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Outdoor airborne allergens: Characterization, behavior and monitoring in Europe

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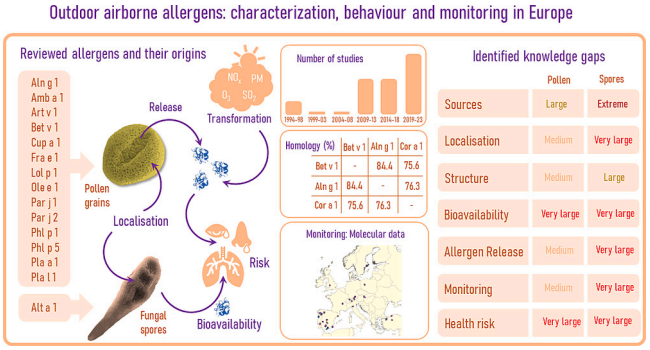
HIGHLIGHTS

- Airborne allergens (aeroallergens) represent a major health problem worldwide.
- Outdoor aeroallergens are derived mainly from pollen grains and fungal spores.
- Current knowledge of allergens structure, localization, and exposure is summarised.
- Methods for aeroallergens monitoring are listed and comprehensively presented.
- Knowledge gaps and challenges associated with allergen analysis are described.

GRAPHICAL ABSTRACT



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ABSTRACT

Aeroallergens or inhalant allergens, are proteins dispersed through the air and have the potential to induce allergic conditions such as rhinitis, conjunctivitis, and asthma. Outdoor aeroallergens are found predominantly in pollen grains and fungal spores, which are allergen carriers. Aeroallergens from pollen and fungi have seasonal emission patterns that correlate with plant pollination and fungal sporulation and are strongly associated with atmospheric weather conditions. They are released when allergen carriers come in contact with the respiratory system, e.g. the nasal mucosa. In addition, due to the rupture of allergen carriers, airborne allergen molecules may be released directly into the air in the form of micronic and submicronic particles (cytoplasmic debris, cell wall fragments, droplets etc.) or adhered onto other airborne particulate matter. Therefore, aeroallergen detection strategies must consider, in addition to the allergen carriers, the allergen molecules themselves. This review article aims to present the current knowledge on inhalant allergens in the outdoor environment, their structure, localization, and factors affecting their production, transformation, release or degradation. In addition, methods for collecting and quantifying aeroallergens are listed and thoroughly discussed. Finally, the knowledge gaps, challenges and implications associated with aeroallergen analysis are described.

1. Introduction

The term "allergen" was coined in 1906 by Von Pirquet to describe the agent causing adverse immune reactions, and in 1923, Coca and Cooke introduced the concept of "atopy" as a sensitized state (Blumenthal and Rosenberg, 2004; Coca and Cooke, 1923; Shulman, 2017; Von Pirquet, 1906). The discovery of immunoglobulin E (IgE) in 1967 advanced understanding of allergic mechanisms (Chang et al., 2007). By the 1980s, numerous allergens inducing IgE-mediated atopic allergies were identified, and in 1986, the International Union of Immunological Societies (IUIS) proposed standardized allergen nomenclature (Marsh et al., 1986). Presently, the IUIS/WHO database lists 1095 allergenic molecules from diverse sources (Dramburg et al., 2022; "WHO/IUIS Allergen Nomenclature,", n.d.), including 541 (49.4 %) that are airborne.

Aeroallergen lacks a universal definition from a functional standpoint. It refers to an airborne external antigen without intrinsic pathogenic properties, capable of IgE-binding as shown by immunoassays (Kleine-Tebbe et al., 2016). However, this disregards that atopy (IgE sensitization) isn't synonymous with allergy. Atopy is a genetic predisposition for IgE responses, but allergen-specific IgE presence alone can't predict clinical symptoms (Hamilton and Kleine-Tebbe, 2022). Thus, allergens are the molecules involved in atopy that induce the production of specific IgE antibodies.

Inhalant allergy is characterized by specific reactivity to allergens in the nose or bronchi, linked to atopy (Bentabol-Ramos et al., 2022). The fact that a molecule becomes an allergen is a process in which many factors intervene on the genetic basis of the immune response. The intensity of the allergic response can be influenced by environmental risk factors such as duration and degree of exposure to the allergen, air pollution, and those that can derive from the effects of climate change (Kleine-Tebbe et al., 2016; Papadopoulos, 2020).

2. Source for outdoor allergens

Allergic diseases are a growing global health concern, especially in low and middle-income countries (Pawankar, 2014). Allergic patients generate specific IgE antibodies when exposed to certain allergens (Eckl-Dorna et al., 2019). Major sources of outdoor inhalant allergens include pollen from seed plants (Spermatophyte) and fungal spores (Burge and Rogers, 2000). External exposure to aeroallergens significantly impacts the prevalence and severity of allergies (Papadopoulos, 2020). This section examines the localization of aeroallergen sources as a crucial factor for prolonged outdoor allergen exposure, using Europe as a case study.

2.1. Pollen grains

Pollen contains the male gametophyte, which takes part in the fertilisation process in seed plants. Wind-pollinated plants produce enormous amounts of small, light, and dry pollen, which often causes allergies (pollinosis) (Weryszko-Chmielewska, 2004). In the WHO/IUIS allergen database, there are listed 152 pollen airborne allergens from Eudicots, 68 from Monocots and 20 from Gymnosperms (http://allergen.org/index.php).

In Europe, the major allergenic plants belong to botanical families such as Poaceae (grasses), Betulaceae (birch, hazel, alder), Oleaceae (olive, ash) and Asteraceae (ragweed, mugwort) (D'Amato et al., 2007). These plants are widely distributed across Europe, though specific source area data is often missing. Birch (*Betula* sp.), ragweed (*Ambrosia*

artemisiifolia), and olive (*Olea europaea*) show the most confident source area distribution (Skjøth et al., 2008; Pauling et al., 2012; Sofiev et al., 2015). Birch forests are densest in Scandinavia, Baltic regions, and Russia, declining towards southern Europe. Recent national studies have enhanced understanding for the UK (McInnes et al., 2017; Skjøth et al., 2015), Ireland (Maya-Manzano et al., 2021), and Belgium (Dujardin et al., 2022), particularly in homogenous landscapes (Skjøth et al., 2015; Stas et al., 2021). Olive has well-defined source distribution due to Corine Land Cover data (Fernández-Rodríguez et al., 2014), allowing continental-scale mapping (Sofiev et al., 2017). However, this excludes smaller olive groves outside the main areas. Limited information exists for other trees despite studies covering Spain (Oteros et al., 2017) and the UK (McInnes et al., 2017; Skjøth et al., 2015). Uncertainty remains to weather pollen concentrations align with these maps. Trees like *Carpinus betulus* (Betulaceae) and *Fraxinus excelsior* (Oleaceae) have been mapped in forestry but are not well-studied in aerobiology. They do however have cross-reactive proteins with birch and olive pollen allergens (Weber, 2003). Some, like *Platanus* spp., produce allergenic pollen but are not in official inventories due to their ornamental status (Galle et al., 2021). Others suspected allergenic ornamental species, such as *Liquidambar styraciflua*, *Ailanthus altissima*, *Baccharis halimifolia*, *Eucalyptus camaldulensis* (Cariñanos and Marinangeli, 2021; Magyar et al., 2022), lack source data, similar to *Platanus* spp.

Pollen grains from grasses are Europe's most prevalent sensitizing agents (Burbach et al., 2009). These plants are widespread in rural settings like meadows (McInnes et al., 2017) and roadsides (Skjøth et al., 2013), and across diverse urban climates (Charalampopoulos et al., 2021; Hugg et al., 2017; Skjøth et al., 2013; Werchan et al., 2017). Numerous grass species produce varying amounts of pollen allergens (e.g. Gangl et al., 2015; Jung et al., 2018), flowering at different times (Brennan et al., 2019), collectively impacting overall pollen concentration (Romero-Morte et al., 2018). Grass pollen tends to stay localized, with local sources significant for urban exposure (Frisk et al., 2022; Frisk et al., 2023). Quantifying emissions is complex as mowing can alter source areas (Skjøth et al., 2013). For Denmark and Belgium, grass source data's operational use requires further research (Verstraeten et al., 2021), underlining the need to prioritize governing processes that affect emissions, focusing on city scale variations.

Ragweed is the only weed where substantial knowledge concerning source strength and source distribution exists. A number of detailed studies covering the Pannonian Plain (Šikoparija et al., 2009; Skjøth et al., 2011), Italy (Bonini et al., 2018), Austria (Karrer et al., 2015) and France (Thibaudon et al., 2014) as well as localized studies (Mimić et al., 2021), has led to continental scale inventories (Schaffner et al., 2020) relying on pollen data using a so-called top-down approach (Skjøth et al., 2019). Other clinically relevant weeds such as *Parietaria* spp., *Salsola* spp., *Chenopodium* spp. or *Artemisia* spp. have little information beyond generalised data from pollen traps (e.g. pollen calendars) (Ciprandi et al., 2018; Grewling et al., 2012; Martínez-Bracero et al., 2015; Villalba et al., 2014).

The provided information concerns the present range of major allergenic species in Europe. However, species distribution has changed significantly in the past decades due to climate change, urbanization, and land-use (Pompe et al., 2008), with projections of change set to accelerate. For example, ragweed may spread in Northern Europe (Cunze et al., 2013), while Mediterranean species such as *Olea europea* (Harrison et al., 2006) and *Parietaria judaica* (Bakkenes et al., 2002) could increase in central Europe. Conversely, some (e.g., birches) may retreat to Northern Europe's favorable habitats (Dyderski et al., 2018). Elevated CO_2 levels could intensify pollen seasons, raising production and allergenicity (Ziska and Beggs, 2012; Ziska, 2020). Recent changes in plant distribution and allergen exposure will undoubtedly impact both the prevalence of allergies and the severity of seasonal symptoms, as has been observed with numerous introduced and invasive species (Asero, 2002; Gassner et al., 2014; Ariano et al., 2015).

2.2. Fungal spores

Fungi are widespread eukaryotes, adaptable to diverse environments, potentially numbering 3.8 million species, with many yet unknown (Hawksworth and Lücking, 2017). Their spores, released into the air, are year-round atmospheric residents, influenced by weather and location (Martínez-Bracero et al., 2022). Fungal spore counts can surpass pollen levels by 1000-fold (Hughes et al., 2022), inhaled indoors and outdoors throughout life (Vitte et al., 2022). Fungal aeroallergens span 3 major Fungi Phyla: Basidiomycota, Ascomycota, and Zygomycota. Ascomycota, holding nearly 50 % of named species, includes ~80 % of medically relevant fungi (Murray et al., 2021). In the WHO/IUIS allergen database, there are 95 molecules of Ascomycota listed, which trigger an IgE-response. The majority of these molecules (91 allergens, 96 %) belong to airborne allergens. Basidiomycota includes 23 known allergens, out of which only 10 are airborne. As for Zygomycota, currently, only two allergenic molecules are classified, and both of them are inhalant allergens (http://allergen.org/index.php).

Prominent allergenic species include *Aspergillus fumigatus*, *Alternaria alternata*, *Cladosporium herbarum*, and *Penicillium notatum* (all from Ascomycota) (Burbach et al., 2009; López Couso et al., 2021). *A. fumigatus* drives allergic fungal airway disease and IgE sensitization (Wardlaw et al., 2021). *A. alternata* leads in fungi-associated asthma (Denning et al., 2006; Salo et al., 2006), with 12 allergens described (www.allergen.org). Alt a 1, a major allergen, induces IgE responses in ~80 % of *Alternaria*-allergic patients (Chruszcz et al., 2012). *Cladosporium* spp. has nine molecular allergens, *Aspergillus* spp. 35, and *Penicillium* spp. 13 (http://allergen.org/index.php). Unfortunately, commercially available extracts for common indoor allergenic fungi like *Aspergillus versicolor*, *Chaetomium*, and *Acremonium* spp. are lacking, impeding research and diagnostics.

Despite progress, fungal spores remain aeroallergens with the most limited data for allergenic properties and sources. Harvesting's role as an *Alternaria* spore source is noted in a number of studies (Apangu et al., 2020; Skjøth et al., 2012). In the UK, croplands are considered a major source of *Alternaria* spores (Sadyś et al., 2015; O'Connor et al., 2014), while cites crops and orchards are sources in Spain (Fernández-Rodríguez et al., 2015). Specific land cover's allergen source importance varies regionally. Existing large-scale maps cover *Alternaria* spp. presence-absence mapping (Sadyś et al., 2015; Fernández-Rodríguez et al., 2015; Apangu et al., 2022) and *Cladosporium* spp. (Olsen et al., 2019), yet their comprehensiveness is uncertain. Other spores, such as *Aspergillus fumigatus*, known to be associated with composting processes, or *Epicoccum*, expected to originate from similar ecosystems as *Alternaria* and *Cladosporium*, have not been mapped. Quantifying fungal spore sources proves more challenging than grass pollen due to management data gaps and limited spore-source studies.

Knowledge gaps and future challenges:

- Limited information on the localization of the allergen sources of such plant genera as *Fraxinus*, *Corylus*, *Alnus*, *Platanus*, *Artemisia* and those species with cross-reactivity to the aforementioned species (e.g. *Carpinus betulus*).
- The need to quantify urban and near urban sources of pollen and spores with high spatial detail (e.g. below 10 m resolution).
- Lack of quantitative mapping covering fungal spores, primarily *Alternaria* and *Cladosporium*, but also other clinically important spores, such as *Aspergillus*.

3. Localisation of allergens

3.1. Plant allergens

Pollen grains are primary sources of plant-released inhalant allergens. Major allergenic proteins, mainly intracellular, locate in sites of protein metabolism like ribosome-rich cytoplasm, endoplasmic

reticulum cisternae, and Golgi vesicles (Table 1) (Alche et al., 1999; Grote et al., 1999, 1998; Miki-Hirosige et al., 1994). Storage sites for grass and birch pollen allergens include starch granules and polysaccharide-containing wall-precursor bodies (p-particles) (Behrendt and Becker, 2001; El-Ghazaly et al., 1996; Staff et al., 1999). Some allergens exist in pollen wall exine and intine (Grote et al., 2008; Suárez-Cervera et al., 2003).

Allergenic proteins extend beyond pollen grains. Notably, orbicules (Ubisch bodies), tiny particles (0.3–4.0 μm), that originate from pollen sac tapetum and may attach to pollen or exist individually (El-Ghazaly et al., 1996; Huysmans et al., 1998; Osada and Okano, 2021; Takahashi et al., 1995). Orbicules disperse upon anther release and have been seen in daily aerobiological samples (Ruggiero and Bedini, 2018). They may be much more numerous than pollen grains, especially in the Cupressaceae family (Miki-Hirosige et al., 1994; Takahashi et al., 1995; Vinckier and Smets, 2001). Allergenic proteins are confirmed in orbicules of *Cryptomeria japonica* (Cry j 1) (Miki-Hirosige et al., 1994), *Cupressus arizonica* and *C. sempervirens* (Cry j 1-homolog) (Suárez-Cervera et al., 2003), *Betula pendula* (Bet v 1) (El-Ghazaly et al., 1996), and *Corylus avellana* (Bet v 7-homolog) (Vinckier et al., 2005). Yet, some plants lack orbicules, e.g., Asteraceae and Oleaceae family (Vinckier et al., 2005). In others, e.g. grasses, orbicules are not easily removed from the anthers' surface; consequently, the number emitted to the atmosphere is low (Dinis et al., 2007).

Additionally, during pollen germination and tube growth, small nanovesicles known as pollensomes (28 to 60 nm in diameter) may release (García Ponce et al., 2014; Prado et al., 2014). In olive pollen, these carry allergens (Ole e 1, Ole e 11, and Ole e 12). Allergen-loaded pollensomes were isolated from other species, like birch (*Betula pendula*) and ryegrass (*Lolium perenne*) (Prado et al., 2015). Allergen homologs are also found in vegetative parts of some allergenic plants, e.g., grass (Fernandez-Caldas et al., 1992) and ragweed (Agarwal et al., 1984). Theoretically, fragmentary leaves or aerosolized plant debris (e.g., by mowing) might trigger allergy responses. Limited information exists on plants hosting allergens within their tissue.

3.2. Fungal allergens

Fungal spores are the naturally sensitizing part of fungi containing the highest concentration of allergens (Bouziane et al., 2005). Mycelium, from which spores develop, may also contain allergenic molecules, concentration of such molescules is generally lower in hyphae (Aukrust et al., 1985; Bouziane et al., 2005). Likely, specific allergens exist for spores and mycelium, dependent on protein type and function (Bouziane et al., 2005). In *A. alternata*, the primary allergen Alt a 1, is crucial in plant infection (Garrido-Arandia et al., 2016; Gómez-Casado et al., 2014) and primarily resides in older spores' melanin layer, not cytoplasm, hyphae, or in young spores (Twaroch et al., 2012). Conversely, Alt a 8 locates solely in hyphae's cytoplasm, absent in spores (Twaroch et al., 2012).

Roughly 25 % of hyphal fragments express detectable allergens, mainly released from terminal ends (Green et al., 2006a). Aerosolized mycelium fragments, abundant bioaerosols outdoors (Levetin et al., 2009; Almaguer et al., 2020; Apangu et al., 2023) and indoors (Cho et al., 2005; Górny et al., 2002; Reponen et al., 2007), vary widely in shape and size, often smaller than spores. Although these fragments display immunological reactivity, their role as an additional fungal allergen source and allergy trigger needs clarification (Alan, 2023; Górny et al., 2002; Green et al., 2006a, 2005a; Grewling et al., 2020b; Simon-Nobbe et al., 2008).

Knowledge gaps and future challenges:

- Production and storage sites of some major pollen allergens, e.g. Amb a 1, and the majority of fungal allergens have not been determined so far.

Table 1
Localization of the major plant inhalant allergens.

Site		Plant	Allergen	References
Pollen	Pollen wall (exine or intine)	*Artemisia annua*, *A. argyi*, *A. capilaris* and *A. sieversiana*	Homologs of Art v 1 and Art v 3	Gao et al., 2019
		Artemisia capilaris and *A. sieversiana*	Homologs of Art v 2	Gao et al., 2019
		Betula verrucosa	Bet v 1	El-Ghazaly et al., 1996
		Betula verrucosa	Bet v 4 sparse	Grote et al., 1999
		Cryptomeria japonica	Cry j 1	Miki-Hirosige et al., 1994
		Cupressus sp.	Cry j 1-homolog	Suárez-Cervera et al., 2003
		Grasses, weeds, and trees	Phl p 7 and Phl p 7-homologs	Grote et al., 2008
		Parietaria judaica	Par j 1	Vega-Maray et al., 2006
		Phleum pratense	Phl p 4	Fischer et al., 1996
		Plantago lanceolata	Pla l 1	Castro et al., 2007
		Platanus acerifolia	Pla a 2	Suarez-Cervera et al., 2005
	Cytoplasm (often within ribosome rich area)	*Artemisia vulgaris*, grass, birch	Art v 7 (60kDa) and its homologs	Grote et al., 1998
		Betula verrucosa	Bet v 1	Grote et al., 1999
		Grasses, weeds, and trees	Phl p 7 and Phl p 7-homologs	Grote et al., 2008
		Lolium perenne	Lol p 1 and Lol p 5	Staff et al., 1999
		Phleum pratense	Phl p 4	Fischer et al., 1996
	Around or inside nucleus	*Artemisia annua*, *A. argyi*, *A. capilaris* and *A. sieversiana*	Homologs of Art v 2 and Art v 7-homolog	Gao et al., 2019
		Artemisia vulgaris, grass, birch	Art v 7 (60kDa) and its homologs	Grote et al., 1998
		Betula verrucosa	Bet v 4 and Bet v 1	Grote et al., 1999
		Grasses, weeds, and trees	Phl p 7 and Phl p 7-homologs	Grote et al., 2008
	Golgi bodies	*Cryptomeria japonica*	Cry j 1	Miki-Hirosige et al., 1994
		Cupressus sp.	Cry j 1-homolog	Suárez-Cervera et al., 2003
		Platanus acerifolia	Pla a 2	Suarez-Cervera et al., 2005
	Endoplasmic reticulum	*Betula verrucosa*	Bet v 4 and Bet v 1	Grote et al., 1999
		Olea europaea	Ole e 1	Alche et al., 1999; Alché et al., 2002, 2004
		Platanus acerifolia	Pla a 1 and Pla a 2	Suarez-Cervera et al., 2005
	Mitochondria	*Artemisia vulgaris*, grass, birch	Art v 7 (60kDa) and its homologs	Grote et al., 1998

(*continued on next page*)

Table 1 (*continued*)

Site	Plant	Allergen	References
	Betula verrucosa	Bet v 4	Grote et al., 1999
	Grasses, weeds, and trees	Phl p 7 and Phl p 7-homologs	Grote et al., 2008
Starch granules	*Betula verrucosa*	Bet v 1	El-Ghazaly et al., 1996
	Cryptomeria japonica	Cry j 2	Osada and Okano, 2021
	Lolium perenne	Lol p 5	Staff et al., 1999
	Lolium perenne	Lol p IX	Taylor et al., 1994
	Phleum pratense	Phl p 4	Fischer et al., 1996
polysaccharide-containing wall-precursor bodies (P-particles)	*Phleum pratense*	Phl p 6	Vrtala et al., 1999
Orbicules (Ubisch bodies)	*Betula pendula*	Bet v 7	Vinckier et al., 2005
	Cryptomeria japonica	Cry j 1	Miki-Hirosige et al., 1994
	Cryptomeria japonica	Cry j 1	Osada and Okano, 2021
	Cupressus sp.	Cry j 1-homolog	Suárez-Cervera et al., 2003
Pollensomes	*Olea europaea*	Ole e 1, Ole e 11, Ole e 12	Prado et al., 2014, 2015

- Scarce information about the homologs of pollen allergens and the possibility of aerosolized vegetative parts of plants causing allergic reactions.
- The abundance and allergenic significance of hyphal fragments in the outdoor air require clarification.

4. Biochemical characterization of airborne allergens

Most pollen or fungal allergens are glycoprotein proteins, with molecular weights from 10,000 to 80,000 Da (Horner et al., 1995; Kurup and Banerjee, 2000; Shah and Grammer, 2012). These allergens fall into a few protein classes (Radauer et al., 2008a). About 25 % of plant allergens in the Official Allergen Database of the IUIS - are pathogenesis-related proteins (PR-proteins), induced by stress, pathogens, and abiotic stimuli (Hoffmann-Sommergruber, 2002). This diverse group is split into 14 families, including PR-protein families 2, 3, 4, 5, 8, 10, and 14 (Hoffmann-Sommergruber, 2002). Plant and fungal allergens also belong to calcium-binding proteins (CBPs, e.g. pollen polcalcins) (Hauser et al., 2010), profilins (Jimenez-Lopez et al., 2012), enzyme inhibitors (e.g. trypsin and invertase inhibitors like Pla a 1) (Asturias et al., 2003), transport proteins (fungi lipocalins, pollen PR-14 group Lipid Transport Proteins (LTPs)), enzymes from various catalysis groups, and regulatory proteins (fungi heat-shock proteins) (Tiwari et al., 2015).

Certain allergens are pollen-specific (Pablos et al., 2016), spore-specific (Aukrust and Borch, 1979; Horner et al., 1993), or found in various organs. For instance, pollen-only polcalcins, are widely distributed profilins across plant organs, and also found in fruits or seeds (Asero et al., 2008; Hauser et al., 2010). Many allergens belong to protein families known as panallergens, leading to structural similarity (Table 2) and shared IgE binding motifs causing cross-reactivity (Fig. 1 for examples) across species, including pollen, fungi, and plant-derived foods (Ferreira et al., 2004; Hauser et al., 2010). The understanding of allergenicity and cross-reactivity hinges on the similarity and conservation of IgE binding domains. Phylogenetic analysis has been done for specific allergens like Ole e 1 (Jiménez-López et al., 2011), profilin (Jimenez-Lopez et al., 2012), Bet v 1 (Radauer et al., 2008b), pectate

Table 2
Main pollen allergen families. The allergens are grouped according to their protein families based on biological function and phylogeny. Sensitization has been demonstrated for all molecular allergens presented in the table (references in the table). The biological and molecular characteristics were obtained from allergome.org (a) and uniprot.org (b) databases and/or the references presented.

Protein family & Biological function[a, b]	Organism	Pollen Allergen	MW (kDa)[b]	References
Profilins	*Chenopodium album*	Che a 2	14	Barderas et al., 2004
Actin-binding Proteins	*Olea europaea*	Ole e 2	15	Quiralte et al., 2005
	Fraxinus excelsior	Fra e 2	14	Hemmer et al., 2000; Mas et al., 2014; Poncet et al., 2010
	Poaceae	Group 12	14	Andersson and Lidholm, 2003; Hatzler et al., 2012
	Plantago lanceolata	Pla l 2	15	Moya et al., 2017
	Salsola Kali	Sal k 4	14	Assarehzadegan et al., 2010
	Betula pendula	Bet v 2	15	Movérare et al., 2002; Offermann et al., 2016
	Ambrosia artemisiifolia	Amb a 8	14	Offermann et al., 2016
	Artemisia vulgaris	Art v 4	14	Offermann et al., 2016; Wopfner et al., 2002
Polcalcins	*Chenopodium album*	Che a 3	10	Barderas et al., 2004
Calcium-binding Proteins (CBPs)	*Betula pendula*	Bet v 3	24	Seiberler et al., 1994
		Bet v 4	7–8	
	Olea europaea	Ole e 3	9	Batanero et al., 1996
		Ole e 8	21	
	Fraxinus excelsior	Fra e 3	9	Hemmer et al., 2000; Mas et al., 2014; Poncet et al., 2010
	Phleum pratense	Phl p 7	6	Andersson and Lidholm, 2003; Niederberger et al., 1999
	Ambrosia artemisiifolia	Amb a 9	9	Zbîrcea et al., 2023
		Amb a 10	17	
	Artemisia vulgaris	Art v 5	10	Asero et al., 2006; Zbîrcea et al., 2023
	Salsola Kali	Sal k 7	8.5	Burgos-Montero et al., 2019
Lipid Transfer Proteins (LTPs)	*Olea europaea*	Ole e 7	9.5	Tejera et al., 1999
	Platanus acerifolia	Pla a 3	10	Lauer et al., 2007
Member of the PR14 family	*Ambrosia artemisiifolia*	Amb a 6	10	Roebber et al., 1983
	Artemisia vulgaris	Art v 3	12	Lombardero et al., 2004; Sánchez-López et al., 2014
	Arabidopsis thaliana	Ara t 3	14	Chardin et al., 2003
	Parietaria judaica	Par j 1	15	Costa et al., 1994
		Par j 2	10–14	
Thaumatin-like Proteins (TLPs)	*Cupressus arizonica*	Cup a 3	21	Cortegano et al., 2004; Palacín et al., 2012
Member of the PR5 group	*Olea europaea*	Ole e 13	23	Palomares et al., 2008
	Platanus acerifolia	Pla a TLP	25	Palacín et al., 2012
	Artemisia vulgaris	Art v TLP	25	Palacín et al., 2012
	Juniperus ashei	Jun a 3	30	Midoro-Horiuti et al., 2000

(*continued on next page*)

Table 2 (*continued*)

Protein family & Biological function[a, b]	Organism	Pollen Allergen	MW (kDa)[b]	References
Pectate lyases	*Ambrosia artemisiifolia*	Amb a 1	38	Adolphson et al., 1978; Pichler et al., 2015; Zbîrcea et al., 2023
	Artemisia vulgaris	Art v 6	44	Asero et al., 2006; Pichler et al., 2015
	Cupressus sempervirens	Cup s 1	43	Feliu et al., 2013
	Cryptomeria japonica	Cry j 1	41	Pichler et al., 2015
	Cupressus arizonica	Cup a 1	43	Pichler et al., 2015
	Juniperus ashei	Jun a 1	43	Pichler et al., 2015
Ole e 1 - like	*Olea europaea*	Ole e 1	16	Barber et al., 2008
	Chenopodium album	Che a 1	19	Flores et al., 2012; Panzner et al., 2014
Trypsin Inhibitors	*Fraxinus excelsior*	Fra e 1	20	Hemmer et al., 2000; Poncet et al., 2010
	Phleum pratense	Phl p 11	20	Andersson and Lidholm, 2003; Marknell DeWitt et al., 2002
	Plantago lanceolata	Pla l 1	22	Panzner et al., 2014
	Salsola Kali	Sal k 5	18	Castro et al., 2014
Bet v 1 – like	*Betula pendula*	Bet v 1	17	Ipsen and Løwenstein, 1983
Ribonucleases	*Alnus glutinosa*	Aln g 1	19	Blankestijn et al., 2017; Hauser et al., 2011
Member of the PR10 group	*Carpinus betulus*	Car b 1	17	Hauser et al., 2011
	Castanea sativa	Cas s 1	22	Hauser et al., 2011
	Corylus avellana	Cor a 1	17	Blankestijn et al., 2017; Hauser et al., 2011
	Fagus sylvatica	Fag s 1	17	Hauser et al., 2011
	Quercus alba	Que a 1	17	Hauser et al., 2011; Niederberger et al., 1998
Art v 1 - like	*Artemisia vulgaris*	Art v 1	28	Barber et al., 2008; Lombardero et al., 2004; Zbîrcea et al., 2023
Defensins	*Parthenium hysterophorus*	Par h 1	12	Pablos et al., 2017
	Ambrosia artemisiifolia	Amb a 4	30	Léonard et al., 2010

lyase (Pichler et al., 2015), and Alt a 1 (Achatz et al., 1995; Zhang et al., 2019). Yet, a comprehensive analysis of various allergen proteins from different families is lacking. Many allergens share biological functions and belong to homologous protein groups (Table 2). This review presents protein phylogenetic trees, homology analysis, and sequence alignment for major European airborne allergens (Ole e 1-like, polcalcin, Bet v 1-like, and Alt a 1).

4.1. Pollen allergens

Ole e 1-like allergens are trypsin inhibitors implicated in pollen-stigma and pollen tube-style cell recognition (Fernández-González et al., 2020b; Alché et al., 2004). Ole e 1, the most studied trypsin inhibitor, is expressed late in pollen development and up-regulated during germination and pollen tube growth (Fernández-González et al., 2020b; Alche et al., 1999). Maturing in the endoplasmic reticulum, it gains three disulphide bonds (between residues 19–90, 22–131, and 43–78) for its final 3D structure, marked by an alpha helix and beta strand motifs (Fig. 1I). Glycosylation, a marker signifying later germination-phase secretion, also occurs (Lara-Mondragón et al., 2022). Despite varying homology (30–92 %) within the Ole 1-like protein family, greater phylogenetic distance correlates with higher homology (e.g., Ole e 1 and Phl p 11 share 32.8 %). Despite these differences, the proteins maintain structural similarity and conserved IgE-binding domains (Fig. 1I).

Conversely, the polcalcin family comprises calcium-binding proteins found in the pollen of flowering plants, including grasses, trees, and weeds, with roles in pollen-tube growth regulation (Niederberger et al., 1999; Wopfner et al., 2007). Highly conserved across the plant kingdom, this allergen is unambiguously categorized as a panallergen. Sequence alignment reveals conserved domains, including the IgE-recognition region, and >67.1 % homology among analyzed species, despite differing phylogenetic distances. Structurally, polcalcins exhibit two distinct EF-hand motifs (domain 1–35 and domain 35–70), forming a helix–loop–helix topology where Ca^{2+} ions bind ligands in the loop (Fig. 1II).

Bet v 1, a member of the pathogenesis-related 10 (PR-10) protein family, belongs to 15–18 kDa acidic cytoplasmic proteins involved in plant defense (Radauer et al., 2008b). Initially demonstrated in ginseng PR-10 proteins, ribonuclease activity is seen in various PR-10 members, including Bet v 1. With a possible nucleic acid binding role, a conserved glycine-rich loop (P-loop) lies between the 2nd and 3rd strands (3D structure in Fig. 1III). Homology among Bet v 1-like family ranged from 54.7 % to 84.4 %, highlighting conserved domains and IgE-recognition epitopes (Fig. 1III).

4.2. Fungal allergens

The fungal allergen Alt a 1 is a dimeric protein (30 kDa dimer with 16.4 kDa and 15.3 kDa subunits), present in *Alternaria* spores' cell walls and hyphal fragments (Table 3). A significant part of the Pleosporaceae family's secretory machinery, it might influence spore germination (Teifoori et al., 2019; Mitakakis et al., 2001). Alt a 1 forms an 11-strand β-barrel (Fig. 1IV) with a hydrophobic middle segment. Five cysteine residues form disulfide bridges, two intramolecular stabilizing the β-barrel, and the third (Cys30) creating a dimer in a 'butterfly-like' arrangement (Fig. 1IV). The Alt a 1 dimer's stability comes from the disulfide bridge and hydrophobic/polar interactions, involving N- and C-terminal regions. Although not universally conserved (Chruszcz et al., 2012), Cys30's role in dimer formation suggests its limited influence on allergen expression/structure.

Besides Alt a 1, only Ste. b 1 and Ulo b 1, few homologs are known and sequenced outside the *Alternaria* genus (De Vouge et al., 1998; Moreno et al., 2016). Homologous protein sequences in dominant airborne fungi like *Cladosporium* and *Aspergillus* are currently unavailable. Sequence alignment of Alt a 1 family reveals conserved domains, including Cys30 and the IgE-recognition region, with >80 % homology among analyzed species. The antibody-binding epitope, spanning amino acids 4–23 of the mature protein, remains consistent across Alt a 1 and homologs (Breitenbach and Simon-Nobbe, 2002; Zhang et al., 1995) (Fig. 1IV).

In summary, the phylogenetic trees, homology analysis and sequence alignment of four relevant major airborne allergens in Europe interestingly evidenced that cross-reactivity is dependent not only on the homology levels as a whole but also dependent on the homology among specific sequences in the proteins, most probably corresponding to IgE-binding sites (Fig. 1 – blue squares). These aspects should be further explored for a better understanding of mechanisms governing the allergenic properties of proteins and to better predict species cross-reactivity.

Knowledge gaps and future challenges:

- Minimal systematic and comprehensive classification of allergens, limitations in allergy diagnostics and in the understanding of cross-reactivity.

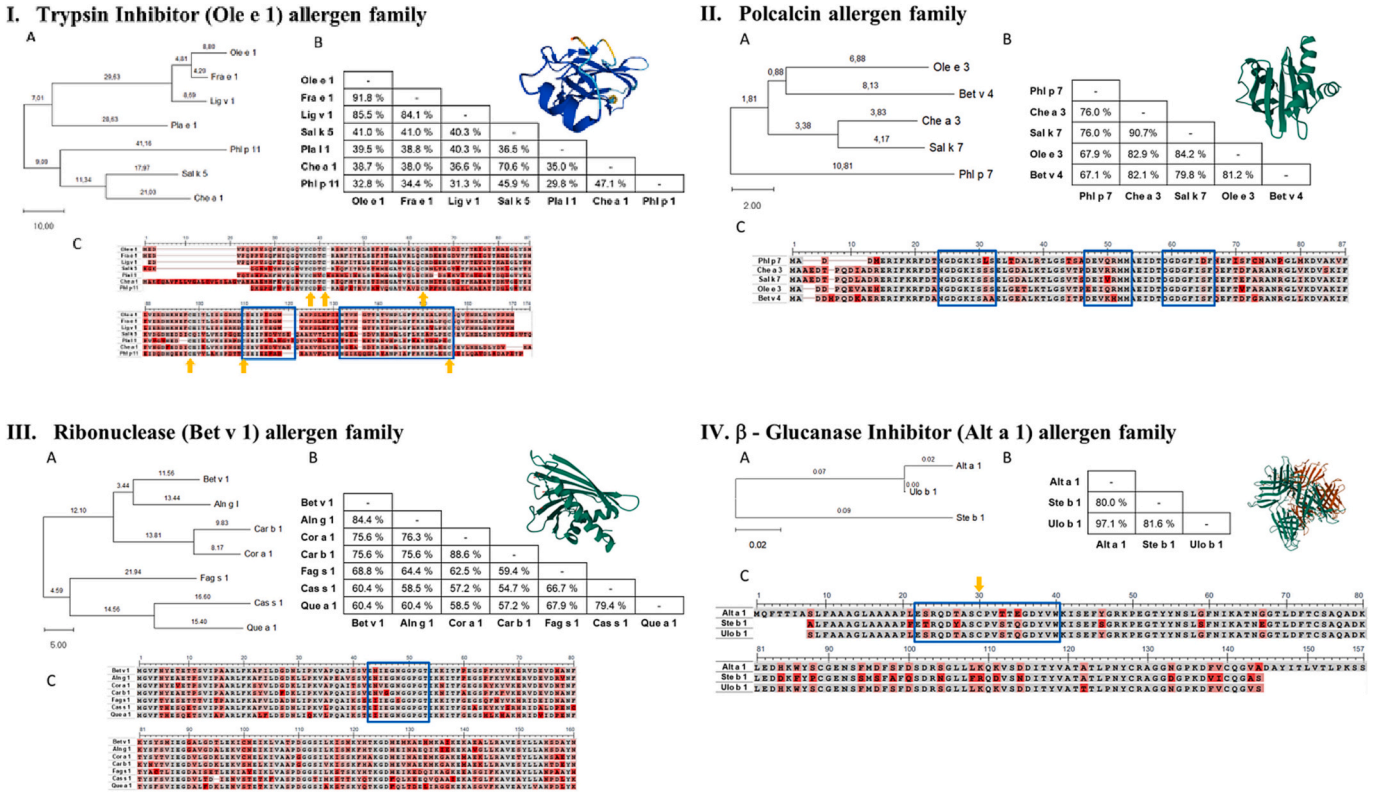

Fig. 1. Phylogenetic and similarity analysis of pollen and fungal dominant allergens in Europe. A) phylogenetic tree - the evolutionary history was inferred using the Neighbor-Joining method (Saitou and Nei, 1987). The optimal tree is shown. The tree is drawn to scale, with branch lengths in the same units as those of the evolutionary distances used to infer the phylogenetic tree. The evolutionary distances were computed using the number of differences method (Nei et al., 2000) and are in the units of the number of amino acid differences per sequence. This analysis involved 7 (1), 5 (2), 7 (3) and 3 (4) amino acid sequences. All ambiguous positions were removed for each sequence pair (pairwise deletion option). Evolutionary analyses were conducted in MEGA11 (Tamura et al., 2021) B) the Calculated percentage of homology conducted in NCBI; Predicted 3D-structure of Ole e 1 (I, Jumper et al., 2021), Polcalcin (II), Bet v 1 (III) and Alt a 1 (IV) allergens(Berman et al., 2000) C) Multiple alignments of the amino acid sequences conducted in Constraint-based Multiple Alignment Tool (COBALT) from NCBI (Papadopoulos and Agarwala, 2007). Orange arrows represent cysteines which are conserved in the sequence of these proteins and seemed to be involved in disulphide bonds (I, The UniProt Consortium, 2023; IV, Breitenbach and Simon-Nobbe, 2002; Zhang et al., 1995). Blue boxes identify immunodominant IgE-bindig epitopes (I, The UniProt Consortium, 2023; II, Moghaddam et al., 2019; III, Atanasio et al., 2022; Spangfort et al., 2003; IV, The UniProt Consortium, 2023).

Table 3
Main fungal spore allergen families. The allergens are grouped according to their protein families based on biological function and phylogeny. Sensitization and/or cross-reactivity has been demonstrated for all molecular allergens presented in the table (references in the table). The biological and molecular characteristics were obtained from allergome.org (a) and uniprot.org (b) databases and/or the references presented.

Protein family & Biological Function[a, b]	Organism	Fungal Allergen	MW (kDa)[b]	References
Alt a 1	*Alternaria alternata*	Alt a 1	30 - dimeric (16.4 + 15.3)	De Vouge et al., 1998
β-glucanase inhibitor				
(Inhibits PR5 activity of the host plant)	Stemphylium botryosum	Ste b 1	17	Moreno et al., 2016
	Ulocladium botrytis	Ulo b 1	17	Moreno et al., 2016
Serine Proteases	Penicillium oxalicum	Pen o 18*	34	Shen et al., 1999
(*Vacuolar)	*Aspergillus fumigatus*	Asp f 18*	34	Shen et al., 2001
	Cladosporium cladosporioides	Cla c 9*	36	Chou et al., 2008
	Epicocum purpurascens	Epi p 1	30	Bisht et al., 2004

- The difference in allergenicity within the protein family members is not yet completely understood; changes in peptide sequences in the IgE-binding site may be a key factor that should be widely investigated.
- There are many plant taxa without exact information on their relevance in allergy (Magyar et al., 2022), but immunogenicity is suspected based on the consideration of its close taxonomic position to allergenic taxa.

5. Impacts and changes in aeroallergens properties

The qualitative and quantitative traits of allergens are influenced by external factors, including both abiotic and biotic environmental stressors (Behrendt et al., 1997; Behrendt and Becker, 2001) (Fig. 2, Table S1). The bioavailability of proteins is determined by their abundance, localization (Section 3), structure, solubility and stability (Foo and Mueller, 2021; Schenk et al., 2009; Vrtala et al., 1993). Allergen production and release can be influenced even by a single stimulus, and while certain conditions may lead to the active expression of one allergen, they may not be optimal for another allergen (Pfeiffer et al., 2022). The environmental impact is observed throughout the life cycle of the allergen: during its expression, transformation, and degradation (Behrendt et al., 1997; Cabrera et al., 2020). Processes and factors affecting allergenic properties of proteins are described below.

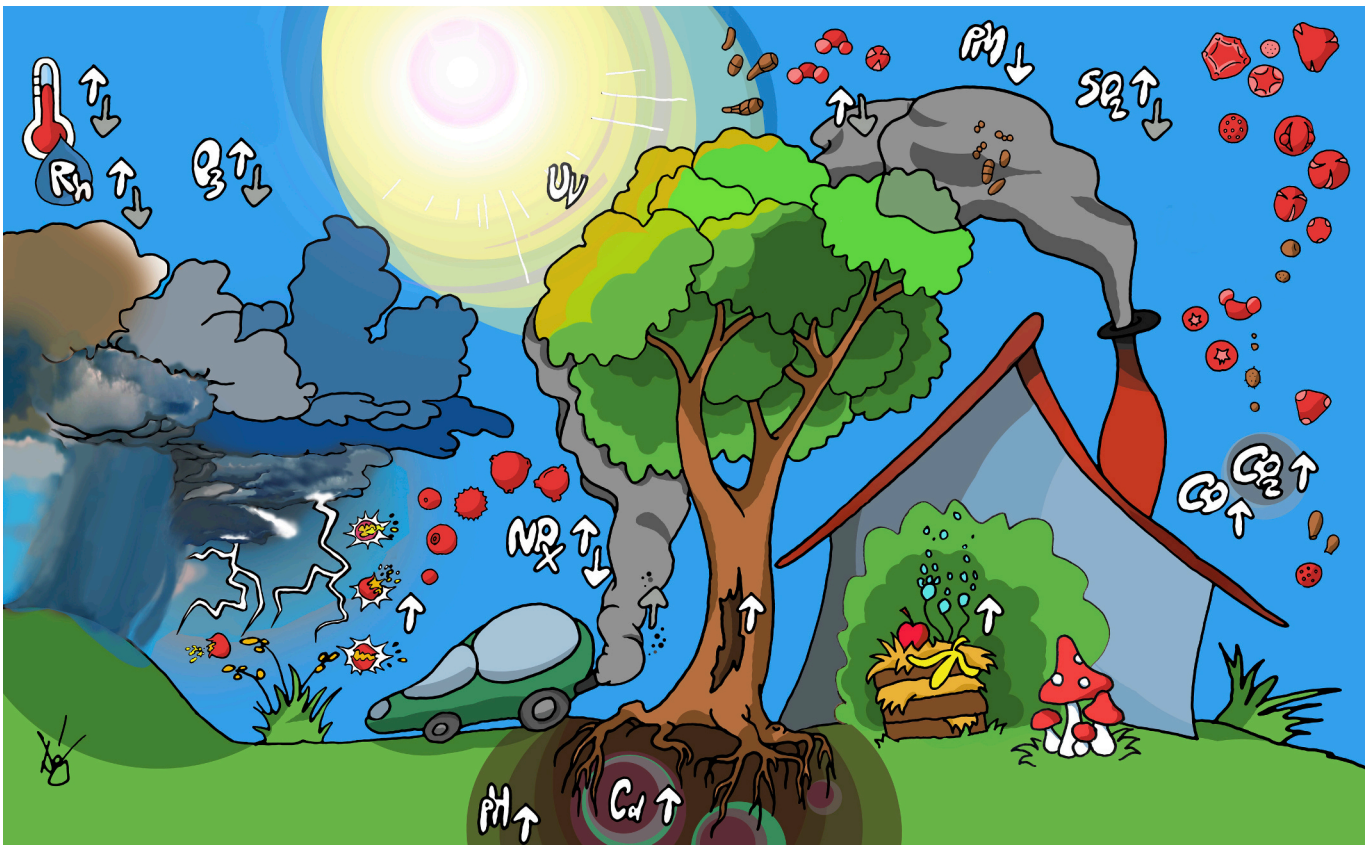

Fig. 2. The environmental effects on airborne allergens. Effects increasing or decreasing the allergenicity of the particles (spores, intact and broken pollen grains) are represented by arrows pointing up or down, respectively. White and grey arrows represent dominant and less common effects, respectively. No arrow: no significant effect. The depicted environmental factors are: temperature, relative humidity, ultraviolet radiation, storms and lightning, PM10, diesel exhaust carbon particles, character of sites ("pollution" effect, represented by combustion fumes), ozone, carbon monoxide, carbon dioxide, sulphur dioxide, nitrogen oxides, ozone, mechanical shock (wound on the tree trunk), microbiome (represented by molds), soil pH and cadmium. For references, see Table S1.

5.1. Pollution

Air pollution significantly influences allergenic protein expression, with species- and protein-specific effects resulting from pollutant concentration and exposure time (Frank and Ernst, 2016; Ribeiro et al., 2017). Pathogenesis-related proteins, like Bet v 1, are particularly sensitive, often overexpressed due to various stressors (Midoro-Horiuti et al., 2001; Sinha et al., 2014). Higher pollution levels, including PM_{10} (Ziemianin et al., 2021) and O_3 (Beck et al., 2013), correlate with increased Bet v 1 in birch pollen. Similarly, Cup a 3, a PR-5 protein from *Cupressus arizonica* pollen, shows elevated expression in pollution (Cortegano et al., 2004; Suárez-Cervera et al., 2008). Pollutant impact on allergens varies by species and allergen (Table S1). For instance, O_3 and/or NO_2 fumigation on pollen has diverse effects on grass, ragweed, and birch pollen allergens (Rogerieux et al., 2007; Pasqualini et al., 2011; Cuinica et al., 2014; Ribeiro et al., 2014). Results, however, require careful interpretation due to varied experimental conditions (e.g., pollutant dose, exposure duration). Additionally, in some experiments, whole plants were exposed to high pollutants concentrations (Masuch et al., 1997; Eckl-Dorna et al., 2010; Kanter et al., 2013; Albertine et al., 2014), whereas in others, only freshly collected pollen or pure allergen extracts were considered (Motta et al., 2006; Hong et al., 2018; Galveias et al., 2021a, 2021b; Zhou et al., 2021) (Table S1).

CO_2's effect on pollen allergens was primarily studied in ragweed plants (Choi et al., 2018; El Kelish et al., 2014; Singer et al., 2005). Elevated CO_2 generally raised major ragweed allergen levels and transcripts, with exceptions like Amb a 6 (Choi et al., 2018; El Kelish et al., 2014; Kim et al., 2018; Singer et al., 2005). The only other studies focusing on the effect of CO_2 on pollen allergen content were conducted on *Phleum pratense* (Albertine et al., 2014) and *Quercus acutissima* (Kim et al., 2018). Given the importance of climate change and rising CO_2, the limited studies are surprising.

Other factors, such as heavy metals in the air and soil, could also alter the pollen allergen profile, as observed for *Poa annua* exposed to cadmium-contaminated soils (Aina et al., 2010). In polluted environments, more heavy metals (e.g., lead, mercury, manganese, and iron) get deposited on the pollen grain's surface (Kalbande et al., 2008; Smiljanic et al., 2019). It is suggested that these chemical elements may be absorbed through the microchannels in the pollen wall and further bioconcentrated in pollen grains, leading to distinct changes in pollen metabolism. These changes may, in turn, affect the qualitative and quantitative traits of pollen allergens (Bartra et al., 2007; Mousavi et al., 2019). Pollution modifies allergens through transcriptome, proteome, and metabolome changes, including oligomerization, oxidation, acidification, and nitration (Backes et al., 2021; Franze et al., 2005; Gruijthuijsen et al., 2006; Hong et al., 2018; Rogerieux et al., 2007; Zhou et al., 2021). Although the mechanisms behind these modifications are not fully understood, they modulate allergens recognition and bioavailability. Instantly, after exposure of ragweed pollen to NO_2, a changed nitrosylation pattern of the pollen proteome and increased IgE reactivity, was observed (Zhao et al., 2016). NO_2/O_3 jointly impacted allergens, modifying Pla a 3 (Zhou et al., 2021) and rHum j 1 (Hong et al., 2018) structures, and enhancing IgE recognition (e.g. Group 5) of *Dactylis glomerata* (Galveias et al., 2021a, 2021b). Conversely, *Phleum pratense* pollen exposed to NO_2/SO_2 experienced minimal protein profile change but reduced IgE recognition (Rogerieux et al., 2007). *Aspergillus fumigatus* conidia's allergenicity increased briefly with NO_2/O_3 exposure via nitration, followed by lessened allergenicity due to deamidation

(Lang-Yona et al., 2016).

5.2. Temperature

High temperatures enhance pollen allergenicity in arborescent (Fernández-González et al., 2013b; Ahlholm et al., 1998; Hjelmroos et al., 1995) and herbaceous pollen (Fernández-González et al., 2019a). For instance, Bet v 1's activity during pollen development is positively temperature-regulated, indicating environmental gene control (Tashpulatov et al., 2004). On the other hand, Bet v 1 showed greater response in trees growing in shaded than open areas (Helander et al., 1997). Very high temperatures can degrade allergens; e.g., Bet v 1-homologs from apples and hazelnuts are heat-sensitive. For example, hazelnut allergen activity dropped within 15 min at 100–185 °C (undetectable at 170 °C) (Siekierzynska et al., 2021; Wigotzki et al., 2000).

Temperature likely impacts fungal allergen expression. *A. fumigatus* major allergen (Asp f 1) increased as sporulation temperature decreased from 32 °C to 17 °C, altering IgE binding (Low et al., 2011). Heat shock repressed 11 *A. fumigatus* genes moderately (Fraczek et al., 2011). Conversely, sunlight and UV (254 nm, 0.25–12 h) didn't affect *Alternaria alternata* allergen content (Mitakakis et al., 2003).

5.3. Biotic factors

Pollen's outer layer often features microcavities filled with a diverse coating of lipids and proteins called pollenkitt (Dahl, 2018). This layer plays roles in pollen-stigma interactions, UV protection, and microorganism habitation (Wolters-Arts et al., 1998; Dickinson et al., 2000; Dahl, 2018; Prado et al., 2023). Pollen hosts unique microbial communities, with different species having distinct bacterial and fungal compositions (Manirajan et al., 2018). The microbiome and its bioactive lipids, like lipopolysaccharides (endotoxins) from Gram-negative bacteria or glycolipids from Gram-positive bacteria, influence allergen recognition, impacting the human immune response (Heydenreich et al., 2012; Zasloff, 2017; Manirajan et al., 2022). *Artemisia* pollen's endotoxin induced sensitization and lung inflammation in an animal model (Oteros et al., 2019). As many allergens are PR-proteins (Section 4), interactions with microorganisms can influence allergen expression. The total microbial species on birch pollen correlated with Bet v 1 concentration, but fungal composition didn't correlate with allergenicity (Obersteiner et al., 2016).

Fungi, in turn, can impact pollen allergen degradation. *Fusarium* extract rapidly erased allergen-specific antibodies for Phl p 5, with Phl p 1 detectable until day 15; all allergenic components vanished after 60 days (Hoff et al., 2002). *Alternaria* extract reduced pollen allergen potency (*Cynodon dactylon, Phleum pratense*) after three months at 4 °C and pollen allergen degradation increases with protease-containing extracts (Nelson et al., 1996). *A. fumigatus* allergen gene expression changed in complex ways with macrophage co-culture (Fraczek et al., 2011).

5.4. Other factors

Many other factors, such as oxidative stress, UV, and chemical agents can affect aeroallergens by modifying their expression and stability (Terada et al., 2009; Tammineedi et al., 2013; Wigotzki et al., 2000). Under anoxic conditions and fungal lipid growth as a sole carbon source, *A. fumigatus* allergen-coding genes were moderately induced (Fraczek et al., 2011). However, cultivating fungi (*Alternaria, Ulocladium*) on different growth media showed no expression changes for major allergens (Alt a 1, Ulo c 1) (Pfeiffer et al., 2022). Strong chemical agents like chlorine bleach (NaOCl) or chlorine dioxide (ClO_2) can directly destroy some antigens (Morino and Shibata, 2014; Terada et al., 2009). NaOCl effectively denatured allergenic material of *A. alternata*, *C. herbarum*, and *A. fumigatus* (Barnes et al., 2009; Martyny et al., 2005).

Although, the major allergens belong to one of the most stable pollen proteins (Cabrera et al., 2020), the pollen protein content may markedly decrease over time, even within days (Siriwattanakul and Songnuan, 2014). Dehydrated pollen may, however, maintain its allergenic potency for several years at room temperature; also, the Ig-E binding profiles of old and fresh pollen grains remained similar (Ariano et al., 2006).

It is worth noting, that allergenic proteins are never found in a purified form in the allergen source, but as part of complex particles where lipids (e.g. originated from pollen coat, see Section 5.3.) are also present in high concentrations (Woodfolk et al., 2015). Certain classes of lipids, such as free fatty acids, glycerolipids, glycerophospholipids, and sphingolipids have the inherent capacity to induce and modulate allergic reactions (Bublin et al., 2014). Bioactive lipids can potentially enhance allergenicity by binding to allergens, acting as adjuvants (González Roldán and Duda, 2020). Many allergens, across protein families, feature hydrophobic domains for binding immunomodulatory lipids (Jappe et al., 2019). Examples include Bet v 1-like family, nsLTPs, lipocalins, and oleosins, which co-bind lipid ligands. Pollen coat's strategic location exposes the lipid layer to gaseous pollutants like NO_2 and O_3. While O_3 increases protein allergenicity and impacts lipid composition, the influence of oxidized lipids on allergenicity remains unclear (Farah et al., 2020).

Knowledge gaps and future challenges:

- The pattern of gene expression coding the majority of pollen and fungal spore allergens is not known.
- The impact of pollution on the transformation of fungal allergens is barely studied.
- The stability and lifespan of allergens in natural outdoor conditions have rarely been investigated so far.

6. Allergen release into the environment

6.1. Pollen allergens

To provoke allergy reactions, pollen allergens need to be transferred from the inside of the pollen grain to the outside, and water availability plays a key role in this process. Under aqueous conditions, allergens migrate rapidly to pollen surfaces (Siriwattanakul and Songnuan, 2014; Suarez-Cervera et al., 2005; Vrtala et al., 1993), taking just 30 s for Bet v 4 (Grote et al., 1999). This is linked to initial cytoplasm changes (Vega-Maray et al., 2003). Transport occurs via apertural intine microchannels, shown for Par j 1 (Vega-Maray et al., 2004). The process depends on allergen, dose, and time (Behrendt et al., 1999, 1997; Hoidn et al., 2005; Vega-Maray et al., 2004), differing between species without a common dependence on pH, salt, or osmolality (Hoidn et al., 2005). Less-allergenic proteins release slowly or not at all, unlike major allergens, linked to their solubility in grains (Vrtala et al., 1993).

Under high humidity conditions, pollen can burst, releasing cytoplasmic contents that trigger IgE responses in asthmatics (Galveias et al., 2021a, 2021b; Suphioglu et al., 1992). The allergenicity and quantity of sub-pollen particles released are species-specific, and the combination of these factors determines the level of hazard posed to allergic individuals (Cecchi et al., 2021). Osmotic shock during processes like germination or tube bursting releases fine allergenic particles (Grote et al., 2003; Schäppi et al., 1997; Suphioglu et al., 1992), that can become airborne under the action of dry air, wind and turbulence (Taylor et al., 2004, 2002). Humidity correlates with fine pollen allergen fraction outdoors (Buters et al., 2015), linked to "thunderstorm asthma" where sensitized individuals inhale concentrated allergens (D'Amato et al., 2021; Suphioglu, 1998). This phenomenon, associated with asthma epidemics, results from osmotic shock-released particles concentrated by thunderstorm outflows (Thien et al., 2018). Inhalation of high concentrations of these aeroallergens by sensitized individuals can induce early asthmatic responses with a late inflammatory phase. This phenomenon has been reported in several locations over the last few decades and has a proven association with epidemics of allergic asthma (D'Amato et al., 2007; Emmerson et al., 2021; Price et al., 2021; Suphioglu, 1998; Thien et al.,

2018).

Mechanical forces may also damage the pollen wall: after pollen impaction into physical obstacles, small particles of 1.0–2.5 μm were released. The number of released particles increased with the impaction velocity and with the pollen's water content (Visez et al., 2015). Also, high wind speed provoked a mechanical shock leading to *Ambrosia* pollen grains rupture and enhanced release of allergen-containing sub-pollen particles (Caronni et al., 2021). Finally, air pollution may also cause allergen release and the formation of fine allergen-containing particles (Behrendt et al., 1997; Motta et al., 2006; Shahali et al., 2009). This process resembles that seen during the activation of pollen under humid conditions (Behrendt and Becker, 2001).

6.2. Fungal allergens

Fungal allergens are water-soluble and are easily liberated from spores (Horner et al., 1995; Bouziane et al., 1989). Their release peaks during spore germination (Asturias et al., 2005; Mitakakis et al., 2001). Some, like Alt a 1, aid plant tissue infection and are secreted during colonization (Gómez-Casado et al., 2014). A similar process is supposed to occur during allergic reactions as viable and germinating fungal spores were isolated from nasal cavities (Sercombe et al., 2006). Alt a 1's release depends on pH (5.0–6.5) (Garrido-Arandia et al., 2016), varying among species due to spore wall traits, which can be clinically significant (Horner et al., 1993). Fungal allergen release can also result from spore and hypha fragmentation, akin to pollen (Green et al., 2006a).

Knowledge gaps and future challenges:

- Most of the allergens are glycoproteins (Huby et al., 2000), and are meant for excretion, despite being found in many subcellular spaces (Table 1). Nevertheless, a limited understanding of the mechanisms of regulation of expression and release of the allergens from pollen grains and fungal spores poses a huge limitation in forecasting the variation in airborne allergen concentrations.
- Despite the significant increase in research on the "thunderstorm-asthma" phenomenon, further studies are needed to elucidate its mechanism, e.g. to clarify the role of fungal spores (Dales et al., 2003; Hughes et al., 2022; Idrose et al., 2020).
- The importance of airborne sub-pollen and sub-spore particles as allergy triggers requires clarification.

7. Aeroallergen monitoring

Airborne pollen/fungal spore concentrations have been considered the most feasible proxy of allergen exposure (Baksay et al., 2020; Pfaar et al., 2020), and their quantification can be done by manual (EN 16868:2019; ISO 16000-17:2014; Sarda-Estève et al., 2019; Sarda Estève et al., 2018; O'Connor et al., 2014) or automatic taxonomic identification based on specific morphological or chemical characteristics (Buters et al., 2022; Tummon et al., 2021a, 2021b; Markey et al., 2022). Sensitization occurs through allergen contact with the respiratory system, making pollen/spore counts unreliable indicators of allergenic epitope concentration (Buters et al., 2010; Galán et al., 2013; Moreno-Grau et al., 2006). Allergen content varies greatly between pollen/spores of different years, regions, and cultivars (Buters et al., 2012, 2008; Lara et al., 2023; Ribeiro et al., 2013). Microscopy analyzes only a fraction of samples, leading to mismatches (Galán et al., 2014). Also, non-pollen/spore sources contribute to allergen levels. Hence, screening aeroallergen molecules, not just pollen or spore counts, is crucial. Effective allergen avoidance (Cecchi, 2013) requires detecting inhalant allergens (across particulate matter fractions) and their airborne concentrations swiftly and accurately. Presently, only the information of airborne pollen/fungal spores count, and often forecasting, is available for general dissemination, provided by regional and national monitoring networks (public or private) on several media platforms, complemented by single-image calendars reporting their seasonality (Tummon et al., 2021a, 2021b). Several websites or mobile apps are available that compile this information, allowing in some cases the inclusion of symptom tracking and forecasting (Beggs et al., 2023 and references within), facilitating end-users allergy self-management (Tummon et al., 2021a, 2021b; Beggs et al., 2023).

Airborne allergen detection is crucial for managing and preventing allergic diseases. Immunoassays in molecular aerobiology have been the primary method for exposure assessment. This review found 47 European studies (Fig. 3, Table S2) across 30 locations, with 91 % focused on pollen allergens and only 4 on fungal allergens. Most studies cover 1–2 seasons (35), while 12 span over 3 seasons. Data collection dates back to 1989 (Turku, Finland), but the majority occurred in the last 5 years (2019–2023) (Fig. S1). Studies mainly reported 1–2 allergens, covering 15 different types, with only Alt a 1 from fungi. Commonly studied allergens included Phl p 5 (14), Ole e 1, and Bet v 1 (12 and 10, respectively). Collection employed cascade impactors (e.g. Chemvol, Andersen) or multi-vial cyclone samplers, often quantified using ELISA. Predominantly, the Iberian Peninsula (12 locations) and Central Europe (Southern Germany, Austria, Switzerland, Northern Italy, Eastern France) were studied, leaving many European countries understudied.

7.1. Immunoassays

Airborne allergens are present in the atmosphere in the pg/m^3 to ng/m^3 range, and their measure, being widely accepted, is the use of immunological assays as standard methods for allergen quantification, that requires highly sensitive techniques (Raulf et al., 2014).

ELISA quantifies outdoor and indoor aeroallergen loads effectively (Fernández-González et al., 2019b; Xue et al., 2023). It's widely used for soluble proteins with varied protocols based on purpose or sample type (Hosseini et al., 2018). Sandwich ELISA is preferred for aeroallergens, binding the allergen between non-interfering 'capture' and biotin-labelled 'detection' antibodies. Streptavidin-enzyme conjugates (e.g., HRP, AP) cause color reaction proportional to bound allergen after substrate addition (Zahradnik and Raulf, 2019). Extraction buffer, enzyme conjugate, and substrate choice affect sensitivity (García-Sánchez et al., 2019). Allergens like Amb a 1, Art v 1, Bet v 1, etc., were quantified in total daily ambient air samples or fractions ($>PM_{10}$, $PM_{10–2.5}$, $PM_{2.5–0.12}$) to assess exposure. Allergen content correlated significantly with carrier particle count (Buters et al., 2012; Çelenk, 2019; Feo Brito et al., 2012; Fernández-González et al., 2013a, 2019b; Galán et al., 2013; Grewling et al., 2020a, 2020b).

Halogen Immunoassay (HIA) detects diverse airborne allergens swiftly, including elusive spores, fragments, and particles hard to spot with ELISA (Green et al., 2005a, 2005b, 2006a, 2006b; Rivera-Mariani et al., 2014). HIA uses human serum IgE for immunostaining, allowing fluorescence-confocal microscopy-based identification and quantification of particles (Popp et al., 1988; Rivera-Mariani et al., 2014). HIA combined with field emission scanning electron microscopy (FESEM) enhances microscopic resolution, spotting sub-micrometer immunolabeled particles (Afanou et al., 2015; Sercombe et al., 2006). HIA can address limitations in *Alternaria* spore monitoring (e.g., Galán et al., 2021). However, these methods are costly, time-consuming, lack multiplexing, and hinder continuous allergen content monitoring (Galán et al., 2021; Rivera-Mariani et al., 2014).

7.2. Immunosensors

Efforts in recent years have been engaged towards the development of new tools and analytical methods to improve the precision, specificity, and sensitivity for airborne allergens detection. Immunosensing technology primarily focuses on point-of-care allergy testing, but it also offers potential for direct allergen detection in air samples, although its applications in this area are limited. Immunosensors are a subset of biosensing technologies, compact and integrated devices that detect specific biological targets like allergens (Bhalla et al., 2016). By

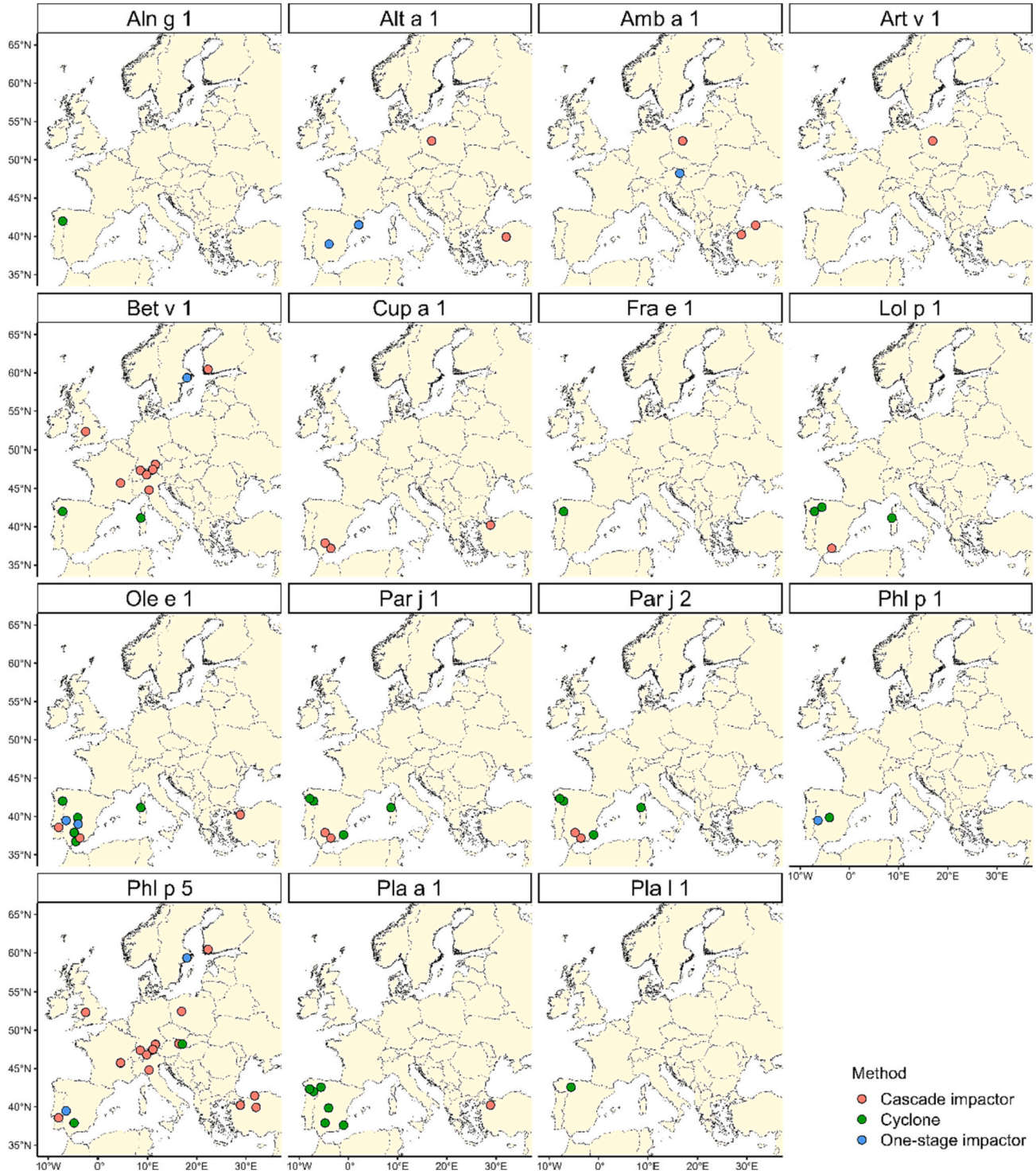

Fig. 3. Location of sites with continuous molecular monitoring of pollen and fungal spores allergens in outdoor air of Europe.

combining a biological recognition component with a transducer, they generate a measurable signal proportional to the target's concentration (Bhalla et al., 2016). Notably, piezoelectric immunosensors (e.g., QCM), surface acoustic wave SPR immunosensors, and DNA-based biosensors have been explored for aeroallergen detection.

In real-time detection, a surface plasmon resonance system achieved a 5 ng/ml sensitivity for airborne *Cryptomeria japonica* pollen allergens (Cry j 1), with 30-min determination of airborne allergen concentration (Takahashi et al., 2001). Similarly, Kim et al. (2016) developed a nanomaterial-based biosensor using carbon nanotube field-effect transistors (CNT-FETs) for real-time capturing and monitoring of *Aspergillus niger* and *Alternaria alternata* allergens. This approach integrated sensor-cooling and microfluidics for device maintenance, although it primarily targeted fungal fragments rather than spores or hyphae.

Aptasensors, a type of DNA-based biosensors, utilize DNA/RNA aptamers in place of antibodies as the recognition unit (Toh et al., 2015). These synthetic single-stranded sequences (25 to 90 nucleotides) fold into specific secondary structures, exhibiting high specificity and affinity for various molecules. Aptamers offer advantages such as greater

binding efficiency due to increased surface density, less spatial blocking, and stability across temperatures and storage conditions (Toh et al., 2015). While initially applied to indoor allergen detection like *Aspergillus fumigatus* Asp f 1 (Low et al., 2009) and *Dermatophagoides pteronyssinus* Der p 2 allergens (Shen et al., 2017), the potential for outdoor allergen detection was demonstrated with Cry j 2 (Chang et al., 2019; Ogihara et al., 2015). Although aptasensors are relatively new for complex air samples, their promising outcomes highlight their utility for both indoor and outdoor allergen detection.

Knowledge gaps and future challenges:

- The number of studies focusing on pollen allergens highly surpasses those on fungal spores, hampering the knowledge of real fungal allergen exposure and its correlation with spore counts in different biogeographical areas.
- Further comprehensive studies are needed to assess the potential of specific antibodies detecting other allergens from the same protein family with sequence similarities and high levels of structural homology, e.g. the case of Bet v 1 antibodies to detect Aln g 1 allergens in the atmosphere (Fernández-González et al., 2020a) and how this particularity could impact the detection of plant/fungal species with concomitantly occurring seasons.
- Improve allergen monitoring resolution towards multiplex detection and/or real-time detection. Immunosensing technology development can become a state-of-the art alternative assay. Still, they lack the robustness and stability necessary for operational field deployment.

8. Aeroallergen health risk-assessment

Proper health-risk assessment for aeroallergens, like other air pollutants, involves two main steps: estimating exposure patterns and health impact and identifying impacting allergens. Exposure calculation relies on detailed data about allergen distribution, source inventory, and factors influencing allergen behavior (Sections 2, 5, and 6), supported by monitoring networks (Section 7). To assess allergy risk, information about both allergen exposure and associated sensitization and symptom patterns is crucial. Unlike pollutants, allergen dose-response relationships are underdeveloped. Thresholds for outdoor aeroallergen-induced symptoms and inflammation are yet to be established, currently limited to proxy pollen/spore counts (de Weger et al., 2013). Large-scale studies, like the Patient's Hayfever Diary data (Karatzas et al., 2014), show symptom scores correlate well with pollen counts, but vary across seasons, years, and countries (Bastl et al., 2020). This variability is due to factors like season and species-specific allergenicity (Buters et al., 2008; Buters et al., 2015; Grewling et al., 2020a, 2020b; Jung et al., 2018; Galán et al., 2013) and the priming effect.

The link between aeroallergens and symptoms has long posed a diagnostic challenge in seasonal allergies. Initial diagnosis involves atopy tests (skin prick test (SPT) and serum allergen-specific (s)IgE) (Ansotegui et al., 2020; Heinzerling et al., 2013). Nevertheless, the positivity of either test only denotes sensitization (presence of sIgE) which often does not translate into airway allergy (Cardona et al., 2018; Klimek et al., 2020). Of note, many atopic patients with asthma do not experience symptoms upon exposure to the allergen they are sensitized to (atopic non-allergic patients). Thus, the assessment and identification of clinically relevant sensitizations represent a main challenge in the clinic and are usually based on either the clinical history or using allergen challenges (Agache et al., 2022; Augé et al., 2018). The former might suffice in patients with intermittent or persistent mild symptoms (e.g. seasonal symptoms in a patient sensitized to a perennial allergen rules out the need of allergy diagnosis), whereas the latter is commonly required for individuals with persistent moderate-to-severe disease (Testera-Montes et al., 2021). Clinically relevant sensitization patterns can be identified by allergen provocations, i.e.: i) in vivo, e.g. by the SPT, the nasal or bronchial allergen challenges (Agache et al., 2022; Augé et al., 2018; Eguiluz-Gracia et al., 2019; Eguiluz-Gracia et al., 2021), ii) ex vivo with basophil activation test (BAT) using flow cytometry to measure peripheral basophils' activation after incubation with an allergen of interest (Eguiluz-Gracia et al., 2020; Hemmings et al., 2018), and iii) in vitro basophil (BAT) and a mast cell activation test (MAT) (Antunes et al., 2017; Buters et al., 2012; Santos et al., 2018). In vivo allergen provocation represents the gold standard for airway allergy diagnosis. Nevertheless, these are laborious procedures requiring technical resources and trained personnel (Agache et al., 2022; Augé et al., 2018). In addition, despite being a relevant tool in allergy diagnosis, ethical issues may arise for determining the allergen thresholds and the dose-response relation and identifying unknown allergens, limiting its broader application in research. Compared to immunoassays, the BAT and MAT inform about the presence and functionality of allergen-specific IgE and constitute a safe and useful tool to assess clinically relevant sensitization in airway allergy without raising the ethical issues associated with the in vivo testing (Ansotegui et al., 2020; Santos et al., 2018). The relevance of identifying the allergic triggers of airway diseases relies on the possibility of further implementation of specific interventions (e.g., allergen immunotherapy), which are only effective in bona fide allergic individuals.

Knowledge gaps and future challenges:

- Despite having a wide range of allergen monitoring and exposure data, thresholds and biological dose-response to aeroallergens are not really known, hampering the allergy risk assessment and forecast;
- In vitro systems capable of a specific allergen-induced mediator release may be a tool to safely assess the dose-dependent effect of known allergens and identify new allergens in the future.

9. Conclusions

Current knowledge on important outdoor sources of inhalant aeroallergens - pollen grains and fungal spores and their distribution were addressed using Europe as an example. Major allergenic plants and fungal spores are well identified, e.g. grasses, birch, hazel, alder, olive, ash, *Parietaria* spp., ragweed or mugwort, *Alternaria* spp. and *Cladosporium* spp. However, precise source area distribution is still often lacking for pollen, with a manifest deficiency in urban environments, while for fungal spores is limited to large-scale presence-absence maps of *Alternaria* spp. and *Cladosporium* spp. Source distribution needs to be quantified with greater spatial detail, particularly at the urban and near-urban scales, where most of the population suffering from allergies inhabit. For fungal spores, detailed information is completely missing.

The major allergens of pollen grains and fungal spores belong to a relatively small number of protein families with molecular weight from 10 to 80 kDa: pathogenesis-related protein families (PR-proteins), calcium-binding proteins (CBPs), profilins, enzyme inhibitors, transport proteins, enzymes from several catalysis groups and regulatory proteins. Many exhibit high levels of structural homology responsible for inter-species IgE cross-reactivity. In pollen, they are located intracellularly, mainly related to protein metabolism areas, in the exine and intine, or in pollensomes released during pollen germination and tube growth. Other plant parts, such as the orbicules, are also allergen carriers. In fungi, allergens are mainly found in the melanin layer of the spore's cell wall and the cytoplasm of the hyphae. Knowledge of precise production, storage sites and the abundance and allergenic significance of other aerosolized vegetative parts of plants or hyphal fragments needs to be determined. Furthermore, a lack of sufficient understanding regarding the differences in allergenicity among protein family members and the cross-reactivity between protein families can impede the diagnosis and treatment of allergies. Many plant taxa with suspected immunogenicity are starting to emerge, and exact information on their relevance in allergy is absent.

To provoke allergy reactions, allergens must be released from pollen grains and fungal spores. Hydration is critical, and elution profiles have

been reported to be allergen-, dose-, time and medium-dependent. For fungal spores, germination is the predominant pathway. Osmotic and mechanical shocks are also pointed responsible for allergen released. Knowledge gaps concerning the regulation of expression and allergens release mechanisms, the so-called "thunderstorm asthma" phenomenon and the role of airborne sub-pollen and sub-spore particles in allergy triggering and exacerbation need clarification. In addition, throughout allergens' life cycle, their bioavailability (abundance, structure, solubility and stability) is impacted by abiotic and biotic stressors, influencing expression, transformation, and degradation. Air pollution has been the most studied factor, reported to induce transcriptome, proteome, and metabolome changes, which may alter allergen structure and cause modifications like oligomerization, oxidation, acidification, and nitration. The pattern and mechanisms behind these modifications still need to be fully understood, as it has been pointed out to be species- and protein-dependent according to the pollutant concentration and exposure duration. For fungal spores, this subject has been poorly addressed. The influence on allergen bioavailability, particularly in its stability and lifespan in outdoor conditions, of the developmental stage, oxidative stress, growth medium, high air temperature, UV, emergent chemicals and association or binding of bioactive lipids acting as adjuvants to allergens remains poorly investigated. More recently, attention has been drawn to the pollen microbiome, but it is still not understood how it can determine the recognition of otherwise innocuous proteins as allergens.

Outdoor pollen allergens have been monitored in several parts of Europe, particularly in the last five years, but few included analysis of fungal spores, and knowledge of the real fungal allergen exposure is missing. Sampling equipment has been cascade impactors of different types or a multi-vial cyclone sampler followed by ELISA for quantification. Technological developments seeking higher precision, specificity, and sensitivity for detection have been engaged, such as biosensing technologies and further experiments are needed to consider them as substitute assays. Also, knowledge concerning the potential of specific antibodies detecting other allergens and exploring multiplex and/or real-time allergen detection are future challenges that will undoubtedly improve allergy management.

Finally, sensitization patterns and airway allergy diagnosis have been well characterized by allergen provocation tests. However, allergen dose-response functions have not been developed, so threshold values for allergy symptoms are difficult to be established. Scientific developments on this subject are critical and prone to benefit aeroallergen risk assessment and forecast, and in vitro systems could be an alternative to assess the dose-dependent effect of known allergens and identify new allergens.

CRediT authorship contribution statement

Łukasz Grewling: Conceptualization, Formal analysis, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Methodology. **Helena Ribeiro**: Conceptualization, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Term. **Celia Antunes**: Conceptualization, Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Visualization, Methodology, Term. **Godfrey Philliam Apangu**: Writing - Review & Editing. **Sevcan Çelenk**: Writing - Original Draft, Writing - Review & Editing. **Ana Costa**: Formal analysis, Investigation, Visualization. **Ibon Eguiluz-Gracia**: Formal analysis, Writing - Original Draft, Writing - Review & Editing, Term. **Ana Galveias**: Formal analysis, Writing - Original Draft, Writing - Review & Editing, Investigation, Visualization. **Nestor Gonzalez Roldan**: Writing - Original Draft, Writing - Review & Editing, Term. **Mirela Lika**: Formal analysis, Writing - Review & Editing. **Donát Magyar**: Conceptualization, Formal analysis, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization, Term. **Moises Martinez-Bracero**: Formal analysis, Writing - Original Draft, Writing - Review & Editing, Data Curation. **Pia Ørby**: Conceptualization, Writing - Original Draft, Writing - Review & Editing, Term. **David O'Connor:** Writing - Review & Editing. **Alexandra Marchã Penha**: Formal analysis, Investigation, Visualization. **Sónia Pereira**: Formal analysis, Investigation. **Rosa Pérez-Badia:** Formal analysis, Writing - Original Draft, Writing - Review & Editing, Term. **Victoria Rodinkova:** Conceptualization, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Term. **Merita Xhetani**: Formal analysis, Writing - Review & Editing. **Ingrida Šauliene**: Formal analysis, Writing - Review & Editing. **Carsten Ambelas Skjøth**: Conceptualization, Formal analysis, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Funding acquisition, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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