D5.2. Generation of a consensus definition for single- and multipollutant exposure and for other variables that impact airway allergy outcomes

CLIMATE CHANGE AND AIR CONTAMINATION:
ARTIFICIAL INTELLIGENCE APPLIED ON THE CORRELATION BETWEEN AIR POLLUTANTS AND NON-COMMUNICABLE RESPIRATORY DISEASES IN EUROPE

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▪ Have followed the required conventions in referencing the thoughts, ideas and texts made outside the Project.

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EXECUTIVE SUMMARY

This deliverable (D5.2) is connected to the activities of WP5 and task 5.1 and aims to establish a consensus definition for the different environmental conditions in which the patients recruited in ClimAIr will be allocated. This allocation is necessary to investigate the effect of pollution, pollen exposure and climate factors on the clinical expression of pollen-driven allergic rhinitis. After a comprehensive landscape analysis, the pollutants of interest have been identified. The pollen the patients are allergic to is established by inclusion criteria and the climate factors are defined by the cities the patients are living in (restricted to those of the participating clinical centers). Thus, two categories are defined for pollutants (single/multiple exposure) and for pollens (single/multiple exposure) whereas four categories have been established for climate (warm and humid, warm and dry, cold and humid, cold and dry). Other WP of ClimAIr will collect data from the pollen, pollution and climate monitoring stations relevant for the patients and will use this information to identify the category of the three domains each patients has to be allocated to.

1. INTRODUCTION

1.1 Background for the selection of the relevant pollutants and variables.

Environmental Pollution and Respiratory Allergies

Since the onset of the Industrial Revolution, urbanisation and industrial development have profoundly reshaped environmental exposures, with significant consequences for respiratory health. More than 90% of the global population currently resides in areas where air quality falls short of the World Health Organisation (WHO) guidelines (1). This situation has led to a growing global burden of respiratory diseases, among which allergic rhinitis (AR) and asthma are the most prevalent. Both conditions share overlapping pathophysiological pathways (2, 3) and demonstrate a rising incidence in tandem with westernized lifestyles and increasing environmental degradation (4-6). The ubiquitous exposure of the respiratory mucosa to environmental agents, collectively termed the "exposome" (7), makes these tissues particularly vulnerable to both outdoor and indoor pollutants, allergens, and microbial agents (8, 9).

Environmental pollution, comprising outdoor (traffic, industry, agriculture) and indoor (tobacco smoke, biomass, volatile organic compounds) sources, plays a pivotal role in modulating immune responses in the airways. Moreover, climate change and biodiversity loss further influence the composition of the exposome and contribute to the growing incidence and severity of allergic diseases (8, 10). Despite growing public health awareness and limited policy interventions, air pollution remains one of the leading causes of premature death worldwide (11, 12), with profound implications for allergic airway diseases.

Outdoor Pollution and Respiratory Allergies

Long-term exposure to outdoor air pollution has been consistently linked to impaired respiratory health across all age groups (13-25). Major pollutants, including particulate matter (**PM**)**2.5**, **PM10**, nitrogen dioxide (**NO_2**), and ozone (**O_3**), originate primarily from traffic, industrial emissions, and fossil fuel combustion. The European ESCAPE project, which studied several birth and adult cohorts, revealed that children exposed to higher levels of **NO_2** and **PM2.5** had a greater risk of developing asthma during adolescence (26). Furthermore, a meta-analysis covering studies from 1999 to 2016 confirmed a strong association between traffic pollution and childhood asthma (27-29), and long-term exposures to **PM2.5** posed a significant risk of asthma prevalence and airway inflammation in a community-based population of children (30). In adults, higher exposures to **NO** and **PM10** are associated with decreased lung function and increased asthma prevalence (31-34). **PM2.5** exposure alters microRNA

expression profiles in nasal mucosa of allergic rhinitis models, affecting pathways such as IgE receptor signaling, T cell receptor signaling, and inflammatory pathways. This provides insight into gene regulation mechanisms by which air pollution exacerbates allergic rhinitis and mucosal inflammation (24, 25, 35).

The relationship between air pollution and AR is less consistently documented than with asthma, especially in adults. Nonetheless, studies suggest a higher prevalence of AR in urban environments compared to rural or suburban areas (36-38), and associations between residential proximity to major roadways and allergic respiratory outcomes have been identified (39-43). This may reflect the synergistic effects of pollution and aeroallergens in urban settings, as well as the inflammatory potential of pollutants themselves. For instance, **PM10** particles activate inflammatory pathways in airway epithelial cells, including inflammasome components like NLRP3, leading to cytokine release and enhanced immune activation (44, 45). **Diesel exhaust** and **PM** further exacerbate this response, particularly in patients with severe asthma phenotypes (46-49). Pollutants can also modulate gene expression through epigenetic mechanisms, especially during early development. Studies in pediatric populations have demonstrated that **black carbon** exposure is linked to changes in DNA methylation in genes such as IL-4, which is central to allergic inflammation (50, 51). These changes may predispose individuals to enhanced IgE-mediated responses and greater susceptibility to allergens.

An international expert consensus highlights the impact of air pollution on allergic rhinitis and the importance of reducing pollutant exposure alongside guideline-based treatment. The antihistamine fexofenadine has been shown to improve symptoms aggravated by pollution; however, more studies on pharmacological management are needed (52).

Indoor Pollution and Allergic Rhinitis

In Western societies, individuals spend nearly 80% of their time indoors, emphasizing the critical importance of indoor air quality for respiratory health (53, 54). Indoor air is influenced by outdoor pollution, building materials, heating, cooking activities, smoking, and the presence of allergens such as mold, dust mites, and pet dander (55-58).

One major indoor pollutant is second-hand tobacco smoke (SHS), which contains over 4,500 toxic chemicals, including fine **PM**, oxidative gases, and heavy metals (59). SHS exposure during pregnancy and infancy significantly increases the risk of developing asthma and allergic diseases in children (60-64), with some studies suggesting that epigenetic changes induced by SHS could have transgenerational impacts (65). Beyond the immunological consequences, SHS alters the airway microbiota, potentially disrupting the delicate microbial-immune balance within the respiratory tract (66-69). These

disruptions may contribute to chronic inflammation, increased mucus production, and airway remodeling (70-73), all of which exacerbate allergic and asthmatic responses.

Other indoor pollutants such as **NO_2**, carbon monoxide (**CO**), and volatile organic compounds (**VOCs**) from building materials, air fresheners, and consumer products have been associated with increased respiratory symptoms, including exacerbations of AR and asthma (74, 75).

Moreover, indoor allergen exposure plays a central role in allergic sensitization. House dust mites (HDMs), molds, and pet dander are among the most common indoor allergens and are linked to more severe phenotypes of airway allergy compared to outdoor seasonal allergens (76-80). Dampness, a frequent issue in 10–15% of households, can foster mold and cockroach proliferation, further worsening indoor air quality and sensitization rates (81, 82).

Significantly, indoor air pollution is also prevalent in non-residential settings such as schools. Large-scale projects like SINPHONIE and HESE have revealed that European schoolchildren are commonly exposed to **PM10**, **CO_2**, and mold allergens at levels exceeding WHO recommendations (83-86). These exposures are especially pronounced in schools located in urban and industrial areas, suggesting that outdoor pollutants readily infiltrate indoor environments and contribute to an increased burden of respiratory allergic diseases in children.

Environmental Interactions and Pollen Allergenicity

Environmental pollutants not only affect host immune responses but also enhance the allergenicity of environmental antigens, particularly pollens and fungal spores. Pollutants like **O_3** and **nitrogen oxides** can alter plant physiology, increase pollen production, and induce structural modifications that enhance their immunogenicity (10, 87-92). For instance, urban ragweed plants exposed to high **CO_2** levels produce more potent pollen and flower earlier than rural counterparts (89). Likewise, birch trees subjected to elevated **O_3** levels produce more of the allergenic protein Bet v 1 and pollen-associated lipid mediators, which activate Th2 cells and promote IgE synthesis (90, 93). Platanus pollen exposed to **NO_2** and **O_3** shows increased release of allergen Pla a 3, with structural modifications enhancing its immunogenicity and stability, which aggravates pollen-induced pneumonia in vivo (94). These findings suggest that environmental pollution may amplify the sensitizing potential of aeroallergens.

However, the clinical significance of these findings remains debated. While some epidemiological studies report a synergistic effect of pollutants and pollen on asthma and rhinitis symptoms (95, 96), others fail to detect a significant association (97). These discrepancies may stem from limitations in measuring personal pollutant and allergen exposures in large-scale population studies.

Climate Change and the Future of Allergic Rhinitis

Climate change and air pollution are deeply interlinked through shared origins, primarily the **combustion** of **fossil fuels**, and exert combined effects on respiratory health (98-102). Global **warming** increases plant biomass and lengthens the growing season of allergenic species like ragweed, thereby elevating airborne pollen concentrations and the geographic range of allergenic flora (103-107). Additionally, climate-related phenomena such as increased **rainfall**, **humidity**, and **extreme weather events** foster mold proliferation and indoor dampness (81, 108). These conditions create an ideal environment for the exacerbation of allergic rhinitis symptoms and complicate disease management.

Furthermore, climate change is anticipated to alter the spread of **respiratory infections**(109, 110), influence allergenic species distribution (111-116), and intensify heat-related respiratory morbidity (117-121). Notably, **thunderstorm** asthma, an acute and severe form of exacerbation linked to sudden releases of aeroallergens, has been increasingly reported and is likely to rise with ongoing climatic instability (122-125).

Summary of findings

In conclusion, the complex interplay between environmental pollution, allergen exposure, and climate change significantly contributes to the increasing burden of allergic rhinitis and respiratory diseases worldwide. Both indoor and outdoor pollutants not only exacerbate symptoms but also enhance the allergenic potential of common airborne particles, while epigenetic and immunological mechanisms further amplify individual susceptibility. Addressing this multifaceted challenge requires integrated public health policies focused on improving air quality, reducing pollutant emissions, and managing indoor environments, alongside continued research into the biological effects of pollution and climate-driven changes. Only through such comprehensive efforts can we effectively reduce the growing impact of allergic airway diseases and improve respiratory health outcomes globally.

1.2 WPS AND TASKS RELATED WITH THE DELIVERABLE

This deliverable refers to Task 5.1 included in “WP5: Mechanistic Research & Clinical Study”

2. Consensus definitions

2.1 Introduction

The grant agreement defines D5.2 in the following manner: "*Report providing standardized definitions and criteria for assessing both single and combined pollutant exposures, as well as other variables influencing airway allergy outcomes. This deliverable will establish a unified framework for interpreting data extracted from electronic records, ensuring consistency and accuracy in the subsequent AI analysis and research*".
The ClimAIr project will integrate clinical data from allergic rhinitis patients with environmental variables extracted from climate, pollen, and pollution monitoring stations located in the areas where the individuals are living and working: Malaga (Spain), Berlin (Germany), Toulouse (France), Lodz (Poland), Brasov (Romania), Thessaloniki (Greece), Luxembourg (Luxembourg), Milan (Italy) and Chernivtsi (Ukraine).

2.2 Valid sources and variables to collect

The following sources will be considered valid monitoring stations:

A. Public or private universities
B. Governmental agencies (local, regional, or national)
C. Science or natural science museums
D. Public hospitals
E. Municipality-owned monitoring stations

The following information will be collected from the monitoring stations:

1. Pollution monitoring stations (only focusing on outdoor air pollution): PM2.5 and PM10 (both $\mu g/m^3$), O_3, NO, NO_2, CO, CO_2, SO_2, VOCs, methane (CH4), N_2O and ammonia (NH_3) (all ppb), and radon (Bq/m^3).
2. Pollen monitoring stations: pollen grains from the endemic species in any of the nine participating centers (*Betula verrucosa*, *Phleum pratense*, *Lolium perenne*, *Olea europaea*, *Parietariajudaica*, *Artemisia vulgaris*, *Platanus acerifolia*, *Chenopodium album*, *Plantago lanceolata*, *Salsola kali, Cupressus arizonica, Ambrosia artemisiifolia)*. The unit that will be used is pollen grains/m^3.
3. Climate monitoring stations: temperature (^oC), humidity (grams of water vapor/m^3), barometric pressure (hPa), partial pressure of O and CO_2 (kPa), cumulative rainfall (liters of rain water/m^2 during a year), rate of storms and thunderstorms (events/year).

2.3 Categorization of patients into environmental conditions

Outdoor pollution

Disclaimer: virtually all patients recruited to ClimAIr will be exposed to ≥1 polluting compound. Thus, their categorization into single- or multiple-pollution conditions will be done on the basis of exposure to different pollution sources rather than to one or more specific compounds.
Definitions: a patient participating in ClimAIr will be considered to be exposed to the following types of pollution (1-4 as elaborated below) if the outdoor ambient air levels of ≥2 compounds have been above the level recommended by the WHO (126) for ≥6 months during the last year, provided that ≥1 pollutant is a **signature compound** (in bold letters) of that pollution category.

1. Industry and construction: PM2.5, PM10, VOCs, O_3, NO, NO_2, **SO_2**
2. Transportation: PM2.5, PM10, VOCs, NO, NO_2, **CO**, **CO_2**
3. Agriculture and waste: PM2.5, PM10, **methane**, **N_2O** and **ammonia**
4. Natural sources (dust, wildfires, etc.): PM10 and **radon**

After the identification of the types of pollution the patients are exposed to, they will be further categorized into the following exposure groups:

1. **Single pollution**: individuals exposed to only one pollution type
2. **Multiple pollution**: individuals exposed to 2-4 pollution types

Pollen

Disclaimer: by recruitment criteria, the patients are exposed to relevant levels of *Phleum pratense*, *Olea europaea* and/or *Betula verrucosa* during the corresponding pollen seasons. Thus, exposure to ≥1 of these primary species is assumed for every patient. To further categorize the individuals, the level of the other pollens will be quantified. A patient will be considered to be exposed to a specific species when the corresponding pollen grain is detected (i) at any level (ii) in the relevant monitoring station (iii) and during the pollen season of the primary species driving rhinitis in the patient. The pollen levels detected outside the pollen seasons of the three primary species will not be taken into account.
Definitions: after the identification of the types of pollution the patients are exposed to, they will be further categorized into the following exposure groups:

3. **Single pollen**: individuals exposed only to the primary sensitizing pollen(s)
4. **Multiple pollen**: individuals exposed to ≥1 additional pollen species

Climate

A patient recruited to ClimAIr will be considered to be exposed to the following types of climate (1-4 as elaborated below) on the basis of the average temperature and the cumulative rainfall during the previous year.

1. **Warm and humid**: average annual temperature ≥21ºC and cumulative annual rainfall ≥500 L/m^2
2. **Warm and dry**: average annual temperature ≥21ºC and cumulative annual rainfall <500 L/m^2
3. **Cold and humid**: average annual temperature <21ºC and cumulative annual rainfall ≥500 L/m^2

4. **Cold and dry**: average annual temperature <21ºC and cumulative annual rainfall <500 L/m^2

3. CONCLUSION

After applying these definitions, every patient participating in ClimAIr will be allocated to one of two pollution condition, one of two pollen condition and one of four climate condition. By matching these conditions with the relevant clinical outcomes of rhinitis, the impact of the environment on the disease can be clarified.

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