Science of the Total Environment 893 (2023) 164801

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Review

Impact of environmental nitrogen pollution on pollen allergy: A scoping review

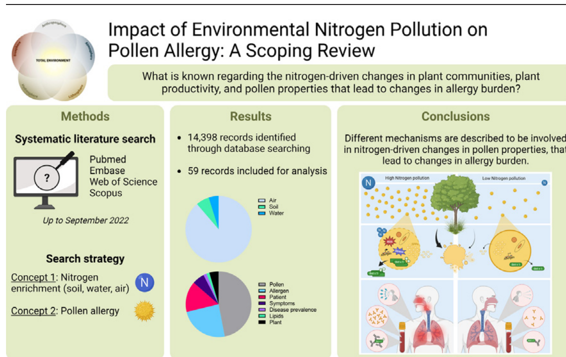
Paulien Verscheure [a], Olivier Honnay [b], Niko Speybroeck [c], Robin Daelemans [b], Nicolas Bruffaerts [d], Brecht Devleesschauwer [e,f], Tobias Ceulemans [b,g], Laura Van Gerven [a,h,i], Raf Aerts [b,j], Rik Schrijvers [a,k,*]

[a] Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, KU Leuven, Leuven, Belgium
[b] Department of Biology, Division Ecology, Evolution and Biodiversity Conservation, KU Leuven, Leuven, Belgium
[c] Institut de Recherche Santé et Société, UC Louvain, Louvain-la-Neuve, Belgium
[d] Department of Mycology & Aerobiology, Sciensano (Belgian Institute for Health), Brussels, Belgium
[e] Department of Epidemiology and Public Health, Sciensano (Belgian Institute for Health), Brussels, Belgium
[f] Department of Translational Physiology, Infectiology and Public Health, Ghent University, Merelbeke, Belgium
[g] Department Biology, UAntwerpen, Antwerpen, Belgium
[h] Department of Otorhinolaryngology, Head & Neck Surgery, University Hospitals Leuven, Leuven, Belgium
[i] Department of Neurosciences, Experimental Otorhinolaryngology, Rhinology Research, KU Leuven, Leuven, Belgium
[j] Risk and Health Impact Assessment, Sciensano (Belgian Institute for Health), Brussels, Belgium
[k] Department of General Internal Medicine, Division of Allergy and Clinical Immunology, University Hospitals Leuven, Leuven, Belgium

HIGHLIGHTS

- Comprehensive literature overview on the nitrogen-driven impact on pollen allergy
- Systematic literature search to map the available literature and knowledge gap
- Review takes a wide angle at the interfaces between the different spheres (air, soil, and water).
- Atmospheric nitrogen pollution affects various aspects of pollen allergy.
- Limited research on soil or aqueous nitrogen pollution yielding no clear conclusions

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Jay Gan

Keywords:
Allergic disease
Environmental pollution
Nitrogen
OneHealth
Pollen
Planetary health

ABSTRACT

The current rise in the prevalence of allergies to aeroallergens is incompletely understood and attributed to interactions with environmental changes and lifestyle changes. Environmental nitrogen pollution might be a potential driver of this increasing prevalence. While the ecological impact of excessive nitrogen pollution has been widely studied and is relatively well understood, its indirect effect on human allergies is not well documented. Nitrogen pollution can affect the environment in various ways, including air, soil, and water. We aim to provide a literature overview of the nitrogen-driven impact on plant communities, plant productivity, and pollen properties and how they lead to changes in allergy burden. We included original articles investigating the associations between nitrogen pollution, pollen, and allergy, published in international peer-reviewed journals between 2001 and 2022. Our scoping review found that the

Abbreviations: H_2O_2, Hydrogen peroxide; HLA, Human leukocyte antigen complex; HNO_2, Nitrous acid; HNO_3, Nitric acid; HSP, Heat shock proteins; IFN, Interferon; Ig, Immunoglobulin; IL, Interleukin; LPS, Lipopolysaccharides; N, Nitrogen; N_2O, Nitrous oxide; NH_3, Ammonia; NH_4^+, Ammonium; NK cells, Natural killer cells; NO, Nitrogen oxide; NO_2, Nitrogen dioxide; NO_3^-, Nitrate; NO_x, Nitrogen oxides; N_r, Reactive nitrogen; ns-LTPs, Non-specific lipid transfer proteins; O_3, Ozone; $ONOO^-$, Peroxynitrite; OVA, Ovalbumin; PALMs, Pollen-associated lipid mediators; PCGs, Pollen cytoplasmic granules; PR, Pathogenesis-related; PRISMA-ScR, Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews; ROS, Reactive oxygen species; sIgE, Specific IgE; SO_2, Sulfur dioxide; SO_4^{2-}, Sulfate; SPPs, Sub-pollen particles; Th, T helper; WOS, Web of Science.

* Corresponding author at: Department of General Internal Medicine, University Hospitals Leuven, Herestraat 49, B-3000 Leuven, Belgium.
E-mail address: rik.schrijvers@uzleuven.be (R. Schrijvers).

http://dx.doi.org/10.1016/j.scitotenv.2023.164801
Received 22 March 2023; Received in revised form 30 May 2023; Accepted 8 June 2023
Available online 14 June 2023

majority of studies focus on atmospheric nitrogen pollution and its impact on pollen and pollen allergens, causing allergy symptoms. These studies often examine the impact of multiple atmospheric pollutants and not just nitrogen, making it difficult to determine the specific impact of nitrogen pollution. There is some evidence that atmospheric nitrogen pollution affects pollen allergy by increasing atmospheric pollen levels, altering pollen structure, altering allergen structure and release, and causing increased allergenic reactivity. Limited research has been conducted on the impact of soil and aqueous nitrogen pollution on pollen allergenic reactivity. Further research is needed to fill the current knowledge gap about the impact of nitrogen pollution on pollen and their related allergic disease burden.

Contents

1. Introduction

Allergic rhinitis, allergic asthma, and food allergy are among the most common (chronic) diseases globally with a prevalence of 20 to 30 % in adults and up to 40 % in children, usually persisting throughout life (Brożek et al., 2017; D'Amato et al., 2007; Hoyte and Nelson, 2018; Savouré et al., 2022). Allergic rhinitis is a common presentation of an immunoglobulin E (IgE)-mediated type I hypersensitivity reaction to foreign, generally harmless substances and is caused by the inhalation of aeroallergens, such as different types of pollen, spores, or particles from pets or dust mites (Bernstein et al., 2016; Dispenza, 2019). Because of its life-long impact, allergic rhinitis is associated with an important disease-, social- and economic burden and has a significant negative impact on the patient's quality of life (Hoyte and Nelson, 2018; Wallace and Dykewicz, 2017; Zuberbier et al., 2014). There is no teleological evidence, and there is limited evidence that allergic rhinitis used to be a problem in earlier times as well. We traditionally still consider an allergy as an "unwanted" immune response and the hygiene hypothesis, "old friends" hypothesis, the barrier hypothesis, and even the biodiversity hypothesis emerged as explanations for the rise in allergy prevalence, including pollen allergy (Celebi Sozener et al., 2022; Haahtela, 2019; Lambrecht and Hammad, 2017; Pfefferle et al., 2021). This rise in allergy prevalence is expected to increase even further and is due to various interactions between lifestyle changes and other environmental changes, e.g. rising temperatures and air pollution (Asam et al., 2015; D'Amato and Cecchi, 2008; Doll et al., 2019; Gilles et al., 2018; Lake et al., 2017; Reinmuth-Selzle et al., 2017).

Environmental nitrogen pollution could be an additional potential driver of increasing aeroallergen prevalence and severity, but there is still a need to determine its impact (Ceulemans et al., 2023). Nitrogen (N) is a chemical element that is present in all organisms, primarily in amino and nucleic acids. The atmosphere consists of 78 % of N_2 gas, however, this inert form of nitrogen is unavailable for biological processes and must be converted into reactive nitrogen (N_r) to be utilized. N_r includes biologically, radiatively, and/or photochemically active forms of nitrogen such as nitrate (NO_3^-) and ammonium (NH_4^+), the dominant forms for organism uptake, and the gasses ammonia (NH_3), nitrogen oxide (NO_x) and nitrous oxide (N_2O) (Galloway et al., 1995) which all contribute to a range of different environmental and human health problems (Erisman et al., 2013; Galloway et al., 2008). This N_2-fixation into biologically available forms naturally only occurs through the activity of nitrogen-fixing microorganisms or by lightning strikes at a rate of ±150Tg N year^{-1}, and is crucial for the functioning of the Earth's ecosystems (Galloway et al., 2008). Anthropogenic activities have dramatically changed the rate of N_2-fixation into N_r up to an additional 200Tg N year^{-1} and rising (Galloway et al., 2008).

Environmental nitrogen pollution originates from multiple sources (Fig. 1). First of all, fossil fuel combustion by industrial processes and vehicle traffic releases NO_x emissions into the air. Furthermore, N_2 is brought into the biosphere in large quantities via synthetic fertilizer production through the Haber-Bosch process, which converts atmospheric nitrogen into ammonia through a catalytic reaction with hydrogen. Excessive fertilizer use in agriculture results in NO_3^- pollution and N_2O emission, while the application of organic fertilizers and livestock raising causes NH_3

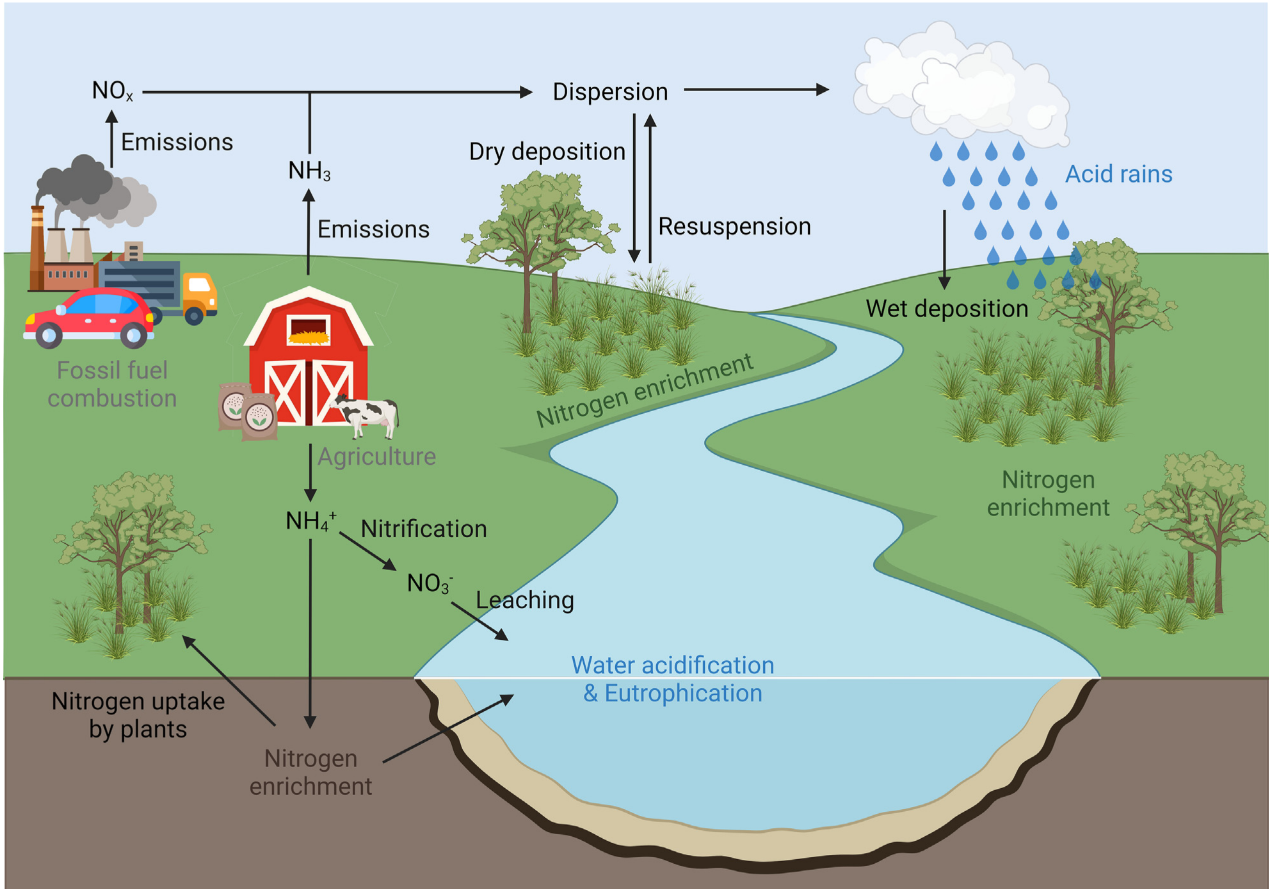


Fig. 1. Nitrogen cycle, the relationship between air, soil, and water nitrogen pollution. Nitrogen emissions from fossil fuel combustion and agriculture lead to dispersion of nitrogen air pollutants. Uptake of nitrogen by plants and environment via dry- and wet deposition, leading to environmental nitrogen enrichment. Additionally, direct agricultural fertilizer application leads to soil nitrogen enrichment and increased nitrogen uptake by plants. Nitrogen pollution reaches the water via leaching from the soil, causing water acidification and eutrophication.

emissions. Those emitted nitrogen gasses can get deposited into ecosystems via rainfall, fog, and snow (wet deposition) or via the free fall and airflow (dry deposition). Soil leaching of excess nitrogen into streams and rivers leads to nitrogen water pollution, causing water acidification and eutrophication (Greaver et al., 2012). Fig. 1 also illustrates the relationship between air, soil, and water nitrogen pollution. Nitrogen is transported through these different phases (i.e. air, water, and soil) and can have an effect in each of them.

Additionally, a potential interaction between atmospheric nitrogen deposition and the shifting seasonality leads to different trends in atmospheric- and soil nitrogen chemistry (Murray et al., 2022). Nitrogen deposition appears to follow seasonal patterns, just as pollen exposure, and both can be impacted by climate change through changing rainfall patterns. Furthermore, pollen as biogenic aerosols themselves may be a relevant factor for the seasonal carbon and nitrogen cycling through direct deposition and canopy exchange in forest systems (Liptzin et al., 2022). This means that pollen is not solely a downstream component impacted by nitrogen pollution, but may also be a relevant component within the nitrogen cycle.

These combined factors create an input of N_r from the atmosphere to the biosphere, leading to biosphere enrichment and a whole range of associated environmental impacts (Galloway et al., 2008; Peñuelas et al., 2012). For instance, the effects of nitrogen deposition on ecosystems are well documented and lead to vegetation biodiversity loss (Galloway et al., 2008; Peñuelas et al., 2012), mainly through creating more productive ecosystems which tend to be dominated by a few highly competitive plant species (Bobbink et al., 2010; Ceulemans et al., 2014; Damgaard et al., 2011; Stevens et al., 2010; Tilman et al., 2001; Wang et al., 2018). As nitrogen pollution is associated with increased plant productivity, it may change the entire pollen-allergenic landscape and subsequently the burden of disease. We hypothesize that environmental nitrogen enrichment, caused by soil and water nitrogen pollution, can impact the pollen allergic disease burden through a combination of direct and indirect effects. Nitrogen enrichment has a known impact on the environment (e.g. change in soil nutrient availability), ecosystem functioning (e.g. increased plant productivity), biodiversity (e.g. biodiversity loss and shift in plant community composition), and aeroallergens (e.g. altered biochemical composition of plant pollen) (Ceulemans et al., 2023). We hypothesize that the combination of all these factors could lead to increased allergy risk. This results in exposure to higher concentrations of certain pollen types that have potentially higher allergenic reactivity leading to a higher allergic disease burden. However, the effects on human health and the mechanisms involved are at present not well documented. We aim to identify and map the available literature and the associated knowledge gaps in this field. In this paper, we present a comprehensive review of the literature on how nitrogen pollution affects pollen allergies and the mechanisms behind it.

2. Methods

The protocol was drafted and the review was reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Tricco et al., 2018). We selected the scoping review protocol to scope a body of literature on our topic and provide a comprehensive overview of the available literature and its focus of it (Munn et al., 2018).

2.1. Information sources and search method

A search strategy was defined based on our research question. The nitrogen-driven impact on biodiversity, the environment, and ecosystem functioning (under the present "biodiversity-ecosystem functioning" paradigm) is well defined (Ceulemans et al., 2023). We aimed to evaluate what is known regarding (a) the nitrogen-driven changes in plant communities that lead to changes in allergy burden (e.g. shift towards more allergenic plant species), (b) the nitrogen-driven changes in plant productivity that lead to changes in allergy burden (e.g. via pollen abundance), and (c) the nitrogen-driven changes in pollen properties that lead to changes in allergy burden (e.g. allergenic protein modifications). A literature search was performed in PubMed, Embase, Web of Science (WOS) Core Collection, and Scopus databases. We conducted a search strategy using MeSH terms for PubMed and Emtree terms for Embase. Manuscripts published between January 1, 2001, and August 31, 2022, were eligible for inclusion. The search terms used for each database and the number of results for each database are listed in Table S1. Results of the literature search were exported into Endnote (Clarivate Analytics, Philadelphia, USA), which was used to detect and remove duplicates.

2.2. Screening selection

Relevant publications were selected by title and abstract screening by PV. Potentially suitable publications for this review were screened for eligibility based on full-text screening by PV. Additional publications were included by "snowballing" the references of the selected studies. We excluded non-English language, non-peer-reviewed articles, and other non-article publications or publications that were inaccessible through reasonable searching protocols. Review articles were also excluded from the analysis, but they were used for reference screening.

Publications that were deemed relevant progressed to extraction. Relevant information was collected from each article using a pre-designed data collection table: (a) nr., (b) title, (c) first author, (d) year of publication, (e) study location, (f) study period, (g) plant taxon producing the pollen, (h) allergen studied, (i) study population, (j) measure for nitrogen impact, (k) method for measuring nitrogen impact, (l) type of nitrogen pollution, (m) pollen-nitrogen exposure method, (n) conclusion nitrogen impact, (o) additional information, (p) type nitrogen pollution (Air-/Soil-/Water-borne), (q) impact on … (Pollen/ Allergen/ Patients/ …), (r) disease type investigated (allergic rhinitis, respiratory disease, asthma, pollen allergy…), (s) mechanism of action. For further analysis, the impact of nitrogen pollution was divided into several categories: pollen (study of pollen characteristics and properties), allergen (specific allergen was studied), patients (patient-specific characteristic e.g. IgE levels), symptoms, disease prevalence, lipids (lipid profile of pollen grains), and the pollen-producing plant taxon. All articles were carefully read and all relevant information was included in the text.

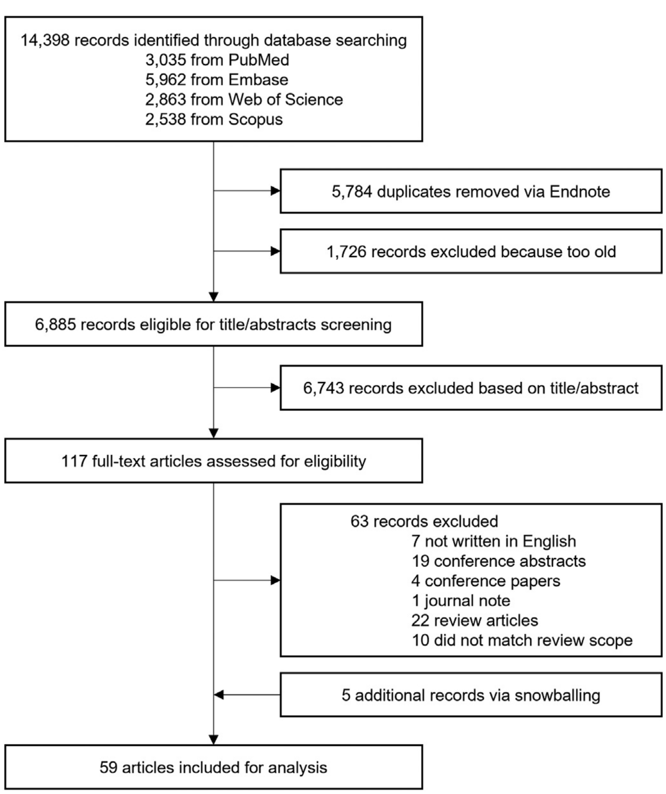


Fig. 2. Flow diagram of publication selection.

3. Results

Our search resulted in a total of 14,398 records. After duplicate removal and exclusion of articles that were published before our inclusion period, 6885 records remained eligible for further screening. Title and abstract screening resulted in 118 records, of which 59 were included in the further analysis according to our pre-defined inclusion criteria. Most of the excluded full-text articles were not peer-reviewed research articles or did not match the scope of the review (for example because they did not focus on nitrogen pollution specifically or did not study the impact regarding allergy) (Fig. 2). Most the records found were research articles performed in Europe, mainly in Germany, Spain and Sweden (Fig. 3). During the last decade, an increase in the number of articles is apparent, with the highest number of articles dating from 2021. The majority of articles focused on the impact of airborne nitrogen pollution on pollen, pollen allergens, or pollen-allergic patients (Fig. 4). Research about the impact of soil or water nitrogen pollution on pollen allergy was limited, representing 6.8 % and 5.1 % of selected articles, respectively. Some articles also reported more than one type of pollution or focused on several impact parameters or pollen types. The most frequently studied pollen types, of variable allergenic reactivity, were *Betula* (birch) and *Phleum* (timothy-grass), but also *Ambrosia* (ragweed), *Platanus* (plane), *Pinus* (pine), and *Humulus* (hop) pollen. Since our review focuses on aeroallergen exposure and respiratory allergies, the most relevant pollen taxa are from anemophilous or wind-pollinating plants. Pollen types investigated differed according to the region where the research was performed (Table 1).

3.1. Impact of airborne nitrogen pollution

The impact of atmospheric nitrogen pollution was evaluated in 55 of the 59 articles. From these, 31 records focused on pollen, 15 on specific pollen allergens, and 14 investigated patient response, symptoms, and disease prevalence (Fig. 5). Few papers focused on multiple aspects. Most papers focused on environmental exposure to multiple co-occurring pollutants, not only on atmospheric nitrogen pollution, while some specifically investigated experimental exposure to only nitrogen pollutants. The most commonly investigated types of nitrogen pollutants were NO_x, including nitrogen dioxide (NO_2) and nitrogen oxide (NO). Other atmospheric pollutants studied in the included studies were O_3, SO_2, and SO_4^{2-}. We specifically looked at the impact of atmospheric nitrogen pollutants on various parameters in pollen and their allergenic reactivity.

We found evidence that atmospheric nitrogen pollution can affect various aspects contributing to pollen allergy (Table 2) and identified nine different mechanisms of interest detailed below. We found differences in atmospheric pollen concentrations, probably caused by changes in biodiversity and plant productivity. Next, there was evidence for changes in the pollen grain membrane and pollen grain morphology, leading to changes in allergen release. Also, differences in pollen viability and germination were found in relation to nitrogen pollution. We found evidence for changes in the allergenic properties of pollen via changes in oxidative defense mechanisms, allergenic proteins, and immune-stimulatory/modulatory mediators, their structure, expression levels, and allergenic reactivity. This was also described concerning

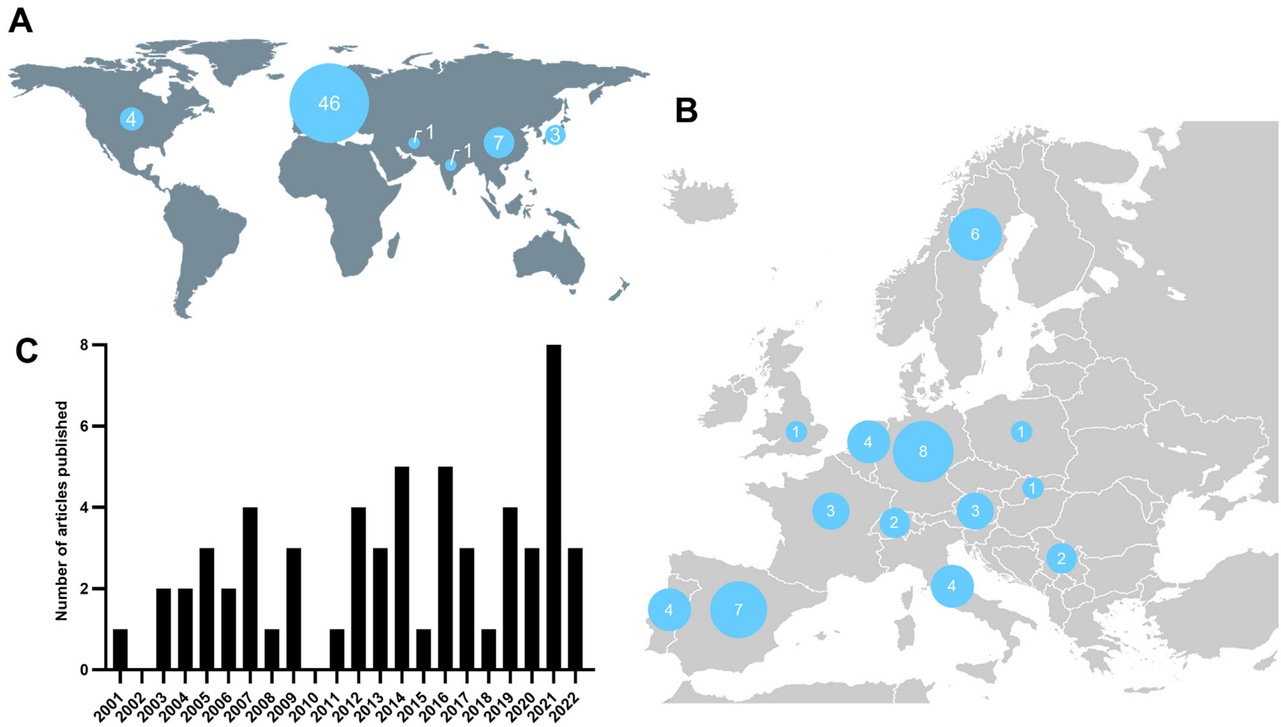


Fig. 3. Global (A) and European (B) distribution of original articles, included in this scoping review, investigating associations between nitrogen pollution, pollen, and allergy, published in international peer-reviewed journals between 2001 and 2022 (C).

the pollen-allergenic burden, specifically showing differences in patient symptoms, allergy severity, and allergy prevalence. (Fig. 6).

3.1.1. Airborne pollen exposure

Significant positive correlations were found in Poland between NO_x and pollen concentrations of *Betula* and *Fraxinus* (Puc, 2012). Also, strong positive correlations were found in Subotica in Serbia between NO_2 concentrations and Urticaceae pollen concentrations (Sabo et al., 2016). In Bratislava on the other hand, atmospheric NO_2 pollution in 2019 was found to be negatively associated with *Phleum pratense* pollen (Ščevková et al., 2021). In the Madrid region, a negative correlation between NO_2 and *Olea* and *Pinus* pollen was observed as well when studying various airborne pollutants and different tree pollen (Chico-Fernández and Ayuga-Téllez, 2022). Rahman et al. found that NO_2 concentrations were both

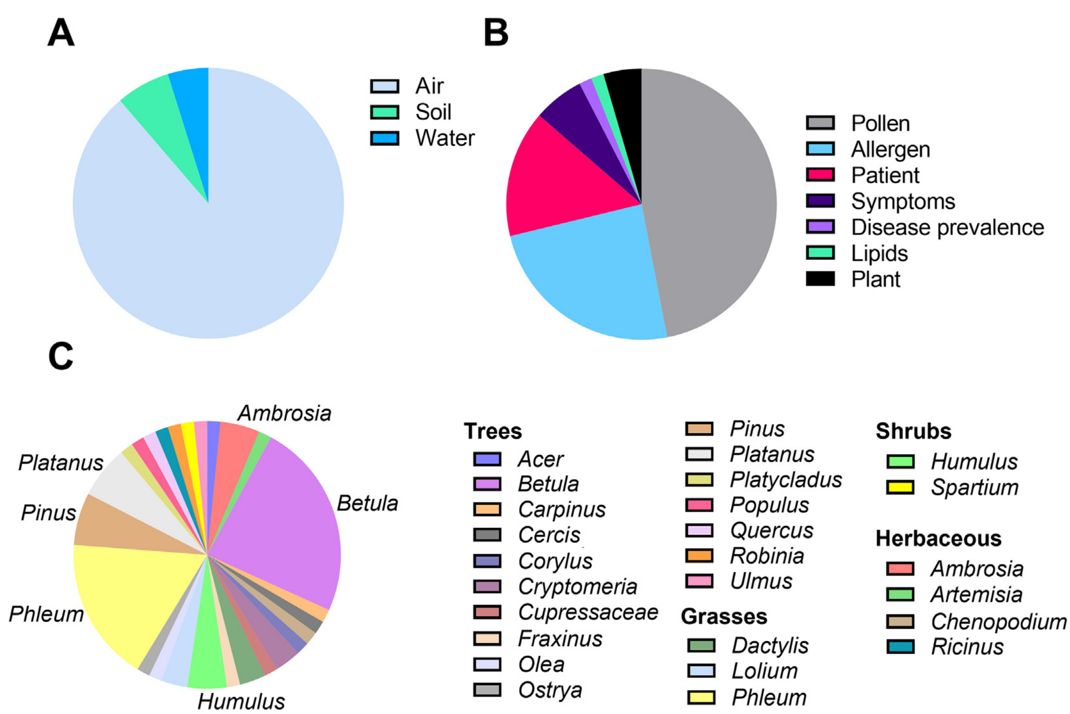


Fig. 4. Distribution of articles investigating associations between nitrogen pollution, pollen, and allergy published between 2001 and 2022 in international peer-reviewed journals according to (A) the source of nitrogen pollution investigated, (B) the parameter used to measure the nitrogen impact, and (C) the pollen taxa investigated.

Table 1
Distribution of articles investigating associations between nitrogen pollution, pollen, and allergy published between 2001 and 2022 in international peer-reviewed journals according to the location (country) of the research group where specific pollen taxa were studied (colors same from Fig. 4).

Pollen type (plant taxon)	Country
Trees	
Acer	Portugal
Betula	Austria, France, Germany, Portugal, Poland, Sweden, Switzerland,
Carpinus	Portugal
Cercis	Italy
Corylus	Italy
Cryptomeria	Japan
Cupressaceae	Spain
Fraxinus	Poland
Olea	Spain
Ostrya	Portugal
Pinus	Italy, Spain
Platanus	China, Portugal, Spain
Platycladus	Iran
Populus	Spain
Quercus	China
Robinia	Italy
Ulmus	Spain
Herbaceous	
Ambrosia	Austria, Germany
Artemisia	China
Chenopodium	China
Ricinus	India
Grasses	
Dactylis	France, Portugal
Lolium	Spain
Phleum	France, Germany, Italy, Serbia, Slovakia, Spain, Sweden, The Netherlands
Shrubs	
Humulus	China
Spartium	Italy

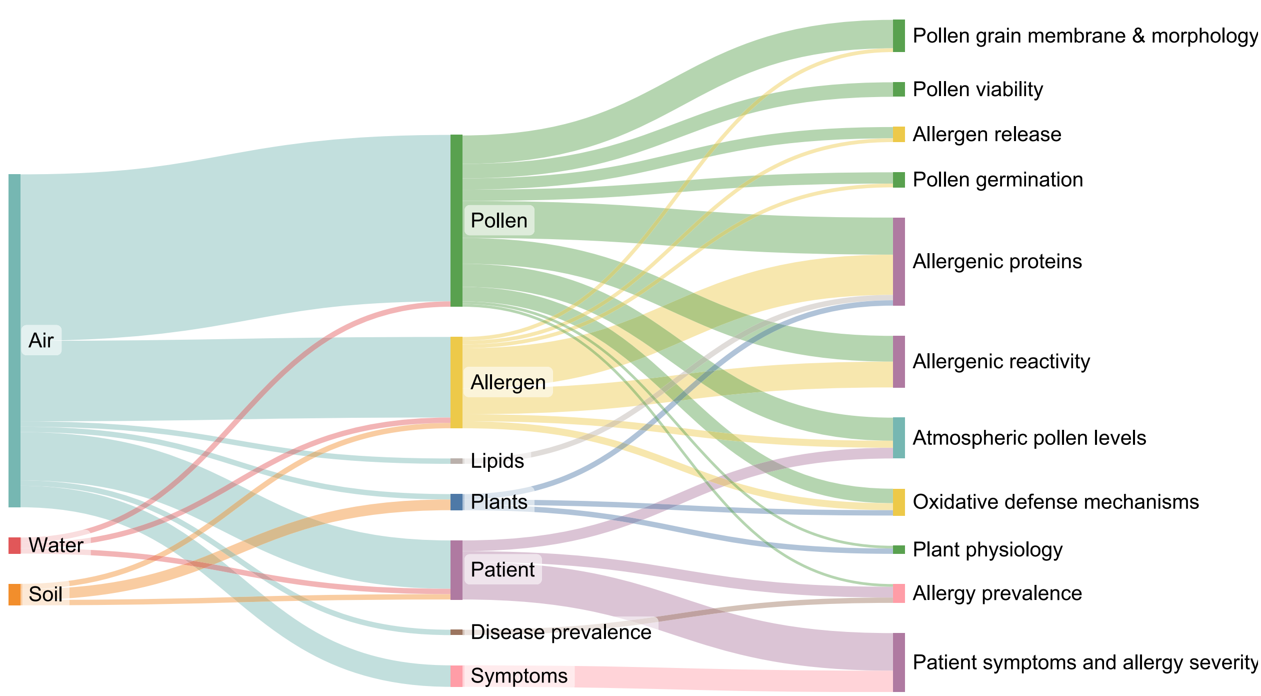


Fig. 5. Flow diagram (Sankey diagram) divided into three primary nodes related to the spheres of the different types of nitrogen pollution, the parameter used to measure the nitrogen impact, and the different response levels (anthroposphere) described in the articles included in this scoping review. The width of connections or flows between nodes is proportional to the number of articles described in this scoping review.

Table 2
Overview of articles describing the 'impact of airborne nitrogen pollution' published between 2001 and 2022 in international peer-reviewed journals. The number of articles (#articles) is shown according to the specific pathway(s) they discuss.

	Pathway impacted by nitrogen pollution	#articles
3.1.1	Atmospheric pollen abundance	7
3.1.2	Pollen grain membrane and morphology	10
3.1.3	Allergen release	4
3.1.4	Pollen viability	5
3.1.4	Pollen germination	4
3.1.5	Oxidative defense mechanisms	4
3.1.6	Allergenic proteins and immune-stimulatory/modulatory mediators	21
3.1.7	Allergenic reactivity	14
3.1.8	Patient symptoms and allergy severity	12
3.1.9	Allergy prevalence	3

negatively and positively correlated with various pollen types in Guangzhou, China (Rahman et al., 2019). Together, this could indicate that atmospheric nitrogen pollution can correlate both positively and negatively with pollen concentrations, possibly depending on the pollen type and/or region of evaluation. However, this could give a (false) impression of a direct (causal) relationship between atmospheric nitrogen pollution and atmospheric pollen concentrations. Yet, high airborne nitrogen pollution levels are associated with an increase in nitrogen deposition, leading to nitrogen enrichment of the biosphere and a subsequent shift in plant communities. On the one hand, this means that certain plants become dominant (e.g. Urticaceae) and their increased biomass entails higher pollen production, thus higher atmospheric pollen concentrations. On the other hand, some plants might be outcompeted, resulting in lower pollen production and lower atmospheric pollen concentrations (e.g. *Phleum pratense*). Therefore, the correlations described here are indicative of an indirect pathway through nitrogen biosphere enrichment.

3.1.2. Pollen grain membrane and morphology

Another potential mechanism of how atmospheric pollutants could affect pollen and their allergenic reactivity is through a direct impact on the pollen cell properties (Table 3). Different articles describe how atmospheric pollutants, including NO_2, affect pollen grains by interacting with the pollen membrane. Lu et al. showed the attachment of pollutant particles on the surface of pollen grains (Lu et al., 2014). Wang et al. found higher amounts of atmospheric pollution particles (NO_3^-, sulfate (SO_4^{2-}) and NH_4^+) and gaseous pollutants (NO_2, sulfur dioxide (SO_2) and NH_3) deposited on *Cryptomeria japonica* pollen grains from urban environments (Wang et al., 2009). Okuyama et al. describe the adsorption of atmospheric pollutants on the surface of *C. japonica* pollen from urban vs mountainous sites and

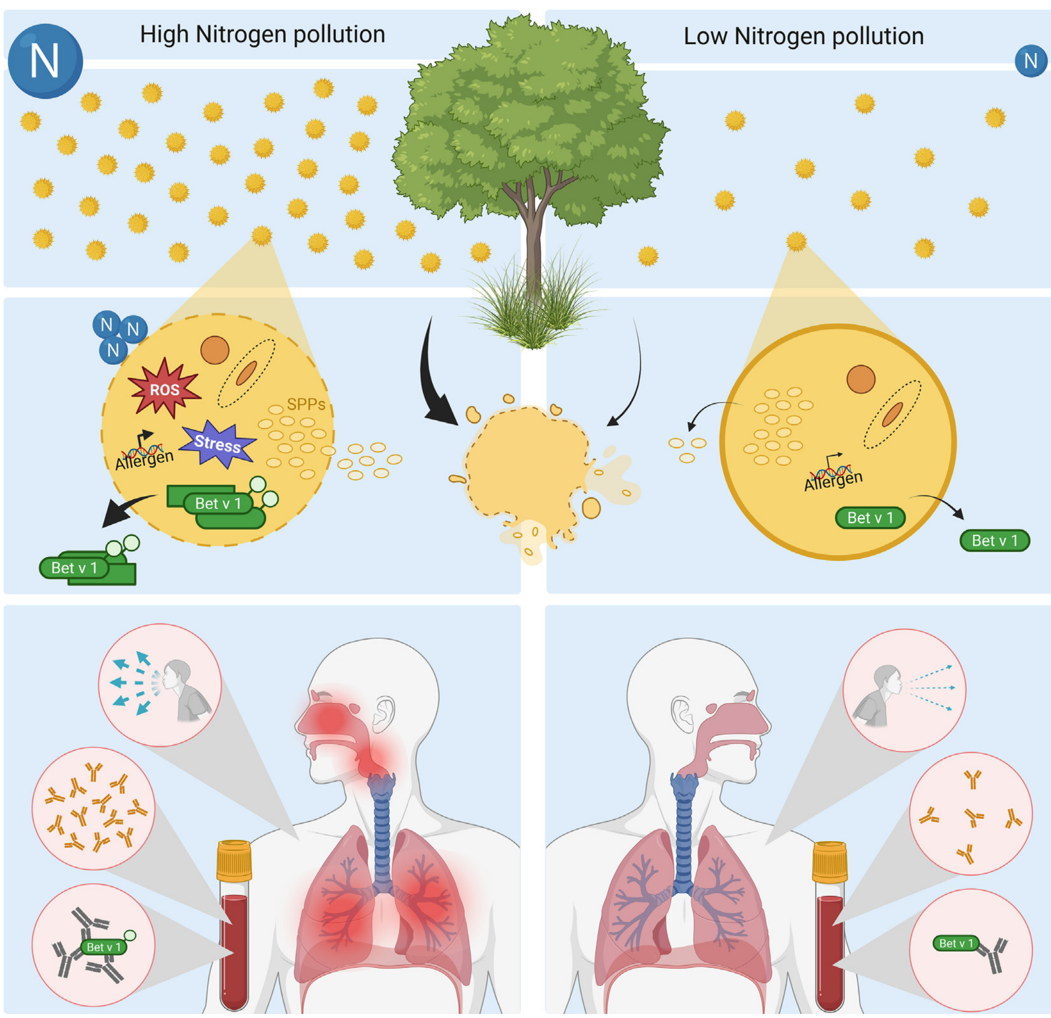


Fig. 6. Schematic overview of the potential impact of nitrogen pollution on pollen and their allergenic activity. High nitrogen pollution concentrations can lead to higher emissions of airborne pollen (upper panel), and result in changes such as thinner pollen cell wall, more pollen damage, attachment of pollutant particles on the surface, a greater degree of oxidative stress, increased sub-pollen particle (SPP) release, increased amount of allergenic proteins and increased release of allergenic proteins, post-translational modifications and structural changes of allergenic proteins, upregulation of stress-related genes and proteins, and enhanced allergenic transcript amounts (middle panel). These changes can affect the allergenic reactivity in humans via: increased irritation of the airway mucosa which facilitates pollinosis, increased sensitization, and allergic rhinitis prevalence, higher sIgE levels, and higher IgE recognition (bottom panel).

Table 3
Overview of mechanisms impacting the pollen grain membrane and morphology.

Mechanism of action	References
Attachment of pollutant particles on the surface of pollen grains	(Lu et al., 2014; Wang et al., 2009)
Absorption of atmospheric pollutants on the surface of pollen	(Okuyama et al., 2007)
Pollen surface acidification, leading to increased airway mucosa irritation	(Okuyama et al., 2007)
Pollen membrane damage, reduced pollen integrity, and more allergen release	(Zhou et al., 2021)
Pollen membrane damage and breakdown of pollen grain	(Chassard et al., 2015; Motta et al., 2006; Ouyang et al., 2016)
Membrane damage stimulates synthesis of membrane repair-related factors with allergenic potential	(Zhou et al., 2021)
Morphological pollen changes	(Lu et al., 2014; Rezanejad, 2009)
Pollen wall modifications leading to compromised pollen function	(Ribeiro et al., 2017; Smiljanic et al., 2019)

found significantly higher amounts of anthropogenic particles on the surface of pollen from the urban site. Also, NH_3 and certain acids (e.g. nitrous acid (HNO_2), and nitric acid (HNO_3)) are adsorbed and acidify the surface, which may increase irritation of the airway mucosa and may facilitate pollinosis (Okuyama et al., 2007). Other articles describe pollen membrane damage and therefore also reduced pollen integrity leading to more allergen release. Gaseous experimental NO_2 pollutant exposure, together with ozone (O_3), caused a damaged integrity of the *Platanus* pollen cell membrane, leading to more Pla a 3 allergen release (Zhou et al., 2021). Membrane damage could also stimulate the synthesis of membrane repair-related factors, such as the non-specific lipid transfer proteins (nsLTPs) Pla a 3, which could explain an increase of this allergenic protein in pollen (Zhou et al., 2021). Combined short-term experimental exposure of *Quercus mongolica* pollen to NO_2 and SO_2 significantly increased their fragility and disruption, ranging from increased fissure or breaks in the exine (the outer layer of a living pollen grain) leading to complete breakdown and release of cytoplasmic granules (Ouyang et al., 2016). Motta et al. observed fissures in the exine or complete breaking of the *Phleum pratense* pollen grains after experimental NO_2 exposure, while Chassard et al. did not observe any visual damage on the exine of *Phleum pratense* pollen after experimental NO_2 exposure (Chassard et al., 2015; Motta et al., 2006). However, Chassard et al. used pre-treated pollen from a commercial supplier which could explain the difference. Additionally, other morphological changes and membrane alterations have been described. *Thuja orientalis* pollen collected from polluted areas were smaller and more fragile, and the exines split faster (Rezanejad, 2009). Experimental exposure of *Platanus orientalis* pollen to pollutant gasses (NO_2, SO_2, NH_3) showed that pollen became swollen (Lu et al., 2014). In vitro exposure of *Platanus acerifolia* pollen to short-term atmospheric concentrations of NO_2/O_3 suggested that the atmospheric pollutants induced pollen wall modifications, which can compromise the pollen function (Ribeiro et al., 2017). *Phleum pratense* pollen collected in a polluted environment, with higher NO_2 concentrations, showed areas where the exine wall was thinner compared to pollen from a non-polluted area (Smiljanic et al., 2019).

Table 4
Overview of mechanisms impacting allergenic proteins and immune-stimulatory/modulatory mediators.

Mechanism of action	References
Post-translational modifications of allergenic proteins	
Oligomerization	(Backes et al., 2021)
Nitration	(Ackaert et al., 2014; Backes et al., 2021; Franze et al., 2005; Zhou et al., 2021)
Nitrosylation	(Zhao et al., 2016)
Oxidation	(Smiljanic et al., 2019; Zhou et al., 2021)
Protein structure changes	(Hong et al., 2018; Zhou et al., 2021)
Altered allergenic protein expression	(Beck et al., 2013; Bist et al., 2004; Lu et al., 2014; Obersteiner et al., 2016; Ribeiro et al., 2017; Ščevková et al., 2021; Zhao et al., 2016)
Altered transcript levels of allergenic proteins	(García-Gallardo et al., 2013; Lucas et al., 2020; Zhao et al., 2017)
Stress-related reactivity	(García-Gallardo et al., 2013; Lucas et al., 2020; Lucas et al., 2019; Rezanejad, 2009)

3.1.3. Allergen release

Pollen can also release allergens in the form of pollen cytoplasmic granules (PCGs), also called sub-pollen particles (SPPs). These small vesicles with a diameter of 0.1-1.0 μm can reach the lower airways. There are different types of SPP described, including starch granules, polysaccharide particles, and small amyloplast vesicles surrounded by a lipid membrane (Burkart et al., 2021; Visez et al., 2021). SPPs can be released upon rapid or excessive hydration, leading to pollen rupture and pollen bursting (Božič and Šiber, 2022; Burkart et al., 2021). An increase in membrane damage caused by nitrogen pollution can therefore lead to an increase in SPP release. Increased SPP release was already observed in *Phleum pratense* pollen collected in a polluted environment (Smiljanic et al., 2019). Also, *Phleum pratense* pollen that was experimentally exposed to high NO_2 concentrations showed an increased release of SPPs (Motta et al., 2006). Gaseous NO_2 pollutant exposure, together with O_3, damaged the integrity of the *Platanus* pollen cell membrane, leading to more SPP release (Zhou et al., 2021). Experimental NO_2 exposure, together with SO_2, caused damaged *Quercus mongolica* pollen leading to subsequent SPP release (Ouyang et al., 2016).

3.1.4. Pollen viability and germination

NO_2 exposure has been described to attribute to a decreased viability of *Betula pendula*, *Ostrya carpinifolia*, *Carpinus betulus, Quercus mongolica*, *Cercis siliquastrum,* and *Pinus nigra* pollen (Cuinica et al., 2014; Duro et al., 2013; Gottardini et al., 2008; Gottardini et al., 2004; Ouyang et al., 2016). Environmental NO_x exposure was negatively correlated with the pollen viability of *Pinus nigra* pollen (Gottardini et al., 2004). No difference in *Humulus* pollen viability was measured in samples collected over four locations with different atmospheric pollutant concentrations (including NO_2) in the atmosphere (Lu et al., 2020). Additionally, the pollen germination capacity was affected by nitrogen pollution. Experimental NO_2 exposure was described to decrease the pollen germination of *Betula pendula*, *Ostrya carpinifolia*, *Carpinus betulus*, and *Acer negundo* pollen (Cuinica et al., 2014; Sousa et al., 2012). Duro et al. found a negative correlation between the germination capacity of *Cercis siliquastrum* and environmental NO_2 but no affected capacity of *Spartium junceum* and *Robinia pseudoacacia*, while Galveias et al. found an increased germination capacity of *Dactylis glomerata* pollen by experimental NO_2 exposure, suggesting different pollen species sensitivity (Duro et al., 2013; Galveias et al., 2021). Taken together, nitrogen pollution generally leads to a decrease in pollen viability and depending on the pollen species to a decrease, increase, or no impact at all on the pollen germination capacity. It remains unknown how these changes could affect pollen allergenic reactivity, but a decreased viability could be accompanied by an increased allergen release, similar to when pollen membrane damage is occurring. The decrease in viability could also be an additional effect of pollutant attachment to the membrane, rather than a potential cause of increased allergen release.

3.1.5. Oxidative defense mechanisms

Exposure to atmospheric nitrogen pollution enhances allergenic activity by activating pollen oxidative defense mechanisms. Galveias et al. exposed *Dactylis glomerata* pollen in vitro to NO_2 and O_3 and established increased levels of reactive oxygen species (ROS) scavenging enzymes and an

Table 5
Overview of mechanisms impacting the allergenic reactivity.

Mechanism of action	References
Mouse/rat models	
Elevated antibody levels	(Gruijthuijsen et al., 2006; Zhou et al., 2021)
Enhanced inflammatory mediator production	(Gruijthuijsen et al., 2006; Zhou et al., 2021)
Promoted allergen sensitization via airway priming	(Bevelander et al., 2007)
Increased IgE-binding affinity	(Hong et al., 2018)
Human	
Elevated antibody levels	(Gruijthuijsen et al., 2006)
Altered IgE recognition	(Cuinica et al., 2014; Rogerieux et al., 2007; Smiljanic et al., 2019; Sousa et al., 2012; Zhao et al., 2016)
Enhanced inflammatory mediator production	(Chassard et al., 2015)
Adapted cellular response	(Ackaert et al., 2014; Chassard et al., 2015; Karle et al., 2012)
Higher skin prick test reactivity	(García-Gallardo et al., 2013)

elevated allergenic activity, described as amplified IgE-recognition of certain allergenic proteins (Galveias et al., 2021). They suggest this might be caused by a change in protein expression levels in response to the induced stress by pollutants, or to a change in antigen-antibody recognition patterns as a result of chemical modifications by pollutants, or a combination of both (Galveias et al., 2021). Smiljanic et al. found elevated antioxidative defense-related enzyme levels in *Phleum pratense* pollen collected from a highly polluted area, including NO_2 (Smiljanic et al., 2019). These articles support the hypothesis that nitrogen pollutants cause stress in pollen, leading to altered expression, including increased defense proteins of which many are allergens. Examples are Bet v 1, a pathogenesis-related (PR) protein upregulated upon infection and stress, or e.g. Pla a 3, an ns-LTP involved in stress-induced membrane adaptations (Yamada et al., 2020; Zhou et al., 2021).

3.1.6. Allergenic proteins and immune-stimulatory/modulatory mediators

We also found evidence that nitrogen pollutants can cause structural changes to allergenic proteins and immune-modulatory and -stimulatory pollen-associated lipid mediators (PALMs) in or released by the pollen grains (Table 4). Different post-translational modifications were found in *Phleum pratense* pollen collected from a polluted environment, which affected specific allergens by oxidative modifications (Smiljanic et al., 2019). The grass pollen allergen Phl p 5 showed chemical modifications, including oligomerization and nitration, after experimental O_3, NO_2, and peroxynitrite ($ONOO^-$) exposure (Backes et al., 2021). Also, enhanced protein nitrosylation was observed in ragweed pollen from plants grown under experimentally elevated NO_2 conditions (Zhao et al., 2016). Franze et al. showed that the birch pollen allergen Bet v 1 can be efficiently nitrated by polluted air exposure, which could provide a molecular rationale for the promotion of allergies by traffic-related atmospheric pollution (Franze et al., 2005). In vitro nitration of the major birch pollen allergen Bet v 1 lead to protein oligomerization and nitration of tyrosine residues involved in ligand binding of Bet v 1, possibly interfering with the ability of ligand-binding to Bet v 1 (Ackaert et al., 2014). As an example, they describe how lipopolysaccharides (LPS) would no longer be able to bind the hydrophobic cavity of Bet v 1. In an ex vivo T-cell line system, this resulted in reduced secretion of T helper (Th) 1-priming cytokines needed to counter-balance Th2 inflammation, thus potentially enhancing the immunogenicity of nitrated Bet v 1 (Ackaert et al., 2014). Surprisingly, pollen collected from high NO_2 exposed birch trees showed no difference in Bet v 1 content, and no difference in PALM content, including prostaglandin E_2 and leukotriene B_4 (Beck et al., 2013).

In the *Platanus* pollen allergen Pla a 3, experimental NO_2/O_3 exposure was reported to result in the oxidation of methionine at sites 1 and 17, and nitration of tyrosine at site 106 (Zhou et al., 2021). This could change the protein spatial structure, with a looser Pla a 3 structure but increased stability (Zhou et al., 2021). Hong et al. found a novel disulfide bond between oxidized sulfhydryl groups of two neighboring cysteine molecules in the profilin protein Hum j 1 after experimental exposure to NO_2 and O_3, leading to an increased IgE-binding affinity and allergenic reactivity (Hong et al., 2018). The adapted protein structure was looser, which facilitates the exposure of more internal epitopes, but also more stable, enabling them to remain in the air for a longer time (Hong et al., 2018). Experimental NO_2 exposure was shown to be unreactive with the external lipid fraction of birch pollen grains, but it could promote the release of cytoplasmic lipids by facilitating pollen rupture (Farah et al., 2021). Obersteiner et al. showed that on-site nitrogen pollution was correlated with the microbial load of pollen, and also partly correlated to different allergenic reactivity parameters (e.g. Bet v 1 content and PALMs). This suggests that microbial diversity could impact the expression of allergenic proteins and immune-modulatory and -stimulatory PALMs in pollen (Obersteiner et al., 2016). Increasing flavonoid levels were observed in *Thuja orientalis* pollen collected from polluted areas, suggesting a protective plant response including an increase in antioxidant enzymes and protection-related secondary metabolite genes (e.g. flavonoids which can induce pollen development, germination, and tube growth) (Rezanejad, 2009). *Lolium perenne* pollen collected in Madrid (in Spain, among the cities with the worst air quality in terms of NO_2) showed significantly higher stress-related enzymatic activity, including NADPH oxidase activity and hydrogen peroxide (H_2O_2) levels, than pollen collected in Ciudad Real (a city with less NO_2 pollution). It has been demonstrated previously that NADPH oxidase activity and H_2O_2 levels can augment IgE production and allergic airway inflammation induced by pollen allergens, suggesting a higher allergenic reactivity of pollen-related to higher atmospheric pollution (Lucas et al., 2019). All these articles describe several alterations in both structure and availability of various allergy-stimulation mediators, which could contribute to increased pollen-allergenic reactivity.

Additionally, several studies described increasing allergenic protein expression levels in pollen caused by nitrogen pollution. Experimental pollutant gas exposure of pollen in the form of NO_2 has been shown to increase the allergenic proteins Pla a 1 and Pla a 2 (Lu et al., 2014; Ribeiro et al., 2017). Experimental exposure of *Ambrosia* to increased NO_2 concentrations resulted in a changed proteomic pattern, including an up-regulation of several Amb a 1 isoforms (Zhao et al., 2016). In Bratislava, it has been observed that NO_2 in the air could increase the Phl p 5 allergen concentration per pollen, described as pollen potency (Ščevková et al., 2021). On the other hand, Beck et al. did not find any correlation between Bet v 1 content and environmental NO_2 exposure (Beck et al., 2013). Bist et al. even showed that the total soluble protein content of *Ricinus communis* pollen after experimental NO_2 exposure had a significant decrease compared to unexposed pollen (Bist et al., 2004). Overall, most pollen show increased allergenic protein levels after nitrogen pollutant exposure. However, the effects differed between different pollen types.

Furthermore, studies evaluated transcript levels of allergenic proteins related to nitrogen pollution. Experimental NO_2-fumigation was shown to induce stress in *Ambrosia* plants and enhance allergenic transcript amounts (‘Amb a’ allergen encoding transcripts including Amb a 1, Amb a 3, Amb a 8, Amb a 9 and Amb a 11) (Zhao et al., 2017). Also, *Pinus radiata* pollen collected in a highly polluted environment showed an upregulation of three stress-related genes (García-Gallardo et al., 2013). This could indicate that pollutants cause stress on plants, affect their protein expression, and increase the production of PR proteins (García-Gallardo et al., 2013). Moreover, *Lolium perenne* pollen collected in Madrid, under higher concentrations of NO_2 and SO_2 compared to Ciudad Real, showed overexpression of heat shock proteins (HSP), glycoside hydrolase family 17, proteins with EF-HAND motifs, pectinesterases, LTPs, and thaumatin (Lucas et al., 2020). All these proteins have a potential relation to other allergenic proteins but have not been described as possible allergens of *L. perenne* (Lucas et al., 2020). Specifically, HSP are upregulated in stress situations and have been described as an allergy-causing agent e.g. the hazelnut pollen allergen Cor a 10 (HSP70). The glycoside hydrolase family 17 includes several enzymes, including the 1,3-beta-glucanase known as the olive pollen allergen Ole e 9. Proteins with EF-HAND motifs are Ca^{2+} binding proteins and have been described as allergens, e.g. the birch pollen allergen Bet v 3 (polcalcin-like protein with 4 EF-HAND motifs). The pectinesterase enzyme known as Sal k 1 (pectin methylesterase), is a major saltwort pollen allergen. LTPs and thaumatin proteins are described as PR proteins, eg. the hazelnut allergen Cor a 8 (ns-LTP type 1) and the olive pollen allergen Ole e 13 (thaumatin). The exact mechanism of how atmospheric pollutants lead to protein upregulation remains unknown but is generally proposed to be stress-induced.

3.1.7. Allergenic reactivity

Atmospheric nitrogen pollutants can also affect the allergenic reactivity of pollen allergens (Table 5). First, several studies showed in mice and rat models elevated antibody levels towards allergens from a nitrogen-polluted condition, and increased allergic disease measurements. Evaluation of the allergenic reactivity of Pla a 3 after experimental NO_2 exposure revealed an enhanced ability to induce an immune response in mice, characterized by more IgG and IgE antibody production, more severe allergic symptoms in the lung tissue (more inflammatory cells, and more oxidative stress) and higher interferon (IFN)-gamma and interleukin (IL)-4 levels, indicating the significantly higher allergenic reactivity of the exposed Pla a 3 protein (Zhou et al., 2021). Atmospheric nitrogen pollution has previously been shown to be able to induce nitration in proteins, hence studies also investigated the impact of in vitro protein nitration on its allergenic reactivity. The immunogenic and allergenic properties of in vitro nitrated rBet v 1a were analyzed by Gruijthuijsen et al. and they found elevated specific IgE (sIgE), IgG1, and IgG2a levels in sensitized mice and enhanced IL-5 production, IFN-gamma production and proliferation of murine splenocytes (Gruijthuijsen et al., 2006). Other studies also investigated the impact of atmospheric nitrogen pollution to prime the airways and increase reactivity towards inhaled particles. It has been shown by Bevelander et al. that NO_2 exposure of C75BL/6 mice promotes allergen sensitization, resulting in allergic airway disease in response to the otherwise not harmful inhaled antigen ovalbumin (OVA) (Bevelander et al., 2007). Increased IgE-binding affinity was found in immunized rats towards rHum j 1 after experimental NO_2 exposure (Hong et al., 2018). On the contrary, no relationship was found between the allergenic reactivity of *Humulus* pollen, measured from sensitized rat's serum against *Humulus* allergens, environmental NO_2 pollutant levels (Lu et al., 2020). However, pollen was collected from four different locations and there was almost no difference in NO_2 concentration between them (Lu et al., 2020).

In humans, *Betula pendula*, *Ostrya carpinifolia*, *Carpinus betulus*, and *Acer negundo* pollen, experimentally exposed to NO_2 levels, showed higher IgE recognition by patient sera sensitized to pollen (Cuinica et al., 2014; Sousa et al., 2012). Also, *Ambrosia* pollen from experimentally NO_2-treated plants showed significantly higher IgE recognition (Zhao et al., 2016). On the contrary, *Phleum pratense* pollen collected from a polluted environment showed lower IgE binding to pollen extracts in several patients, compared to pollen from a less polluted environment (Smiljanic et al., 2019). In line with this, Rogerieux et al. found that experimental exposure of *Phleum pratense* pollen to gaseous pollutants (including NO_2) led to a decrease in allergen IgE recognition by pollen-allergic patient sera (Rogerieux et al., 2007). They explain that they found acidification of several allergens and that these modifications might affect allergen-IgE detection, or that the decreased recognition is due to allergen loss during treatment (Rogerieux et al., 2007). Chassard et al. found that human dendritic cells, exposed to *Phleum pratense* pollen after experimental NO_2 exposure, favored the production of CCL22 which is known to promote Th2-cell responses and diminished CXCL10 production related to Th1-cell responses (Chassard et al., 2015). This demonstrates that NO_2 uptake by *Phleum pratense* pollen directly correlates with an increased Th2-cell response in human dendritic cells (Chassard et al., 2015). *Pinus radiata* pollen allergenic reactivity measured by skin prick testing was observed to be higher in pollen collected in a rural area, compared to an area near a high-traffic road (García-Gallardo et al., 2013). However, higher O_3 exposure values were measured in the rural area, which might also affect the allergenic reactivity (García-Gallardo et al., 2013). Several studies also took a closer look at the impact of protein nitration on its allergenic reactivity in humans. Gruijthuijsen et al. analyzed sera from birch pollen-allergic patients and found higher amounts of functional sIgE against in vitro nitrated rBet v 1a compared to untreated rBet v 1a. Additionally, a competition assay suggested that these patients may possess some IgE specifically recognizing the nitrated epitopes of Bet v 1a (Gruijthuijsen et al., 2006). In vitro nitration of Bet v 1a has also been shown to enhance both the quantity and quality of allergen-derived human leukocyte antigen complex (HLA-DR)-associated peptides, which suggests that nitration of Bet v 1a alters the antigen processing and presentation via HLA-DR (Karle et al., 2012). Lastly, in vitro nitrated Bet v 1 showed an enhanced proliferation of birch pollen-specific T cell lines, a prolonged resistance towards endolysosomal degradation, and a decreased secretion of Th1- and pro-inflammatory cytokines by dendritic cells, which corroborates with the possible involvement in the observed increased allergenic reactivity (Ackaert et al., 2014).

3.1.8. Patient symptoms and allergy severity

Various studies describe how atmospheric nitrogen pollution can impact patient allergic symptoms and disease severity (Table 6). Melén et al. investigated associations between IgE sensitization towards common food and inhalant allergens, and atmospheric pollution exposure in 4 European birth cohorts in Sweden, Germany, and The Netherlands. According to their results, atmospheric pollution did not seem to increase the overall risk of allergic sensitization, but sensitization to birch pollen as well as the grass pollen allergen Phl p 1 was associated with specific pollutants (NO_2 and $PM_{2.5}$, respectively) (Melén et al., 2021). Association between NO_2 and elevated IgE levels and skin prick test reactivity were found for indoor allergens but not for outdoor allergens, including grass and tree pollen (Janssen et al., 2003). Riediker et al. found that rhinoconjunctivitis symptoms in pollen-allergic individuals were strongly influenced by atmospheric pollutants, including NO_x, and suggest that rhinoconjunctival tissue is highly sensitive to irritant stimuli during an ongoing inflammation which could also increase the susceptibility towards allergens (Riediker et al., 2001). Berger et al. analyzed the relationship of patient symptom data to pollen with air quality parameters but only found positive associations with O_3 (Berger et al., 2020). A categorical principal component analysis by Cabrera et al. revealed a weak relationship between patient symptom scores and NO_2 concentrations (Cabrera et al., 2021). Pollen-allergic asthmatic patients living in a more polluted region, including higher NO_2 concentrations, presented more symptoms and had a worse clinical course (Feo Brito et al., 2007). Carlsen et al. unexpectedly observed a negative association between atmospheric NO_x exposure and allergic symptoms in birch pollen-allergic asthmatic patients (Carlsen et al., 2022). Feo-Brito et al. compared symptoms and medication requirements of asthmatic patients allergic to grass pollen from Madrid (high urban pollution) and

Table 6
Overview of parameters used to evaluate patient symptoms and allergy severity.

Mechanism of action	References
Rhino-conjunctivitis symptoms	(Barck et al., 2005a; Berger et al., 2020; Cabrera et al., 2021; Carlsen et al., 2022; Feo Brito et al., 2007; Feo-Brito et al., 2022; Riediker et al., 2001)
Elevated IgE levels	(Janssen et al., 2003)
Skin prick test reactivity	(Janssen et al., 2003)
Medication requirements	(Feo-Brito et al., 2022; Grundström et al., 2017)
Allergen-induced inflammatory response	(Barck et al., 2005b; Barck et al., 2005a; Feo-Brito et al., 2022; Steerenberg et al., 2003)

Ciudad Real (low pollution) (Feo-Brito et al., 2022). Patients from the Madrid region had a worse clinical evolution because of higher NO_2 concentrations, which was linked with a higher capacity of pollen to activate T-CD8$^+$ and natural killer (NK)-cells (Feo-Brito et al., 2022). Grundström et al. found that the over-the-counter sales of antihistamines were higher during situations with simultaneously high birch pollen and high atmospheric pollution concentrations, including NO_2 (Grundström et al., 2017). Barck et al. found no differences in symptoms and pulmonary function of allergic asthmatic patients after experimental NO_2 exposure, compared to purified air (Barck et al., 2005a). However, they did find evidence that experimental NO_2 exposure can prime circulating eosinophils and enhance their activity, which could relate to enhanced airway inflammatory reactions (Barck et al., 2005a). They also investigated the effect of short-term experimental NO_2 exposure on the upper airways after nasal allergen challenge and found no noticeable priming effect on inflammatory cells and mediators in the upper airways of the subsequent allergic response (Barck et al., 2005b). Lastly, Steerenberg et al. did not observe any additional pro-inflammatory effect of environmental NO_2 pollution in pollen-allergic children, indicating it did not facilitate allergen-induced inflammatory responses (Steerenberg et al., 2003).

3.1.9. Allergy prevalence

A cross-sectional study from the U.S. found that poor air quality, marked by elevated NO_2 concentrations, was correlated with an increased prevalence of allergic rhinitis (Bhattacharyya, 2009). In another study, correlation analysis indicated that NO_x was significantly associated with the daily number of grass pollen-positive patients in Beijing, and with pollen concentrations of *Artemisia, Humulus,* and *Chenopodium* (Ouyang et al., 2019). While Gruzieva et al. found that traffic-related atmospheric pollution (including NO_x) did not impact the overall risk of allergic sensitization in children, an increased pollen sensitization at the age of 4 was associated with atmospheric pollution exposure during the first year of life (Gruzieva et al., 2012).

3.2. Impact of soil nitrogen pollution

Only three studies found with our search strategy focused on the impact of nitrogen soil pollution on pollen allergy, two of which focused on changes in plant physiology while only one article described changes in an allergenic protein. First of all, Wan et al. investigated how an increase in soil nitrogen nutrition affects the composition and spatial location of ω-gliadins of wheat grains (Wan et al., 2014). They suggest that the increased accumulation of these proteins can be due to the increase in gene expression, resulting from the transport of surplus nitrogen (amino acids) into these cells under conditions of excess nitrogen supply (Wan et al., 2014). The ω-gliadins are major allergenic proteins of wheat and are often causing severe food allergy symptoms in wheat-allergic patients. However, they are not implicated in allergic rhinitis or allergic asthma after wheat pollen exposure. In a meta-analysis by Peñuelas et al., increased gluten and gliadin levels in wheat crops grown under elevated nitrogen conditions were observed, which positively correlated with coeliac disease prevalence (Penuelas et al., 2020). Similar mechanisms could be involved in plants that are producing allergenic pollen. Jamieson et al. described how nitrogen enrichment positively affected plant performance and defense traits of *Linaria dalmatica*, suggesting an influence of nitrogen enrichment on plant invasiveness (Jamieson et al., 2012). As described before, many proteins involved in plant defense mechanisms are described to be allergenic proteins, which could contribute to the increased allergenic reactivity. Nitrate, an important agricultural fertilizer, is also widely found in leafy vegetables and is taken up by the human body via various mechanisms (Zhu et al., 2021). Different studies have already found associations between these chemicals and human health, which could also be a possible mechanism leading to increasing allergenic reactivity. However, Zhu et al. did not find any association between urinary nitrate levels and allergic symptoms, only positive associations with eczema were found (Zhu et al., 2021). Taken together, there is some evidence that nitrogen soil pollution, mainly in the form of fertilization, could affect allergenic proteins and contribute to an increase in allergenic reactivity. However, the literature is limited and there is a need for definite observational and experimental studies directly linking N fertilization with pollen allergenicity.

3.3. Impact of aqueous nitrogen pollution on pollen allergy

Nitrogen pollution in the water is mainly caused by the wet deposition of atmospheric nitrogen pollution and soil leaching of excess nitrogen fertilizers into streams and rivers. We found only two articles that dealt with the possible impact of nitrogen pollution through water on human health or pollen allergy specifically. Similarly as described in the previous paragraph, Zhu et al. described how nitrates can be found in contaminated water and taken up by the human body (Zhu et al., 2021). However, no associations were found with allergic-related outcomes (Zhu et al., 2021). Increased water nitrogen levels are known to be able to overstimulate aqueous plant growth, but Ghiani et al. also found the ability to modify allergenic proteins. They showed how nitrate ions in an aqueous solution can result in protein nitration of the Phl p 2 allergen (Ghiani et al., 2016). Immunoblot analysis using sera from grass pollen-allergic patients showed modifications in the allergic response after allergen treatment with nitrate solutions. They generally observed an enhanced IgE reactivity towards the nitrated Phl p 2 protein, suggesting that protein nitration could occur in a polluted water environment.

4. Discussion

Nitrogen pollution can be air-, soil-, or waterborne. Our scoping review indicates that the majority of studies focus on the impact of atmospheric nitrogen pollution on pollen, pollen allergens, and their allergenic reactivity (Table S2).

There is ample evidence that atmospheric nitrogen pollution affects pollen allergy in many ways and via various mechanisms. The most prominently described are increasing airborne pollen emissions, modifications of pollen structure and cell wall integrity, increasing allergen expression and release, and increased pollen allergenic reactivity leading to more symptoms in patients (Table 2). Most studies look at the impact of multiple atmospheric pollutants in concert, not just nitrogen because, in typical polluted environments, multiple pollutants co-occur. This could affect the results concerning the impact of nitrogen exposure alone, as the interactions between different atmospheric pollutants and the health effects of exposure to multiple pollutants are insufficiently known. Different atmospheric pollutants can have synergistic or antagonistic effects, leading to differences in pollen (allergen) characteristics that would not occur when using only nitrogen pollutants (Galveias et al., 2021; Ribeiro et al., 2017; Shiraiwa et al., 2012). This complicates disentangling the impact of only airborne nitrogen pollution. Therefore, studies focusing on nitrogen pollution alone can provide better insights (Chassard et al., 2015; Cuinica et al., 2014; Zhao et al., 2016). Also, experimental exposure concentrations of the pollutants sometimes far exceed those observed during normal exposure, questioning their relevance (Bist et al., 2004; Galveias et al., 2021; Hong et al., 2018; World Health Organization, 2021; Zhou et al., 2021). For example, NO_2 exposure in different experimental (in vitro) setups can range from 80 ppm to 200 ppm for polluted conditions, while other studies reported values ranging from 400 to even more than 1000 ppb (Table S3). Additionally, in studies investigating the differences between pollen from highly polluted regions and less polluted regions, also variability between the pollutant exposure levels was encountered. For example, Scevkova et al. evaluated the relationship between pollen levels and air pollution parameters and found a negative correlation with NO_2 exposure levels (Ščevková et al., 2021). The annual average NO_2 measurements were 18.9 μg/m^3 (2019) and 16.6 μg/m^3 (2020). On the contrary, Sabo et al. found a positive correlation with NO_2 exposure and measured an average value of 31.9 μg/m^3 (2009-2013). (Sabo et al., 2016). The exact impact of varying NO_2 exposure levels in these settings remains to be determined but could (in part) explain the observed differences. Additionally, observational studies on the impact of environmental pollution are subject to a great amount of potentially confounding factors (e.g. weather conditions, temperature, humidity), making it even more difficult to draw firm conclusions. This might also partly explain why some studies found no correlation between airborne pollen concentrations and atmospheric pollutant concentrations. Next, most studies focus on the effect of atmospheric nitrogen pollutants on pollen that are already atmospherically dispersed. This could have a different effect, compared to when pollen is not released yet and the plant itself is exposed to higher nitrogen pollutant levels, for example through N fertilization.

Remarkably, a few contradictory articles might indicate that the effect caused by nitrogen pollution could be plant species dependent. Some outcome parameters were different among pollen types showing that nitrogen pollution could have opposite effects on pollen from different taxa (García-Gallardo et al., 2013; Sousa et al., 2012). Additionally, there could also be a difference between a possible direct effect and the indirect effect of nitrogen deposition caused by atmospheric pollution. High nitrogen pollution levels are also associated with an increase in nitrogen deposition leading to nitrogen soil enrichment. This means that atmospheric nitrogen pollution could also have an indirect effect on pollen properties and their allergenic reactivity. This could also explain differences between pollen species, as plants react differently to nitrogen enrichment. Some species may thrive under high nitrogen conditions, suppressing other less dominant species.

One of the most often described mechanisms behind the increasing allergenic reactivity caused by atmospheric nitrogen pollution is protein nitration. Many studies have shown that atmospheric pollution can cause protein nitration, affecting its allergenic reactivity. However, some studies use proteins affected by nitrogen pollution, while others use in vitro nitrated proteins. According to Reinmuth-Selzle et al., the efficiency and specific location of nitration can vary based on the type of nitrating agent and reaction conditions used. (Reinmuth-Selzle et al., 2014). This could lead to different allergenic proteins with different post-translational modifications, which could have different effects on their reactivity. This should be considered when evaluating studies on the impact of nitration on pollen allergens and their allergenic reactivity.

This scoping review found limited information on the effects of soil and water nitrogen pollution on pollen allergenicity. Although some possible mechanisms were identified, more research is needed in this area to fill the gap in current knowledge (Ceulemans et al., 2023). E.g., explore the identified mechanisms in existing literature, or discover additional pathways of soil and aqueous nitrogen pollution and how they can affect pollen allergenic reactivity and the related disease burden. In our review, we found many post-production effects of nitrogen on pollen or pollen allergens. Additional research on pre-production effects, in the plant, during the processes leading to the pollen formation, might be more informative, especially regarding soil and water effects.

Due to the wide variety of processes that are studied in the literature on nitrogen and pollen allergy, it was not feasible to conduct a meta-analysis to estimate the overall effect of nitrogen pollution on pollen allergenicity or pollen allergic disease burden. Also, the broad meaning of the environmental impact of nitrogen pollution led to a large number of search results with an important amount of noise.

5. Conclusion

Our scoping review showed that atmospheric nitrogen pollution affects various aspects of pollen allergy, including airborne pollen concentrations, pollen grain morphology, allergen release, pollen viability and germination, oxidative defense mechanisms, allergen protein content and its allergenic reactivity, patient symptoms, disease severity, and prevalence. However, research on soil or aqueous nitrogen pollution is scarce and does not provide clear conclusions. Moreover, there is a lack of controlled studies evaluating the impact of nitrogen pollution on pollen allergy, making it difficult to establish a cause-and-effect relationship. Taken together, the evidence documented in our review highlights an important role of nitrogen in pollen allergy, but further studies are needed to elucidate the precise causal pathways.

Funding sources

The authors acknowledge funding of the NITROPOL-BE project (B2/212/P1/NITROPOL-BE) by the Belgian Science Policy Office (BELSPO) in the framework of Belgian Research Action through Interdisciplinary Networks (BRAIN-be 2.0). RS is supported by an FWO senior clinical investigator fellowship (1805518N, 1805523N). Funders had no role in the design and preparation of the manuscript.

CRediT authorship contribution statement

Paulien Verscheure: Methodology, Writing – original draft, Visualization. **Olivier Honnay:** Writing – review & editing. **Niko Speybroeck:** Writing – review & editing. **Robin Daelemans:** Writing – review & editing. **Nicolas Bruffaerts:** Writing – review & editing. **Brecht Devleesschauwer:** Writing – review & editing. **Tobias Ceulemans:** Writing – review & editing. **Laura Van Gerven:** Writing – review & editing. **Raf Aerts:** Writing – review & editing. **Rik Schrijvers:** Conceptualization, Writing – review & editing, Supervision.

Data availability

No data was used for the research described in the article.

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.

Acknowledgments

The authors would like to thank Thomas Vandendriessche, Anouk D'Hont, and Eline Vancoppenolle, the biomedical reference librarians of the KU Leuven Libraries – 2Bergen – learning Centre Désiré Collen (Leuven, Belgium), for their help in conducting the systematic literature search. We would also like to thank Nicolas Dendoncker from the NITROPOL-BE consortium for his suggestions on the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.164801.

References

Ackaert, C., Kofler, S., Horejs-Hoeck, J., Zulehner, N., Asam, C., von Grafenstein, S., Fuchs, J.E., Briza, P., Liedl, K.R., Bohle, B., Ferreira, F., Brandstetter, H., Oostingh, G.J., Duschl, A., 2014. The impact of nitration on the structure and immunogenicity of the major birch pollen allergen bet v 1.0101. PLoS One 9, 1–11. https://doi.org/10.1371/journal.pone.0104520.

Asam, C., Hofer, H., Wolf, M., Aglas, L., Wallner, M., 2015. Tree pollen allergens-an update from a molecular perspective. Allergy 70, 1201–1211. https://doi.org/10.1111/all.12696.

Backes, A.T., Reinmuth-Selzle, K., Leifke, A.L., Ziegler, K., Krevert, C.S., Tscheuschner, G., Lucas, K., Weller, M.G., Berkemeier, T., Pöschl, U., Fröhlich-Nowoisky, J., 2021. Oligomerization and nitration of the grass pollen allergen phl p 5 by ozone, nitrogen dioxide and peroxynitrite: reaction products, kinetics and health effects. Int. J. Mol. Sci. 22.

Barck, C., Lundahl, J., Halldén, G., Bylin, G., 2005a. Brief exposures to NO2 augment the allergic inflammation in asthmatics. Environ. Res. 97, 58–66.

Barck, C., Lundahl, J., Holmström, M., Bylin, G., 2005b. Does nitrogen dioxide affect inflammatory markers after nasal allergen challenge? Am. J. Rhinol. 19, 560–566.

Beck, I., Jochner, S., Gilles, S., McIntyre, M., Buters, J.T.M., Schmidt-Weber, C., Behrendt, H., Ring, J., Menzel, A., Traidl-Hoffmann, C., 2013. High environmental ozone levels lead to enhanced allergenicity of birch pollen. PLoS One 8, e80147. https://doi.org/10.1371/journal.pone.0080147.

Berger, M., Bastl, K., Bastl, M., Dirr, L., Hutter, H.P., Moshammer, H., Gstöttner, W., 2020. Impact of air pollution on symptom severity during the birch, grass and ragweed pollen period in Vienna, Austria: importance of O3 in 2010–2018. Environ. Pollut. 263.

Bernstein, D.I., Schwartz, G., Bernstein, J.A., 2016. Allergic rhinitis: mechanisms and treatment. Immunol. Allergy Clin. N. Am. 36, 261–278. https://doi.org/10.1016/J.IAC.2015.12.004.

Bevelander, M., Mayette, J., Whittaker, L.A., Paveglio, S.A., Jones, C.C., Robbins, J., Hemenway, D., Akira, S., Uematsu, S., Poynter, M.E., 2007. Nitrogen dioxide promotes allergic sensitization to inhaled antigen. J. Immunol. 179, 3680–3688. https://doi.org/10.4049/JIMMUNOL.179.6.3680.

Bhattacharyya, N., 2009. Air quality influences the prevalence of hay fever and sinusitis. Laryngoscope 119, 429–433.

Bist, A.P., It, T., Bhatnagar, A.K., Singh, A.B., 2004. Variability in protein content of pollen of Castor bean (Ricinus communis) before and after exposure to the air pollutants SO2 and NO2. Grana 43, 94–100. https://doi.org/10.1080/00173130410019316.

Bobbink, R., Hicks, K., Galloway, J., Spranger, T., Alkemade, R., Ashmore, M., Bustamante, M., Cinderby, S., Davidson, E., Dentener, F., Emmett, B., Erisman, J.-W., Fenn, M., Gilliam, F., Nordin, A., Pardo, L., de Vries, W., 2010. Global assessment of nitrogen deposition effects on terrestrial plant diversity: a synthesis. Ecol. Appl. 20, 30–59. https://doi.org/10.1890/08-1140.1.

Božič, A., Šiber, A., 2022. Mechanics of inactive swelling and bursting of porate pollen grains. Biophys. J. 121, 782–792. https://doi.org/10.1016/J.BPJ.2022.01.019.

Brożek, J.L., Bousquet, J., Agache, I., Agarwal, A., Bachert, C., Bosnic-Anticevich, S., Brignardello-Petersen, R., Canonica, G.W., Casale, T., Chavannes, N.H., Correia de Sousa, J., Cruz, A.A., Cuello-Garcia, C.A., Demoly, P., Dykewicz, M., Etxeandia-Ikobaltzeta, I., Florez, I.D., Fokkens, W., Fonseca, J., Hellings, P.W., Klimek, L., Kowalski, S., Kuna, P., Laisaar, K.-T., Larenas-Linnemann, D.E., Lødrup Carlsen, K.C., Manning, P.J., Meltzer, E., Mullol, J., Muraro, A., O'Hehir, R., Ohta, K., Panzner, P., Papadopoulos, N., Park, H.-S., Passalacqua, G., Pawankar, R., Price, D., Riva, J.J., Roldán, Y., Ryan, D., Sadeghirad, B., Samolinski, B., Schmid-Grendelmeier, P., Sheikh, A., Togias, A., Valero, A., Valiulis, A., Valovirta, E., Ventresca, M., Wallace, D., Waserman, S., Wickman, M., Wiercioch, W., Yepes-Nuñez, J.J., Zhang, L., Zhang, Y., Zidarn, M., Zuberbier, T., Schünemann, H.J., 2017. Allergic rhinitis and its impact on asthma (ARIA) guidelines-2016 revision. J. Allergy Clin. Immunol. 140, 950–958. https://doi.org/10.1016/j.jaci.2017.03.050.

Burkart, J., Gratzl, J., Seifried, T.M., Bieber, P., Grothe, H., 2021. Isolation of subpollen particles (SPPs) of birch: SPPs are potential carriers of ice nucleating macromolecules. Biogeosciences 18, 5751–5765. https://doi.org/10.5194/bg-18-5751-2021.

Cabrera, M., Subiza, J., Fernández-Caldas, E., Garzón García, B., Moreno-Grau, S., Subiza, J.L., 2021. Influence of environmental drivers on allergy to pollen grains in a case study in Spain (Madrid): meteorological factors, pollutants, and airborne concentration of aeroallergens. Environ. Sci. Pollut. Res. Int. 28, 53614–53628.

Carlsen, H.K., Haga, S.L., Olsson, D., Behndig, A.F., Modig, L., Meister, K., Forsberg, B., Olin, A.C., 2022. Birch pollen, air pollution and their interactive effects on airway symptoms and peak expiratory flow in allergic asthma during pollen season – a panel study in Northern and Southern Sweden. Environ. Health 21.

Celebi Sozener, Z., Ozdel Ozturk, B., Cerci, P., Turk, M., Gorgulu Akin, B., Akdis, M., Altiner, S., Ozbey, U., Ogulur, I., Mitamura, Y., Yilmaz, I., Nadeau, K., Ozdemir, C., Mungan, D., Akdis, C.A., 2022. Epithelial barrier hypothesis: effect of the external exposome on the microbiome and epithelial barriers in allergic disease. Allergy 77, 1418–1449. https://doi.org/10.1111/all.15240.

Ceulemans, T., Stevens, C.J., Duchateau, L., Jacquemyn, H., Gowing, D.J.G., Merckx, R., Wallace, H., van Rooijen, N., Goethem, T., Bobbink, R., Dorland, E., Gaudnik, C., Alard, D., Corcket, E., Muller, S., Dise, N.B., Dupré, C., Diekmann, M., Honnay, O., 2014. Soil phosphorus constrains biodiversity across European grasslands. Glob. Chang. Biol. 20, 3814–3822. https://doi.org/10.1111/gcb.12650.

Ceulemans, T., Verscheure, P., Shadouh, C., Van Acker, K., Devleesschauwer, B., Linard, C., Dendoncker, N., Speybroeck, N., Bruffaerts, N., Honnay, O., Schrijvers, R., Aerts, R., 2023. Environmental degradation and the increasing burden of allergic disease: the need to determine the impact of nitrogen pollution. Front. Allergy 4, 6. https://doi.org/10.3389/FALGY.2023.1063982.

Chassard, G., Choel, M., Gosselin, S., Vorng, H., Petitprez, D., Shahali, Y., Tsicopoulos, A., Visez, N., 2015. Kinetic of NO2 uptake by Phleum pratense pollen: chemical and allergenic implications. Environ. Pollut. 196, 107–113.

Chico-Fernández, J., Ayuga-Téllez, E., 2022. Analysis of pollen concentrations from various tree pollen types and their interrelation with different airborne pollutants in the Madrid region (Spain). Sustainability 14. https://doi.org/10.3390/su14095259.

Cuinica, L.G., Abreu, I., Esteves da Silva, J., 2014. Effect of air pollutant NO_2 on Betula pendula, Ostrya carpinifolia and Carpinus betulus pollen fertility and human allergenicity. Environ. Pollut. 186, 50–55. https://doi.org/10.1016/j.envpol.2013.12.001.

D'Amato, G., Cecchi, L., 2008. Effects of climate change on environmental factors in respiratory allergic diseases. Clin. Exp. Allergy 38, 1264–1274. https://doi.org/10.1111/j.1365-2222.2008.03033.x.

D'Amato, G., Cecchi, L., Bonini, S., Nunes, C., Annesi-Maesano, I., Behrendt, H., Liccardi, G., Popov, T., van Cauwenberge, P., 2007. Allergenic pollen and pollen allergy in Europe. Allergy 62, 976–990. https://doi.org/10.1111/j.1398-9995.2007.01393.x.

Damgaard, C., Jensen, L., Frohn, L.M., Borchsenius, F., Nielsen, K.E., Ejrnæs, R., Stevens, C.J., 2011. The effect of nitrogen deposition on the species richness of acid grasslands in Denmark: a comparison with a study performed on a European scale. Environ. Pollut. 159, 1778–1782. https://doi.org/10.1016/j.envpol.2011.04.003.

Dispenza, M.C., 2019. Classification of hypersensitivity reactions. Allergy Asthma Proc. 40, 470–473. https://doi.org/10.2500/AAP.2019.40.4274.

Doll, R.J., Joseph, N.I., McGarry, D., Jhaveri, D., Sher, T., Hostoffer, R., 2019. Epidemiology of Allergic Diseases BT - Allergy and Asthma: The Basics to Best Practices. Springer International Publishing, Cham, pp. 31–51 https://doi.org/10.1007/978-3-030-05147-1_2.

Duro, A., Piccione, V., Zampino, D., 2013. Air quality biomonitoring through pollen viability of Fabaceae. Environ. Monit. Assess. 185, 3803–3817.

Erisman, J.W., Galloway, J.N., Seitzinger, S., Bleeker, A., Dise, N.B., Petrescu, A.M.R., Leach, A.M., de Vries, W., 2013. Consequences of human modification of the global nitrogen cycle. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 368, 20130116. https://doi.org/10.1098/rstb.2013.0116.

Farah, J., Choël, M., de Nadaï, P., Balsamelli, J., Gosselin, S., Visez, N., 2021. Organic and aqueous extraction of lipids from birch pollen grains exposed to gaseous pollutants. Environ. Sci. Pollut. Res. Int. 28, 34527–34538.

Feo Brito, F., Mur Gimeno, P., Martínez, C., Tobías, A., Suárez, L., Guerra, F., Borja, J.M., Alonso, A.M., 2007. Air pollution and seasonal asthma during the pollen season. A cohort study in Puertollano and Ciudad Real (Spain). Allergy: Eur. J. Allergy Clin. Immunol. 62, 1152–1157.

Feo-Brito, F., Alfaya Arias, T., Amo-Salas, M., Somoza Álvarez, M.L., Haroun Díaz, E., Mayorga Mayorga, C., Fernández Santamaría, R., Urra Ardanaz, J.M., 2022. Clinical impact and immunological alterations in asthmatic patients allergic to grass pollen subjected to high urban pollution in Madrid. Clin. Exp. Allergy 52, 530–539.

Franze, T., Weller, M.G., Niessner, R., Pöschl, U., 2005. Protein nitration by polluted air. Environ. Sci. Technol. 39, 1673–1678. https://doi.org/10.1021/es0488737.

Galloway, J.N., Schlesinger, W.H., Levy, H., Michaels, A., Schnoor, J.L., 1995. Nitrogen fixation: anthropogenic enhancement-environmental response. Glob. Biogeochem. Cycles 9, 235–252. https://doi.org/10.1029/95GB00158.

Galloway, J.N., Townsend, A.R., Erisman, J.W., Bekunda, M., Cai, Z., Freney, J.R., Martinelli, L.A., Seitzinger, S.P., Sutton, M.A., 2008. Transformation of the nitrogen cycle: recent trends, questions, and potential solutions. Science 320, 889–892. https://doi.org/10.1126/science.1136674.

Galveias, A., Arriegas, R., Mendes, S., Ribeiro, H., Abreu, I., Costa, A.R., Antunes, C.M., 2021. Air pollutants NO2- and O3-induced Dactylis glomerata L. pollen oxidative defences and enhanced its allergenic potential. Aerobiologia (Bologna) 37, 127–137. https://doi.org/10.1007/S10453-020-09676-2.

García-Gallardo, M.V., Algorta, J., Longo, N., Espinel, S., Aragones, A., Lombardero, M., Bernaola, G., Jauregui, I., Aranzabal, A., Albizu, M.V., Gastaminza, G., 2013. Evaluation of the effect of pollution and fungal disease on pinus radiata pollen allergenicity. Int. Arch. Allergy Immunol. 160, 241–250.

Ghiani, A., Bruschi, M., Citterio, S., Bolzacchini, E., Ferrero, L., Sangiorgi, G., Asero, R., Perrone, M.G., 2016. Nitration of pollen aeroallergens by nitrate ion in conditions simulating the liquid water phase of atmospheric particles. Sci. Total Environ. 573, 1589–1597.

Gilles, S., Akdis, C., Lauener, R., Schmid-Grendelmeier, P., Bieber, T., Schäppi, G., Traidl-Hoffmann, C., 2018. The role of environmental factors in allergy: a critical reappraisal. Exp. Dermatol. 27, 1193–1200. https://doi.org/10.1111/exd.13769.

Gottardini, E., Cristofolini, F., Paoletti, E., Lazzeri, P., Pepponi, G., 2004. Pollen viability for air pollution bio-monitoring. J. Atmos. Chem. 49, 149–159. https://doi.org/10.1007/s10874-004-1221-z.

Gottardini, E., Cristofori, A., Cristofolini, F., Maccherini, S., Ferretti, M., 2008. Ambient levels of nitrogen dioxide (NO2) may reduce pollen viability in Austrian pine (*Pinus nigra* Arnold) trees–correlative evidence from a field study. Sci. Total Environ. 402, 299–305. https://doi.org/10.1016/J.SCITOTENV.2008.04.048.

Greaver, T.L., Sullivan, T.J., Herrick, J.D., Barber, M.C., Baron, J.S., Cosby, B.J., Deerhake, M.E., Dennis, R.L., Dubois, J.J.B., Goodale, C.L., Herlihy, A.T., Lawrence, G.B., Liu, L., Lynch, J.A., Novak, K.J., 2012. Ecological effects of nitrogen and sulfur air pollution in the US: what do we know? Front. Ecol. Environ. 10, 365–372. https://doi.org/10.1890/110049.

Gruijthuijsen, Y.K., Grieshuber, I., Stöcklinger, A., Tischlera, U., Fehrenbach, T., Weller, M.G., Vogel, L., Vieths, S., Pöschl, U., Duschl, A., 2006. Nitration enhances the allergenic potential of proteins. Int. Arch. Allergy Immunol. 141, 265–275.

Grundström, M., Dahl, Å., Ou, T., Chen, D., Pleijel, H., 2017. The relationship between birch pollen, air pollution and weather types and their effect on antihistamine purchase in two Swedish cities. Aerobiologia (Bologna) 33, 457–471. https://doi.org/10.1007/S10453-017-9478-2.

Gruzieva, O., Bellander, T., Eneroth, K., Kull, I., Melén, E., Nordling, E., van Hage, M., Wickman, M., Moskalenko, V., Hulchiy, O., Pershagen, G., 2012. Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. J. Allergy Clin. Immunol. 129, 240–246.

Haahtela, T., 2019. A biodiversity hypothesis. Allergy all.13763. https://doi.org/10.1111/all.13763.

Hong, Q., Zhou, S., Zhao, H., Peng, J., Li, Y., Shang, Y., Wu, M., Zhang, W., Lu, S., Li, S., Yu, S., Wang, W., Wang, Q., 2018. Allergenicity of recombinant Humulus japonicus pollen allergen 1 after combined exposure to ozone and nitrogen dioxide. Environ. Pollut. 234, 707–715.

Hoyte, F.C.L., Nelson, H.S., 2018. Recent advances in allergic rhinitis. F1000Res 7, 1333. https://doi.org/10.12688/f1000research.15367.1.

Jamieson, M.A., Seastedt, T.R., Deane Bowers, M., 2012. Nitrogen enrichment differentially affects above- and belowground plant defense. Am. J. Bot. 99, 1630–1637.

Janssen, N.A.H., Brunekreef, B., van Vliet, P., Aarts, F., Meliefste, K., Harssema, H., Fischer, P., 2003. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. Environ. Health Perspect. 111, 1512. https://doi.org/10.1289/EHP.6243.

Karle, A.C., Oostingh, G.J., Mutschlechner, S., Ferreira, F., Lackner, P., Bohle, B., Fischer, G.F., Vogt, A.B., Duschl, A., 2012. Nitration of the pollen allergen bet v 1.0101 enhances the presentation of bet v 1-derived peptides by HLA-DR on human dendritic cells. PLoS One 7.

Lake, I.R., Jones, N.R., Agnew, M., Goodess, C.M., Giorgi, F., Hamaoui-Laguel, L., Semenov, M.A., Solmon, F., Storkey, J., Vautard, R., Epstein, M.M., 2017. Climate change and future pollen allergy in Europe. Environ. Health Perspect. 125, 385–391. https://doi.org/10.1289/EHP173.

Lambrecht, B.N., Hammad, H., 2017. The immunology of the allergy epidemic and the hygiene hypothesis. Nat. Immunol. 18:10 (18), 1076–1083. https://doi.org/10.1038/ni.3829.

Liptzin, D., Boy, J., Campbell, J.L., Clarke, N., Laclau, J.P., Godoy, R., Johnson, S.L., Kaiser, K., Likens, G.E., Karlsson, G.P., Markewitz, D., Rogora, M., Sebestyen, S.D., Shanley, J.B., Vanguelova, E., Verstraeten, A., Wilcke, W., Worrall, F., McDowell, W.H., 2022. Spatial and temporal patterns in atmospheric deposition of dissolved organic carbon. Glob. Biogeochem. Cycles 36, e2022GB007393. https://doi.org/10.1029/2022GB007393.

Lu, S., Ren, J., Hao, X., Liu, D., Zhang, R., Wu, M., Yi, F., Lin, J., Shinich, Y., Wang, Q., 2014. Characterization of protein expression of Platanus pollen following exposure to gaseous pollutants and vehicle exhaust particles. Aerobiologia (Bologna) 30, 281–291.

Lu, S., Yao, C., Zhou, S., Lin, Y., Zhang, L., Zeng, J., Rao, L., Zhang, W., Dai, Y., Li, H., Wang, W., Wang, Q., 2020. Studies on relationships between air pollutants and allergenicity of Humulus Scandens pollen collected from different areas of Shanghai. J. Environ. Sci. (China) 95, 43–48. https://doi.org/10.1016/j.jes.2020.03.037.

Lucas, J.A., Gutierrez-Albanchez, E., Alfaya, T., Feo-Brito, F., Gutiérrez-Mañero, F.J., 2019. Oxidative stress in ryegrass growing under different air pollution levels and its likely effects on pollen allergenicity. Plant Physiol. Biochem. 135, 331–340. https://doi.org/10.1016/j.plaphy.2018.12.018.

Lucas, J.A., Gutierrez-Albanchez, E., Alfaya, T., Feo Brito, F., Gutierrez-Mañero, F.J., 2020. Search for new allergens in Lolium perenne pollen growing under different air pollution conditions by comparative transcriptome study. Plants (Basel) 9. https://doi.org/10.3390/plants9111507.

Melén, E., St, M., Gehring, U., Altug, H., Antó, J.M., Berdel, D., Bergström, A., Bousquet, J., Heinrich, J., Koppelman, G.H., Kull, I., Lupinek, C., Markevych, I., Schikowski, T., Thiering, E., Valenta, R., van Hage, M., von Berg, A., Vonk, J.M., Wickman, M., Wijga, A., Gruzieva, O., 2021. Air pollution and IgE sensitization in 4 European birth cohorts—the MeDALL project. J. Allergy Clin. Immunol. 147, 713–722.

Motta, A.C., Marliere, M., Peltre, G., Sterenberg, P.A., Lacroix, G., 2006. Traffic-related air pollutants induce the release of allergen-containing cytoplasmic granules from grass pollen. Int. Arch. Allergy Immunol. 139, 294–298.

Munn, Z., Peters, M.D.J., Stern, C., Tufanaru, C., McArthur, A., Aromataris, E., 2018. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Med. Res. Methodol. 18, 1–7. https://doi.org/10.1186/S12874-018-0611-X/TABLES/1.

Murray, D.S., Shattuck, M.D., McDowell, W.H., Wymore, A.S., 2022. Nitrogen wet deposition stoichiometry: the role of organic nitrogen, seasonality, and snow. Biogeochemistry 160, 301–314. https://doi.org/10.1007/S10533-022-00966-0/FIGURES/5.

Obersteiner, A., Gilles, S., Frank, U., Beck, I., Häring, F., Ernst, D., Rothballer, M., Hartmann, A., Traidl-Hoffmann, C., Schmid, M., 2016. Pollen-associated microbiome correlates with pollution parameters and the allergenicity of pollen. PLoS One 11.

Okuyama, Y., Matsumoto, K., Okochi, H., Igawa, M., 2007. Adsorption of air pollutants on the grain surface of Japanese cedar pollen. Atmos. Environ. 41, 253–260.

Ouyang, Y., Xu, Z., Fan, E., Li, Y., Zhang, L., 2016. Effect of nitrogen dioxide and sulfur dioxide on viability and morphology of oak pollen. Int. Forum Allergy Rhinol. 6, 95–100.

Ouyang, Y., Yin, Z., Li, Y., Fan, E., Zhang, L., 2019. Associations among air pollutants, grass pollens, and daily number of grass pollen allergen-positive patients: a longitudinal study from 2012 to 2016. Int. Forum Allergy Rhinol. 9, 1297–1303.

Peñuelas, J., Sardans, J., Rivas-ubach, A., Janssens, I.A., 2012. The human-induced imbalance between C, N and P in Earth's life system. Glob. Chang. Biol. 18, 3–6. https://doi.org/10.1111/j.1365-2486.2011.02568.x.

Penuelas, J., Gargallo-Garriga, A., Janssens, I.A., Ciais, P., Obersteiner, M., Klem, K., Urban, O., Zhu, Y.-G., Sardans, J., 2020. Could global intensification of nitrogen fertilisation increase immunogenic proteins and favour the spread of coeliac pathology? Foods 9. https://doi.org/10.3390/foods9111602.

Pfefferle, P.I., Keber, C.U., Cohen, R.M., Garn, H., 2021. The hygiene hypothesis – learning from but not living in the past. Front. Immunol. 12, 632. https://doi.org/10.3389/FIMMU.2021.635935/BIBTEX.

Puc, M., 2012. Influence of meteorological parameters and air pollution on hourly fluctuation of birch (Betula L.) and ash (Fraxinus L.) airborne pollen. Ann. Agric. Environ. Med. 19, 660–665.

Rahman, A., Luo, C.X., Khan, M.H.R., Ke, J.Z., Thilakanayaka, V., Kumar, S., 2019. Influence of atmospheric PM2.5, PM10, O-3, CO, NO2, SO2, and meteorological factors on the concentration of airborne pollen in Guangzhou, China. Atmos. Environ. 212, 290–304. https://doi.org/10.1016/j.atmosenv.2019.05.049.

Reinmuth-Selzle, K., Ackaert, C., Kampf, C.J., Samonig, M., Shiraiwa, M., Kofler, S., Yang, H., Gadermaier, G., Brandstetter, H., Huber, C.G., Duschl, A., Oostingh, G.J., Pöschl, U., 2014. Nitration of the birch pollen allergen bet v 1.0101: efficiency and site-selectivity of liquid and gaseous nitrating agents. J. Proteome Res. 13, 1570–1577.

Reinmuth-Selzle, K., Kampf, C.J., Lucas, K., Lang-Yona, N., Fröhlich-Nowoisky, J., Shiraiwa, M., Lakey, P.S.J., Lai, S., Liu, F., Kunert, A.T., Ziegler, K., Shen, F., Sgarbanti, R., Weber, B., Bellinghausen, I., Saloga, J., Weller, M.G., Duschl, A., Schuppan, D., Pöschl, U., 2017. Air pollution and climate change effects on allergies in the Anthropocene: abundance, interaction, and modification of allergens and adjuvants. Environ. Sci. Technol. 51, 4119–4141. https://doi.org/10.1021/acs.est.6b04908.

Rezanejad, F., 2009. Air pollution effects on structure, proteins and flavonoids in pollen grains of Thuja orientalis L. (Cupressaceae). Grana 48, 205–213. https://doi.org/10.1080/00173130902949417.

Ribeiro, H., Costa, C., Abreu, I., Esteves da Silva, J.C.G., 2017. Effect of O3 and NO2 atmospheric pollutants on Platanus x acerifolia pollen: immunochemical and spectroscopic analysis. Sci. Total Environ. 599, 291–297.

Riediker, M., Monn, C., Koller, T., Stahel, W.A., Wüthrich, B., 2001. Air pollutants enhance rhinoconjunctivitis symptoms in pollen-allergic individuals. Ann. Allergy Asthma Immunol. 87, 311–318.

Rogerieux, F., Godfrin, D., Sénéchal, H., Motta, A.C., Marlière, M., Peltre, G., Lacroix, G., 2007. Modifications of Phleum pratense grass pollen allergens following artificial exposure to gaseous air pollutants (O3, NO2, SO2). Int. Arch. Allergy Immunol. 143, 127–134.

Sabo, N.Č., Kiš, T., Janaćković, P., Đorđević, D., Popović, A., 2016. Pollution by Urticaceae pollen-influence of selected air pollutants and meteorological parameters. Environ. Sci. Pollut. Res. Int. 23, 10072–10079. https://doi.org/10.1007/s11356-016-6163-x.

Savouré, M., Bousquet, J., Jaakkola, J.J.K., Jaakkola, M.S., Jacquemin, B., Nadif, R., 2022. Worldwide prevalence of rhinitis in adults: a review of definitions and temporal evolution. Clin. Transl. Allergy 12, e12130. https://doi.org/10.1002/CLT2.12130.

Ščevková, J., Vašková, Z., Sepšiová, R., Kováč, J., 2021. Seasonal variation in the allergenic potency of airborne grass pollen in Bratislava (Slovakia) urban environment. Environ. Sci. Pollut. Res. Int. 28, 62583–62592.

Shiraiwa, M., Selzle, K., Yang, H., Sosedova, Y., Ammann, M., Pöschl, U., 2012. Multiphase chemical kinetics of the nitration of aerosolized protein by ozone and nitrogen dioxide. Environ. Sci. Technol. 46, 6672–6680.

Smiljanic, K., Prodic, I., Apostolovic, D., Cvetkovic, A., Veljovic, D., Mutic, J., van Hage, M., Burazer, L., Cirkovic Velickovic, T., 2019. In-depth quantitative profiling of post-translational modifications of Timothy grass pollen allergome in relation to environmental oxidative stress. Environ. Int. 126, 644–658.

Sousa, R., Duque, L., Duarte, A.J., Gomes, C.R., Ribeiro, H., Cruz, A., Esteves da Silva, J.C., Abreu, I., 2012. In vitro exposure of Acer negundo pollen to atmospheric levels of SO_2 and NO_2: effects on allergenicity and germination. Environ. Sci. Technol. 46, 2406–2412. https://doi.org/10.1021/es2034685.

Steerenberg, P.A., Bischoff, E.W.M.A., De Klerk, A., Verlaan, A.P.J., Jongbloets, L.M.N., Van Loveren, H., Opperhuizen, A., Zomer, G., Heisterkamp, S.H., Hady, M., Spieksma, F.T.M., Fischer, P.H., Dormans, J.A.M.A., Van Amsterdam, J.G.C., 2003. Acute effect of air pollution on respiratory complaints, exhaled NO and biomarkers in nasal lavages of allergic children during the pollen season. Int. Arch. Allergy Immunol. 131, 127–137.

Stevens, C.J., Duprè, C., Dorland, E., Gaudnik, C., Gowing, D.J.G., Bleeker, A., Diekmann, M., Alard, D., Bobbink, R., Fowler, D., Corcket, E., Mountford, J.O., Vandvik, V., Aarrestad, P.A., Muller, S., Dise, N.B., 2010. Nitrogen deposition threatens species richness of grasslands across Europe. Environ. Pollut. 158, 2940–2945. https://doi.org/10.1016/j.envpol.2010.06.006.

Tilman, D., Fargione, J., Wolff, B., D'Antonio, C., Dobson, A., Howarth, R., Schindler, D., Schlesinger, W.H., Simberloff, D., Swackhamer, D., 2001. Forecasting agriculturally driven global environmental change. Science 1979 (292), 281–284. https://doi.org/10.1126/science.1057544.

Tricco, A.C., Lillie, E., Zarin, W., O'Brien, K.K., Colquhoun, H., Levac, D., Moher, D., Peters, M.D.J., Horsley, T., Weeks, L., Hempel, S., Akl, E.A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M.G., Garritty, C., Lewin, S., Godfrey, C.M., MacDonald, M.T., Langlois, E.V., Soares-Weiser, K., Moriarty, J., Clifford, T., Tunçalp, Ö., Straus, S.E., 2018. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann. Intern. Med. 169, 467–473. https://doi.org/10.7326/M18-0850/SUPPL_FILE/M18-0850_SUPPLEMENT.PDF.

Visez, N., de Nadaï, P., Choël, M., Farah, J., Hamzé, M., Sénéchal, H., Pauwels, M., Frérot, H., Thibaudon, M., Poncet, P., 2021. Biochemical composition of Phleum pratense pollen grains: a review. Mol. Immunol. 136, 98–109. https://doi.org/10.1016/J.MOLIMM.2021.05.014.

Wallace, D.V., Dykewicz, M.S., 2017. Seasonal allergic rhinitis: a focused systematic review and practice parameter update. Curr. Opin. Allergy Clin. Immunol. 17, 286–294. https://doi.org/10.1097/ACI.0000000000000375.

Wan, Y., Gritsch, C.S., Hawkesford, M.J., Shewry, P.R., 2014. Effects of nitrogen nutrition on the synthesis and deposition of the ω-gliadins of wheat. Ann. Bot. 113, 607–615.

Wang, Q., Gong, X., Nakamura, S., Kurihara, K., Suzuki, M., Sakamoto, K., Miwa, M., Lu, S., 2009. Air pollutant deposition effect and morphological change of Cryptomeria japonica pollen during its transport in urban and mountainous areas of Japan. Environ. Health Risk V 14, 77-+. https://doi.org/10.2495/ehr090081.

Wang, W.J., He, H.S., Thompson, F.R., Spetich, M.A., Fraser, J.S., 2018. Effects of species biological traits and environmental heterogeneity on simulated tree species distribution shifts under climate change. Sci. Total Environ. 634, 1214–1221. https://doi.org/10.1016/j.scitotenv.2018.03.353.

World Health Organization, 2021. WHO Global Air Quality Guidelines: Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. World Health Organization, Geneva.

Yamada, Y., Kidoguchi, M., Yata, A., Nakamura, T., Yoshida, H., Kato, Y., Masuko, H., Hizawa, N., Fujieda, S., Noguchi, E., Miura, K., 2020. High-yield production of the major birch pollen allergen bet v 1 with allergen immunogenicity in Nicotiana benthamiana. Front. Plant 11, 344.

Zhao, F., Elkelish, A., Durner, J., Lindermayr, C., Winkler, J.B., Ruëff, F., Behrendt, H., Traidl-Hoffmann, C., Holzinger, A., Kofler, W., Braun, P., von Toerne, C., Hauck, S.M., Ernst, D., Frank, U., 2016. Common ragweed (Ambrosia artemisiifolia L.): allergenicity and molecular characterization of pollen after plant exposure to elevated NO2. Plant Cell Environ. 39, 147–164.

Zhao, F., Durner, J., Winkler, J.B., Traidl-Hoffmann, C., Strom, T.M., Ernst, D., Frank, U., 2017. Pollen of common ragweed (Ambrosia artemisiifolia L.): Illumina-based de novo sequencing and differential transcript expression upon elevated NO2/O3. Environ. Pollut. 224, 503–514. https://doi.org/10.1016/J.ENVPOL.2017.02.032.

Zhou, S., Wang, X., Lu, S., Yao, C., Zhang, L., Rao, L., Liu, X., Zhang, W., Li, S., Wang, W., Wang, Q., 2021. Characterization of allergenicity of Platanus pollen allergen a 3 (Pla a 3) after exposure to NO2 and O3. Environ. Pollut. 278.

Zhu, F., Jiao, J., Zhuang, P., Huang, M., Zhang, Y., 2021. Association of exposures to perchlorate, nitrate, and thiocyanate with allergic symptoms: a population-based nationwide cohort study. Environ. Pollut. 283.

Zuberbier, T., Lötvall, J., Simoens, S., Subramanian, S.V., Church, M.K., 2014. Economic burden of inadequate management of allergic diseases in the European Union: a GA2LEN review. Allergy 69, 1275–1279. https://doi.org/10.1111/ALL.12470.