From MASK-air® and SILAM to CATALYSE (Climate Action to Advance HeaLthY Societies in Europe)

Running title: Pollen in climate change (CATALYSE)

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Abstract

Plant species vary under different climate conditions and the distribution of pollen in the air and their trends can be used to assess the impact of climate change on public health. In 2015, MASK-air® (Mobile Airways Sentinel networK for rhinitis and asthma) was launched as a project of the European Innovation Partnership on Active and Healthy Ageing (EIP-on-AHA, DG Santé and DG CONNECT). This project aimed to develop a warning system to inform patients about the pollen season onset. SILAM (System for Integrated modeLling of Atmospheric composition), a global-to-meso-scale dispersion model was developed by the Finnish Meteorological Institute (FMI). It provides quantitative information on atmospheric pollution of anthropogenic and natural origins, particularly on allergenic pollens. POLLAR (Impact of Air Pollution on Asthma and Rhinitis, EIT Health) has combined MASK-air clinical data with SILAM forecasts. A new Horizon Europe grant, CATALYSE (Climate Action to Advance HeaLthY Societies in Europe; grant agreement number 101057131), which started in September 2022, aims at better understanding climate change and finding ways to counteract it. One objectives of this project is to develop early warning systems and predictive models to improve the effectiveness of adaptation strategies to climate change. One of warning system is focused on allergic rhinitis (CATALYSE Task 3.2). with a collaboration between the FMI (Finland), Porto University (Portugal), MASK-air SAS (France), ISGlobal (Spain), Hertie School (Germany) and the University of Zurich (Switzerland). It is to be implemented with the support of EAACI. This paper reports the planning of CATALYSE Task 3.2.

Key words: Catalyse. MASK-air. SILAM. Pollen. Climate change.

Resumen

Las especies de plantas varían según las diferentes condiciones climáticas y la distribución del polen en el aire y sus tendencias pueden utilizarse para evaluar el impacto del cambio climático en la salud pública. En 2015, se lanza MASK-air® (Mobile Airways Sentinel network for rhinitis and asma) como un proyecto de la Asociación Europea de Innovación sobre Envejecimiento Activo y Saludable (EIP-on-AHA, DG Santé y DG CONNECT) que tenía como objetivo desarrollar un sistema de alerta para informar a los pacientes sobre el inicio de la temporada de polen. Paralelamente, SILAM (Sistema para el modelado integrado de la composición atmosférica), un modelo de dispersión de escala global a meso ha sido desarrollado por el Instituto Meteorológico de Finlandia (FMI) y proporciona información cuantitativa sobre la contaminación atmosférica de origen antropogénico y natural, en particular sobre los pólenes alergénicos. El proyecto POLLAR (Impacto de la contaminación del aire en el asma y la rinitis, EIT Health) combina los datos clínicos de MASK-air con las previsiones de SILAM. Una nueva subvención de Horizon Europe, CATALYZE (Climate Action to Advance HeaLthY Societies in Europe; acuerdo de subvención número 101057131), que comenzó en septiembre de 2022, tiene como objetivo comprender mejor el cambio climático y encontrar formas de contrarrestarlo. Uno de los objetivos de este proyecto es desarrollar sistemas de alerta temprana y modelos predictivos para mejorar la eficacia de las estrategias de adaptación al cambio climático. Uno de los sistemas de alerta se centra en la rinitis alérgica (CATALYSE Task 3.2) siendo desarrollado mediante una colaboración entre la FMI (Finlandia), la Universidad de Oporto (Portugal), MASK-air SAS (Francia), ISGlobal (España), Hertie School (Alemania) y la Universidad de Zúrich (Suiza) y se implementará con el apoyo de la EAACI. Este documento centra en la planificación de CATALYZE Task 3.2.

Palabras clave: Catalyse. MASK-air. SILAM. Polen. Cambio climático.

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Introduction and concept

Allergic diseases (e.g., allergic rhinitis (AR), asthma, rhinoconjunctivitis, urticaria and eczema) are among the most common diseases in the world[1]. They display a substantial burden on social life, work and school performance [2, 3, 4, 5]. Many patients are untreated and symptoms are often uncontrolled [6, 7].

Climate change is associated with an increased prevalence and severity of rhinitis and asthma [8, 9]. Plant species vary under different climate conditions, and the distribution of pollen can be used to assess the impact of climate change. Worsening ambient air pollution, changes in temperature, humidity or wind for the atmospheric transport (leading to altered local and regional allergen production [10]) as well as reduction in biodiversity may also play a decisive role in the worsening of rhinitis and asthma symptoms, with potentially relevant implications for the clinical practice and public health planning. [11] The 2022 Europe report of the *Lancet* Countdown on health and climate change towards a climate-resilient future has proposed allergenic trees as an indicator of climate change [12].

mHealth apps can help to better understand and mitigate climate change. One such example is that of MASK-air®, which was launched in 2015 as a project of the European Innovation Partnership on Active and Healthy Ageing (EIP-on-AHA, DG Santé and DG CONNECT). At that time, it envisioned not only the possibility of patients reporting their daily allergy symptoms and medication through an mHealth app, but also the development of an SMS-based early warning system informing patients about the beginning and the peak of the pollen season (Figure 1). This has been reflected in the following statements: [7] *"For patients allergic to pollen, knowledge of the season onset is of vital importance to start their treatment to control symptoms and avoid severe disease including asthma. When they travel, patients are often concerned about potential symptoms outside their usual symptom 'window'. It is therefore of great importance to forecast the onset of the pollen season as well as to characterize seasons in different places."*

While this SMS-based early warning system has not yet been developed, some advances have been achieved towards the prediction of allergy risk for sensitive individuals at the European level. SILAM provides air quality forecasts at the global scale, but pollen predictions are currently limited by Europe due to the absence of representative (good resolution) habitation maps of allergenic plants and pollen observations in other regions. The expansion of SILAM pollen forecasts to other continents is planned. In particular, a combination of operational forecasts of air quality and pollen concentrations of the SILAM dispersion model (http://silam.fmi.fi) was used to reproduce the complex interaction of exacerbating factors of environmental allergy (Figure 2). Since air pollutants are known to worsen pollen-related allergy, the allergy risk index formulation includes the pollen levels amplified locally by poor air-quality conditions [13].

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A new Horizon Europe grant, CATALYSE (Climate Action to Advance HeaLthY Societies in Europe; grant agreement number 101057131), began in September 2022. Its aim is to better understand climate change and to find ways to counteract it. One of the specific objectives of this project is to develop early warning systems and predictive models to improve the effectiveness of adaptation strategies to climate change. One of the early warning systems to be developed is focused on AR (CATALYSE Task 3.2). It stems from a collaboration between the Finnish Meteorological Institute (FMI), Porto University, MASK-air SAS, ISGlobal, Hertie School and the University of Zurich. The development of this early warning system will encompass (i) the integration of information technology tools for climate, weather, air pollution and aerobiology in MASK-air®, along with patients' previously-reported symptoms and (ii) social media data (Google Trends and Twitter data) [14]. EAACI will support its implementation and assist further development with the expertise of the major European allergy societies. Citizens will thus be informed of personal environmental threats, which may also be linked to the indicators of Planetary Health and sustainability.

There is, therefore, a direct link and cross-fertilisation between the aims and the achievements of MASK-air®, SILAM and CATALYSE. The MASK-air® functionality, enriched with the SILAM developments in the POLLAR project [12], will form the background to building an early warning system for AR within CATALYSE. On the other hand, CATALYSE will provide extremely important tools in order to bring the MASK-air® predictions to the new technological level, particularly the development of an alert system which utilises the internet search activity and severity of reported allergy/rhinitis symptoms of individual app users across Europe.

1- Existing CATALYSE allergy-related technologies

1-1- MASK-air® (Annex I)

MASK, the Phase 3 ARIA (Allergic Rhinitis and its Impact on Asthma) [3, 15] initiative, is a flexible e-platform for AR and asthma and includes the MASK-air® app. It is operational in 27 countries and 19 languages. Over 58,000 users have been registered.

MASK-air® is a validated mHealth app (Medical Device regulation Class IIa) and a Good Practice of DG Santé on digitally-enabled, patient-centred care (Annex 1) [16]. It is also a candidate Good Practice of OECD (Organisation for Economic Co-operation and Development). The maturity level of MASK-air® tools assessed by the Technology Readiness Level (TRL) [17] ranges from 7 to 9/9 [18]. The vision of MASK-air® has led to a strategic overview that was initiated by ARIA in 1999. It includes WHO-associated projects[3, 19] as well as EU grants and projects [20, 21, 22, 23, 24, 25, 26].

MASK-air® data has enabled the discovery and characterisation of novel phenotypes, as well as novel insights into the management of AR (Table 1). MASK-air® data has shown that most AR patients (i) are

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not adherent and do not follow guidelines, (ii) use as-needed treatment, (iii) do not take medication when they are well, (iv) increase their treatment based on symptoms, (v) do not use the recommended treatment and (vi) do not always report better control (symptoms, work productivity, educational performance) when using medications. A combined symptom-medication score (ARIA-EAACI-CSMS) has been developed and validated for clinical practice and trials. The implications of the novel MASK-air® information should lead to change management in rhinitis and asthma [27].

1-2- Embedding SILAM predictions in MASK-air®: POLLAR: Impact of air POllution on Asthma and Rhinitis (EIT Health)

Allergic rhinitis is impacted by allergens and air pollution, but interactions between air pollution, sleep and allergic diseases have been insufficiently understood. POLLAR (Impact of air POLLution on Asthma and Rhinitis), a project of the European Institute of Innovation and Technology (EIT Health) and a demonstration project of GARD (Global Alliance against Chronic Respiratory Diseases, WHO) [28, 29], used MASK-air® to investigate these relationships in Northern and Central European users in 2017 and 2018 [26]. A total of 3323 geolocated individuals [36,440 VAS days) were studied. Associations between uncontrolled rhinitis and pollutants were stronger during the grass pollen season [30]. There was an interaction between ozone and grass but not birch pollen. A similar trend was found for particulate matter with a diameter of less than 2.5 μm, especially in 2017. These results suggest that the relationship between uncontrolled AR and air pollution is modified by the presence of grass pollens and favour the inclusion of pollen and pollution data in MASK-air®.

Following the POLLAR study, and within that framework, a new index developed by the FMI has been made available in MASK-air® [13]. For geolocated users, MASK-air® provides a daily prediction of pollen levels indicated for the current day and for the next day. Geolocation-based forecasts of pollution levels are available within MASK-air®. In CATALYSE, the predictive model for the user symptoms will be built depending on the personal sensitiveness to the complex of environmental factors (AQ+pollen). It will be based on an updated symptom prediction model including, in particular, individual changes of user symptoms as a reaction to the changes ("increment") of environmental conditions.

1-3-SILAM® pollen predictions (Annex II)

Pollen forecasting models for alder, birch, grass, mugwort, olive and ragweed are integral parts of the System for Integrated modeLling of Atmospheric coMposition (SILAM [31] http://silam.fmi.fi/, open-source code https://github.com/fmidev/silam-model/ visited 25.10.2022). This advanced atmospheric composition model is in operational use in Finland. It also routinely provides air quality and pollen forecasts to the Copernicus Atmospheric Monitoring Service CAMS (https://atmosphere.copernicus.eu/) and to various research and application projects. The pollen lifecycle in the atmosphere within SILAM (such as

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release, transport, mixing and removal) is formulated in the same way as for a chemically non-reactive aerosol, taking into account the density and aerodynamic diameter of pollen grains. To reproduce the natural biological cycles of pollen presentation, maturation and release by plants, two types of phenological models were developed in SILAM. The parametrisation of tree phenology (for alder, birch and olive) is based on the concept of accumulated heat as the main trigger and driver of the flowering season [32, 33, 34]. The pollen season characteristics for herbaceous plants were empirically derived from the long-term aerobiological pollen measurements and used in the model as a fixed pollen calendar. The habitat maps for every taxon delineate the geographical areas where SILAM initiates the pollen release from allergenic plants. The propagation of the pollen season is modulated by the actual meteorological conditions.

The quality of SILAM AQ predictions is regularly evaluated by direct comparison of model forecasts with the air quality and pollen measurements within the scope of several international projects and operational services, such as (i) the Copernicus Atmospheric Monitoring Service (CAMS, https://atmosphere.copernicus.eu/, visited 22.11.2022), (ii) the International Cooperative for Aerosol Prediction ICAP [35] (https://doi.org/10.1002/qj.3497), (iii) the World Meteorological Organization Global Air Quality Forecasting and Information System (WMO GAFIS https://hpfx.collab.science.gc.ca/~svfs000/na-aq-mm-fe/dist/, visited 22.11.2022), (iv) the WMO Sand and Dust Storm Warning Advisory and Assessment System WMO SDS-WAS (https://dust.aemet.es, visited 24.11.2022) and (v) other national and international evaluation projects.

2- CATALYSE

2-1-Pollen in climate change

Exposure to sensitising pollens, one of the main triggers of AR symptoms, is predicted to increase due to climate-change-induced increases in the duration of allergenic pollen seasons, pollen concentrations and allergenicity [36, 37, 38, 39]. This is not unexpected since the timing of the life cycle events for plants is generally sensitive to temperature, with atmospheric pollen levels and pollen spread also being influenced by humidity and carbon dioxide levels [37]. In particular, higher temperatures and increased carbon dioxide levels have been found to be associated with higher pollen production in greenhouse or growth chamber experimental studies, with some longer-term observational studies having found correlations between temperature and pollen concentrations or pollen season length [36, 40].

2-2-CATALYSE task 3.2 – Early warning system for allergic rhinitis

The primary objective of CATALYSE task 3.2 is to develop an early warning system for AR, rhinoconjunctivitis and asthma. This system is set to incorporate data on meteorological forecasting, air quality (including air pollution), allergenic pollen levels, previously-reported symptoms and Internet users'

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activity. These data will then allow for the generation of early warnings on the possibility of short-term exacerbations due to environmental conditions.

More specifically, the SILAM model will provide hourly forecasts of air quality, meteorological parameters (e.g., temperature and humidity) and pollen concentrations over Europe with a horizontal resolution of about 10km x 10km for six relevant allergic pollen species in Europe: alder, birch, grass, mugwort, olive and ragweed (Figure 3). These data will form the basis to construct the space-resolving models, indicating the overall risk of short-term respiratory allergy exacerbations for each European region. The SILAM pollen/allergy risk forecasts will be generated on the regular Mercator (longitude-latitude grid with horizontal resolution about 10 km x 10 km). Using these gridded forecasts, we can interpolate/aggregate the predictions to any NUTS levels. Such models will be interconnected with MASK-air® and further personalised by including patients' previously-reported symptoms in MASK-air®. For patients who had previously reported a small amount of data to MASK-air®, we may - for model personalisation - use (i) data from other users reporting MASK-air® data in the same region and (ii) Twitter posts and internet search activity data (assessed by Google Trends, https://trends.google.es/trends/) on AR. The latter will be particularly useful for regions where MASK-air®-reported data are sparse and will be based on previous studies that have indicated that Google Trends searches correlate well with surveillance data on rhinitis and asthma or with asthma hospitalisations [14, 41]. The Bayesian multilevel estimation with poststratification approaches will be used to address limitations in the representativeness of social media data, particularly at the higher level of geographical granularity relevant for MASK-air® users.

The predictive skill of the early warning system will be initially tested on the retrospective data sets of MASK-air®, with the assessment and prediction for patients and regions reporting larger and smaller volumes of data. This system will be further validated in terms of real-world utility through three case studies in different regions of Europe (Southern, Central and Northern). The validation will involve a randomised trial to assess the utility of personalised messages delivered through the MASK-air® early warning system to improve patients' symptom management. In brief, enrolled patients will be using MASK-air® and will be randomised to receive (i) personalised messages based on early warning systems or (ii) "neutral" general messages that may help patients to adopt protective measures. The primary outcome will consist of the recently-developed and validated EAACI-ARIA allergy combined symptom-medication scores for allergic diseases (CSMS) [42]. Secondary outcomes will include reported VASs on allergy symptoms and medication use.

2-3- Supporting studies

The development of the early warning system will require supporting studies to be conducted, gaps in current knowledge to be filled and possibly the development of the early warning system to be optimised. Such supporting studies include:

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1. Assessment of the MASK-air® reporting patterns according to the social and economic development of the region: Using data from geolocated European users, we may understand whether the region in which the patient lives influences the patterns of using MASK-air®, as well as the reporting of symptoms and medication. This may inform on (i) the representativeness of MASK-air® reported days, (ii) health policies to reduce inequalities within and between countries and (iii) gender inequalities.

2. Study of the characteristics of reported *vs* unreported days in MASK-air®: In order to assess the potential selection biases associated with the days on which patients report MASK-air® data, we shall assess whether reported and unreported days differ substantially depending on environmental exposure variables (e.g., pollen and pollution). Pollens can induce nasal and/or ocular symptoms within a few minutes as shown by allergen challenge [42]. This study may also enable the development of imputation using models accounting for unreported days in MASK-air®: (i) further facilitating the implementation of longitudinal studies, (ii) better assessment of climate change and (iii) clinical trials.

3. Assessment of the birch or grass pollen levels in European MASK-air® users associated with different levels of AR and asthma using defined cut-offs for low, medium and high symptoms.[43] This study should result in the identification of pollen level thresholds that may elicit personalised and regionalised warnings of pollen levels, potentially inducing symptoms or severe symptoms. It will be very important in clinical trials.

2-4- Potential limitations

There are some relevant approaches to consider in the development of this task.

In particular, MASK-air® is only available in 22 European countries, limiting the coverage of the personalised early warning system to those countries. However, the countries in which MASK-air® is available comprise 90% of the population of the European Union. Another limitation may stem from the relatively low number of users reporting a high frequency of MASK-air® data, limiting the total number of users receiving fully-personalised information on their allergy risk.

SILAM pollen forecasts - currently available for 12 pollen species - appear to be of higher accuracy in Northern and Central Europe than in Southern Europe, where human-controlled local watering significantly affects the phenology of the plants [43, 44]. The connection of the gridded atmospheric information (resolution 10 km x10 km) with individual-level health data (MASK-air®) needs to be tested. It will be established for every grid cell separately. Multi-user contribution per grid cell will be averaged and combined with the "neutral"/"background" allergy risk value (which is computed based on health data and Pollen Indices).

Conclusion

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In 2015, when MASK-air® was launched, the development of a personalised early warning system (warning patients about the possibility of rhinitis exacerbations) had been envisioned [7]. While some steps were taken to achieve this goal (with the incorporation, in MASK-air®, of geolocalised forecasts for pollen levels), such a warning system is still lacking. CATALYSE presents an opportunity for the development and validation of a personalised early warning system incorporating environmental, symptoms and online activity data. The inclusion of a task on allergic respiratory diseases in CATALYSE reflects not only the burden of this disease but also the expected increase in its prevalence and severity as a result of climate change.

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Conflicts of interest

JB reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach, other from KYomed-Innov, other from Mask-air-SAS, outside the submitted work.
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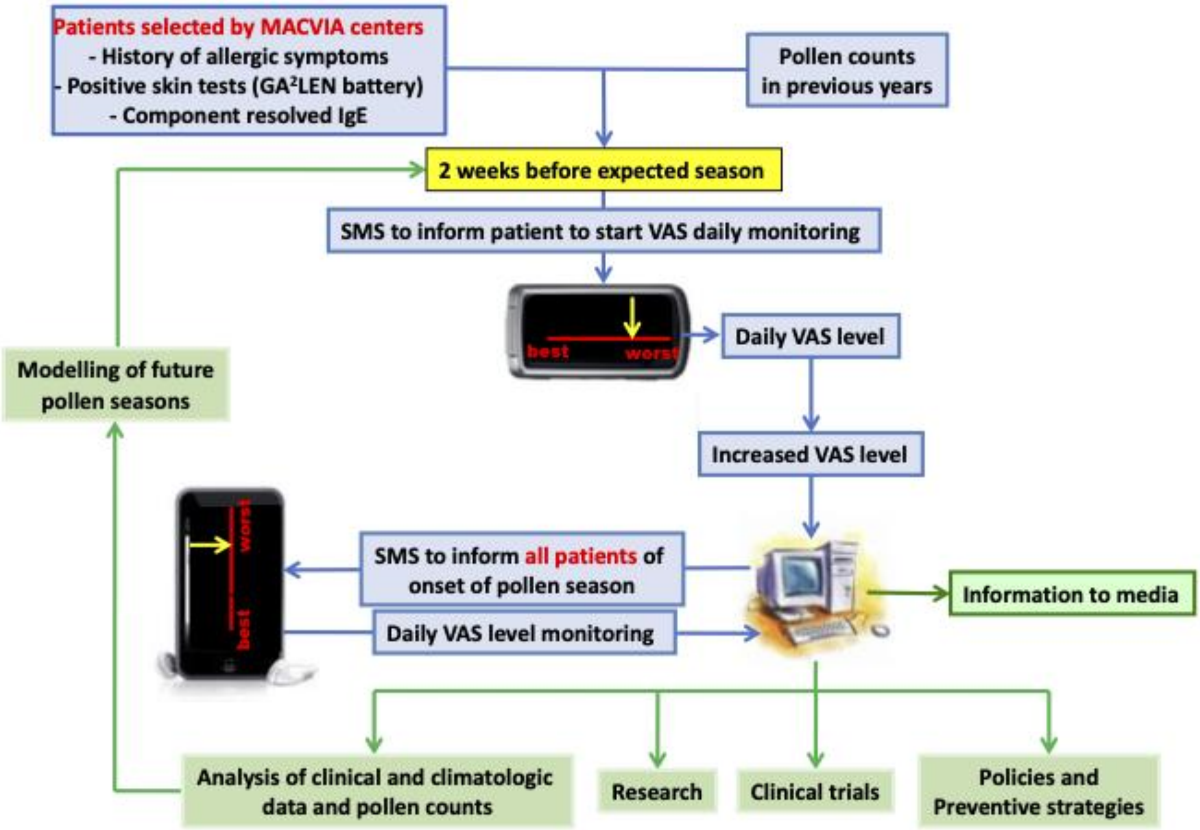
Figures

Figure 1. The MASK-air® sentinel network proposed in 2015 (from [7]).



MACVIA-LR: EIP on AHA reference site.

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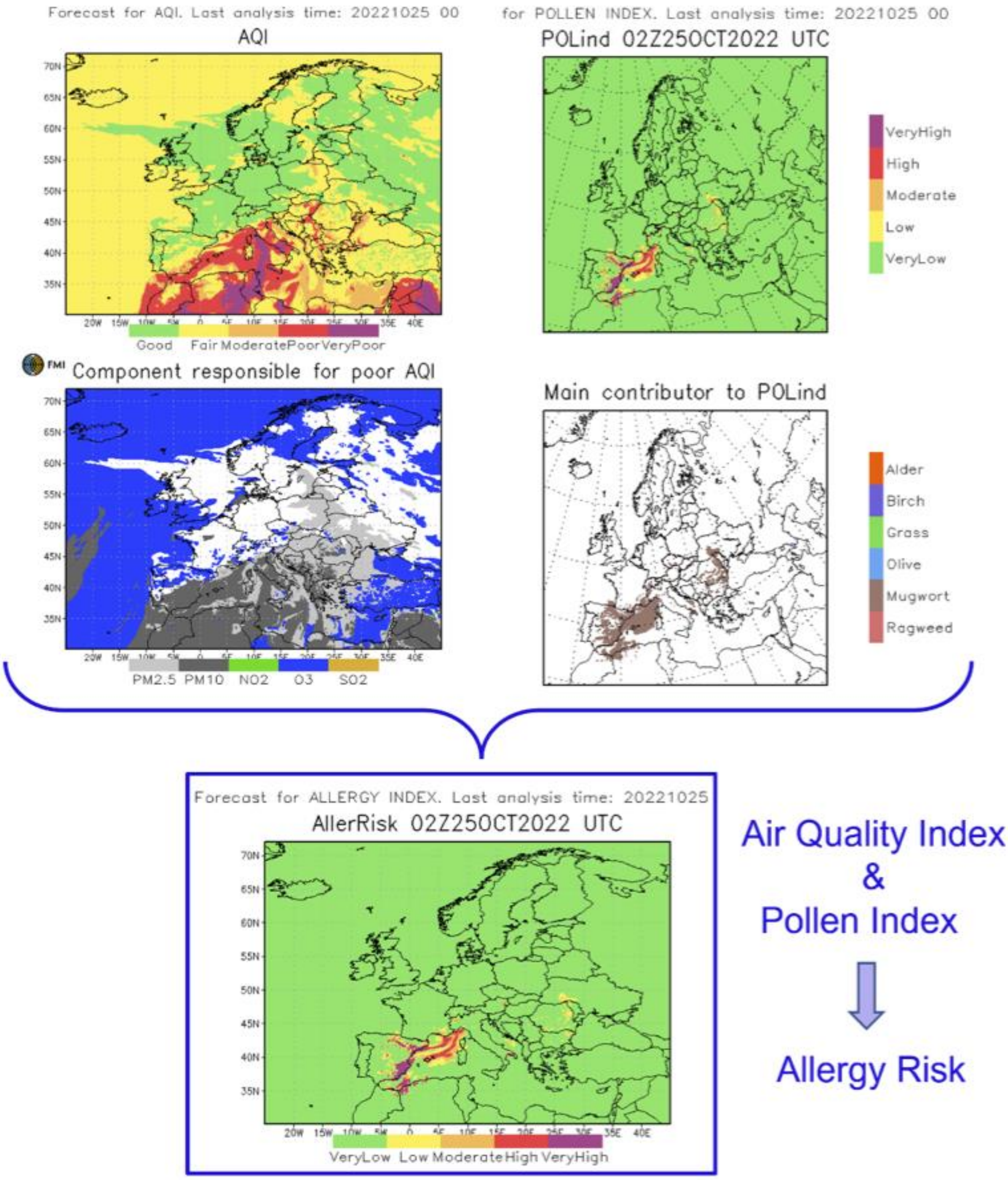
Figure 2. Allergy risk prediction by the SILAM model: single forecast example for 25 Oct 2022.



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