Supplementary material 1

THE INTERCONNECTION BETWEEN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): A PATHOLOGICAL AND THERAPEUTIC CONTINUUM

Asthma and Chronic Obstructive Pulmonary Disease (COPD) have long been considered distinct nosological entities, defined by different pathophysiological, clinical and epidemiological characteristics.

Asthma is classically described as chronic eosinophilic inflammation of the airways, characterized by reversible bronchial obstruction and bronchial hyperresponsiveness, typically manifesting at a young age [ginasthma.org, 2025].

COPD, on the other hand, is traditionally associated with long-term exposure to harmful substances, primarily cigarette smoke, and characterized by neutrophilic inflammation and persistent and progressive bronchial obstruction, typical of adulthood and advanced age [goldcopd.org, 2025].

However, growing clinical and research evidence has challenged this clear separation, revealing a significant overlap between the two pathologies and suggesting the existence of a pathological continuum. This led to the definition of the so-called "*Asthma-COPD Overlap*" (ACO), a condition that has characteristics of both diseases [ginasthma.org, 2025; goldcopd.org, 2025].

Asthma as a risk factor for COPD

Longitudinal epidemiological studies have conclusively demonstrated that asthma, especially if infantile or long-lasting, or in patients born prematurely, constitutes an independent and significant risk factor for the development of COPD in adulthood and advanced age.

The mechanisms underlying this association are multiple and complex [Agustí et al., 2019]. Persistent, even if low-grade chronic inflammation typical of asthma can induce airway remodeling. This process involves permanent structural changes, such as thickening of the reticular basement membrane, subepithelial fibrosis and bronchial smooth muscle hyperplasia.

Such alterations, over time, can lead to a loss of reversibility of bronchial obstruction, evolving towards a fixed and progressive airflow limitation, which is the hallmark of COPD [Pavord et al., 2018]. In practice, chronic "asthma-related" inflammation accelerates the decline of lung function over the course of life, predisposing the individual to reach the diagnostic threshold for COPD at an earlier age, especially in the presence of other risk factors such as cigarette smoking which also entail a risk of increased mortality from respiratory causes [Lemmetyinen et al., 2018; Modak et al., 2025].

From the concept of ACO to the approach for "tractable traits"

The recognition of the ACO has highlighted the limits of a rigidly categorical diagnostic and therapeutic approach [Leung et al., 2017]. The management of patients who are in this overlapping zone is often complex, as traditional guidelines for asthma or COPD may not be fully adequate.

To overcome this impasse, a paradigm shift has been proposed: moving from a management based on the diagnostic label (asthma or COPD) to a multidimensional approach based on "*treatable traits*". This personalized model focuses on the identification and treatment of phenotypic (clinical) and endotypic (mechanistic) characteristics specific to each individual patient, regardless of formal diagnosis [McDonald et al., 2019].

Tractable traits can be divided into several categories:

- *Lung tracts:*
    - Type 2 (T2) inflammation: characterized by eosinophilia in the blood or sputum and a high fraction of exhaled nitric oxide (FeNO). This trait, typical of allergic asthma,

responds well to therapy with inhaled corticosteroids (ICS) and targeted biological drugs (e.g. anti-IgE, anti-IL5/5R, anti-IL4/13R).
    - Significant bronchodilation: a marked reversibility of FEV1 following administration of a bronchodilator, suggesting a benefit from optimized therapy with long-acting bronchodilators (LABA/LAMA).
    - Bronchial hyperresponsiveness: an accentuated sensitivity to bronchoconstrictive stimuli.
    - Frequent exacerbations: which may have infectious (bacterial, viral) or inflammatory (eosinophilic) triggers, requiring differentiated therapeutic approaches (e.g., antibiotics, systemic steroids, or targeted preventive therapies).
    - Chronic sputum production: often associated with neutrophilic inflammation and chronic bacterial infections.
- *Extra-pulmonary tracts and comorbidities:*
    - Cigarette smoking: requires targeted cessation interventions.
    - Obesity: which impacts on respiratory mechanics and systemic inflammation.
    - Skeletal muscle dysfunction and deconditioning: needing pulmonary rehabilitation programs.
    - Cardiovascular disease, gastroesophageal reflux, anxiety and depression: comorbidities that affect symptoms and quality of life and require integrated management.

This approach makes it possible to deconstruct diagnostic complexity and build a tailor-made treatment plan.

For example, an elderly patient, smoker, with a diagnosis of COPD but with a high blood eosinophilic count and tendency to exacerbates, will benefit from a therapy that includes inhaled corticosteroids, typically reserved for asthma, in addition to standard bronchodilator therapy for COPD [goldcopd.org, 2025].

In contrast, a patient with long-standing asthma and fixed obstruction, but without evidence of T2 inflammation, may not benefit from high doses of ICS and require intensification of bronchodilator therapy [ginasthma.org, 2025; McDonald et al., 2024].

Table S1 shows the main characteristics of Asthma, COPD and ACO.

Table S1. Key features of Asthma, COPD and ACO.

Clinical and pathophysiological feature	**Asthma (classic form)**	**COPD (classic form)**	**ACO (Asthma-COPD Overlap)**
Etiology / Main Risk Factors	Genetic predisposition, allergies, early environmental factors.	Cigarette smoking (>80% of cases), occupational exposures, pollution, alpha1-antitrypsin deficiency.	Often long-standing asthma (risk factor) superimposed on cigarette smoke or harmful exposures.
Typical age of onset	Generally in pediatric or juvenile age.	Generally after the age of 40.	Often > 40 years old, but with a history of

			respiratory symptoms (asthma) that began at a younger age.
Prevalent type of inflammation	Eosinophilic (Type 2), mast cell.	Neutrophilic, macrophage.	Mixed (often eosinophilic and neutrophilic).
Principal place of damage	Mainly the airways (bronchi and bronchioles).	Lung parenchyma (emphysema) and small airways (obstructive bronchiolitis).	Both airway and, potentially, parenchyma (variable).
Airflow limitation (Spirometry)	Reversible obstruction (completely or near-complete) after bronchodilator. High variability.	Persistent and progressive obstruction (poorly or non-reversible). FEV_1/FVC post-bronchodilator < 0.70.	Persistent obstruction (such as COPD) but with significant reversibility (such as Asthma).
Prevalent symptomatology	Episodic: wheezing, shortness of breath, cough (often at night or after exertion). Asymptomatic intercritical periods.	Persistent and progressive: dyspnoea on exertion, chronic productive cough.	Persistent symptoms (dyspnoea, cough) with marked daily variability and/or frequent exacerbations (often more similar to asthma).
Response to inhaled corticosteroids (ICS)	Generally excellent. First-line therapy for control.	Generally poor or limited (except in the presence of eosinophilia or frequent exacerbations).	Generally good (better than "pure" COPD), especially if "T2 traits" (e.g. eosinophils) are present.

The view of asthma and COPD as two chronic obstructive diseases expressing different etiopathogenetic mechanisms but sometimes with a functional and clinical overlap, with asthma representing an important risk factor for the development of fixed bronchial obstruction, has transformed our understanding of chronic respiratory diseases.

The adoption of a multidimensional management approach based on "treatable traits" enables precision medicine, overcoming the limitations of traditional diagnostic labels.

This model allows for personalization of treatment, optimizing therapeutic efficacy and improving clinical *outcomes* for patients across the spectrum of obstructive pulmonary disease.

Supplementary material 2

METHODS IN AEROBIOLOGY

Aerobiological monitoring networks in Italy

In Italy, pollen monitoring is carried out through monitoring centers distributed throughout the country. The data flow into national networks (POLLnet, R.I.M.A.[@], AAIITO). Monitoring centres often coordinate several sampling stations within the regional territory. Monitoring centres can transfer data to one or more national networks.

The Italian monitoring centres are part of the System of Regional Environmental Protection Agencies (ARPA), Local Health Authorities, hospitals, universities, research institutes and scientific societies.

The historical reference is represented by the R.I.M.A. network.[@] (Italian Aerobiological Monitoring Network). The R.I.M.A.[@], which reports to the Italian Society of Aerobiology, Medicine and Environment (SIAMA), operates according to the European technical standard (UNI EN 16868:2019) and provides the data of its Centers to the EAN (*Europaean Aerobiology Network*), based in Vienna.

Sampling techniques

In accordance with the technical standard UNI EN 16868:2019, aerobiological monitoring is conducted primarily according to the Hirst volumetric method**.** The standard defines the type of instrument (Hirst volumetric air sampler), height and place of installation (representative site of the area and exposure criteria), sampling procedures (H24 without interruption during the year), sample preparation protocol, microscopic analysis of samples and data quality control. The aerobiological monitoring samples are analyzed exclusively by qualified personnel, using discriminating morphological criteria for the identification of the gender to which the pollen and fungal spores present in the sample belong. Results are expressed as daily concentration (granules/m^3).

Recently, innovative automatic monitoring systems based on imaging, fluorescence and machine learning algorithms, capable of providing high temporal and near-real-time resolution data, have been considered [Erb et al., 2024]. In the absence of a specific technical standard for these instruments, the data produced by the automatic systems were compared with those obtained by the Hirst method, used as a regulatory reference for calibration and performance validation [Suanno et al., 2022; Farooq et al., 2025; Bastl et al., 2023].

Data analysis and communication

The aerobiological monitoring data, in addition to representing a scientific source of extreme interdisciplinary interest, are processed on a daily and weekly basis for a simple, immediate and disseminatable graphic result in the form of concentration calendars, information bulletins and short-term forecasts.

This information is made available through the *websites* of official channels and specific communications in allergy centres; however, the dissemination of data is not uniform across the country.

Recently, there has been a proliferation of dedicated apps, whose communication is not always controlled or reliable.

Automatic aerobiological monitoring network: the example of Switzerland

In addition to traditional networks based on manual volumetric sampling, Switzerland has developed a national pollen monitoring network that uses automatic instruments with real-time measurements, representing an innovative model at European and global level [Aerobiology.ch].

The network is operated by MeteoSwiss, the country's Federal Office of Meteorology and Climatology, and consists of around 14 monitoring stations distributed in the main Swiss climate and vegetation zones. These automatic instruments are equipped with advanced technologies — such as laser sensors and artificial intelligence algorithms — that identify and count pollen grains in the air with hourly resolution; in some cases, there is the possibility of data being available even a few minutes after the measurement [pollenundallergie.ch].

The Swiss automated system employs devices such as the *Swisens Poleno*, which combines bioaerosol capture, algorithm-based recognition and immediate data transmission, enabling continuous and dynamic monitoring of airborne pollen [swisens.ch].

The benefits of this approach include:

- Real-time access to pollen concentrations, with hourly updates that improve the timeliness of information available to patients and healthcare professionals [pollenundallergie.ch];
- Improved quality of pollen forecasts, thanks to the speed and frequency of measurements [Aerobiology.ch];
- Support for scientific research and analysis of the relationships between pollen exposure and allergic reactions at different time scales [MeteoSwiss.ch].

This infrastructure represents an important step forward compared to traditional methods, which involve weekly analysis of samples managed exclusively by a specialized operator, and is an example of how the integration between digital technologies and environmental sciences can significantly improve the provision of real-time environmental data for public health [Aerobiology.ch].

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