Pollen on Adverse Respiratory Outcomes

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Respiratory diseases such as asthma, allergic rhinitis (AR) and chronic obstructive pulmonary disease (COPD) affect millions worldwide and pose a significant global public health burden. Over the years, changes in land use and climate have increased pollen quantity, allergenicity and duration of the pollen season, thus increasing its impact on respiratory disease.

Keywords: asthma ; allergic rhinitis ; pollen

1. Introduction

1.1. Outdoor Pollen Is a Risk Factor for Respiratory Diseases

Pollen, a type of aeroallergen, is an established risk factor for allergic rhinitis (AR) and asthma [1][2][3], but evidence for a relationship with chronic obstructive pulmonary disease (COPD) is still emerging. Pollen can trigger allergic inflammation which is IgE-dependent, but non-allergic inflammatory changes may still be possible [4]. Due to their micronic sizes, pollen can easily enter the respiratory tract during inhalation. Intact pollen grains are usually >20 μm in size and deposit in the upper respiratory tract [5], but pollen fragments can be less than 1 μm in size and therefore can deposit in the lower airways [1]. Subsequently, this can trigger a cascade of immune responses, leading to adverse respiratory effects. These adverse respiratory effects can result in asthma and COPD hospital presentations, general practice (GP) consultations, self-reported symptoms, or subtle lung function changes. Because pollen exposure can be over the life course, from pre-natal, post-natal, childhood through to adulthood, it is important to understand its impact, so that necessary measures such as behavioural modification and environmental planning can be adopted to reduce the burden of exposure.

1.2. What Do We Know about Pollen?

Pollen is the male gamete of seed-bearing plants, comprised of Angiosperms and Gymnosperms. It is a fine, dust-like substance that can be transported by several methods, including biotic (insect-borne) and abiotic (wind) vectors. The prominent allergenic pollen families are grass, tree and weed. These pollens are produced by wind-pollinated plants and are adapted to have excellent aerodynamic properties, allowing distribution over hundreds of kilometres [6][7]. The primary allergenic pollen differs between countries and regions, due to geographical variations [8][9][10]. For example, the main allergenic pollen family in the Southern Mediterranean is nettle weed [11], but grass is prominent in other temperate regions such as northern Europe and Australia [12]. Temperate grasses (e.g., *Pooideae*) dominate in cooler climates, while subtropical grasses (e.g., *Panicoideae* and *Chloridoideae*) dominate in subtropical climates [13]. Although allergenic pollen only account for approximately 20–30% of the total annual pollen load, they are abundant during the species' flowering seasons [14], thereby triggering symptoms.

Climate change can affect pollen species' distribution and phenology. Over the years, changes in land use and climate, such as rising temperatures and carbon dioxide levels, have led to increased pollen quantity, allergenicity and duration of the pollen season [15][16][17]. In some instances, during thunderstorm activity, pollen can burst into hundreds of sub-pollen particles of paucimicronic size, causing a phenomenon called "thunderstorm asthma" (TA). Scientists predict that climate change will increase the concentration of airborne pollen, as the frequency and intensity of rainfall is also likely to increase [18][19]. As a result, the prevalence and severity of pollen-induced asthma, AR and sensitisation are also expected to increase [19][20][21].

2. Short-Term Impact of Pollen on Adverse Respiratory Outcomes

2.1. Thunderstorm Asthma (TA)

Grass pollen plays a crucial role in thunderstorm asthma (TA), as evidenced by the systematic review [22]. TA is defined by acute bronchospasm that is triggered within minutes or hours following a thunderstorm or convergence line weather event (defined as a band of rain and cloud, formed when winds from opposite directions collide) with or without the presence of lightning [23][24]. TA can perpetuate an early asthmatic response that is severe enough to seek emergency treatment and, in some instances, death [23][25]. It can cause an unforeseen and sudden surge in respiratory-related GP and hospital presentations, therefore imposing a considerable burden on health services. Airway inflammation during TA is characterised by mucus production, mucosal edema and IgE-mediated mast cell degranulation, followed by increased sputum eosinophil cationic protein (ECP), sputum eosinophils and IL-5-positive cells [26]. These changes caused by TA are similar to asthma, which is why it has the same ICD code (J45, J45.0, J45.1, J45.8, J45.9 and J46) [27]. TA effects were less severe in those who had no previous diagnosis of asthma or hay fever, such that the majority did not require emergency medical assistance [28][29]. Nonetheless, this reveals a hidden at-risk population and an urgent need for early warning systems where, delivery of real-time pollen information is readily accessible by at-risk communities.

Seasonal peaks in asthma admissions have been reported during spring so TA might only be the worst of a seasonal phenomenon [30]. Of the 20 studies included in the systematic review (up until 15 April 2019), 15 presented some evidence of an association between pollen and TA, with nine demonstrating lagged effects of up to four days [22]. Elliot and colleagues [23], who investigated the recent 2021 TA event in England, also reported high grass pollen levels at the time of the occurrence. Because these events usually occurred during pollen seasons, it is hypothesised that there was a priming phenomenon or a prior sensitisation phase, in which people were already exposed and usually pollen-sensitised [31][32].

During a thunderstorm, whole pollen grains (≥20 µm) are disseminated up and horizontally into the air. The convergence line weather events, plus a sudden drop in temperature and air pressure, high humidity, electrical ions, lightning strikes and heavy rainfall, facilitate the rupturing of whole pollen grains into Lol p 5-enriched sub-pollen particles (≤2.5 µm) [24][33][34][35]. The gusty wind then transports the sub-pollen particles over long distances, while the cold downdraft and outflows re-deposit the ruptured pollen grains onto or near to the ground [35][36]. As the sub-pollen particles are several times smaller than intact pollen grains, they can evade filtration by the nasopharynx and penetrate deeper into the airways, provoking primed individuals, even those with no history of diagnosed asthma, to have a more dramatic, asthmatic response [37]. Nonetheless, pollen is not the only factor for TA onset. Other aeroallergens such as fungi can also play a part [38].

Thunderstorm asthma prediction models should consider the role of air quality and its potential synergistic effect with aeroallergens. Darvall et al. [39] demonstrated a sharp increase in PM_{10} concentrations coinciding with the storm front, and although this suggests that more PM_{10} could be stirred up in the winds during a thunderstorm, it could also indicate that ruptured aeroallergens are mistaken for particulate matter (PM) and therefore, are undetectable by volumetric spore traps [22]. To support this, most observational case report studies in the systematic review detailed high intact pollen concentrations in the days preceding the thunderstorm, but the concentrations were low–moderate during the event [22].

2.2. Asthma and COPD Hospital Presentations

2.2.1. Childhood Asthma

To date, three systematic reviews [8][13][40] have evaluated the relationship between ambient pollen and childhood asthma hospital attendances, in which ambient grass and birch pollen were reported to be important risk factors, but only in non-subtropical climates.

Erbas et al. [8], who examined asthma emergency department (ED) presentations, included 14 eligible studies and reported an increased risk of 1% to 14% of ED presentations associated with increasing ambient pollen exposure. There was a minimum threshold of 10 grains/m^3 and some studies demonstrated that the effect flattened after reaching a certain threshold, ranging from 20–50 grains/m^3. This threshold could be population- or location-specific, as it reflects the variation in pollen sensitisation rates, pollen allergenicity and fewer data points at higher pollen concentrations [41][42][43]. Meta-analysis was only possible for grass pollen, demonstrating a 1.88% (95% CI = 0.94%, 2.82%, I^2 = 0%; n = 3) increase in number of asthma ED presentations for every 10 grains/m^3 increase at lag 3.

Shrestha et al. [40], who examined asthma hospitalisations, included 12 eligible studies and demonstrated a relationship with ambient grass and birch pollen. For every 10 grains/m^3 increase in grass pollen at lag 0 and birch pollen at lag 2 and

lag 0–6, there was a 3% (95% CI = 1%, 4%, I^2 = 0%; *n* = 2) and 0.85% (95% CI = 0.4%, 1.3%, I^2 = 0%; *n* = 2) increase in asthma admissions, respectively.

Simunovic et al. [13], who assessed asthma ED presentations and hospitalisations in subtropical climates, reported little to no evidence of an association with grass pollen on the same day or lagged in the six studies that assessed children only. In subtropical regions, grass pollen seasons are longer in duration with multiple peaks and there are probably many different grass pollen species involved, but in temperate regions, the seasons are shorter with a single, relatively higher peak and only one or two dominant grass pollen species [12][44]. This could explain why a strong association could not be detected in the subtropics.

More recent studies from various regions have reported increasing grass [45], tree [45][46][47] and weed [45][46] pollen concentrations to be associated with an increased risk of asthma exacerbations. Of these three studies, two were conducted in temperate climates [45][46] and one was in a subtropical climate [47].

Only one study investigated the role of ambient pollen concentrations on asthma readmissions. Vicendese et al. [48] observed higher rates of readmission within 28 days in boys during the temperate grass pollen season. The authors explained that this could be because boys were more sensitive to pollen, and this may have led to severe asthma reactions that required multiple admissions. Alternatively, it may suggest poorer adherence to treatments in boys, as they accounted for 60% of all admissions.

2.2.2. Adulthood Asthma

Similarly, ambient pollen is an important risk factor for adulthood asthma, but only in non-subtropical climates. Only one systematic review examined the role of outdoor short-term pollen exposure on adult asthma hospital attendances, but it focussed on subtropical climates. Comparable to what was found in children, Simunovic et al. [13] reported little to no evidence of an association between grass pollen (on the same day or lagged) and hospitalisations in the two studies that assessed adults only.

Studies performed in non-subtropical climates have not yet been systematically reviewed. Researchers identified 14 original studies investigating such relationships from the search. Of these, 13 reported some evidence of an association between increasing ambient pollen concentrations and adult asthma hospital attendances [20][46][49][50][51][52][53][54][55][56][57][58][59]. For example, Osborne et al. [57], who conducted a study in London, UK, observed increasing grass pollen concentrations at lag 4 and lag 5 to be associated with increased asthma admission rates. When classified into pollen ‘alert’ levels based on the UK’s Met Office, the authors found ‘very high’ pollen days (vs. low) to be associated with increased admissions 2 to 5 days after, peaking at lag 3 (Incidence rate ratio = 1.45 [95% CI = 1.2, 1.78]) [57]. Although this study did not find an association with tree pollen, others have [20][46][51][53][56]. Contrarily, weed pollen has been shown to be important in Hungary [55][59]. One study indicated a “threshold level”, as the 2nd quartile of pollen distribution imposed the maximum effect on asthma hospital admissions [50]. However, the authors stated that this could be because admissions occurred primarily in pollen-sensitised individuals, so once they were affected, the impact on those not sensitised may be lower. The study [60] that reported no evidence of a relationship failed to do extensive analysis with pollen, and only had 232 attendances recorded that year, so there could be insufficient power to detect associations. Moreover, Oulu is an industrial town, so pollen may not be as important there.

2.2.3. Adulthood COPD

Very few studies investigated the relationship between outdoor pollen concentrations and COPD and this evidence has also not been systematically reviewed. Of the five studies that researchers discovered, two reported some evidence of an association [61][62], while others did not [53][63][64]. Brunekreef et al. [61] observed a small dose–response relationship between average weekly grass pollen concentrations and daily COPD mortality in the Netherlands. Compared to the lowest exposure category (<22 grains/m^3), the moderate (22–77 grains/m^3), high (78–135 grains/m^3) and extreme (>135 grains/m^3) exposure categories were associated with a 1.095 (95% CI = 1.05, 1.14), 1.12 (95% CI = 1.07, 1.18) and 1.15 (95% CI = 1.08, 1.23) increased risk of daily COPD mortality, respectively. These effect sizes were comparable to the association between air pollution and mortality [61]. Additionally, Hanigan et al. [62] showed that for every IQR increase in total pollen concentrations, daily COPD admissions in Darwin, Australia, increased by 33.2% (95% CI = 12.8, 57.3). However, the authors stated that replication of the study findings is needed as the study sample was relatively small (*n* = 334 over 20 months). Studies that reported no evidence of an association [53][63][64] did not provide effect estimates, so researchers could not determine the strength and confidence of the relationships.

2.3. General Practice (GP) Consultations

The relationship between ambient pollen concentrations and GP consultations also has not been systematically synthesised. Of the five studies that researchers found, all reported a positive association with GP consultations for AR [65][66][67][68] and asthma [66][67][69]. One study in Beijing, China, observed the association with AR consultations to be strongest at lag 0 [65] (RR = 2.6; 95% CI = 2.6, 2.7 for every 10 grains/m^3 increase in total pollen). Interestingly, a UK study demonstrated that peak AR consultations coincided with peak grass pollen concentrations, but peak asthma consults occurred only 2–3 weeks later [66], indicating potential differences in disease mechanisms. Comparatively, Huynh et al. [69] observed a strong linear relationship between average weekly grass pollen concentrations and weekly asthma consults (RR = 1.54, 95% CI = 1.33, 1.79 for every IQR increase [i.e., 17.6 grains/m^3]).

2.4. Self-Reported Respiratory Symptoms

In those with pre-existing allergic conditions, even low–moderate levels of pollen are likely to trigger respiratory symptoms on the same day of exposure. Kitinoja et al. [70] recently published a systematic review of 26 studies that assessed the association between pollen concentrations and self-reported respiratory symptoms in allergic and/or asthmatic subjects. Some studies were eligible for a meta-analysis, in which the authors reported a 7% (95% CI = 4%, 9%; n = 3; I^2 = 28.7%) and 1% (95% CI = 0%, 2%; n = 6; I^2 = 68%) increase in the risk of self-reported upper and lower respiratory symptoms, respectively, for every 10 grains/m^3 increase in any pollen. However, all studies included in this systematic review investigated pollen exposure at lag 0 only and there was moderate–high heterogeneity.

The most recent study evaluated the relationship between daily ambient pollen concentrations and respiratory symptoms logged by users of a smartphone application, called AirRater, in Tasmania, Australia [71]. There was a non-linear association of up to 3 days following exposure and no minimum threshold of pollen concentration, indicative of no ‘safe level’, akin to air pollution effects. The lag 0 association was the strongest with an RR of 1.31 (95% CI = 1.26, 1.37 at 50 grains/m^3). Furthermore, more users reported symptoms in the upper respiratory tract compared to the lower respiratory tract, which is consistent with the systematic review by Kitinoja et al. [70]. It is important to note that most of the app users self-identified as having a history of asthma and/or AR, and they were also more likely to be health-literate compared to the public.

2.5. Lung Function Changes

There is little evidence that pollen season or pollen concentrations on the same day were associated with lung function changes, but the four studies that investigated lagged responses reported some evidence of an association. These four studies also suggest that ambient pollen may be associated with different lung function measures, depending on age. It seems like allergenic pollen is more associated with the forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) in children, and the FEV_1/FVC ratio and mid-forced expiratory flow ($FEF_{25–75\%}$) in adults.

Two systematic reviews have been published on this topic [31][70]. In the qualitative review of seven population-based studies that investigated such relationships [31], only the study that measured associations for lagged effects reported evidence of an association, with significant reductions in FEV_1 and FVC in 8-year-old children with increasing grass pollen concentrations at lag 1, lag 0–3 and lag 0–7 [72]. In the quantitative review by Kitinoja and colleagues [70], they found no evidence of a relationship between ambient pollen on the same day and peak expiratory flow (PEF) (n = 2) and FEV_1 (n = 2).

Subsequently, researchers performed a data analysis of the MACS high-risk cohort which consisted of primarily adults and observed increased grass pollen concentrations to be associated with middle–small airway changes 2–3 days after exposure, as reflected by the FEV_1/FVC ratio and $FEF_{25–75\%}$, respectively [73]. Similarly, Lambert et al. [74] observed a reduction in FEV_1 and FVC with increasing concentrations of tree pollen at lag 1 and lag 3 in 8-year-old ‘high-risk’ children residing in Sydney, Australia [74]. The same authors investigated similar relationships in adolescents of the GINIplus and LISA cohorts in Germany, but observed the association to be present only in those who were pollen sensitised [75]. Using an unsupervised approach, another recent study of the PARIS cohort demonstrated that children in the ‘grass pollen’ cluster (i.e., moderate grass pollen exposure and low air pollution exposure) had reductions in FEV_1 and FVC, when compared to children in the ‘low exposure’ cluster (i.e., no pollen exposure and low air pollution exposure) [76].

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