval: 0.95, 1.26) and 0.96 (0.87, 1.05), for 2017 and 2018 respectively) whereas
325   positive associations were found during the grass pollen season (ORs: 1.25 (1.11, 1.41) and 1.14
326   (1.04, 1.25), for 2017 and 2018 respectively) and no pollen season (ORs: 1.08 (1.01, 1.16) and 1.15
327   (1.09, 1.21), for 2017 and 2018 respectively). Associations were stronger during the grass pollen
328   season of 2017 than in 2018. In general, levels of ozone were highest during the grass pollen season
329   and lowest outside the pollen season (Table 1).

330   No association was observed between $PM_{2.5}$ and uncontrolled rhinitis for 2017 overall (Table 1).
331   When the association was stratified by seasons, no association was observed during the birch season
332   whereas a strong positive association was found during the grass pollen season and a weak negative
333   association was found during the no pollen season (ORs: 1.02 (0.96, 1.09), 1.21 (1.09, 1.34) and 0.96
334   (0.93, 0.99), respectively). Levels of $PM_{2.5}$ were highest during the birch pollen season and lowest
335   outside the pollen season (Table 1). A positive association was observed between $PM_{2.5}$ and
336   uncontrolled rhinitis for 2018 overall. When the association was stratified by seasons, similar
337   positive associations were found during the birch and grass pollen seasons but no association was
338   observed during the no pollen season (ORs: 1.11 (1.07, 1.15), 1.11 (1.04, 1.19), 1.00 (0.96, 1.04),
339   respectively).

340   In order to investigate potential confounding by temperature in the associations found between air
341   pollutants and uncontrolled rhinitis, we fitted additional analyses by considering both the pollutant
342   level (ozone or $PM_{2.5}$) and the maximal temperature as exposures in the regression models (Table 2).
343   We observed that, while strong positive associations were found quite consistently throughout the
344   year between temperature and uncontrolled rhinitis, the positive associations found between
345   pollutant levels and uncontrolled rhinitis weakened after accounting for temperature. The association
346   between air pollutant levels (both ozone and $PM_{2.5}$) and uncontrolled rhinitis during the grass pollen
347   season remained statistically significant in 2017 but not in 2018 (Table 2). The associations found
348   for 2018 between ozone and uncontrolled rhinitis during the "no pollen season", and between $PM_{2.5}$

349 and uncontrolled rhinitis during the birch pollen season remained statistically significant. Strong
350 correlations were found quite consistently throughout the year between pollutant levels and
351 temperature. This may lead to unstable estimates when simultaneously included in the same model.
352 The results of the two-pollutant models (i.e. models that include ozone and $PM_{2.5}$ simultaneously as
353 exposures) were similar to the results of the single-pollutant models (Table 3).

354 When the main analyses were repeated by considering a one day-lag, the same tendency in the
355 results was observed, with overall weaker associations (Table E3). When analyses were stratified by
356 urban/rural areas, similar associations as the ones observed in the main analysis were found in urban
357 areas (Table E4), while in rural areas, given the smaller sample size, most of the associations that
358 were observed in the main analyses were no longer significant (Table E5).

359 When we repeated our analyses by considering global VAS as an outcome (instead of uncontrolled
360 rhinitis), similar patterns of association were found (Table E6). When we repeated our analyses by
361 considering ozone and $PM_{2.5}$ in quartiles, the results were consistent with linear trends, with small
362 departures that were not replicated in the different years (Table E7).

363 When we reran our 2017 analyses among the subset of countries for which pollen seasons were
364 assessed in 2018, results remained similar (results not shown).

365
366

367 **Discussion**

368 The results of this study suggest a deleterious effect of air pollution (particularly ozone) on allergic
369 rhinitis control, especially during the grass pollen season. Positive associations were found between
370 air pollutants (ozone and $PM_{2.5}$) and allergic rhinitis symptoms. Differences between pollen seasons
371 were found, suggesting an interaction between air pollution and pollen exposure (i.e. that the
372 deleterious effects of exposure to pollen are magnified by exposure to air pollutants). Results for
373 2017 and 2018 are consistent for ozone, suggesting that ozone increases rhinitis symptoms during the
374 grass pollen season (and outside pollen seasons) but not during the birch pollen season. Results are
375 less consistent for $PM_{2.5}$: results for 2017 suggest that $PM_{2.5}$ increases rhinitis symptoms during the
376 grass pollen season but not during the birch pollen season, whereas results for 2018 suggest a similar
377 deleterious effect of $PM_{2.5}$ in both pollen seasons.

378

379 *Strengths and weaknesses*

380 The current study has many strengths including a large number of observations on daily symptoms
381 and treatment use, with participants from multiple countries. Mobile technology is becoming an
382 important tool for better understanding and managing AR and provides novel information that was
383 not previously available.

384 Other strengths and limitations of MASK have already been reported (16,20). As for all studies using
385 participatory data, potential biases include (i) the likelihood of sampling bias being present and (ii)
386 the lack of generalizability of the study as most users have a moderate to severe disease. In
387 particular, users of the *MASK-air* App might use it mostly when symptoms are present, thus
388 producing missing data in days with mild or no symptoms. This bias is expected to attenuate (i.e.
389 underestimate) the true associations (32).

390 As in previous studies using MASK-air data (16,20), we were not able to conduct any longitudinal
391 study as most users utilize the App intermittently, hence there is no clear pattern of treatment.

392 In the current study, we cannot ascertain that the users are allergic to a given allergen since this
393 information is not available for all patients. The diagnosis of AR was not supported by a physician
394 but was a response to the question: "Do you have allergic rhinitis? Yes/No". Some users with non-
395 allergic rhinitis may therefore have responded "Yes" to the question but >95% of responders
396 declared symptoms of AR by questionnaire. Precise patient characterization is impossible using an
397 App, but every observational study using MASK has been able to identify days with poor control or
398 criteria of severity (16,20). Potential unmeasured confounding arising from the limited amount of
399 information available on users' profile (e.g. socioeconomic status) is another limitation of the present
400 study and cannot be avoided due to privacy regulations.

401 We used MASK, a validated App for the study of allergic rhinitis (16,20). Thus, the data obtained
402 from the patients are of high quality. We defined the severity of rhinitis according to MASK studies
403 (16,20) but other methods may have been used such as symptom-medication scores proposed for
404 allergen immunotherapy (33). Results remained similar when we considered VAS global - which has
405 been used to assess AR severity in previous papers (16,20) - as an outcome. Both VAS global and
406 uncontrolled rhinitis have been found to be highly correlated with work productivity (assessed using
407 a specific VAS score) in *MASK-air* App users (unpublished data), providing internal validity of our
408 results.

409 We only checked the association with ozone and $PM_{2.5}$ since these two pollutants appear to be the
410 most relevant. Interestingly, results for both ozone and $PM_{2.5}$ remained similar after mutual
411 adjustment (i.e. when we conducted two-pollutant models). Other pollutants need to be tested in a
412 further study. A multipollutant air quality index may be appropriate (34).

413 The models used for assigning air pollution exposure had a spatial resolution of 12 by 12 km.
414 Although more spatially resolved models could have been used, our approach is reasonable given
415 that we used a single geolocation point to assign exposure and subjects often move around wider
416 areas around their residence or work address. Actually, without having data on time-activity patterns,
417 using highly spatially-resolved models can introduce more error that using others with lower spatial
418 resolution (35). Nevertheless, the nature of measurement error due to spatial averaging is of Berkson
419 type (36). This error is not expected to bias the exposure-health associations, although it makes it
420 more difficult to detect associations (36).

421

422 *Interpretation of the results*

423 The results observed in this study show that ozone levels are associated with an increased AR
424 severity during the grass pollen season. Positive associations were also found outside the pollen
425 season. No association was found during the birch pollen season. Results are highly consistent across
426 years and outcomes. Additional analyses were conducted without suggesting non-linear effects or lag
427 effects (although the assumption that the geolocation on the previous day was the same as the
428 geolocation on the day the app was used might not be true). Associations stratified by urban *vs* rural
429 areas did not suggest any effect modification by urbanization (although rural areas represented less
430 than 20% of the person days included in our study).

431 We observed stronger positive associations between air pollutants – particularly ozone – and
432 uncontrolled rhinitis in 2017 compared to 2018. A plausible explanation could be that pollen seasons
433 were less clear in 2018 compared to 2017. This might have caused misclassification in the
434 assessment of 2018 pollen seasons using GTs and thus could explain some of the inconsistencies
435 found between 2017 and 2018, more particularly for the birch pollen season and the "no pollen
436 season". Although in 2017 pollen seasons were assessed for a broader range of countries than in
437 2018, results for 2017 remained similar when we restricted our analyses to the subset of countries
438 that were included in the 2018 analyses. This suggests that these inconsistencies are not caused by
439 heterogeneity between geographical regions. Nevertheless, although GTs are not the most precise
440 tool to assess pollen counts, they appear to be more related to symptoms during the pollen season
441 than pollen counts (37, 38). Further studies using pollen counts (that are not available for all our
442 study population yet) are needed to complete our results.

443 These results confirm previous data suggesting that traffic-related pollutants can disrupt pollen, a
444 modification that causes more allergic symptoms (4,5). However, this is the first study to provide
445 daily assessment in a large number of patients using daily reports.

446   The respective role of temperature and ozone is still unclear. Temperature increases grass pollen
447   counts (39) and the effect of ozone may be related to increased temperature in one year. Although
448   the associations we found weakened after accounting for maximal temperature, strong correlations
449   were found between pollutant levels and temperature, quite consistently throughout the year. Given
450   the high correlation, results from models including both terms may be unstable. Although we have
451   found evidence suggesting a deleterious effect of air pollution (particularly ozone) on allergic rhinitis
452   control, especially during the grass pollen season, we cannot rule out (at least partially) confounding
453   by high temperature. Further studies are needed to disentangle the deleterious effects of air pollution
454   and other meteorological factors (temperature, humidity, etc.) on allergic rhinitis control.

455

456
457   **Conclusions**

458   These results show the importance of air pollution and allergen concentrations, as well as their
459   interaction, as predictors of intensity of rhinitis symptoms. They will form the base for the
460   development of predictive models in the next stage of the POLLAR project. The results of MASK-
461   air have been used to propose a DG Santé awarded Good Practice for digitally-enabled, integrated,
462   patient-centred care (40) as we expect to embed aerobiology and air pollution data in care pathways
463   for rhinitis and asthma.

464

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466
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589

Table 1. Associations between ozone and PM$_{2.5}$ levels and uncontrolled rhinitis stratified by pollen/no pollen seasons

Association between ozone and uncontrolled rhinitis				
Period/season	**Levels of ozone, median [p25-p75]**	**OR* (95%CI)**	**P**	**P interaction****
All 2017 (n=18,398)	74.0 [59.5-86.6]	1.17 (1.12, 1.23)	<0.001	
Birch (n=2,133)	83.5 [73.4-94.1]	1.10 (0.95, 1.26)	0.20	
Grass (n=4,397)	85.5 [76.6-97.5]	1.25 (1.11, 1.41)	<0.001	0.13
Between-seasons (n=1,101)	81.8 [74.7-90.2]	1.02 (0.73, 1.42)	0.91	
No pollen season (n=10,767)	64.5 [51.1-76.4]	1.08 (1.01, 1.16)	0.02	
All 2018 (n=18,042)	85.9 [70.9-98.7]	1.14 (1.10, 1.17)	<0.001	
Birch (n=4,371)	90.1 [79.4-99.3]	0.96 (0.87, 1.05)	0.34	0.14
Grass + intermediate seasons (n=4,960)[†]	95.0 [85.3-105.2]	1.14 (1.04, 1.25)	0.005	
No pollen season (n=8,711)	75.1 [59.7-90.4]	1.15 (1.09, 1.21)	<0.001	
Association between PM$_{2.5}$ and uncontrolled rhinitis				
Period/season	**Levels of PM$_{2.5}$, median [p25-p75]**	**OR* (95%CI)**	**P**	**P interaction****
All 2017 (n=18,398)	5.9 [3.0-10.5]	0.99 (0.97, 1.02)	0.63	
Birch (n=2,133)	7.7 [3.3-15.3]	1.02 (0.96, 1.09)	0.47	
Grass (n=4,397)	7.3 [4.4-10.6]	1.21 (1.09, 1.34)	<0.001	0.0003
Between-seasons (n=1,101)	5.2 [3.1-8.2]	0.88 (0.67, 1.15)	0.34	
No pollen season (n=10,767)	5.0 [2.5-10.0]	0.96 (0.93, 0.99)	0.02	
All 2018 (n=18,042)	7.1 [4.4-11.0]	1.08 (1.06, 1.10)	<0.001	

Birch (n=4,371)	8.5 [5.1-14.0]	1.11 (1.07, 1.15)	<0.001	
Grass + intermediate seasons (n=4,960)[†]	7.5 [4.9-11.0]	1.11 (1.04, 1.19)	0.004	0.0001
No pollen season (n=8,711)	6.3 [3.8-9.6]	1.00 (0.96, 1.04)	0.83	

IQR: interquartile range, OR: odds ratio

*per IQR increase in pollutants levels (ozone or $PM_{2.5}$), adjusting for sex, age, country and treatment

** treating pollutants levels (ozone or $PM_{2.5}$) as a continuous variable and the pollen season as a categorical variable

[†]In 2017, for most countries, two GT peaks were observed (i.e. clear "birch" and "grass" peaks) with an in between pollen seasons and no pollen season. In 2018, for most countries, three GT peaks were observed in 2018 (i.e. in addition to the "birch" and "grass" peaks, an intermediate peak was observed). Since there was some uncertainty on the intermediate birch-grass pollen season, pollen counts from Germany, France and Lithuania were assessed and showed that grass pollens were retrieved during this intermediate season. Therefore, for all countries, the grass pollen and the intermediate seasons were studied jointly.

1 **Table 2.** Associations between air pollutants (ozone and $PM_{2.5}$) and uncontrolled rhinitis,
2 considering temperature as a covariate in regression models
3

Association between ozone, temperature and uncontrolled rhinitis					
Period/season	Correlation between ozone and temperature	OR* (95%CI) for ozone	P	OR** (95%CI) for temperature	P
All 2017 (n=18,398)	0.60	1.14 (1.08, 1.20)	<0.001	1.06 (1.01, 1.12)	0.03
Grass (n=4,397)	0.58	1.18 (1.03, 1.35)	0.02	1.23 (1.02, 1.34)	0.03
All 2018 (n=18,042)	0.61	1.11 (1.07, 1.15)	<0.001	1.05 (1.01, 1.10)	0.02
Grass + intermediate seasons (n=4,960)	0.45	1.07 (0.96 1.18)	0.24	1.24 (1.06, 1.46)	0.009
No pollen season (n=8,711)	0.69	1.13 (1.06, 1.20)	<0.001	1.04 (0.97,1.12)	0.23
Association between $PM_{2.5}$, temperature and uncontrolled rhinitis					
Period/season	Correlation between $PM_{2.5}$ and temperature	OR* (95%CI) for $PM_{2.5}$	P	OR** (95%CI) for temperature	P
Grass (n=4,397)	0.59	1.13 (1.00, 1.28)	0.05	1.24 (1.01, 1.51)	0.04
All 2018 (n=18,042)	0.09	1.07 (1.04, 1.09)	<0.001	1.10 (1.06, 1.14)	<0.001
Birch (n=4,371)	0.43	1.07 (1.03, 1.12)	0.001	1.22 (1.09, 1.37)	0.001
Grass + intermediate seasons (n=4,960)	0.32	1.07 (0.99, 1.15)	0.10	1.24 (1.06, 1.44)	0.006

4 IQR: interquartile range, OR: odds ratio

5

6 *per IQR increase in pollutants levels (ozone or $PM_{2.5}$), adjusting for sex, age, country, treatment and
7 maximum temperature

8

9 **per IQR increase in maximum temperature, adjusting for sex, age, country, treatment and
10 pollutants levels (ozone or $PM_{2.5}$)

11
12

13   **Table 3.** Associations between air pollutants (ozone and $PM_{2.5}$) and uncontrolled rhinitis,
14   considering ozone and $PM_{2.5}$ simultaneously as exposures in regression models (i.e. two-
15   pollutant models)
16

Association between ozone, $PM_{2.5}$ and uncontrolled **rhinitis**				
Period/season	**OR* (95%CI) for ozone**	**P**	**OR** (95%CI) for $PM_{2.5}$**	**P**
All 2017 (n=18,398)	1.17 (1.12, 1.23)	<0.001	1.00 (0.98, 1.02)	0.88
Birch (n=2,133)	1.10 (0.95, 1.27)	0.19	1.03 (0.96, 1.10)	0.38
Grass (n=4,397)	1.18 (1.03, 1.34)	0.02	1.14 (1.01, 1.28)	0.04
Between-seasons (n=1,101)	1.06 (0.75, 1.48)	0.75	0.86 (0.65, 1.12)	0.26
No pollen season (n=10,767)	1.07 (1.00, 1.15)	0.04	0.96 (0.93, 1.00)	0.03
All 2018 (n=18,042)	1.13 (1.10, 1.17)	<0.001	1.08 (1.05, 1.10)	<0.001
Birch (n=4,371)	0.93 (0.85, 1.03)	0.15	1.11 (1.07, 1.15)	<0.001
Grass + intermediate seasons (n=4,960)	1.11 (1.01, 1.22)	0.03	1.09 (1.01, 1.17)	0.03
No pollen season (n=8,711)	1.15 (1.10, 1.21)	<0.001	1.00 (0.96, 1.04)	0.87

17   IQR: interquartile range, OR: odds ratio

18   *per IQR increase in ozone levels, adjusting for sex, age, country, treatment and $PM_{2.5}$ levels

19   **per IQR increase in $PM_{2.5}$ levels, adjusting for sex, age, country, treatment and ozone levels

20

21

22 **Figure 1.** Flow chart of the study population

23 *including for days recorded in Italy and France only those above the latitude of Lyon

24 VAS: visual analog scale

25

```
┌─────────────────────────┐
│  190,492 VAS recorded   │
│  between February 2017  │
│    and October 2018     │
└─────────────────────────┘
            │
            ▼   - 4,287 duplicates or multiplicates (for days with > 1 VAS recorded)
┌─────────────────────────┐
│  186,205 single VAS     │
│  person days recorded in│
│     2017 and 2018       │
└─────────────────────────┘
            │
            ▼   - 66,076 days recorded without geolocation
┌─────────────────────────┐
│  120,129 single VAS     │
│  person days recorded in│
│    2017 and 2018 with   │
└─────────────────────────┘
            │
            ▼   - 69,035 days recoded outside Northern or Central Europe
┌─────────────────────────┐
│  51,094 single VAS person│
│  days recorded in       │
│  Northern and Central   │
│  Europe* in 2017 and 2018│
│    with geolocation     │
└─────────────────────────┘
            │   -   1,999 days without air pollution data (SILAM European database)
            ▼
                -   12,655 days without pollen data (Google Trends)
┌─────────────────────────┐
│  36,440 single VAS person│       ┌ 18,398 days in 2017
│  days (3,323 users) in  │       │
│  Northern and Central   │       │
│  Europe in 2017 and 2018│       │
│     with available      │       └ 18,042 days in 2018
│   information on air     │
└─────────────────────────┘
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26   **Figure 2A.** Assessment of pollen seasons by region/countries for 2017 using Google Trends

2017
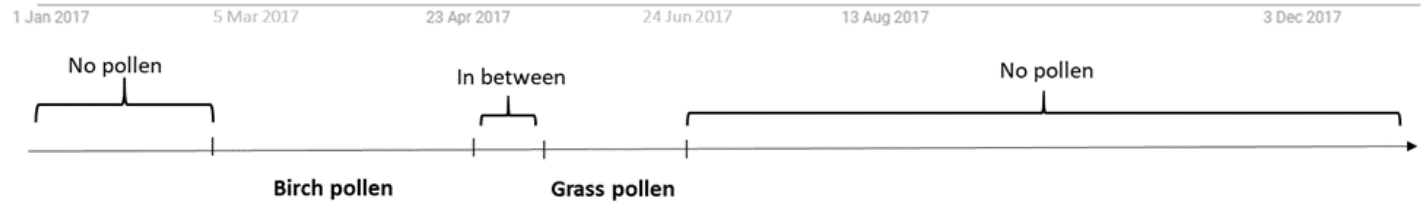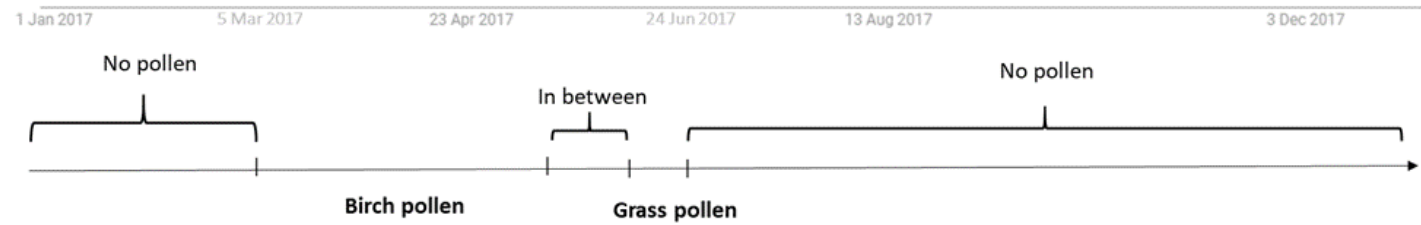
Continental and semi-continental climates
(Germany, Austria, Belgium, France, Netherlands, Poland, Switzerland, Czech Republic, Northern Italy)

1 Jan 2017   5 Mar 2017   23 Apr 2017   24 Jun 2017   13 Aug 2017   3 Dec 2017

No pollen   In between   No pollen

Birch pollen   **Grass pollen**

Northern countries
(Denmark, Finland, Lithuania, Sweden)

1 Jan 2017   5 Mar 2017   23 Apr 2017   24 Jun 2017   13 Aug 2017   3 Dec 2017

No pollen   In between   No pollen

Birch pollen   **Grass pollen**

UK

1 Jan 2017   5 Mar 2017   23 Apr 2017   24 Jun 2017   13 Aug 2017   3 Dec 2017

No pollen   In between   No pollen

Birch pollen   **Grass pollen**
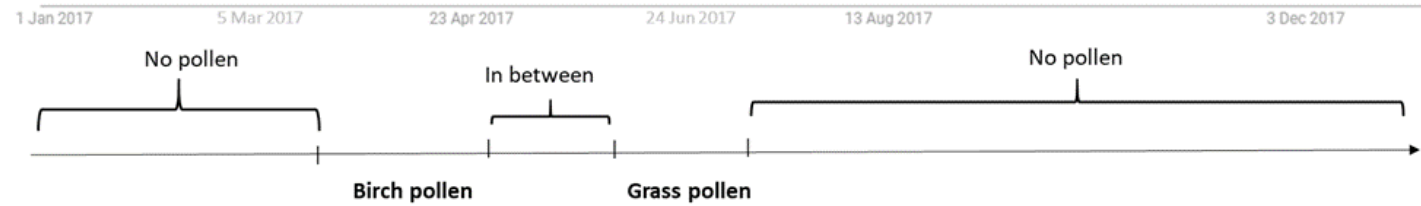
27
28

29

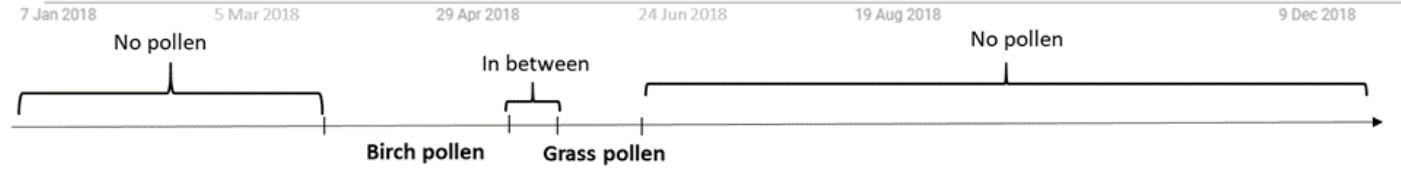30   **Figure 2B.** Assessment of pollen seasons by region/countries for 2018 using Google Trends

31

2018
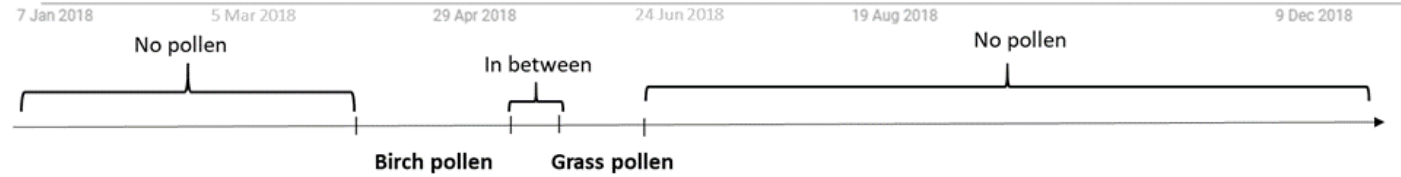
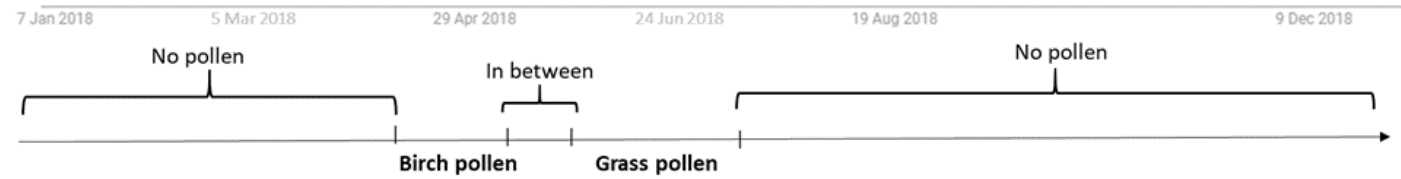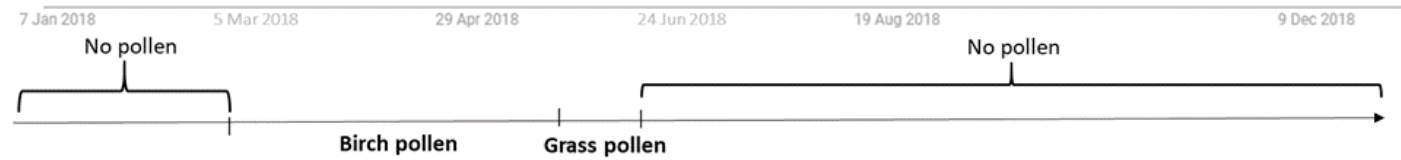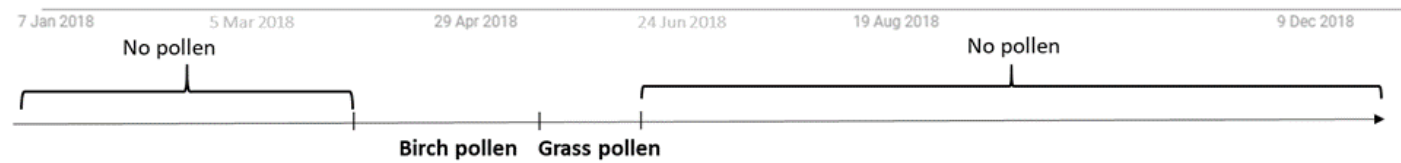33   **Figure 3A:** Assessment of pollen seasons for 2017 using GTs – examples for France,
34   Germany and the UK

35

36   **Figure 3B:** Assessment of pollen seasons for 2018 using GTs – examples for France, Germany and

37   the UK
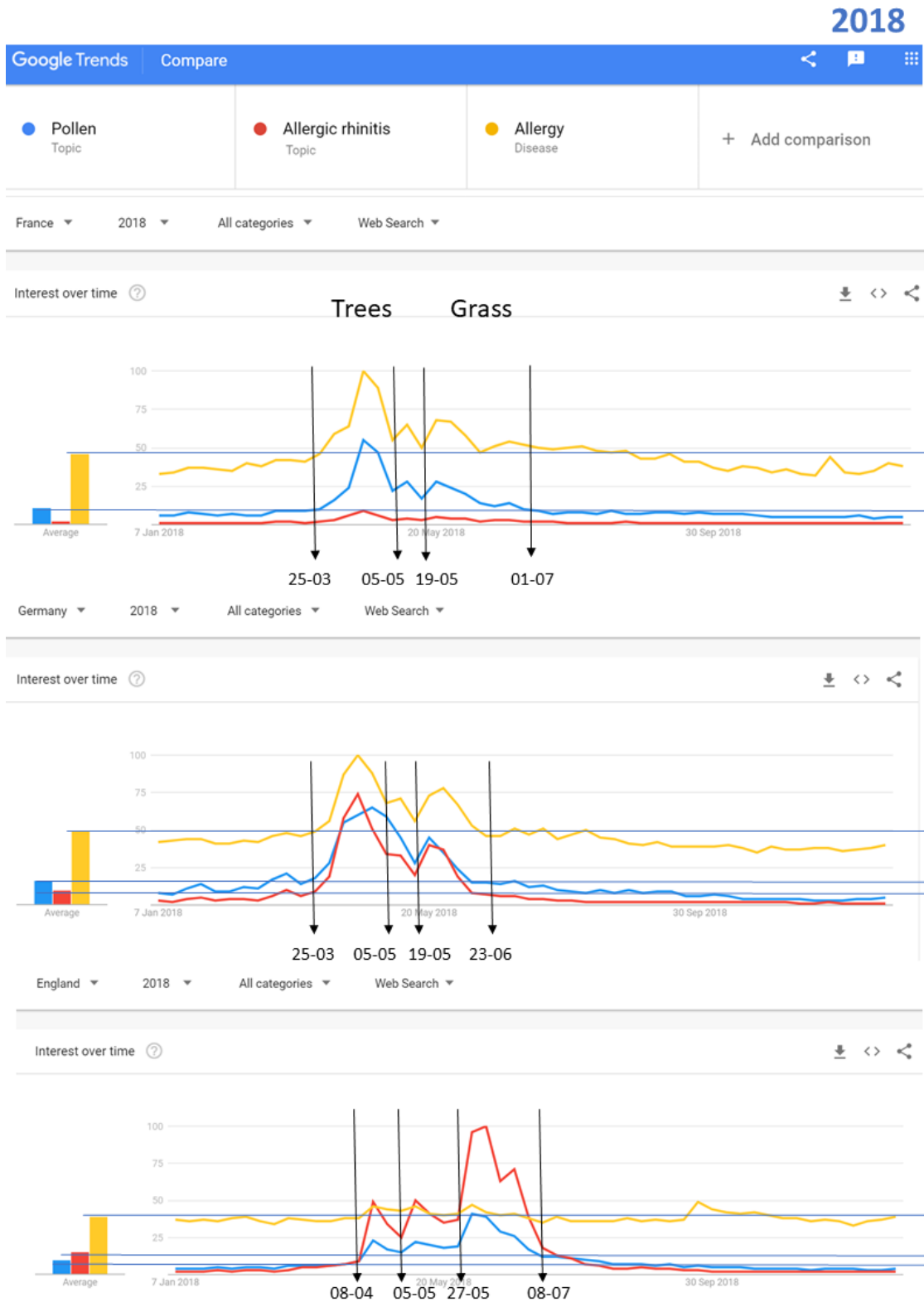
38

39   **Table E1.** Number of days included in the analyses by country and year

Country	Number of days studied		Total days	Total users
	2017	**2018**		
Austria	847	1,435	2,319	199
Belgium	270	311	581	102
Czech Republic	136	0	136	11
Denmark	279	170	449	51
Finland	1,022	0	1,022	160
France	684	2,635	3,319	407
Germany	3,650	3,836	7,486	509
Northern Italy	2,104	0	2,104	125
Lithuania	4,004	0	4,004	203
NA*	252	0	252	73
Netherlands	851	3,998	4,849	541
Poland	1,581	3,462	5,043	428
Sweden	279	0	279	38
Switzerland	598	1,687	2,285	502
United Kingdom	1,804	508	2,312	245
Total	**18,398**	**18,042**	**36,440**	**3,323**

40   *NA: information not available (eg. located on borders etc.)

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Table E2. Usage of the app (number of days used and VAS global) by users' characteristics

Number of days per user$^{\pm}$ (n=3,323)			
	N users (%)	**Median [p25-p75]**	**P***
Sex			
Male	1,514 (45.6)	2 [1-8]	
Female	1,806 (54.4)	2 [1-7]	0.32
Country of residence			
Austria	174 (5.2)	1 [1-5]	
Belgium	74 (2.2)	1 [1-7]	
Czech Republic	7 (0.2)	14 [4-35]	
Denmark	53 (1.6)	3 [1-10]	
Finland	139 (4.2)	2 [1-4]	
France	354 (10.7)	2 [1-4]	0.0001
Germany	428 (12.9)	3 [1-15]	
Northern Italy	129 (3.9)	3 [1-14]	
Lithuania	212 (6.4)	6.5 [2-25]	
Netherlands	535 (16.1)	2 [1-6]	
Poland	405 (12.2)	2 [1-8]	
Sweden	44 (1.3)	2 [1-7]	
Switzerland	487 (14.7)	1 [1-2]	
United Kingdom	230 (6.9)	3 [1-9]	
Year of birth			
≤1974	1,038 (31.3)	2 [1-9]	0.06
1975-1988	1,120 (33.7)	2 [1-6.5]	
≥1989	1,162 (35.0)	2 [1-7]	
VAS global (n=36,440)			
	N person-days (%)	**median [p25-p75]**	**P***
Sex			
Male	18,359 (50.4)	10 [0-28]	
Female	18,078 (49.6)	16 [3-44]	0.0001
Country of residence			
Austria	2,309 (6.3)	5 [0-21]	
Belgium	547 (1.5)	30 [11-56]	
Czech Republic	150 (0.4)	1 [0-18]	
Denmark	471 (1.3)	30 [15-53]	
Finland	997 (2.7)	16 [6-35]	
France	2,939 (8.1)	11 [0-41]	0.0001
Germany	7,391 (20.3)	13 [1-32]	
Northern Italy	2,335 (6.4)	7 [0-25]	
Lithuania	4,098 (11.3)	7 [0-26]	
Netherlands	4,955 (13.6)	21 [6-49]	
Poland	5,023 (13.8)	9 [0-28]	

Sweden	329 (0.9)	11 [0-33]	
Switzerland	2,363 (6.5)	26 [7-57]	
United Kingdom	2,345 (6.4)	16 [6-42]	
Year of birth			
≤1974	13,860 (38.0)	13 [1-32]	
1975-1988	11,874 (32.6)	12 [0-33]	0.0001
≥1989	10,703 (29.4)	15 [1-43]	
Daily treatment			
No	16,756 (46.0)	7 [0-25]	
Yes	19,684 (54.0)	18 [5-43]	0.0001

44   ± The number of days per user recorded between early 2017 and the end of 2018 (hence we

45   do not account for the days that may have been recorded by those users in 2016 for

46   instance).

47   * Kruskal-Wallis tests were used to compare the distribution of continuous variables by

48   categories.

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51 **Table E3.** Associations between ozone and PM$_{2.5}$ levels and uncontrolled rhinitis stratified

52 by pollen/no pollen seasons (lag analysis)

Association between ozone and uncontrolled rhinitis		
Period/season	**OR* (95%CI)**	**P**
All 2017 (n=18,331)	1.12 (1.06, 1.17)	<0.001
Birch (n=2,103)	1.07 (0.94, 1.23)	0.31
Grass (n=4,301)	1.12 (0.99, 1.26)	0.07
Between-seasons (n=1,179)	1.09 (0.79, 1.49)	0.60
No pollen season (n=10,735)	1.03 (0.96, 1.10)	0.44
All 2018 (n=18,012)	1.15 (1.11, 1.19)	<0.001
Birch (n=4,317)	1.09 (0.99, 1.19)	0.08
Grass + intermediate seasons (n=4,942)	1.11 (1.01, 1.22)	0.04
No pollen season (n=8,715)	1.16 (1.10, 1.22)	<0.001
Association between PM$_{2.5}$ and uncontrolled rhinitis		
Period/season	**OR* (95%CI)**	**P**
All 2017 (n=18,331)	1.00 (0.98, 1.02)	0.92
Birch (n=2,103)	1.00 (0.94, 1.07)	0.99
Grass (n=4,301)	1.12 (1.01, 1.24)	0.04
Between-seasons (n=1,179)	1.03 (0.79, 1.34)	0.84
No pollen season (n=10,735)	0.97 (0.94, 1.00)	0.08
All 2018 (n=18,012)	1.08 (1.06, 1.11)	<0.001
Birch (n=4,317)	1.11 (1.08, 1.15)	<0.001
Grass + intermediate seasons (n=4,942)	1.04 (0.97, 1.12)	0.27
No pollen season (n=8,715)	1.00 (0.96, 1.05)	0.85

53 IQR: interquartile range, OR: odds ratio

54 *per IQR increase in pollutants levels (ozone or PM$_{2.5}$), adjusting for sex, age, country and

55 treatment

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58   **Table E4.** Associations between ozone and $PM_{2.5}$ levels and uncontrolled rhinitis stratified

59   by pollen/no pollen seasons (urban area)

Association between ozone and uncontrolled rhinitis		
Period/season	**OR* (95%CI)**	**P**
All 2017 (n=14,610)	1.16 (1.10, 1.22)	<0.001
Birch (n=1,723)	1.07 (0.92, 1.24)	0.38
Grass (n=3,532)	1.22 (1.07, 1.39)	0.002
Between-seasons (n=864)	1.03 (0.71, 1.48)	0.89
No pollen season (n=8,478)	1.08 (1.00, 1.16)	0.05
All 2018 (n=14,672)	1.17 (1.13, 1.21)	<0.001
Birch (n=3,592)	0.99 (0.89, 1.10)	0.82
Grass + intermediate seasons (n=4,068)	1.17 (1.06, 1.29)	0.002
No pollen season (n=6,976)	1.19 (1.12, 1.26)	<0.001
Association between $PM_{2.5}$ and uncontrolled rhinitis		
Period/season	**OR* (95%CI)**	**P**
All 2017 (n=14,610)	1.00 (0.97, 1.02)	0.78
Birch (n=1,723)	1.02 (0.95, 1.09)	0.58
Grass (n=3,532)	1.21 (1.08, 1.36)	0.002
Between-seasons (n=864)	0.86 (0.64, 1.14)	0.30
No pollen season (n=8,478)	0.96 (0.92, 0.99)	0.01
All 2018 (n=14,672)	1.09 (1.07, 1.12)	<0.001
Birch (n=3,592)	1.11 (1.07, 1.16)	<0.001
Grass + intermediate seasons (n=4,068)	1.14 (1.06, 1.23)	0.001
No pollen season (n=6,976)	0.99 (0.94, 1.04)	0.77

60   IQR: interquartile range, OR: odds ratio

61   *per IQR increase in pollutants levels (ozone or $PM_{2.5}$), adjusting for sex, age, country and

62   treatment

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68 **Table E5.** Associations between ozone and PM$_{2.5}$ levels and uncontrolled rhinitis stratified

69 by pollen/no pollen seasons (rural area)

Association between ozone and uncontrolled rhinitis		
Period/season	**OR* (95%CI)**	**P**
All 2017 (n=3,769)	1.31 (1.15, 1.50)	<0.001
Birch (n=393)	1.09 (0.67, 1.78)	0.73
Grass (n=856)	1.44 (1.02, 2.04)	0.04
Between-seasons (n=227)	1.07 (0.48, 2.39)	0.87
No pollen season (n=2,266)	1.18 (0.96, 1.47)	0.12
All 2018 (n=3,334)	1.03 (0.94, 1.13)	0.57
Birch (n=738)	0.75 (0.54, 1.04)	0.08
Grass + intermediate seasons (n=875)	1.02 (0.77, 1.35)	0.91
No pollen season (n=1,715)	1.07 (0.94, 1.22)	0.31
Association between PM$_{2.5}$ and uncontrolled rhinitis		
Period/season	**OR* (95%CI)**	**P**
All 2017 (n=3,769)	0.98 (0.92, 1.05)	0.65
Birch (n=393)	1.06 (0.81, 1.37)	0.68
Grass (n=856)	1.32 (0.99, 1.75)	0.06
Between-seasons (n=227)	1.13 (0.55, 2.32)	0.73
No pollen season (n=2,266)	0.97 (0.87, 1.07)	0.47
All 2018 (n=3,334)	1.04 (0.98, 1.10)	0.19
Birch (n=738)	1.11 (1.00, 1.23)	0.05
Grass + intermediate seasons (n=875)	0.99 (0.79, 1.24)	0.90
No pollen season (n=1,715)	0.99 (0.91, 1.09)	0.88

70 IQR: interquartile range, OR: odds ratio

71 *per IQR increase in pollutants levels (ozone or PM$_{2.5}$), adjusting for sex, age, country and

72 treatment

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76 **Table E6.** Associations between ozone and $PM_{2.5}$ levels and global VAS stratified by pollen/no

77 pollen seasons

Association between ozone and global VAS		
Period/season	**β* (95%CI)**	**P**
All 2017 (n=18,398)	1.86 (1.48, 2.24)	<0.001
Birch (n=2,133)	0.59 (-0.70, 1.87)	0.37
Grass (n=4,397)	2.27 (1.24, 3.29)	<0.001
Between-seasons (n=1,101)	1.81 (-0.71, 4.34)	0.91
No pollen season (n=10,767)	1.15 (0.71, 1.58)	<0.001
All 2018 (n=18,042)	2.37 (1.99, 2.76)	<0.001
Birch (n=4,371)	0.61 (-0.55, 1.78)	0.30
Grass + intermediate seasons (n=4,960)	2.15 (1.18, 3.12)	<0.001
No pollen season (n=8,711)	2.15 (1.70, 2.60)	<0.001
Association between $PM_{2.5}$ and global VAS		
Period/season	**β* (95%CI)**	**P**
All 2017 (n=18,398)	-0.07 (-0.24, 0.09)	0.39
Birch (n=2,133)	0.15 (-0.43, 0.73)	0.62
Grass (n=4,397)	2.08 (1.16, 3.00)	<0.001
Between-seasons (n=1,101)	0.95 (-1.12, 3.02)	0.37
No pollen season (n=10,767)	-0.27 (-0.44, -0.11)	0.001
All 2018 (n=18,042)	0.86 (0.60, 1.13)	<0.001
Birch (n=4,371)	1.53 (1.07, 1.98)	<0.001
Grass + intermediate seasons (n=4,960)	1.24 (0.46, 2.01)	0.002
No pollen season (n=8,711)	-0.36 (-0.71, -0.02)	0.04

78 IQR: interquartile range, β: mean difference in global VAS measure
79 *per IQR increase in pollutants levels (ozone or $PM_{2.5}$), adjusting for sex, age, country and treatment

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82 **Table E7.** Associations between ozone and PM2.5 levels – in quartiles - and uncontrolled

83 rhinitis stratified by pollen/no pollen seasons

Association between ozone and uncontrolled rhinitis, OR (95%CI)				
Period/season	**Q2 vs Q1**	**Q3 vs Q1**	**Q4 vs Q1**	**P trend***
All 2017 (n=18,398)	1.11 (1.03, 1.20)	1.21 (1.11, 1.32)	1.46 (1.31, 1.61)	<0.001
All 2018 (n=18,042)	1.16 (1.07, 1.24)	1.26 (1.18, 1.36)	1.33 (1.23, 1.42)	<0.001
Association between PM$_{2.5}$ and uncontrolled rhinitis, OR (95%CI)				
Period/season	**Q2 vs Q1**	**Q3 vs Q1**	**Q4 vs Q1**	**P trend***
All 2017 (n=18,398)	1.02 (0.95, 1.10)	1.08 (1.00, 1.18)	1.05 (0.96, 1.14)	0.16
All 2018 (n=18,042)	1.05 (0.99, 1.12)	1.09 (1.02, 1.16)	1.23 (1.15, 1.31)	<0.001

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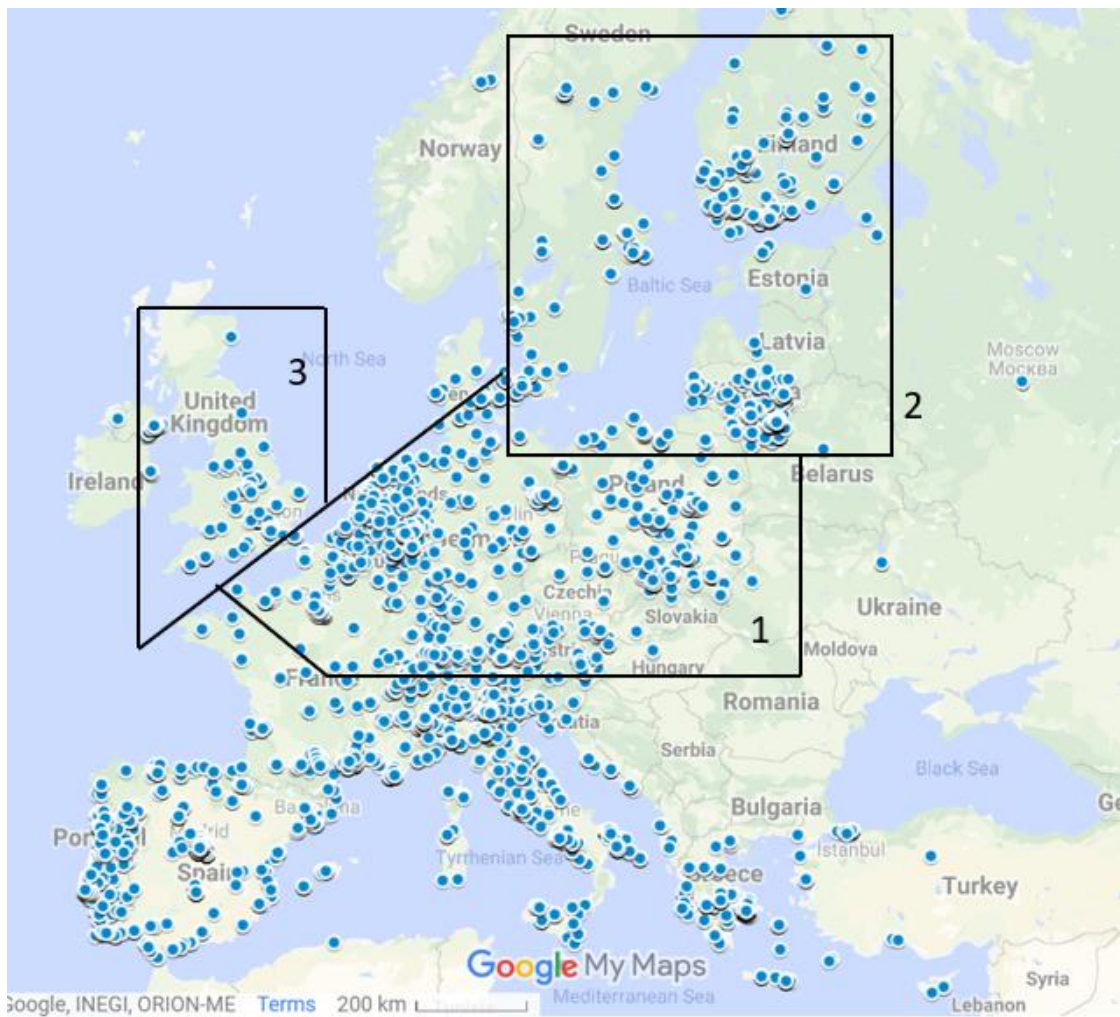85 IQR: interquartile range, OR: odds ratio

86 *per quartile increase in pollutants levels (ozone or PM$_{2.5}$), adjusting for sex, age, country

87 and treatment

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91 **Figure E1.** Areas of the study

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94 1. Continental and semi-continental climate (Germany, Austria, Belgium, Northern France,

95 Netherlands, Poland, Switzerland, Czech Republic, Northern Italy)

96 2. Northern countries (Denmark, Finland, Lithuanian, Sweden)

97 3. The UK

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