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Review article

Allergenic pollen and pollen allergy in Europe

The allergenic content of the atmosphere varies according to climate, geography and vegetation. Data on the presence and prevalence of allergenic airborne pollens, obtained from both aerobiological studies and allergological investigations, make it possible to design pollen calendars with the approximate flowering period of the plants in the sampling area. In this way, even though pollen production and dispersal from year to year depend on the patterns of preseason weather and on the conditions prevailing at the time of anthesis, it is usually possible to forecast the chances of encountering high atmospheric allergenic pollen concentrations in different areas.Aerobiological and allergological studies show that the pollen map of Europe is changing also as a result of cultural factors (for example, importation of plants such as birch and cypress for urban parklands), greater international travel (e.g. colonization by ragweed in France, northern Italy, Austria, Hungary etc.) and climate change. In this regard, the higher frequency of weather extremes, like thunderstorms, and increasing episodes of long range transport of allergenic pollen represent new challenges for researchers. Furthermore, in the last few years, experimental data on pollen and subpollen-particles structure, the pathogenetic role of pollen and the interaction between pollen and air pollutants, gave new insights into the mechanisms of respiratory allergic diseases.

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Pollen allergy has a remarkable clinical impact all over Europe, and there is a body of evidence suggesting that the prevalence of respiratory allergic reactions induced by pollens in Europe has been on the increase in the past decades (1–6). However, recent findings of the phase three of the International Study of Asthma and Allergies in Children (ISAAC) study showed the absence of increases or little changes in prevalence of asthma symptoms, allergic rhinoconjunctivitis and eczema for European centres with the existing high prevalence among the older children (7). The prevalence of pollen allergy is presently estimated to be up 40%. Exposure to allergens represents a key factor among the environmental determinants of asthma, which include air pollution (8). Since airborne-induced respiratory allergy does not recognize national frontiers, the study of pollinosis cannot be limited to national boundaries, as obviously happens with most diseases that can be prevented by avoiding exposure to the causative agent. In Europe, the main pollination period covers about half the year, from spring to autumn, and the distribution of airborne pollen taxa of allergological interest is related to five vegetational areas (Table 1).

Table 1. Vegetational areas and prevalent distribution of allergenic plants in Europe

Arctic: birch
Central: deciduous forest, birch, grasses
Eastern: grasses, mugwort, ragweed
Mountains: grasses (with a pollination season delayed by three-four weeks in comparison with areas at sea level).
Mediterranean: *Parietaria*, olive trees, grasses and also cypress.

Up to date on allergenic pollen in Europe

Gramineae

Grass pollen is the major cause of pollinosis in many parts of the world (9). Although its frequency differs regionally, grass-induced pollinosis is the most common pollen allergy also in Europe. Up to 95% of patients allergic to grass pollen possess IgE specific for group 1 allergens and 80% for group 5 allergens, the two groups that constitute the major grass-pollen allergens (10).

The antigens of grass pollen, like those of the other allergenic pollen grains, are rapidly released when allergen-carrying pollen comes into contact with the oral, nasal, or eye mucosa, thereby inducing the appearance of hay-fever symptoms in sensitized patients. As a consequence, the concentration of airborne grass pollen influences the degree of symptoms in pollinosis patients. In London (UK), the lowest atmospheric concentration of grass pollen able to induce the apparance of hay-fever symptoms was shown to be 10–50 grains/m3 (11).

In Cardiff (Wales), 10% of pollinosis patients experienced symptoms in the presence of 10 grass-pollen grains/m3, and again in London a concentration of more than 50 grains/m3 induced symptoms in all pollinosis patients (12). In Bilbao (Spain), 100% of pollinosis patients experienced symptoms when the pollen count was above 37 grass-pollen grains/m3 (13). In Turku (Finland), a count of less than 30 grass-pollen grains/m3 was significantly correlated with nasal symptoms at the start of the grass-pollen season (14).

The grass family (Gramineae) comprises more than 600 genera and over 10 000 species, of which more than 400 herbaceous, wind-pollinated plants are found in Europe (15). The most abundant airborne grass pollen originates from tall meadow grasses such as timothy (*Phleum pratense*), orchard grass (*Dactylis glomerata*), or meadow foxtail (*Alopecurus pratensis*). Cultivated rye (*Secale cereale*), which has remarkably high pollen production, is another potent source of allergens (16). However, with very few exceptions, all grass- pollen types show a very high degree of cross reactivity (17, 18).

In northern, central and eastern Europe the main grass flowering period starts at the beginning of May and finishes at the end of July. In the Mediterranean area, flowering usually starts and ends 1 month earlier (19). Pollination occurs about 2–3 weeks earlier at sea level than in mountainous regions. As mentioned above, pollen season tends to vary from year to year because of fluctations in climatic factors, but maximum atmosperic concentration of grass pollen usually occurs 1–2 months after the start of the main flowering season. On the whole, in Europe, grass flowering notoriously peaks in June.

Notwithstanding a decreased annual total grass-pollen count, probably because changes in agricultural practices and land use have led to a reduction in grasslands, the frequency of allergic sensitization to grass pollen does not seem to be decreasing (20). Grass allergens induce mostly nasal and conjunctival symptoms. Djukanovic et al. (21) provided evidence that natural exposure to grass pollen may exacerbate asthma, and, so, induce an inflammatory response involving T cells, mast cells and eosinophils.

Trees

The most allergenic tree pollen is produced by birch (*Betula*) in north, central, and eastern Europe, and by Olive (*Olea europaea*) as also cypress (*Cupressus*) in the Mediterranen regions.

Fagales. As in the grass family, there are high levels of allergenic cross-reactivity between the representative plants of the genera of the order Fagales (22). This order comprises three families: Betulaceae, including the genera *Betula* (birch) and *Alnus* (alder); Corylaceae, including the genera *Corylus* (hazel), *Carpinus* (hornbeam), and *Ostrya* (hopbeam); Fagaceae, including the genera *Quercus* (oak), *Fagus* (beech), and *Castanea* (sweet chestnut).

Birch is the major pollen-allergen-producing tree in northern Europe (23). In western Europe, the main flowering period usually starts at the end of March, and in central and eastern Europe, from the beginning to mid-April. Going northward, the flowering season starts, depending on the latitude, from late April to late May (northern Europe) (19, 24). Pollen values peak 1–3 weeks after the start of the season. The duration of the main season is remarkably dependent on temperature and thus varies from 2 to as much as 8 weeks. Far shorter or longer periods, with yearly alternating low and high pollen production, has been observed in various European regions (25).

The Corylaceae trees, hazel and alder, are the first (December–April) to shed pollen in the outdoor air in Europe, followed by birch, hornbeam and hop hornbeam. As a consequence of this early pollination and of allergenic cross-reactivity, hazel and alder can act as primers of allergic sensitization to betulaceae pollen allergens, so that clinical symptoms become more marked during the birch-pollen season.

Similarly, the onset of the oak season in spring, shortly before the beech-pollen season, which is usually quite mild, can prolong the birch season in western, central, and eastern Europe. Sweet-chestnut pollen appear in June

and July in western and central Europe in the mountainous areas of southern Europe. In the central Alpine regions, the highest concentrations of *Alnus viridis* pollen are found at the end of May and in early June (19, 24).

Birch, followed by alder and hazel, has the greatest allergenic potency in this group of allergenic trees. In Europe, the percentage of subjects with a positivity skin prick test to birch allergens range from 5% in The Netherlands to 54% in Zurich (Switzerland). In recent years, the popularity of *Betula* as ornamental plant loved by architects, particularly in northern Italy, has caused a significant increase in allergic sensitization to this allergen (26–28). In a large study of cross-sensitization between allergenic plants in adult patients with asthma or rhinitis, Eriksson and Holmen (15) found that sensitization to birch pollen allergens was frequently associated with other allergens, that it induced mostly nasal symptoms, and that respiratory symptoms started at about 30 years of age. The Eriksson and Holmen study did not confirm the report by Bjorkstén et al. (29) of a correlation between the birth during the months of *Betula* flowering and the subsequent development of respiratory allergy to the same pollen.

Oleaceae. Olive (*Olea europaea*) pollen is considered as one of the most important causes of respiratory allergic disease in the Mediterranean region. In Spain (30), southern Italy (31), Greece (32) and Turkey (33), olive pollen is an important cause of pollinosis. The main pollen season is from April to June. The frequency of olive-induced pollinosis is increasing as a consequence of improved diagnostic procedures and as a result of changes in farming pratices (34) It is of interest that ecoenvironment and crop management are factors able to induce allergological changes, in different varieties or cultivars of olive tree (35).

Olea europaea pollinosis is clinically characterized by rhinoconjunctival symptomatology than bronchial asthma. Moreover, polysensitization to olive pollen is more frequent than monosensitization (34, 36).

In sourthern Italy, the frequency of positivity to *Olea* pollen allergens among all skin prick test-positive patients is 13.49% in adults and 8.33% in children (37). In pollinosis patients of the Naples area, monosensitization to olive was identified in only 1.33% of children and in 2.28% in adults; in all the remaining patients, sensitization to olive pollen was associated with other allergens, mainly derived from pollen grains (34). Interestingly, children and adults with monosensitization to olive and living in the Naples area are frequently affected by year-long symptoms that usually do not increase during the olive-pollen season. A similar finding has recently described in Spanish (30) and Turkish patients (33).

Pollen from other species of the Oleaceae family, e.g. *Fraxinus excelsior* and *Ligustrum vulgare* rarely induce allergic respiratory symptoms (38, 39).

Cupressaceae. The genus *Cupressus* is widely spread in Mediterranean area, where the most common species are *C. sempervirens*, *C. arizonica*, *C. macrocarpa* and *C. lusitanica*. Cypress releases an enormous amount of anemophilous pollen and it has been recognized to be responsible for a large part of total annual amount of airborne pollen in several Mediterranean areas. In the city of Cordoba, southern Spain, Cupressaceae pollen represents at least 30% of the total pollen count during the winter season (40), whereas in Italy and Albania it reaches 20–40% of annual pollen rain (41, 42) In last decades, Cupressaceae pollen has been identified as source of increasing pollinosis in Mediterranean countries such as France (43, 44), Israel (45) Spain (46) and Italy (47, 48). It is also responsible for winter pollinosis in a period of the year when no other allergenic plants are flowering (49, 50).

The period of cypress pollination may last more than 1 month, because of the gradual mechanism of microsporophyllous maturation (from the bottom to the top of the flower) and furthermore because pollination shows an high variability from year to year, depending on meteorological factors (51). Calleja and Farrera (44) showed that the dates of maximum pollination differed by up to 29 days and precocity in pollination seems to run parallel to ongoing global warming. This phenological characteristicts make cypress allergy tricky to treat, due to difficulties in identifying start and duration of pollen season (52).

It should be noted that a high cross-reactivity exists within cupressacace family (*Cupressus, Juniperus* and *Cryptomeria*) and between Cupressacae and Taxacee (53–56) which have quite different pollination seasons, overlapping or preceding the cypress pollination period. This observation is of clinical importance, where cross-reacting and earlier flowering plants (*C.arizonica* is one of the most spread in several European areas) are well represented.

The sensitization rate to Cupressaceae pollen antigens is highly variable depending on the population under study and on the exposure level. While in the general population it goes from 2.4 to 9.6%, the rate is much higher in pollinosis patients, being over 30% in some areas (57). The increasing epidemiological impact of pollinosis induced by Cupressaceae plants is probable related to several factors: an increasing use of *C. arizonica* extracts (easier to prepare and chimically more stable specially in solution than *C. sempervirens* extracts (58) and a better awarness to this allergy, that could be mistaken for viral infections due to its late winter occurrence.

A large French study showed that cypress allergy is characterized by higher prevalence of dry cough and a lower prevalence of conjunctivitis compared with grass pollen allergy (59). However, asthma prevalence in sensitized patients seems to be very low (60).

The latest clinical trials on efficacy of immunotherapy in cypress allergy, using standardized extracts, have led to

significant improvements, using both the subcutaneous and the sublingual routes. However, the effects of specific immunotherapy should be further exploited (57).

Weed

Urticaceae. *Parietaria* is the main allergenic genus of the Urticaceae (nettle) family. The most important species are *Parietaria judaica* and *Parietaria officinalis*. The major allergens of both species are small glycoproteins with molecular weights ranging between 10 and 14 kDa, with high cross-reactivity (61). Recent findings showed that P judaica pollen contains an aminopeptidase which is able to disrupt epithelium barrier, enhancing the delivery of allergenic protein to dendritic cells (62).

Parietaria judaica grows mainly in coastal Mediterranean areas, but has also been found in the UK (63). *Parietaria* pollen varies greatly according to the geographic area.

Pollinosis caused by *Parietaria* is less frequent before the age of 10 years (64–66).

The highest frequency of pollinosis caused by *Parietaria* occurs in subjects aged 10–30 years and is more frequent in population of coastal towns than in those living in rural, noncoastal areas. In Europe (67, 68) and the USA (69), there is a greater frequency of reactivity to *Parietaria*.

The extraordinarily long persistence in the atmosphere of *Parietaria* pollen in the Mediterranean area is responsible for a multiseasonal symptomatology (70). In some areas, like southern Italy, some patients have year-long symptoms.

In a retrospective cohort study, sensitization to *Parietaria judaica* markedly increased the risk of developing asthma, while no associations were shown for sensitization to house dust mite and other pollens (71).

Bronchial asthma or its equivalents, such as cough (severe in some cases) associated with rhinoconjunctivitis, is present in 52% of the monosensitized *Parietaria* patients in central and southern Italy, reaching a peak of 60% in Naples and Rome (72).

Although the correlation was not significant, a higher number of *Parietaria*-monosensitized subjects living in the Naples area were born during the *Parietaria* pollen season and underwent an early exposure to the allergens released by this pollen (66).

The frequency of positivity skin prick test to various types of pollen grains (particularly those of *Parietaria* spp) implicated in pollinosis symptoms in atopic subjects has increased in the Naples area during the last 15 years (72). Severe oral allergy symdrome after the ingestion of pistachio nuts was described in two patients with monosensitization to *Parietaria* and a slight degree of cross-reactivity between *Parietaria* allergens and the pistachio nut was detected in both cases (73).

The treatment of *Parietaria* hay fever is often a frustrating experience for both patients and clinicians because of the prolonged persistance of this pollen in the atmosphere. However, an increasing body of evidence support use of sublingual specific immunotherapy for subjects with symptoms due to *Parietaria* pollen (74, 75). The recent identification of an hypoallergenic fragment of Par j 2, able to upregulate natural immunity receptors (Toll-like receptors) and increase INFγ might disclose new perspectives for immunotherapy (76).

Compositae. The Compositae (Asteraceae), is one of the largest plant families with almost 20 000 species. Ragweed (*Ambrosia*) and mugwort (*Artemisia*) are the most involved in pollenosis The most common species of *Artemisia* are *A. vulgaris* (mugwort), which grows throughout Europe, and *A. Annua* and *A. verlotorum,* which grow mainly in southern Europe. Mugwort is present in both urban and suburban areas. It flowers from late July to the end of August in northwest Europe.

The genus *Ambrosia* (A.), which includes both *A. artemisiifolia* (short or common ragweed) and *A. trifida* (giant ragweed) has long been recognized as a significant cause of allergic rhinitis. A large random skin test survey demonstrated that 10% of the US population was ragweed-sensitive (77). More recently, *Ambrosia* pollen levels were significantly related to asthma and rhinitis in a study based on a symptoms diary and peak expiratory flow rates (78).

The pollen of *A.artemisiifolia* is produced in enormous amounts and one single plant alone may produce millions of pollen grains. Since the pollen grains are small (18–22 μm) they are often involved in episodes of long distance transport (79).

The most representative species, *A.artemisiifolia*, was first signalled in Europe in 1960 (80) and ragweed pollen is increasingly important from an allergological point of view in parts of Central and Eastern Europe. Its distribution covers the area at medium latitude characterized by continental climate and it started its expansion from Hungary, the most ragweed-polluted country (81), Croatia (82), certain areas of France (83) and Italy (84). Furthermore, ragweed has been also detected in Bulgaria (85), Austria (86), Switzerland (87), Czech Republic (88), Slovak Republic (89), Sweden, (90) and Poland (91).

Ragweed and mugwort have nearly identical flowering seasonal periods and high degree of cross-reactivity. In a recent study was shown that patients with both ragweed and mugwort IgE reactivity on RAST and/or skin prick tests are actually co-sensitized. This observation is of clinical relevance especially in patients for whom specific immunotherapy is indicated (92). A large cross-reactivity between short and giant ragweed is also well known. However, recent data suggest the two plants are not allergenically equivalent. Due to this, in subjects sensitized to ragweed, diagnosis and eventually immunotherapy

should be performed according to type of pollen species present in that specific area (93).

Pollens from ornamental plants

In the last decades, the increased use of ornamental plants in parks and gardens, public and work places and houses provided new sources of aeroallergens.

The first report of weeping fig (*Ficus benjamina*) allergy in plants keepers was published about 20 years ago (94). Since then, several cases were also reported among general population and non-atopic subjects (95, 96) and in a series of 2662 patients with a positive skin test to any aeroallergens the 2.5% reacted with *Ficus benjamina* (97). Recent findings showed the source of allergen to be in sap (98). A Ficus-fruit (i.e. fig and other tropical fruits) syndrome was identified in which *Ficus benjamina* latex is the cross-reacting allergen (99).

In a population of 59 subjects with persistent rhinitis and exposed to indoor decorative plants in the domestic environment 78% were sensitized to at least one ornamental plant (weeping fig, yucca, ivy, palm tree and geranium) (100). Authors suggest indoor plants have to be considered as potential allergens causing perennial rhinitis and they should be included into the standard skin prick test panel in exposed patients.

Allergenic pollen in the Mediterranean area

Because of its climatic conditions, characterized by mild winters and sunny days with dry summers, the vegetation of the Mediterranean area is different from that of central and northern Europe. Allergenic-pollen-producing plants typical of the Mediterranean climate are *Parietaria,* Olive and Cupressaceae. However, during the last 30 years or so, aerobiological and allergological studies have been developed rapidly in most parts of Europe and also in the Mediterranean area. This has led to an increased density of observational networks of pollen-counting stations, and also to the need for multilateral exchange and cooperation in aerobiological and allergological studies.

Aerobiological sampling of the pollen content of the atmosphere of various Mediterranean cities has made it possible to identify three pollen seasons (15, 101, 102):

1. A low winter pollen season (from December to the end of March) marked by the presence of the pollens of such trees as Cupressaceae (*Cupressus* and *Juniperus*), Corilaceae (Hazel), Acaciae (*Mimosa*) and some Betulaceae.
2. A high spring-summer pollen season (April–July), of marked allergological interest, dominated by the pollination of Grasses, *Parietaria* and *Olea* (Olive). Partly overlapping with this season, from March to May, *Platanus* flowers have some allergenic importance in some Mediterranean areas as Southern France, Spain etc.
3. A summer–autumn season (August–October) marked by the second, less pronounced, peak of *Parietaria* and sometimes of Gramineae and the pollens of herbaceous plants, such as mugwort (*Artemisia*) and Chenopodiaceae.

Grass pollen is by far the most important cause of pollinosis throughout the European continent, including the Mediterranean area. Between 8% and 35% of young adults in countries of the European Community show IgE serum antibodies to grass pollen allergens (103). It is interesting to note that in various European cities the atmospheric concentration of grass pollen is decreasing (101, 104) while the prevalence of allergic rhinitis and allergic asthma is increasing,. The decrease in grass pollen concentrations has been attributed to substantial decrease in grassland over large areas of the continent. In fact, the last 30 years have seen a reduction in grassland of about 40% (104). However, the observation that cases of allergic rhinitis and asthma induced by grass pollen are increasing is probably related to various factors, including increased air pollution (34, 104, 105).

Parietaria is a genus of the Urticaceae family, and *P. officinalis* and *P. judaica* are the most common allergenic species of this genus.

Parietaria judaica grows in coastal Mediterranean areas such as Spain, southern France, Italy, Yugoslavia, Albania, Greece.This allergenic plant, which is responsible for many cases of severe pollinosis, has two very long flowering periods. Its pollen appears first at the beginning of the spring and persists during the spring and summer months, often reaching a peak level with daily mean values of more than 500 pollen grains per cubic meter of air at the end of April or in May, depending on the climate of the area. A shorter pollination period is observed from the end of August–October.

In the Oleaceae family, the most allergenic pollen is produced by *Olea europaea*, the olive tree, which in the Mediterranean area has been recognized as being one of the most important causes of seasonal respiratory allergy (53). The olive pollination season lasts from April to the end of June and sometimes causes severe symptoms (oculorhinitis and/or bronchial asthma). Olive tree, like birch, has reproductive rhythms of high and low years for the abundance of pollen and subsequent seed. The alternating patterns may be modified or even obscured by the influence of weather during the times of pollen formation and dispersal.

Sensitization to pollen allergens of *Olea* is often associated with other atopic sensitizations such as allergy to grasses and it is frequently difficult to know whether sensitization to grasses or to Olive prevails.

Another interesting aspect of olive allergy is that in subjects with sensitization to the allergens of this pollen the clinical symptoms are frequently not limited to the pollination season (May–June) but are unaccountably present all year round.

As for birch, which is the most potent of the pollen-allergen-producing trees in northern Europe, this arboreal plant is spreading down into the Mediterranean area.

For example, birches are becoming increasingly abundant in northern Italy where landscape artists tend to use them in new urban parks. The typical peaks of birch pollens are recorded in northern Europe during May, whereas in sourthern Europe the birch pollen concentration generally peaks in April. This tendency for spring-pollinating plants, like birch and grass, to flower earlier in the warmer southern regions of Europe is reversed for the autumn-pollinating types such as mugwort (101).

Cypress pollination is characterized by a wide variability with very high concentrations in Mediterranean coastal areas, where it frequently induces rhinoconjunctivitis. This pollen taxon is the most common airborne allergen of the winter months in some Mediterranean cities.

The increasing epidemiologic impact of pollinosis induced by Cupressaceae plants is related to the increasing use of these species for gardening and reforestation (106). So again, as with birch, we have a case of fashion influencing the epidemiology of pollen-induced disorders.

Pollen grains from herbs like mugwort (*Artemisia*) and Plantain (*Plantago*) are of limited but, nevertheless, real clinical importance. Mugwort in particular has a marked sensitizing capacity. In the same Compositae family of mugwort, we also find ragweed (*Ambrosia*), which is colonizing Europe, and not only Central Europe, but also some parts of the Mediterranean area such as northern Italy.

Advances in the pathogenetic role of pollen and air pollution

In the context of allergy, pollen grains have been simply regarded as allergen carriers, and little attention has been devoted to the nonprotein compounds of pollen. However, individuals are rarely exposed to pure allergens, but rather to particles releasing the allergen, such as pollen grains or pollen-derived granules (107–109). Notably, lipids are major components of pollen exine and exsudate (108). In addition, long chain unsaturated fatty acids in pollen, such as linolenic acid, serve as precursors for the biosynthesis of several plant hormones, such as dinor isoprostanes, recently termed phytoprostanes. These phytoprostanes are formed non-enzymatically via autooxidation in plants and structurally resemble prostaglandins and isoprostanes in humans (110–112). Recent results suggest that phytoprostanes might have an evolutionary ancient function in plant host defense (113, 114). Whereas the physiological role of phytoprostanes in the life cycle of plants is just beginning to emerge, virtually nothing is known about their effects on the human immune response in health and disease. It has been demonstrated recently that pollen grain, under physiological exposure conditions, releases not only allergens but also bioactive lipids that activate human neutrophils and eosinophils *in vitro* (115–117). Moreover, intact grains of pollen induce activation and maturation of dendritic cells *in vitro*, suggesting that pollen can act not only as allergen carrier but also as an adjuvant in the induction phase of the allergic immune response (118).

Pollen allergen carrying small particles

Secondary allergen carriers. Pollen grains are the primary carriers of pollen allergens, a fact which explains why the symptoms typical of hay fever are located in the eyes, nose and nasopharynx. Basically, intact pollen grains, which have the aerodynamic size of 15–40 μm, probably cannot enter the lower, thoracic regions of the respiratory tract; instead, they affect the nasal or nasopharyngeal mucous membrane (119, 120). However, symptoms of the bronchial regions, such as cough or wheezing, are not infrequently seen in pollen-allergic patients. Among the various hypotheses put forward to account for the thoracic afflictions in hay fever is the existence of secondary pollen-allergen-carrying particles of much smaller sizes, capable of penetrating the lower respiratory tract. In fact, as early as 1873, Blackley speculated that "free granular matter" floats in the air causing "hay asthma".

Although it is plausible that, in spite of aerodynamic principles, a small number of pollen grains may penetrate into the lower respiratory tract (121), particularly by mouth breathing, there is now strong evidence for the atmospheric presence of pollen-allergen-carrying particles of sizes much smaller than intact pollen grains (122–124).

In the early 1970s, Busse et al. (125) were the first to demonstrate the presence of specific ragweed allergens carried by small particles. By different techniques, this observation was confirmed and extended, first to ragweed-pollen allergen (126–128). Subsequently, the same phenomenon was observed in grass-pollen allergen (129–131), red oak-pollen allergen (132), Japanese cedar-pollen allergen (133), and birch-pollen allergen (134). With cascade impactors or other instruments that fractionate the sampled airborne matter into several size classes, it was established that these small particles range from some micrometers, i.e. 2–10 μm (paucimicronic) to less than 1 μm (submicronic) sizes (127, 128, 131, 133, 134).

Three aspects of the atmospheric presence of pollen-allergenic, paucimicronic, or submicronic particles are of particular interest; i.e. the consequences for the localization of pollinosis-related symptoms, the relationship between the atmospheric pollen concentration and pollen-allergen quantities, and the nature and origin of these small pollen-allergen carriers. Although research and discussion on these aspects have not been concluded, some observations and data are worth considering here.

Pollinosis symptoms in the lower respiratory tract. Several hypotheses have been proposed to account for pollinosis-

related symptoms in the lower respiratory tract, at the level of the bronchi and bronchioli; e.g. absorption of allergen in the nose and subsequent transportation to the bronchi, or reflex mechanisms inducing bronchial involvement after a nasal reaction. Discussion of these hypotheses is beyond the scope of this paper, but it is clear from an aerodynamic point of view that the inhalation and penetration of small particles carrying pollen allergen into the lower respiratory region is a rather direct and not unlikely cause of pollinosis-related symptoms in that region (123, 124).

Atmospheric pollen grains and pollen allergen. The traditional way to measure the presence and quantity of pollen allergen in the atmosphere is to assess the airborne pollen concentration. With the demonstration of substantial quantities of airborne pollen allergen outside the pollen season, the question arises as to whether or not the traditional pollen count is a correct measurement of atmospheric pollen allergen. This point is still being debated because the conclusions drawn by different researchers are not in agreement. Studies on red oak-pollen allergen (132) and for birch-pollen allergen (134, 135) revealed a discrepancy between the numbers of pollen grains and quantities of pollen allergen in the atmosphere. In fact, substantial airborne pollen-allergenic activity has been found, not only after, but even before, the period of presence of pollen grains. On the contrary, there is a good correlation between the presence of pollen grains and pollen allergens, with very little airborne pollen allergen outside the pollen season. The discrepancies detected during the pollen season have been attributed to the occurrence of rainstorms (129, 130, 136, 137). Probably, the final conclusion will depend on the appreciation of the incidental presence of atmospheric allergen outside the pollen season, and its significance for pollinosis symptoms (138). This topic should be investigated, and perhaps studies on the relationship with clinical symptoms of pollinosis will contribute to the discussion.

Nature and origin of the small allergenic particles. The nature and origin of the paucimicronic and the submicronic allergen-carrying particles also have yet to be conclusively defined. Four suggestions or hypotheses have been proposed (123, 124, 138): pollen-grain fragments, starch granules, nonpollen plant parts, and nonplant environmental particles.

Pollen fragments. Because pollen grains generally resist fragmentation, it is unlikely that pollen-grain fragments make a major contribution to the pollen-allergen-carrying particulate matter in the atmosphere, although in the context of a thunderstorm it is possible to observe a pollen rupture by osmotic shock (see paragraph on "Thunderstorm-asthma"). However, abrasion (126), particularly from echinate pollen grains, cannot be ruled out completely.

Starch granules. It has been shown that, under wet conditions, pollen grains may rupture and release part of their content into the atmosphere. An important element of the pollen-grain content is starch granules, which range in size from 0.5 to 2–5 μm. Starch granules appear to be carriers of specific pollen allergen (136, 137). However, the process of the release of allergenic starch granules from pollen grain cannot account for the presence, also under dry conditions, of the larger fraction of the paucimicronic allergenic particles, which range between 5 and 10 μm in size.

Nonpollen plant parts. Several authors have suggested that pollen-allergenic particles originating from plant parts other than pollen can occur in the atmosphere (see paragraph "Thunderstorm-asthma). Parts from inflorescences and/or leaves (128, 132, 139) as well as the so-called orbicules or Ubisch bodies (less than 0.2 μm in size), are capable of carrying specific pollen antigens responsible for the presence of allergenic activity in the atmosphere.

Non-plant particulate matter. Allergen from the surface of the pollen grain could be transferred to other small particles derived or not from pollen grain; e.g. through physical contact or by leaching (136, 140). This process of transfer could take place both in the air and after the pollen has settled to the ground. Particularly in regions with an extra atmospheric load of particular matter as a component of air pollution, this process could be of great clinical importance in view of the possible synergistic effect of exposure to allergen and air pollution (123, 140). The process of transfer of pollen allergen from pollen grains to nonspecific environmental particulate matter might explain the wide range of sizes (from submicronic to paucimicronic) of these secondary pollen-allergen carriers (138).

Pollen/pollutants interaction

Studies have demonstrated that urbanization, high levels of vehicle emissions and westernised lifestyle are correlated with the increasing frequency of pollen-induced respiratory allergy and people who live in urban areas tend to be more affected by pollen-induced respiratory allergy than people living in rural areas (104, 106, 141–143). In urban cities of the Mediterranean area among the components of air pollution such as nitrogen dioxide (NO_2) and inhaled particulate matter (PM_{10} and $PM_{2,5}$) there are frequently high concentrations of ozone favoured by sunny days and ultraviolet radiations. Ozone (O_3) trends in polluted urban atmosphere depend not only on substrate supply (emissions of nitrogen dioxide by cars), but also on weather conditions. Sunny days, which are frequent in Mediterranean area, facilitate the transformation of NO2 into O3, thereby producing the so- called "Summer smog". O_3 is the main component of

photochemical oxidants in cities that enjoy a mild sunny climate, such as several cities of the Mediterranean area.

About 40–60% of the inhaled O_3 is absorbed in the nasal airways, the remainder reaching the lower airways. Exposure to increased atmospheric levels of O_3 induces decrement in lung funcion, increased airway reactivity to bronchoconstrictor agents and is related to an increased risk of asthma exacerbation in asthmatic subjects (144, 145). Epidemiologic studies have provided evidence that high ambient concentrations of this air pollutant are associated with an increased rate of asthma attacks and increased hospital admissions or emergency department visits for respiratory diseases, including asthma (145–148). Several studies suggest that O_3 increases asthma morbidity by enhancing airway inflammation and epithelial permeability (146, 147, 149).

Ozone exposure significantly increases the levels of inflammatory cells (in particular, neutrophils) and mediators, such as IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF) and fibronectin, in bronchoalveolar lavage fluid (BALF) of asthmatic subjects (149, 150).

It has long been speculated that O_3 and other pollutants may render allergic subjects more susceptible to the antigen they are sensitised to (150, 151). Recently, it has been observed that the incidence of new diagnoses of asthma are associated with heavy exercise in communities with high concentrations of O_3, thus, air pollution and outdoor exercise could contribute to the development of asthma in children (152).

However, it is important to consider that exercise in polluted areas results in greater deposition of air pollutants, including allergen-carrying particles, in the lower airways.

There is a growing body of evidence stating that components of air pollution interact with inhalant allergens carried by pollen grains (140, 153, 154) and may enhance the risk of both atopic sensitization and exacerbation of symptoms in sensitized subjects (153), since urban air pollution affects both airborne allergenic pollen and the airways of exposed subjects.

Pollen allergy has been one of the most frequent models used to study the interrelationship between air pollution and respiratory allergic diseases (106, 140, 153–155). Pollen grains or plant-derived paucimicronic components carry allergens that can produce allergic symptoms (156). They may also interact with air pollution (particulate matter, ozone) in producing these effects (Table 2). Furthermore, airway mucosal damage and impaired mucociliary clearance induced by air pollution may facilitate the access of inhaled allergens to the cells of the immune system (153) (Table 3). In addition, vegetation reacts with air pollution and environmental conditions and influence the plant allergenicity. Several factors influence this interaction, including the type of air pollutants, plant species, nutrient balance, climatic factors, degree of airway sensitization and hyperresponsiveness of exposed subjects.

Table 2. The rationale for the interrelationship between agents of air pollution and pollen allergens in inducing respiratory allergy

Air pollution can interact with pollen grains, leading to an increased release of antigens characterized by modified allergenicity.
Air pollution can interact with allergen-carrying paucimicronic particles derived from plants. The paucimicronic particles, pollen-originated or not, are able to reach peripheral airways with inhaled air, so inducing asthma in sensitized subjects.
Air pollution, and in particular ozone, particulate matter and sulphur dioxide, have been shown to have an inflammatory effect on the airways of exposed, susceptible subjects, causing increased permeability, easier penetration of pollen allergens in the mucous membranes and easier interaction with cells of the immune system.
There is also evidence that predisposed subjects have increased airway reactivity induced by air pollution and increased bronchial responsiveness to inhaled pollen allergens.
Some components of air pollution seem to have an adjuvant immunologic effect on IgE synthesis in atopic subjects. In particular diesel exhaust particles (27, 28), which can interact in atmosphere with pollens or paucimicronic particles.

In a recent study in four European cities, allergens from pollens, latex and also β-glucans were shown to be bound to ambient air particles. Thus, combustion particles in ambient air can act as carriers of allergens and as depots of allergens inhaled into the airways (157).

Moreover, in experimental conditions, traffic-related pollutants can trigger the release of allergen- containing granules from *Phleum pratense* (timothy grass) pollen, and increase the bioavailability of airborne pollen allergens (158).

Environmental factors affecting production and diffusion of pollen and pollutants

Climate change

Effects of climate changes on start and length of season, on pollen production and future scenarios. Recent studies showed the potential impact of climate change on aeroallergens and, as a consequence, on allergic diseases. These include impacts on pollen amount, pollen allergenicity, pollen season, plant and pollen distribution, and other plant attributes (159). An analysis of the data from the International Phenological Gardens in Europe (a network of sites covering 69–42°N and 10°W–27°E) has shown that spring events, such as flowering, have advanced by 6 days, and that autumn events have been delayed by 4.8 days, compared with the early 1960s (160).

Table 3. Possible mechanisms of pollutant enhancement of responses to pollen allergens

Increased epitelial permeability
Pollutant induced airway inflammation "priming" the subsequent allergen-induced responses
Enhanced oxidative stress in the airways.

On average, the length of the growing season in Europe increased by 10–11 days during the last 30 years. Trends in pollen amount over the latter decades of the 1900s increased according to local rises in temperature (25, 161–163). Substantial increases in pollen production resulted from exposure to increased CO_2 concentration, in experimental conditions (164–166) and in urban *vs* rural areas; the latter study provides a reliable model for evaluating the effects of global warming (167). Other attributes of allergenic plants are also responsive to CO_2 concentration and/or temperature increases (168, 169). The duration of the pollen season is also extended, especially in summer and in the late flowering species (160). There is some evidence of significantly stronger allergenicity in pollen from trees grown at increased temperatures (170, 171).

An earlier start and peak of the pollen season is more pronounced in species that start flowering earlier in the year. Due to the earlier onset of pollen seasons, the seasons are more often interrupted by adverse weather conditions in late winter/early spring. Anyway, the association between changes in temperature is likely to vary across plant species (annual, more than perennial species and insect pollinators advancing more than wind pollinators).

Changes in climate appear to have altered the spatial distribution of pollens. New patterns of atmospheric circulation over Europe might contribute to episodes of long distance transport of allergenic pollen, increasing the risk of new sensitizations among the allergic population (172). There is growing evidence to show that climate change might also facilitate the geographical spread of particular plant species to new areas, which become climatically suitable. However, the effect of the expected rate of warming (0.5°C per decade) could be less pronounced than effects of land use change the sociocultural changes as well as international transport (173, 174).

Weather

Thunderstorm asthma. "Thunderstorm-associated asthma" was recognized over 15 years ago, and, since then, other asthma outbreaks during thunderstorms were described in UK (175), Australia (176, 177) and Italy (178). A comprehensive review on thunderstorm-associated asthma was recently published by D'Amato et al.(179). The hypotheses underlying the epidemiological observations are: (1) outflow of colder air occurring during thunderstorms sweeps up pollen grains and particles and concentrates them at the ground level. Sensitized subjects who are exposed will inhale a high concentration of allergenic material capable of inducing asthmatic reactions which can also be severe (180); (2) Some authors found that under wet conditions or during thunderstorms, pollen grains may, after rupture by osmotic shock, release part of their content, including respirable, allergen-carrying starch granules (0.5–2.5 μm) into the atmosphere (136, 137); and (3) It has been hypothesized that an increase in fungal spores during a thunderstorm could contribute to asthma epidemics (181).

In the light of the above, subjects affected by pollen allergy should be alert to the danger of being outdoors during a thunderstorm in the pollen season, since such events may be an important cause of severe exacerbations of asthma.

Long-distance transport. Many studies of the dispersal distance of the anemophilous pollen have focused on the deposition of pollen within relatively short distances. However, there are numerous examples of pollen undoubtedly traveling long distances to arrive at a site (182–184) and studied by using air concentration samples or meso-scale dispersion process models (185). Suspended particles are usually transported by the wind, and dispersed by the existing turbulence within the lowest atmospheric layer (boundary layer) where deep convection can bring up particles to free atmosphere and be suspended in an air mass moved by synoptic systems. Depending on the altitude reached, they could be transported and deposited at great distances (186).

Emerging evidence showed that long distance transport might represent a cause of sensitization and of symptoms among the allergic population, in areas far from the source of pollen.

Ragweed seems to be frequently involved in the transboundary transport in Europe (90, 187, 188). In central Italy, several episodes of detection of ragweed pollen appeared to be linked to air mass coming from the Balkans (possibly Hungary) and pollen count often reached the clinical threshold suggesting a possible increase in the sensitization rate and clinical impact on allergic population (172). This hypothesis was supported by a preliminary observation of the increasing trend of ragweed allergy in a neighbouring region where plants are not present, as well. (189)

Furthermore, there is convincing evidence to prove that the long-range transport of pollen from distant regions can significantly modify pollinating seasons (i.e. the start time and duration of high atmospheric pollen concentrations) in many European areas. This is particularly important for northern Europe, where flowering takes place later in the spring. regions (190). In Finland, birch pollen are shown to come from Baltic States, Russia, Germany, Poland and Sweden, depending on the particular meteorological situation. Since the pollen count can reach high levels during these episodes, large-scale forecasting might be useful for the allergic population (186).

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