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To cite this version:

Annabelle Bédard, Mikhail Sofiev, Sylvie Arnavielhe, Josep Antó, Judith Garcia-Aymerich, et al.. Interactions Between Air Pollution and Pollen Season for Rhinitis Using Mobile Technology: A MASK-POLLAR Study. Journal of Allergy and Clinical Immunology: In Practice, 2020, 8 (3), pp.1063-1073.e4. 10.1016/j.jaip.2019.11.022 . hal-03380325

HAL Id: hal-03380325
https://hal.umontpellier.fr/hal-03380325v1

Submitted on 22 Jan 2024

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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Abstract

Background: Several studies have suggested an interaction between air pollution and pollen exposure with an impact on allergy symptoms. However, large studies with real-life data are not available.

Objectives: In the POLLAR (Impact of Air POLLution in Asthma and Rhinitis) project, we investigated associations between major air pollutants (ozone and $PM_{2.5}$) and allergic rhinitis control, during grass and birch pollen seasons as well as outside the pollen season.

Methods: The daily impact of allergic symptoms was recorded by the *Allergy Diary - MASK-air* - App (a validated mHealth tool for rhinitis management), using visual analogue scales (VASs) in Northern and Central Europe users in 2017 and 2018. Uncontrolled allergic rhinitis was defined using symptoms and medications. Pollutant levels were assessed using SILAM (System for integrated modelling of atmospheric composition). Pollen seasons were assessed by regions using Google Trends. Generalized estimating equation models were used to account for repeated measures per user, adjusting for gender, age, treatment and country. Analyses were stratified by pollen seasons to investigate interactions between air pollutants and pollen exposure.

Results: 3,323 geolocated individuals (36,440 VAS days) were studied. Associations between uncontrolled rhinitis and pollutants were stronger during the grass pollen season. Days with uncontrolled allergic rhinitis increased by 25% for an interquartile range increase in ozone levels during the grass season: odds ratio (OR) of 1.25 [95% confidence interval (CI): 1.11-1.41] in 2017 and of 1.14 [95% CI: 1.04-1.25] in 2018. A similar trend was found for PM2.5, especially in 2017.

Conclusions: These results suggest that the relationship between uncontrolled allergic rhinitis and air pollution is modified by the presence of grass pollens. This study confirms the impact of pollutants in grass pollen season but not in birch pollen season.

Conflict of interest

A Bédard has nothing to disclose.

M Sofiev has nothing to disclose.

S Arnavielhe has nothing to disclose.

JM Antó has nothing to disclose.

J Garcia-Aymerich has nothing to disclose.

M Thibaudon has nothing to disclose.

KC Bergmann has nothing to disclose.

R Dubakiene has nothing to disclose.

A Bedbrook has nothing to disclose.

GL Onorato has nothing to disclose.

I Annesi-Maesano has nothing to disclose.

JL Pépin reports grants and personal fees from Resmed, grants and personal fees from Philips, grants from Fisher and Paykel, grants and personal fees from Agiradom, grants and personal fees from Astra Zeneca, grants from Mutualia, grants from Vitalaire, grants from Air Liquide Foundation, grants and personal fees from SEFAM, personal fees from JAZZ, personal fees from ITAMAR, outside the submitted work.

D Laune has nothing to disclose.

S Zeng has nothing to disclose.

J Bousquet reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, outside the submitted work, and KYomed-Innov shares.

Dr. Basagaña has nothing to disclose.

Source of funding

EIT Health (Grant ref: 18354 - Impact of POLLution on Asthma and Rhinitis), Fondation FMC-VIA-LR

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

Abbreviations

AR: Allergic rhinitis

GT: Google Trends

ICT: Information and Communication Technology

INN: International Nonproprietary Names

OTC: over the counter

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

POLLAR: Impact of air POLLution on Asthma and Rhinitis

$PM_{2.5}$: Particulate matter 2.5

RCT: Randomized controlled trial

SILAM: System for integrated modelling of atmospheric composition

VAS: Visual Analogue Scale

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 patients in order to deliver interconnected rhinitis management assistance during peak periods of air pollution and promote measures that help people deal with health and societal consequences of the condition (17). To achieve this, one of the objectives of POLLAR is to investigate the interaction between air pollution and pollen exposure and its impact on AR control. A series of analyses were carried out on the MASK-air data available for 2017 and 2018 in Northern and Central Europe. The aim was to assess the impact of the two major pollutants associated with rhinitis (ozone and $PM_{2.5}$) on the severity of rhinitis during and outside the estimated pollen seasons. To do so, we linked the self-reported rhinitis symptoms obtained via an App with air pollution predictions obtained from the SILAM (System for integrated modelling of atmospheric composition (18)) database. We then conducted analyses separately by pollen seasons derived using Google Trends (GTs). We restricted the study to Northern and Central Europe (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Northern Italy, Lithuania, Netherlands, Poland, Sweden, Switzerland, United Kingdom) since these pollen seasons are better identified than those in Southern Europe. The two major pollen seasons included Betulaceae (i.e. birch) and grass (more details below).

Setting - study population and observations unit

All days recorded by the users of the MASK-air app between February 2017 and October 2018 were included with no exclusion criteria and according to methods previously described (16, 19, 20). The unit of observations used in the present study is person-days (i.e. each day of app use by any user). Some of the users used the app more than once a day to report symptoms. We carefully analyzed this issue and found that the highest recording should be used and this approach was used to eliminate duplicates/multiplicates (16,19).

Days where the App was used in Northern and Central Europe were included in the analyses. Areas were defined as those above the latitude of Lyon (Figure E1). Table E1 summarizes the number of days included in the study by country for each year.

Ethics

The Allergy Diary is CE1 registered. By using k-anonymity, the data were anonymized including the data related to geolocation (21). An Independent Review Board approval was not required since the study is observational and users agree to having their data analysed (terms of use) (16,19,20).

m-health data

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

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

Outcomes

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

1. days with VAS global ≥ 50/100

   or

2. days with VAS global ≥ 35 and use of INCS-containing medication

   or

3. days with VAS global ≥ 20 and use of at least 3 medications

Days were defined as controlled rhinitis otherwise.

Exposure data

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

Air pollution data

Pollutants (ozone and $PM_{2.5}$ concentrations; spatial resolution: 12x12 km grid) for the whole of Europe were obtained from the SILAM (System for integrated modelling of atmospheric composition) database (18,22,23) of the Finnish Meteorological institute (http://silam.fmi.fi). SILAM is a global-to-meso-scale dispersion model that uses anthropogenic emission datasets, information on wild-land fires, meteorological data, as well as embedded emission computations for sea salt, pollen, wind-blown dust, and natural volatile organic compounds to produce the forecasts of several pollutants, including ozone and particulate matter with a diameter of less than 2.5 μm ($PM_{2.5}$). We used forecasts for the same day at noon at a 0.1 degree resolution.

Temperatures

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

Urban *vs* rural area

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

Pollen season

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

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

Statistical analysis

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

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

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

In order to investigate a potential lag-time in the effect of air pollution on allergic rhinitis control, especially in a cross-sectional study, we repeated the analyses of the associations between air pollution and uncontrolled rhinitis, using a 1-day lag (i.e. considering the air pollution levels of the user’s location on the previous day – assuming the geolocation on the previous day was the same as the geolocation on the day the app was used). In order to investigate potential effect modification by urbanization, associations were stratified by rural and urban areas. As a sensitivity analysis, we repeated our main analyses by considering global VAS - which has been used in previous papers (16,20) - as an outcome (instead of uncontrolled rhinitis), using mixed linear regression models (for continuous outcome). In order to investigate potential non-linear effects, we repeated our analyses of the associations between air pollutants and uncontrolled rhinitis, considering ozone and $PM_{2.5}$ in quartiles, testing a linear trend.

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

Results

Demographic characteristics of the users and usage of the app

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

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

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

Estimation of the pollen season

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

For 2018, five patterns of pollen seasons were determined: 1) Germany, France and Switzerland, 2) Belgium, Netherlands and Denmark, 3) the UK, 4) Austria and 5) Poland (Figure 2B). 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 - see examples in Figure 3B). 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.

Associations between pollution and uncontrolled rhinitis

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

No association was observed between $PM_{2.5}$ and uncontrolled rhinitis for 2017 overall (Table 1). When the association was stratified by seasons, no association was observed during the birch season whereas a strong positive association was found during the grass pollen season and a weak negative association was found during the no pollen season (ORs: 1.02 (0.96, 1.09), 1.21 (1.09, 1.34) and 0.96 (0.93, 0.99), respectively). Levels of $PM_{2.5}$ were highest during the birch pollen season and lowest outside the pollen season (Table 1). A positive association was observed between $PM_{2.5}$ and uncontrolled rhinitis for 2018 overall. When the association was stratified by seasons, similar positive associations were found during the birch and grass pollen seasons but no association was 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), respectively).

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

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

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

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

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

Discussion

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

Strengths and weaknesses

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

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

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

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

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

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

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

Interpretation of the results

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

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

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

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

Conclusions

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

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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.

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

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

IQR: interquartile range, OR: odds ratio

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

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

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

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

IQR: interquartile range, OR: odds ratio

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

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

Figure 1. Flow chart of the study population

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

VAS: visual analog scale

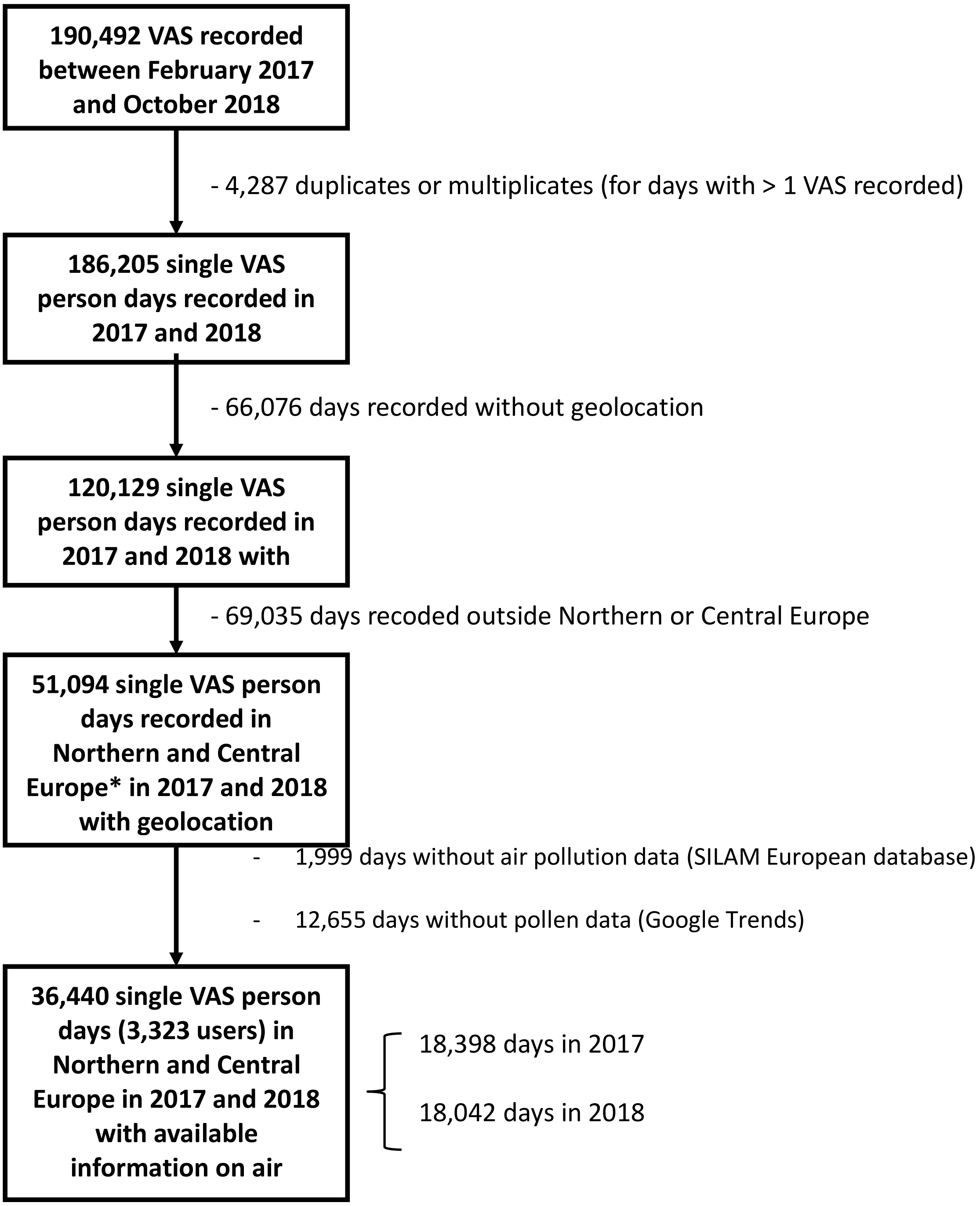


Figure 2A. Assessment of pollen seasons by region/countries for 2017 using Google Trends

2017

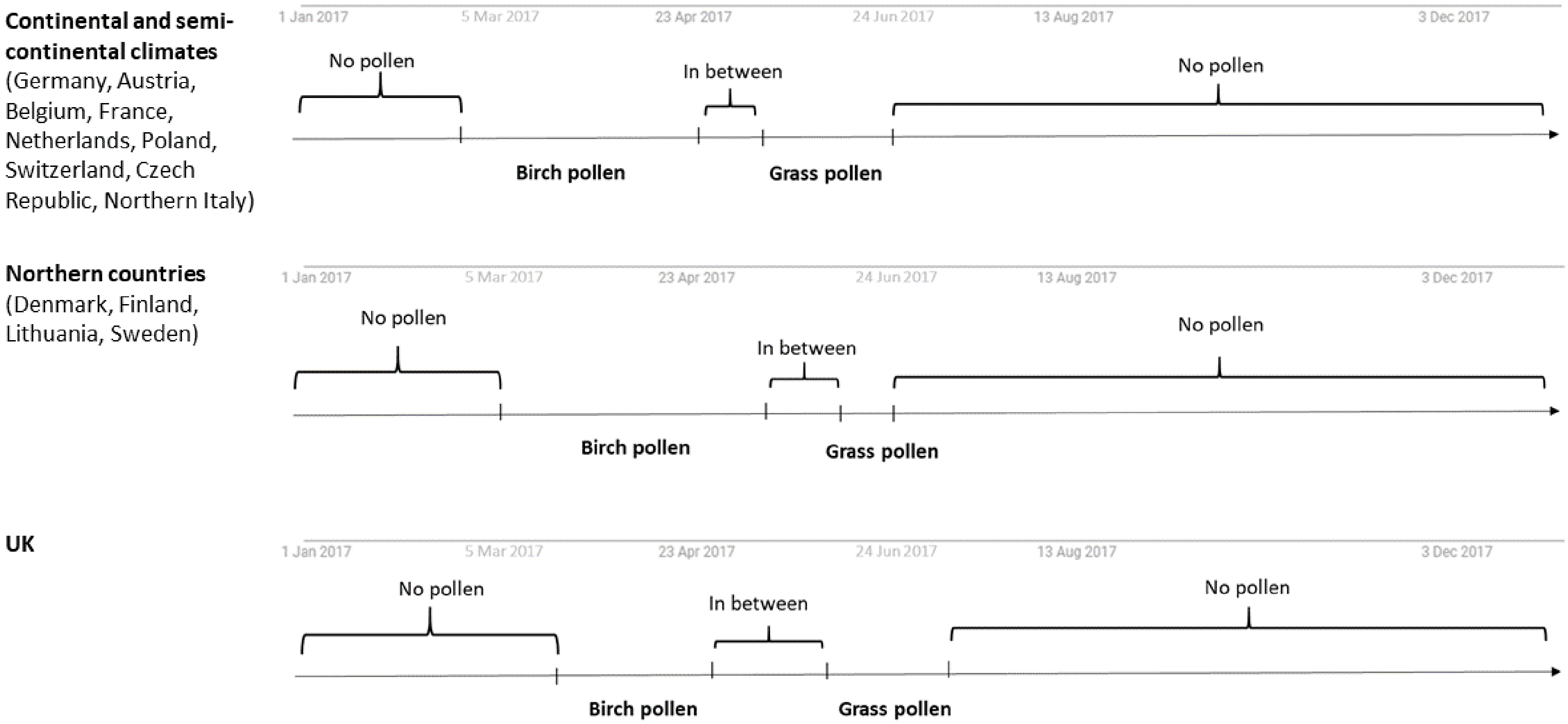

Continental and semi-continental climates
(Germany, Austria, Belgium, France, Netherlands, Poland, Switzerland, Czech Republic, Northern Italy)
1 Jan 2017
5 Mar 2017
23 Apr 2017
24 Jun 2017
13 Aug 2017
3 Dec 2017
No pollen
In between
No pollen
Birch pollen
Grass pollen
Northern countries
(Denmark, Finland, 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

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

2018

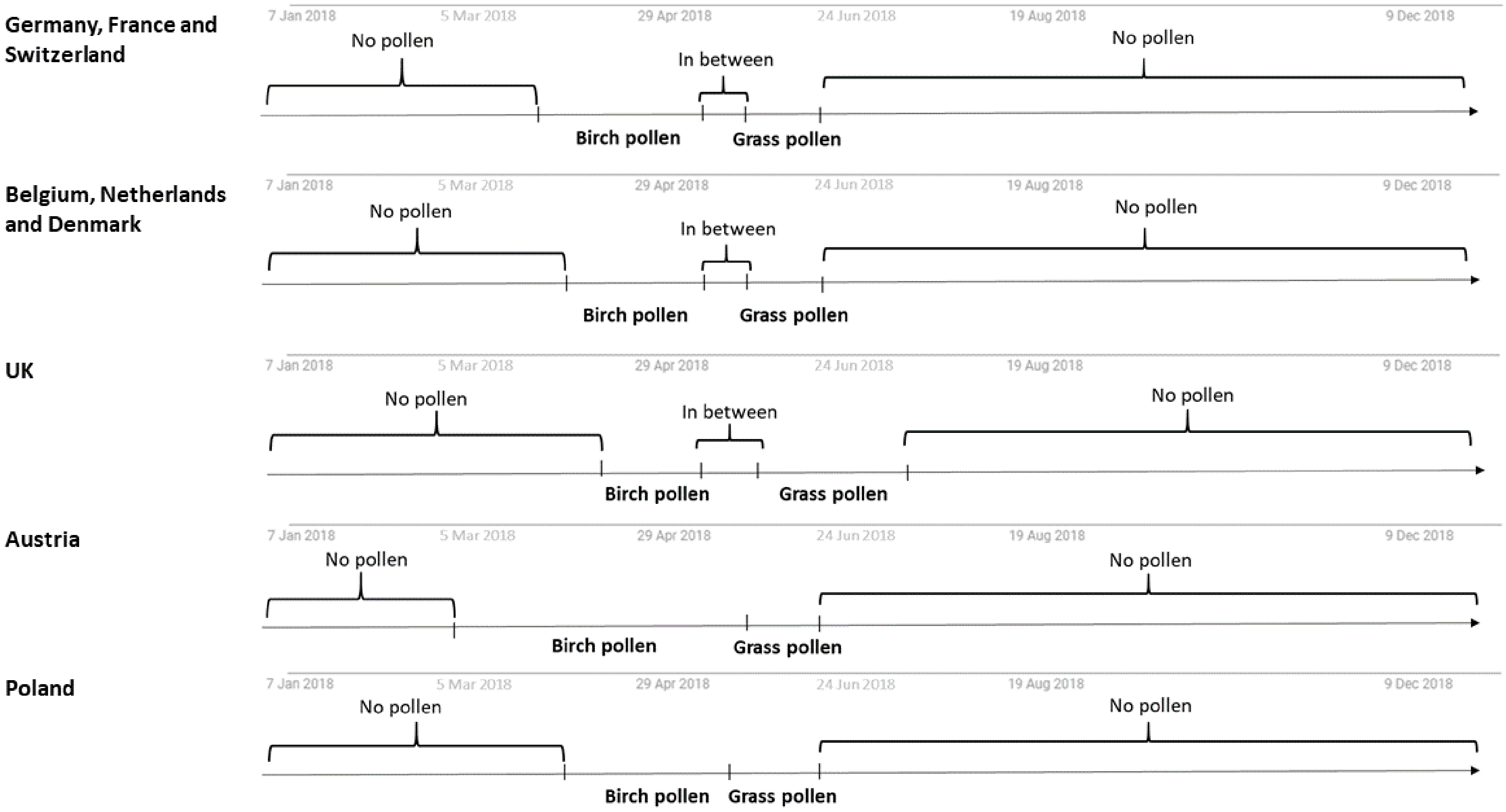

Germany, France and Switzerland
7 Jan 2018
5 Mar 2018
29 Apr 2018
24 Jun 2018
19 Aug 2018
9 Dec 2018
No pollen
In between
No pollen
Birch pollen
Grass pollen
Belgium, Netherlands and Denmark
7 Jan 2018
5 Mar 2018
29 Apr 2018
24 Jun 2018
19 Aug 2018
9 Dec 2018
No pollen
In between
No pollen
Birch pollen
Grass pollen
UK
7 Jan 2018
5 Mar 2018
29 Apr 2018
24 Jun 2018
19 Aug 2018
9 Dec 2018
No pollen
In between
No pollen
Birch pollen
Grass pollen
Austria
7 Jan 2018
5 Mar 2018
29 Apr 2018
24 Jun 2018
19 Aug 2018
9 Dec 2018
No pollen
No pollen
Birch pollen
Grass pollen
Poland
7 Jan 2018
5 Mar 2018
29 Apr 2018
24 Jun 2018
19 Aug 2018
9 Dec 2018
No pollen
No pollen
Birch pollen
Grass pollen

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

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

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

Country	**Number of days studied**			
	2017	**2018**	**Total days**	**Total users**
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.)

41

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

[±] The number of days per user recorded between early 2017 and the end of 2018 (hence we do not account for the days that may have been recorded by those users in 2016 for instance).

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

Table E3. Associations between ozone and $PM_{2.5}$ levels and uncontrolled rhinitis stratified 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

IQR: interquartile range, OR: odds ratio

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

Table E4. Associations between ozone and PM$_{2.5}$ levels and uncontrolled rhinitis stratified 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

IQR: interquartile range, OR: odds ratio

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

Table E5. Associations between ozone and $PM_{2.5}$ levels and uncontrolled rhinitis stratified 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

IQR: interquartile range, OR: odds ratio

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

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

IQR: interquartile range, β: mean difference in global VAS measure

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

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

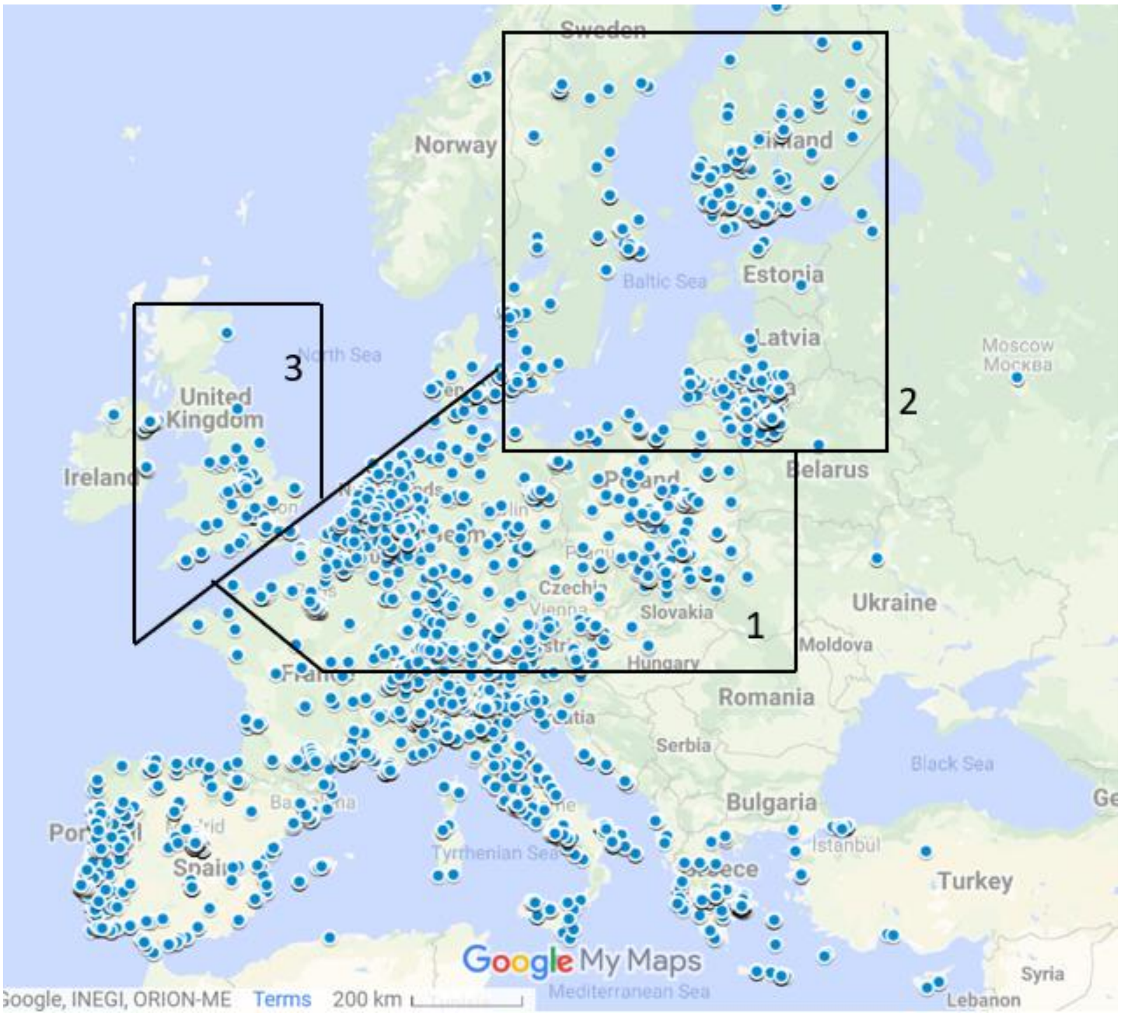
Association between $PM_{2.5}$ ***and uncontrolled rhinitis, OR (95%CI)***

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

IQR: interquartile range, OR: odds ratio

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

Figure E1. Areas of the study



1. Continental and semi-continental climate (Germany, Austria, Belgium, Northern France, Netherlands, Poland, Switzerland, Czech Republic, Northern Italy)

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

3. The UK