

ORIGINAL ARTICLE OPEN ACCESS

Postcode-Level Variation and Environmental Determinants of Respiratory Allergies in a Large German Cohort

Trang Dao-Siebel^{1,2}  | Christoph Knotz³ | Christoph Müller⁴ | Thilo Erbertseder⁵ | Elke Hertig⁶ | Roxana Halbleib² | Evelyn Lamy¹

¹Environmental Health Mechanisms and Exposomics, Medical Faculty, University of Augsburg, Augsburg, Germany | ²Chair of Statistics and Econometrics, Institute of Economics, University of Freiburg, Freiburg, Germany | ³Model-Based Environmental Exposure Science, Faculty of Medicine, University of Augsburg, Augsburg, Germany | ⁴Center for Pediatrics and Adolescent Medicine, Faculty of Medicine, University of Freiburg, Freiburg, Germany | ⁵German Remote Sensing Data Center, German Aerospace Center (DLR), Oberpfaffenhofen, Germany | ⁶Regional Climate Change and Health, Medical Faculty, University of Augsburg, Augsburg, Germany

Correspondence: Evelyn Lamy (evelyn.lamy@med.uni-augsburg.de)

Received: 19 January 2026 | **Revised:** 6 April 2026 | **Accepted:** 3 June 2026

Keywords: environmental factors | PM₁₀ | prevention | respiratory allergies | two-part models

ABSTRACT

Background: Respiratory allergies (RAs) are common conditions with complex, multifactorial etiologies including environmental influences. However, little is known about their spatial variation at small-area levels in Germany. This study aimed to (1) examine variations in respiratory allergy incidence (RAI) and dispensed prescribed medication rate (DPMR) at the municipal level in Baden-Württemberg from 2012 to 2022; (2) assess associations between RAI, DPMR, and environmental factors in Baden-Württemberg to support targeted prevention strategies.

Methods: We used nonparametric tests to examine differences in RAI and DPMR. To assess associations between RAI, DPMR, and environmental factors (e.g., air pollutants, meteorological parameters, pollen), we applied generalized additive two-part models.

Results: Both RAI and DPMR were significantly higher in urban compared to rural areas. The probability of RAs occurrence was significantly associated (p -adjusted < 0.01) with PM₁₀, PM_{2.5}, temperature, as well as alder and birch pollen. O₃, NO₂, and the interaction O₃*NO₂ were additionally significantly linked to cumulative nonzero RAI. Notably, alder pollen played a major role in determining whether RAs occurred, whereas among diagnosed individuals, PM₁₀ concentration was the strongest determinant. Across air pollutants, reducing PM₁₀ to the quarterly threshold of 15 µg/m³ could reduce RAs onset, especially in children aged 0–9. DPMR models yielded similar results, except for those of NO₂ and the interaction O₃*NO₂.

Conclusions: Reducing alder pollen and PM₁₀ exposure could present the most effective environmental intervention for lowering both RAI and DPMR, particularly in young children. Effective health management is required for affected individuals due to exacerbations caused by O₃ and NO₂.

Abbreviations: AME, average marginal effects; AME(PM_{2.5}), average marginal effects of PM_{2.5}; BW, Baden-Württemberg; DPMR, dispensed prescribed medication rate; EFs, environmental factors; NO₂, nitrogen dioxide; O₃, ozone; PM, particulate matter; PM₁₀, particulate matter less than 10 µm; PM_{2.5}, particulate matter less than 2.5 µm; Pr(DPM), probability of receiving medication; prevRA, preventable RAs cases; Pr(RA), probability of RAs occurrence; RAI, RAs incidence; RAs, respiratory allergies.

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2026 The Author(s). *Allergy* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd.

1 | Introduction

Allergic diseases, especially respiratory allergies (RAs) (including allergic rhinitis and allergic asthma), have reached alarming levels, affecting 20–30 million people in Germany [1] and imposing a significant burden on healthcare systems [2]. On average, each person with RAs incurs annual costs of 699 euros [3], which could amount to 20 billion euros per year in total. RAs are common conditions with complex etiologies involving both genetic and environmental contributions [4]. In the context of climate change, the impact of environmental factors (EFs) on RAs is receiving increased attention, especially the ones of meteorological parameters (including temperature and precipitation), air pollutants, as well as pollen.

In Germany, the mean annual air temperature reached 2.1°C above the 1881–1910 baseline by 2013–2022, 0.6°C above the global increase [5]. Mean annual precipitation increased by 7.3% since 1881, with seasonal and spatial variations [5]. Concentrations of nitrogen dioxide (NO₂), particulate matter less than 10 and 2.5 μm (PM₁₀ and PM_{2.5}) declined from 2012 to 2021, and ozone (O₃) levels increased [6]. Additionally, pollen, the most common trigger of RAs [1], also varied in concentration and allergenicity by type and region [7].

At the regional scale, climate change is clearly perceptible, including in Baden-Württemberg (BW), Germany's warmest state [8]. With 35,751 km² and approximately 11.1 million [9], BW is one of Germany's largest, most densely populated, and economically dynamic regions. Its industrial activity, high traffic volumes, mixed urban–rural landscape [10], and ongoing urbanization [11] highlight the need to better understand how EFs contribute to the development and exacerbation of RAs.

Against this background, our study aimed to investigate: (1) potential variations in RAs incidence (RAI) and dispensed prescribed medication rate (DPMR) (including temporal trends, geographical distribution, age and sex differences, and urbanization levels) at the municipal level from 2012 to 2022 in BW; (2) associations between RAs, DPMR, and EFs in BW, to inform targeted prevention and management strategies in the region. We hypothesized spatial/temporal variation in RAI and DPMR across BW. We further hypothesized that higher PM₁₀ and airborne pollen concentrations are associated with higher RAI and DPMR, particularly in children. To date, little is known about regional variation in RAs in Germany, as no studies have examined RAs at a scale smaller than the district level.

2 | Data

The data overview is provided below; for more details, see Appendix S1. Based on quarterly medical claims, the Allgemeine Ortskrankenkasse Baden-Württemberg (AOK BW)—the largest health insurer in BW (>4.6 million) provided aggregated and anonymized counts of newly diagnosed cases and the population at risk stratified by age groups (0–9, 10–19, 20–59, and 60+), sex (male and female), 5-digit postal codes ($n=1192$), and urbanization levels ($n=3$). RAs were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, German modification

(ICD-10-GM-code: J30.1; J30.2; J30.3; and J30.4 for allergic rhinitis; J45.0, J45.8, J45.9 for allergic asthma), covering the period from 2012 to 2022. To assess severity, we observed the number of clients who received dispensed prescribed medication (based on ATC codes; see Table S1) among those diagnosed with RAs in the corresponding quarters.

For this study, daily air pollutant concentrations (NO₂, O₃, PM₁₀, and PM_{2.5}) [12] for the years 2013–2022, as well as quarterly pollen data (alder and birch) [13] for all 5-digit postal codes in BW from 2012 to 2022, were extracted from published datasets. Daily meteorological data (temperature, precipitation, and surface UV) from 2012 to 2022 were provided at the zip code level by the German Aerospace Center based on the ERA5 reanalysis [14].

In this study, quarter one (Q1) refers to January–March; Q2 to April–June; Q3 to July–September, and Q4 to October–December.

3 | Methods

A brief overview of the methods is provided below; full methodological details are available in Appendix S2.

All analyses were conducted using methods and packages within the free software environment R (Version 4.3.2, Germany) and Microsoft Excel Version 2301. First, we calculated quarterly cumulative RAI as the number of new diagnoses within each quarter divided by the population at risk, stratified by age group, sex, and postal code. To compare the incidence and severity of the RAs, we calculated the DPMR as the number of clients receiving dispensed prescribed medication divided by the population at risk. We then analyzed potential variations in RAI and DPMR by age, sex, and geographic location. Differences in RAI and DPMR across urbanization levels were tested by using the Kruskal–Wallis Test, post hoc Dunn's Test, and Wilcoxon Test. To avoid perfect multicollinearity in the regression models, we computed the Spearman Rank correlation among EFs (Table 1). None was perfectly correlated. Hence, to avoid omitting variable bias, we focused on studying the effects of multivariable on the RAI and the DPMR. PM_{2.5}, a subset of PM₁₀, has been receiving increasing attention in relation to RAs. Hence, we also investigated the association with PM_{2.5} by replacing PM₁₀ with PM_{2.5} and PM_{2.5–10} in the models.

Since both RAI and DPMR are semicontinuous with true zeros and right-skewed, we adopted the two-part modeling approach described by Boulton et al. [15]. This allowed us to model (1) the probability of occurrences (binary component) and the intensity among occurrences (continuous component). Here, combined models and, separately, the models stratified by each urbanization level were fitted. In the combined models, the function “bam()” from the package “mgcv” with the method “fREML” was used. Thin plate regression splines were applied to the EFs. Age, sex, and seasonality (quarter) were included as categorical predictors. Postal code was modeled as a random effect smooth term (bs = “re”). In the stratified models, the data were stratified into urban, suburban, and rural areas, and the respective models were applied separately for each group. All models were finally adjusted to achieve

TABLE 1 | Spearman correlations among environmental factors in Baden-Württemberg from 2012 to 2022.

Variables	O ₃	NO ₂	PM ₁₀	Precipitation	Temperature	UV	Birch	Alder
O ₃	1.000	−0.723	−0.380	0.110	0.423	0.827	0.632	0.366
NO ₂	−0.723	1.000	0.608	−0.336	−0.482	−0.662	−0.366	−0.087
PM ₁₀	−0.380	0.608	1.000	−0.417	−0.318	−0.294	−0.025	0.163
Precipitation	0.110	−0.336	−0.417	1.000	−0.047	−0.042	0.047	0.030
Temperature	0.423	−0.482	−0.318	−0.047	1.000	0.625	0.104	−0.328
UV	0.827	−0.662	−0.294	−0.042	0.625	1.000	0.709	0.348
Birch	0.632	−0.366	−0.025	0.047	0.104	0.709	1.000	0.725
Alder	0.366	−0.087	0.163	0.030	−0.328	0.348	0.725	1.000

Notes: Color intensity from white to dark grey indicates the absolute strength of the Spearman rank correlation coefficient.

optimal fitness; here, model's wiggleness was assessed by using “gam.check()” function, and the smooth term collinearity was considered by using the “concurvity()” function. Finally, we estimated the probability of RAs occurrence (Pr(RA)) and probability of receiving medication (Pr(DPM)), as well as the numbers of RAI and DPMR with their confidence interval 95% (95% CI), using the “plot_predictions()” function in package “marginaleffects” and “predict()” function for all significant EFs, with the other variables set to their mean values for each quarter. A significant threshold of p -adjusted $< 0.01^1$ was applied in all models. Furthermore, key determinants were identified by comparing the average marginal effects (AME) and range effects. To identify vulnerable subgroups, age–sex interactions were modeled within the smooth terms of the environmental factor.

4 | Results

4.1 | RAI and DPMR in BW From 2013 to 2022

Over the 11-year study period, there were 1,300,079 RAs new cases, with 556,515 individuals receiving prescribed medication.

RAI and DPMR were significantly higher in Q2 than in the other three quarters during the study period ($p < 2.2e-16$) (Figure 1, left). In Figure 1A (right), the highest average quarterly incidence of RAs was clustered around the city of Schwäbisch Hall. However, this was artificial inflation; hence, we excluded the postcodes from our analyses. Similarly, the DPMR was evenly distributed in BW throughout the study period (Figure 1B, right).

Figure 2 displays the quarterly RAI and DPMR across age groups and sexes. The incidence was highest in younger age groups and showed a marked male predominance, whereas in adulthood, it was higher among females. The DPMR's pattern resembled RAI's, with a notably higher rate in young males, but overall lower than the incidence. This supports our hypothesis that only clients with severe RAs required medication support.

The Kruskal–Wallis test showed significant differences in RAI and DPMR across the three urbanization levels ($p < 2.2e-16$). Our post hoc Dunn's test and Wilcoxon test indicated that the RAI was highest in urban areas, followed by suburban and then

rural areas ($p < 2.2e-16$) (Figure 3A). The same pattern was observed for DPMR ($p < 2.2e-16$) (Figure 3B).

4.2 | Model Outcomes

4.2.1 | RAs Models

Results from our binary component of the two-part models showed significant associations between the Pr(RA) and several EFs, including PM₁₀, PM_{2.5}, temperature, alder, and birch pollen (p -adjusted < 0.01 ; Figure 4). In the continuous component, NO₂, O₃, and interaction O₃*NO₂ were also significantly associated with RAI (p -adjusted < 0.01 ; Figure 5). See Tables S2 and S3 for all models' summaries and effect sizes.

In Figure 4, the binary RAI was positively associated with PM₁₀ and PM_{2.5}, as well as nonlinearly associated with temperature and pollen concentrations. Remarkably, the Pr(RA) was highest at PM₁₀ levels above 20 µg/m³, PM_{2.5} levels above 15 µg/m³, and at alder and birch pollen concentrations of approximately 20 and 80 grains/m³, respectively. Furthermore, the temperature range from 5°C to 10°C was associated with the highest Pr(RA).

In Figure 5, nonzero RAI values were nonlinearly positively associated with PM₁₀, PM_{2.5} (caution ranges² above 13 and 10 µg/m³, respectively), and nonlinearly associated with NO₂ as well as O₃ (caution ranges above 15 and 70 µg/m³, respectively). The combined effect of high O₃ and NO₂ levels showed a synergistic amplification, especially when both were elevated (Figure 5E). Furthermore, temperature showed a nonlinear association (Figure 5F), with two caution ranges at around 5°C–13°C and 16°C–18°C. Alder and birch pollen concentrations were nonlinearly associated with RAI (Figure 5G,H, respectively), with caution ranges from 5 grains/m³ for alder and from 5 to 150 grains/m³ for birch.

Our results on AME showed that the alder pollen concentration played a major role in determining whether at least one case of RAs occurred, whereas among diagnosed individuals, the PM₁₀ concentration was the strongest determinant (Table S4). Specifically, a one-unit increase in the concentrations of alder pollen (grain/m³) and PM₁₀ (µg/m³) was estimated to increase, on average, 0.21 percentage points in the predicted Pr(RA) and 0.1989 new cases of

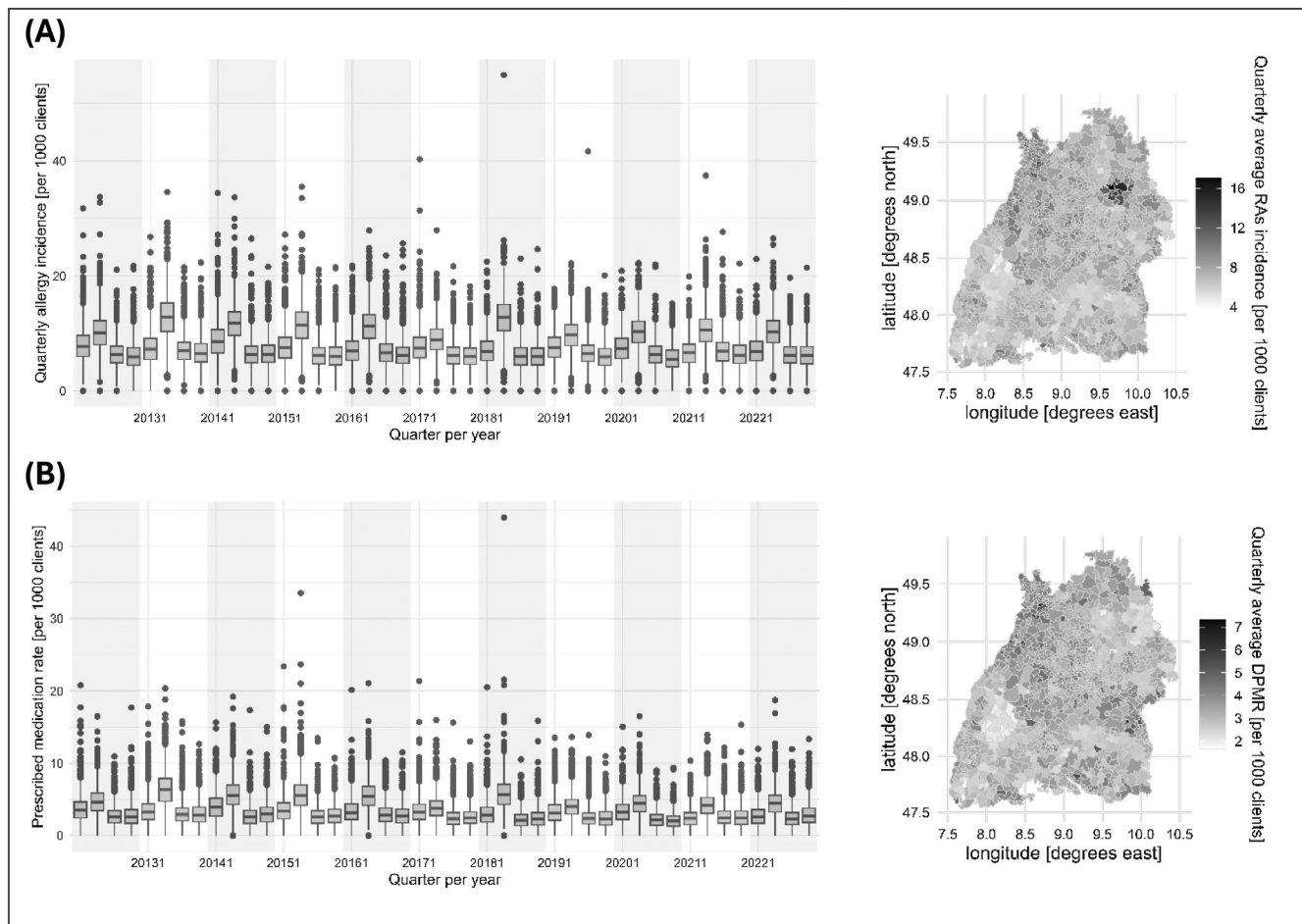


FIGURE 1 | Boxplots (on the left) and geographical distribution (on the right) of (A) incidence, and (B) DPMR of respiratory allergies per postcode for each quarter from 2012 to 2022 in Baden-Württemberg.

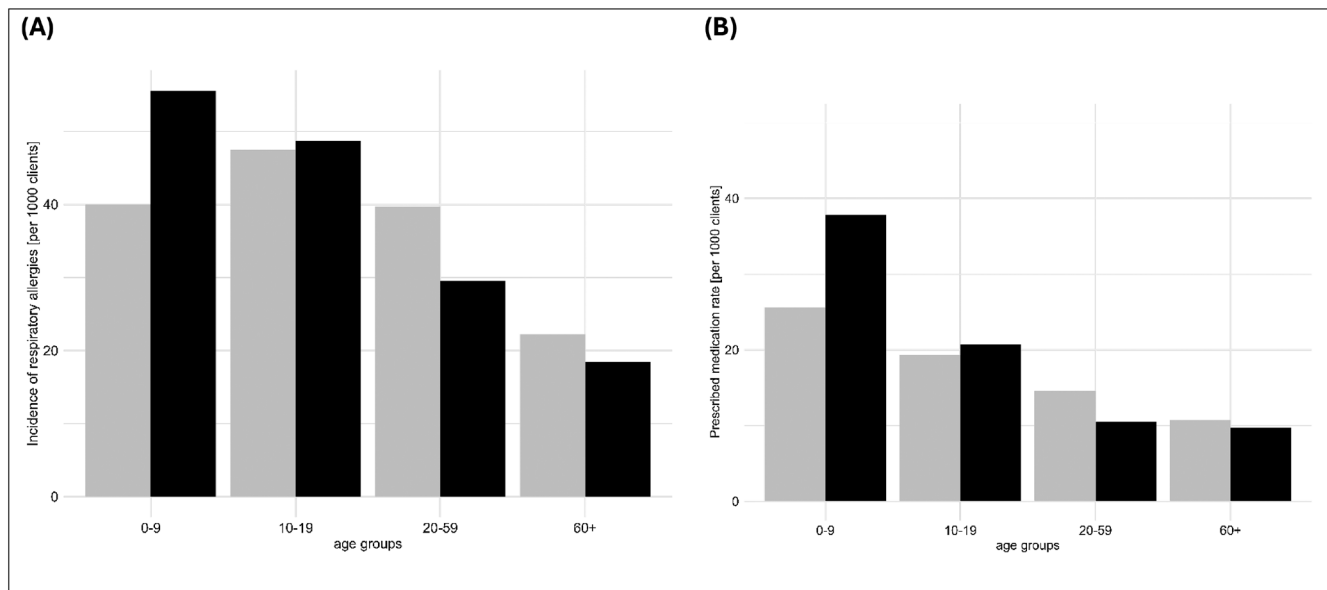


FIGURE 2 | (A) Quarterly incidence and (B) DPMR of respiratory allergies for different age groups and sex. Females and males are represented by grey and black bars, respectively.

RAI per 1000 clients, respectively. Interestingly, the $AME(PM_{2.5})$ is approximately 61.8% of the $AME(PM_{10})$ in the continuous component, suggesting its substantial share.

Notably, among the air pollutants, most of our quarterly caution exposure ranges were higher than WHO AQGs recommended thresholds for long-term (annually) exposure to protect human

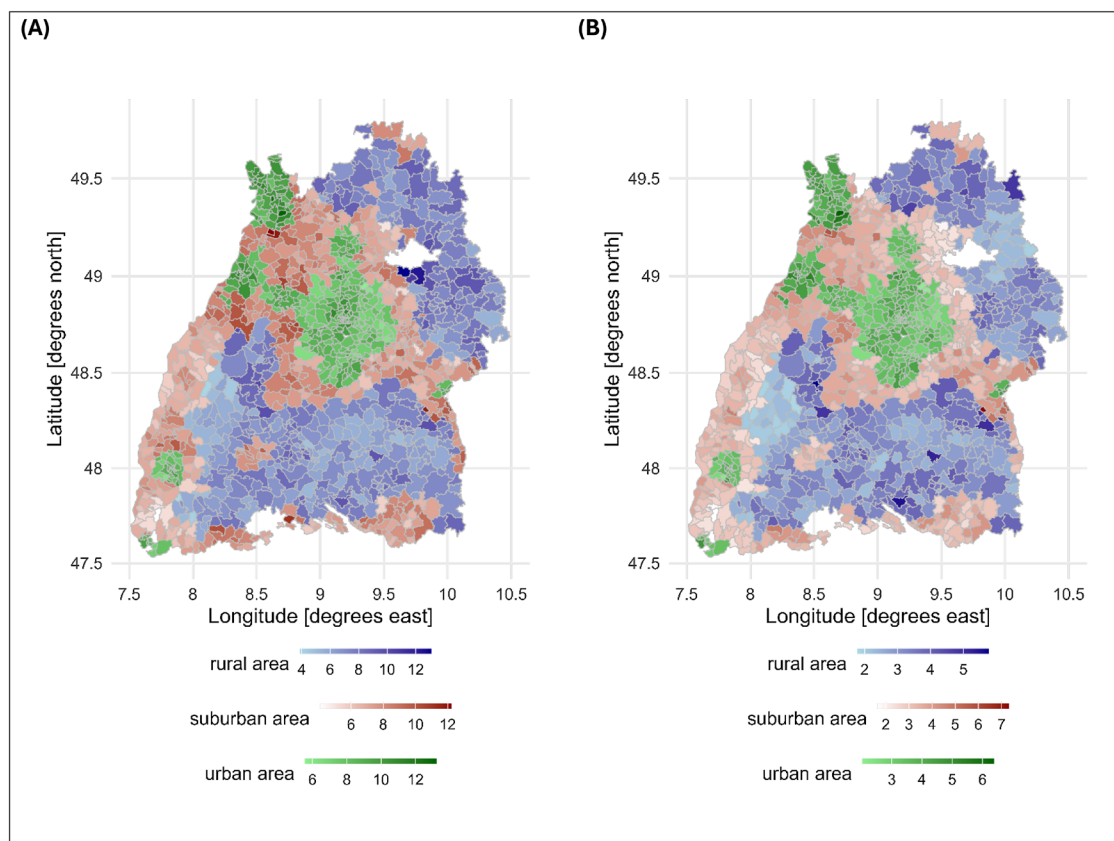


FIGURE 3 | Geographical distribution of quarterly RAs (A) incidence, and (B) DPMR per urbanization levels from 2012 to 2022 in Baden-Württemberg.

health (60, 10 and $5\mu\text{g}/\text{m}^3$ for O_3 , NO_2 , and $\text{PM}_{2.5}$, respectively), except for PM_{10} ($15\mu\text{g}/\text{m}^3$) [16], but remained within EU air quality standards (120 and $40\mu\text{g}/\text{m}^3$ for O_3 and NO_2 , respectively, as well as 40 and $25\mu\text{g}/\text{m}^3$ for PM_{10} and $\text{PM}_{2.5}$, respectively) [17, 18]. As the recommendations apply only to annual thresholds and no quarterly guidelines are provided, we compared the estimated Pr(RA) and intensity at pollutant concentrations above, versus below guideline thresholds to estimate potentially preventable RAs cases (prevRA) due to air pollutant exposure (Table S5). Our results on prevRA did not provide sufficient evidence that reductions in quarterly air pollutants were associated with lower RAI, except in the cases of PM_{10} and $\text{PM}_{2.5}$. Although reducing quarterly particulate matter (PM) concentrations did not alter the Pr(RA), reducing the quarterly values to the targeted annual recommendation in PM_{10} and $\text{PM}_{2.5}$, starting in 2030, may correspond to reductions of 0.602 (0.355; 0.881) and 0.268 (0.134; 0.420) new cases RAs per 1000 clients, respectively. Remarkably, a reduction in quarterly PM_{10} to the WHO annual recommended threshold was potentially associated with a decrease of 0.687 (0.532; 0.872) new cases RAs per 1000 clients.

Our interaction model showed that the associations varied significantly across age-sex strata ($p < 3.22\text{e-}07$). In children aged 0–9, reducing PM_{10} to $15\mu\text{g}/\text{m}^3$ was associated with a reduction of 2.73 (0.948; 4.513) for female, and 2.66 (0.568; 4.761) for male prevRA per 1000 clients, corresponding to relative reductions of 19.2% and 16.1%, respectively (Table 2). No significant evidence of reduced RAI in other age and sex groups associated with lower PM_{10} levels was found.

4.2.2 | DPMR Models

The DPMR model is closely aligned with the RAI results for PM_{10} , $\text{PM}_{2.5}$, O_3 , temperature, and pollen (Appendices S3 and S4). Key differences were that NO_2 and the interaction $\text{O}_3 \cdot \text{NO}_2$ showed significant associations with the DPMR binary component. Although precipitation was statistically significant in the models (p -adjusted < 0.01), its estimated range effects were very small, suggesting limited practical relevance (see Table S3). Hence, we did not discuss this association here. Overall, the Pr(DPM) in response to EFs was lower than the Pr(RA). PM_{10} and alder pollen showed the highest average marginal effects on both the Pr(DPM) and its intensity. For more details, see Tables S2–S4.

4.2.3 | Urbanization Models

Results of our urbanization models were similar to those of the combined models, except for the significant association of NO_2 in rural and suburban areas, as well as the one of O_3 in urban areas.

5 | Discussion

5.1 | RAs and DPMR Between Age and Sex Groups, Geographical Distribution, and Urbanization Levels

Our results revealed notable differences across age and sex groups, in geographical distribution as well as in distinct

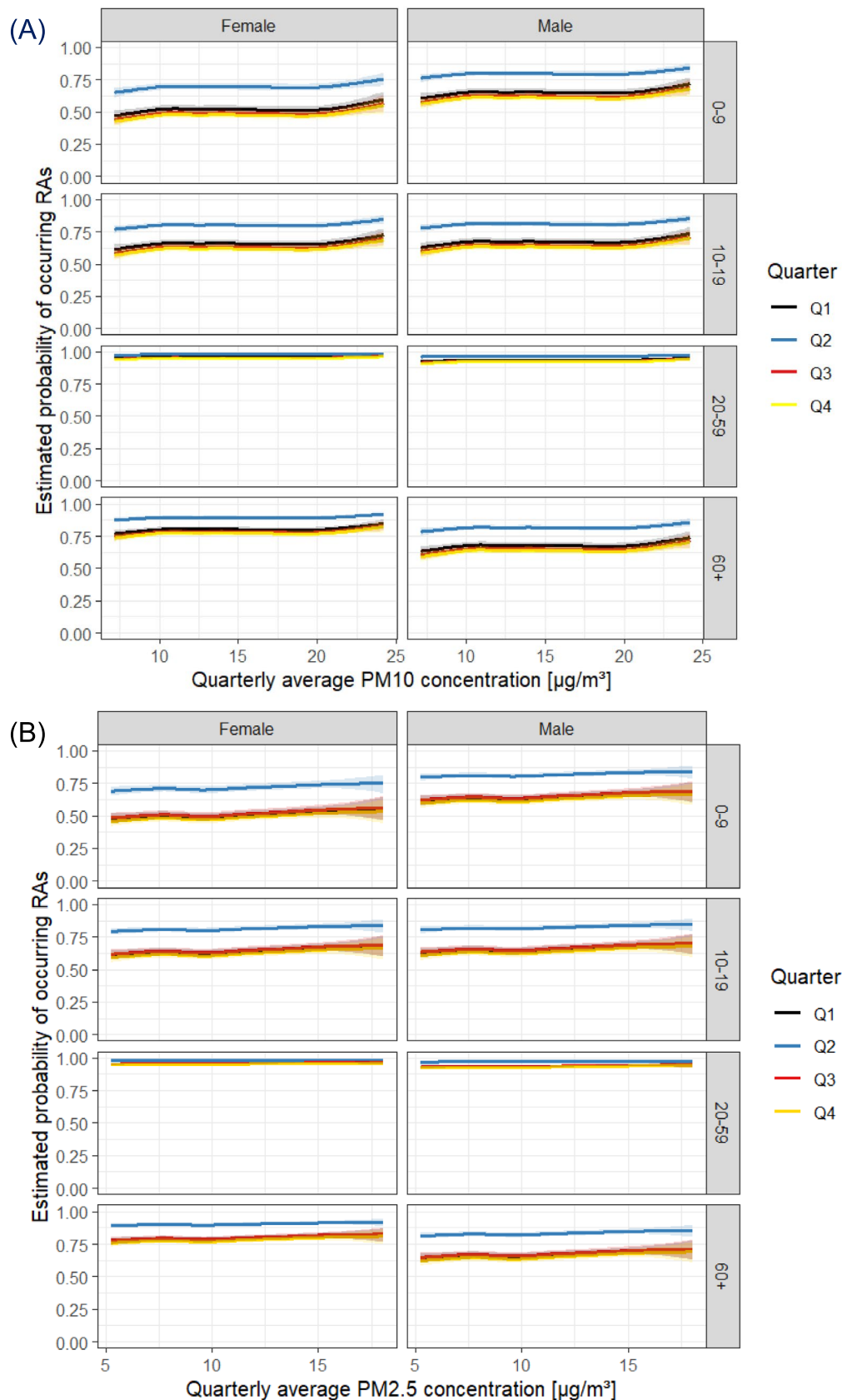


FIGURE 4 | Estimated probability of RAs occurring for each age group and sex in response to variations in environmental factors based on the quarterly data from 2012 to 2022 in BW. (A) The effect of PM₁₀ ($\mu\text{g}/\text{m}^3$). (B) The effect of PM_{2.5} ($\mu\text{g}/\text{m}^3$). (C) The effect of temperature ($^{\circ}\text{C}$). (D) The effect of alder pollen (grains/ m^3). (E) The effect of birch pollen (grains/ m^3). Colored lines represent the associations between EFs and the probability of RAI occurrence. Shaded areas represent the 95% confidence intervals. The associations for each quarter are shown in black for Q1, blue for Q2, red for Q3, and yellow for Q4.

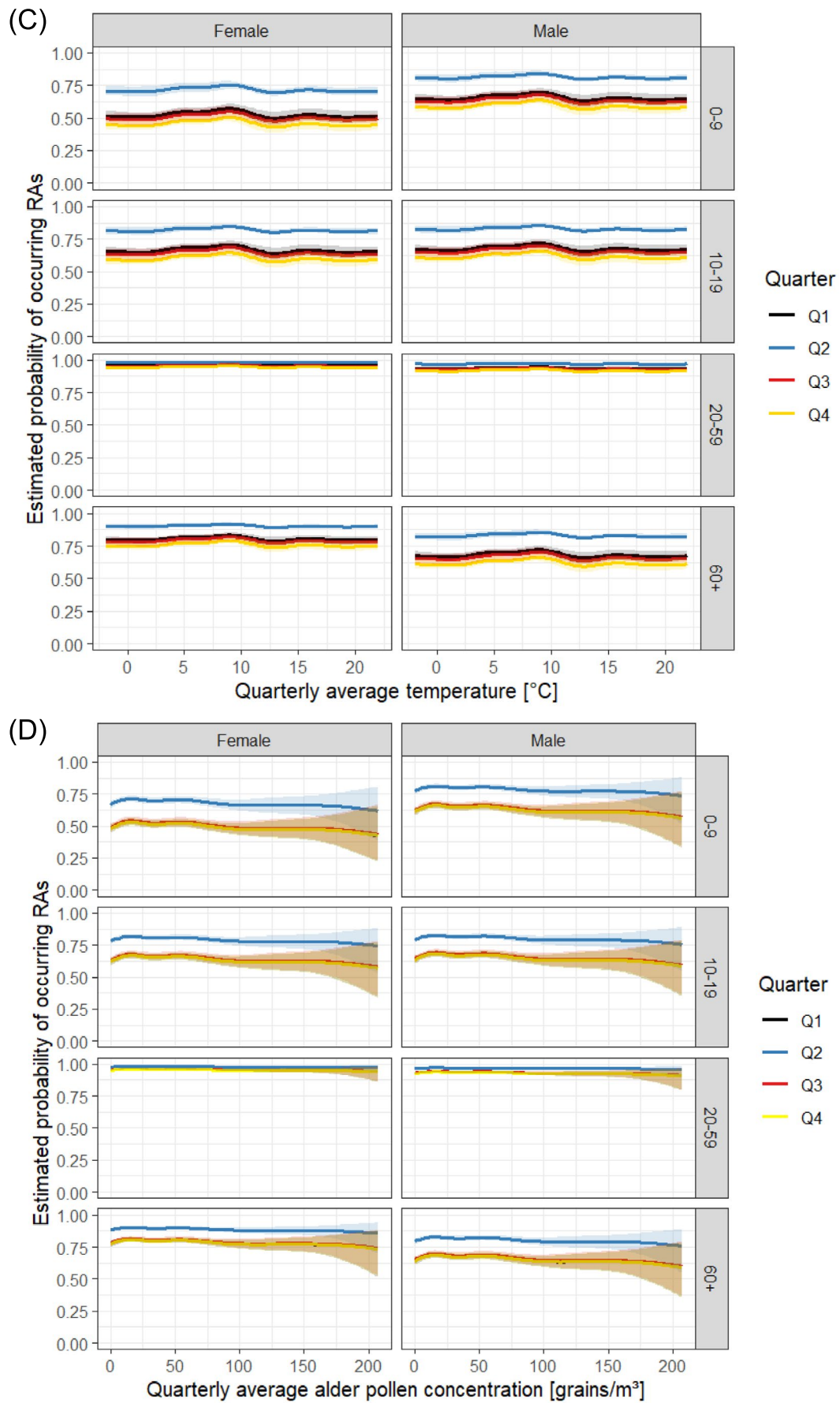


FIGURE 4 | (Continued)

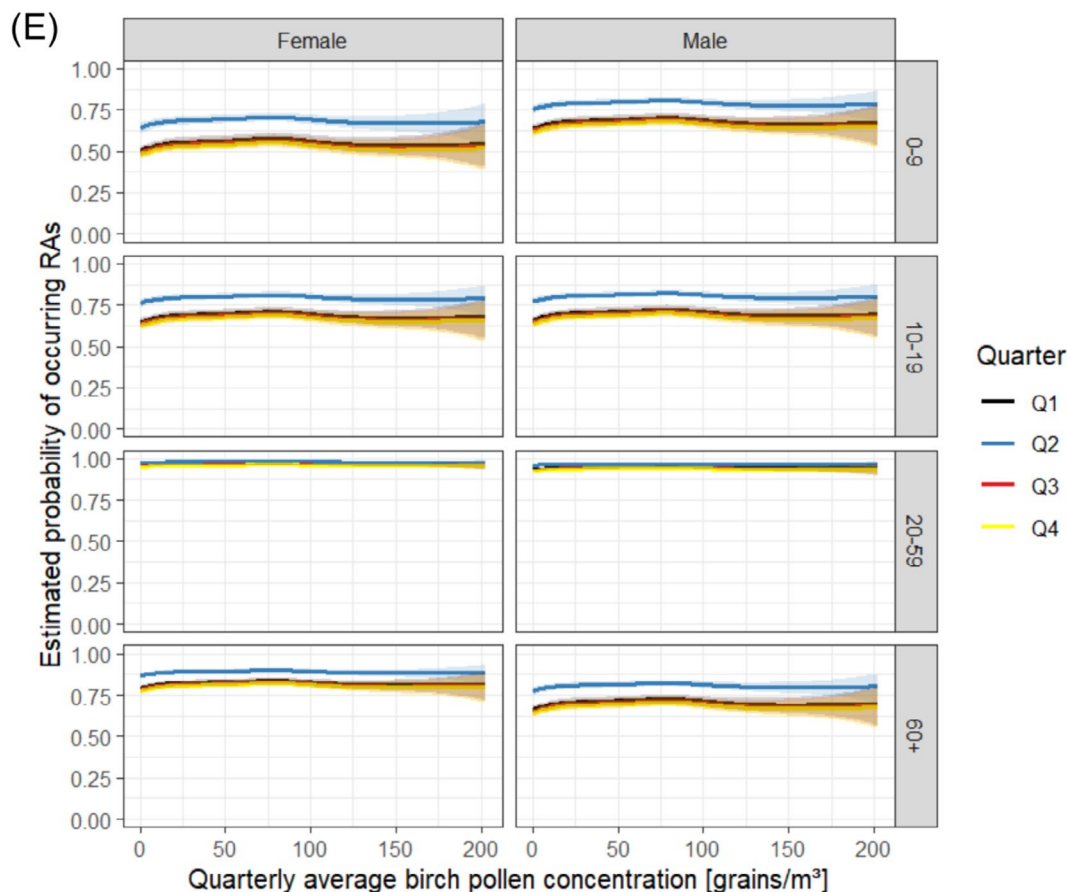


FIGURE 4 | (Continued)

urbanization levels, consistent with previous epidemiological research, and emphasize the RAs' multifactorial nature.

There is increasing clinical evidence for the influence of age and sex hormones on the allergies development [19, 20]. At a young age, more boys develop RAs. This changes rapidly with girls' sexual maturation, leading to a lifelong female dominance in RAs [21, 22]. In prepubertal children, setting of low sex steroid levels, inherent structural differences are more important to sex differences in RAs [19]. For example, early elevation of serum IgE levels [23] and delayed airway growth in boys may contribute to higher RAI in childhood [19]. After puberty, females have smaller airways relative to lung size and show variations in lung mechanics influenced by hormonal changes as compared to males [24]. Estrogen and progesterone aggravate the development and outcome of RAs [25], while androgens such as testosterone can exert a protective role [21], for example, by suppressing group 2 innate lymphoid cells [25]. Additionally, women exhibit stronger immune responses than men [25] and are more sensitive to environmental toxins [21], making them more vulnerable to RAs.

Geographically, our results confirm that RAI and DPMR are lower in rural than urban areas. Rural residents, particularly those exposed to farm environments, are believed to benefit from unique and broader microbial diversity, as well as sustained microbial exposure, which supports immune tolerance [26] and prevents colonization of the lower airways with harmful bacteria [27]. Consumption of raw milk in both farm and nonfarm populations is discussed as one of the most effective

protective factors against RAs development [28]. In contrast, urban residents face higher exposure to traffic-related air pollution and reduced allergen diversity, which may contribute to sensitization and increased symptom severity [20, 29].

5.2 | Association Between RAs and DPMR With Environmental Factors

5.2.1 | Temperature

Temperature influences RAs and DPMR through both direct and indirect ways. Physiologically, our findings align with proposed mechanisms whereby thermal stress increases RAs and elevates DPMR [30]. Cold temperature can disrupt respiratory epithelial barriers [31], increasing susceptibility to allergens and pathogens [32]. A study by He et al. [33] suggested that personal exposure to lower temperatures was associated with higher oxidative stress levels. Such disruptions contribute to the development and exacerbation of RAs.

Behavior matters: In industrialized countries, including in Germany, people spend over 90% of their time indoors, especially in winter [34–36]. Tighter building envelopes and reduced winter ventilation can allow indoor pollutants and allergens to accumulate [35, 37, 38]. Moreover, clinical and epidemiological observations indicate that respiratory viruses, especially RSV, can facilitate allergic sensitization to aeroallergens [39], by interfering with the immune tolerance induction.

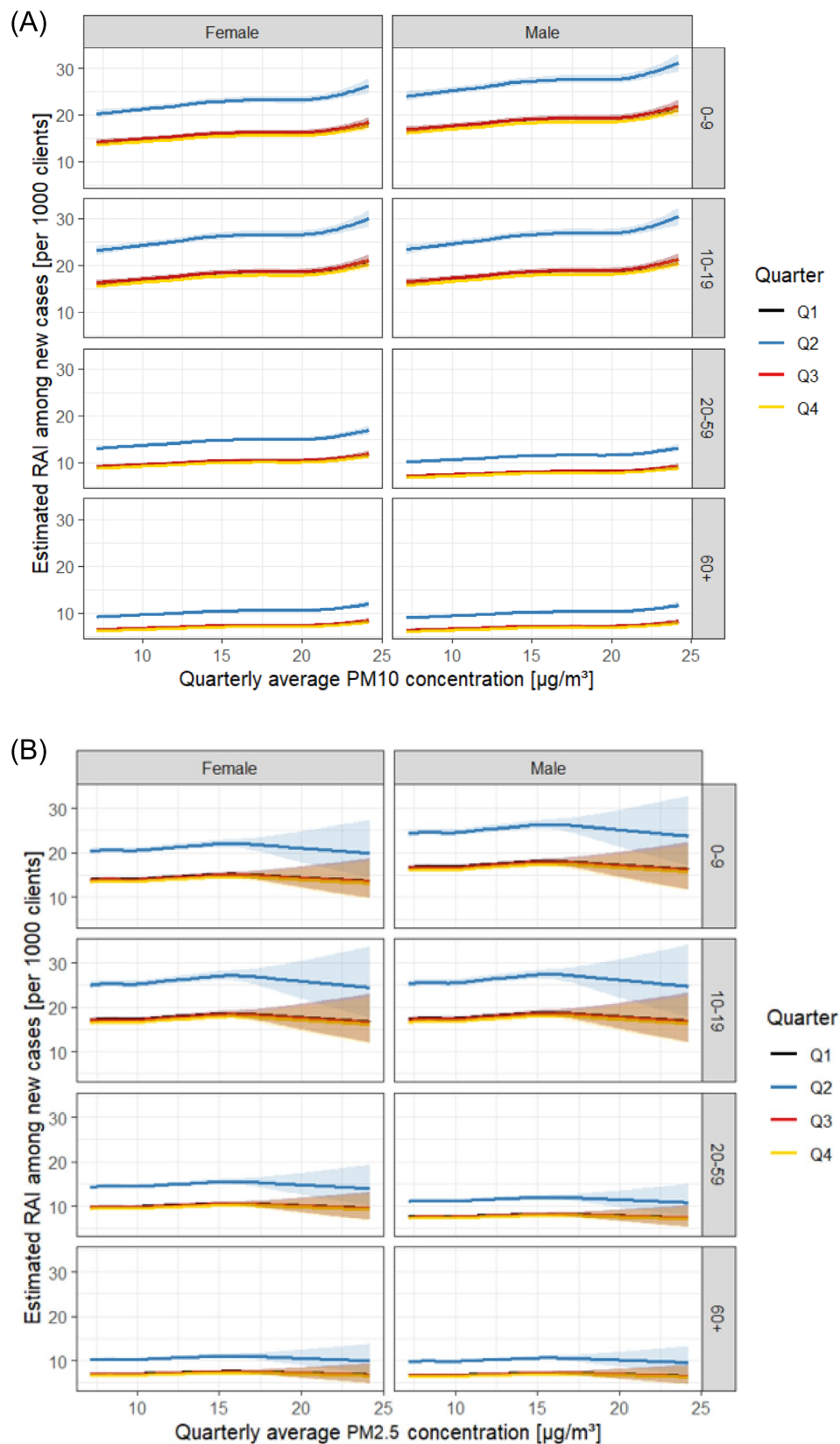


FIGURE 5 | Estimated positive RAI for each age group and sex in response to variations in environmental factors based on the quarterly data from 2012 to 2022 in BW. (A) The effect of PM_{10} ($\mu\text{g}/\text{m}^3$). (B) The effect of $\text{PM}_{2.5}$ ($\mu\text{g}/\text{m}^3$). (C) The effect of O_3 ($\mu\text{g}/\text{m}^3$). (D) The effect of NO_2 ($\mu\text{g}/\text{m}^3$). (E) The effect of interaction $\text{O}_3 \cdot \text{NO}_2$ ($\mu\text{g}/\text{m}^3$). (F) The effect of temperature ($^{\circ}\text{C}$). (G) The effect of alder pollen (grains/ m^3). (H) The effect of birch pollen (grains/ m^3). In the main effect plots, colored lines represent the associations between EFs and RAI. Shaded areas represent the 95% confidence intervals. The associations for each quarter are shown in black for Q1, blue for Q2, red for Q3, and yellow for Q4. In the interaction plot, color intensity from dark blue to yellow indicated lower to higher predicted RAI.

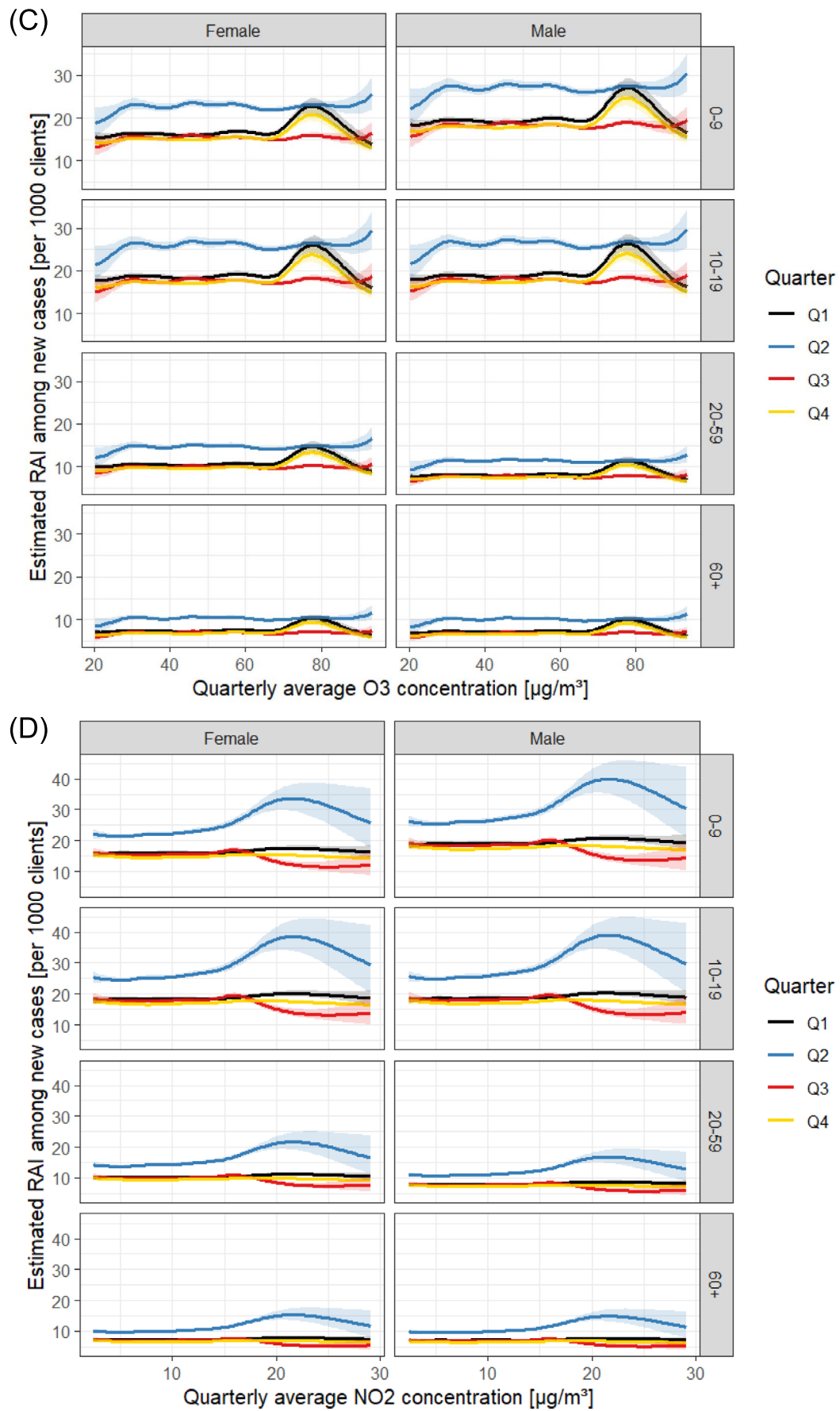


FIGURE 5 | (Continued)

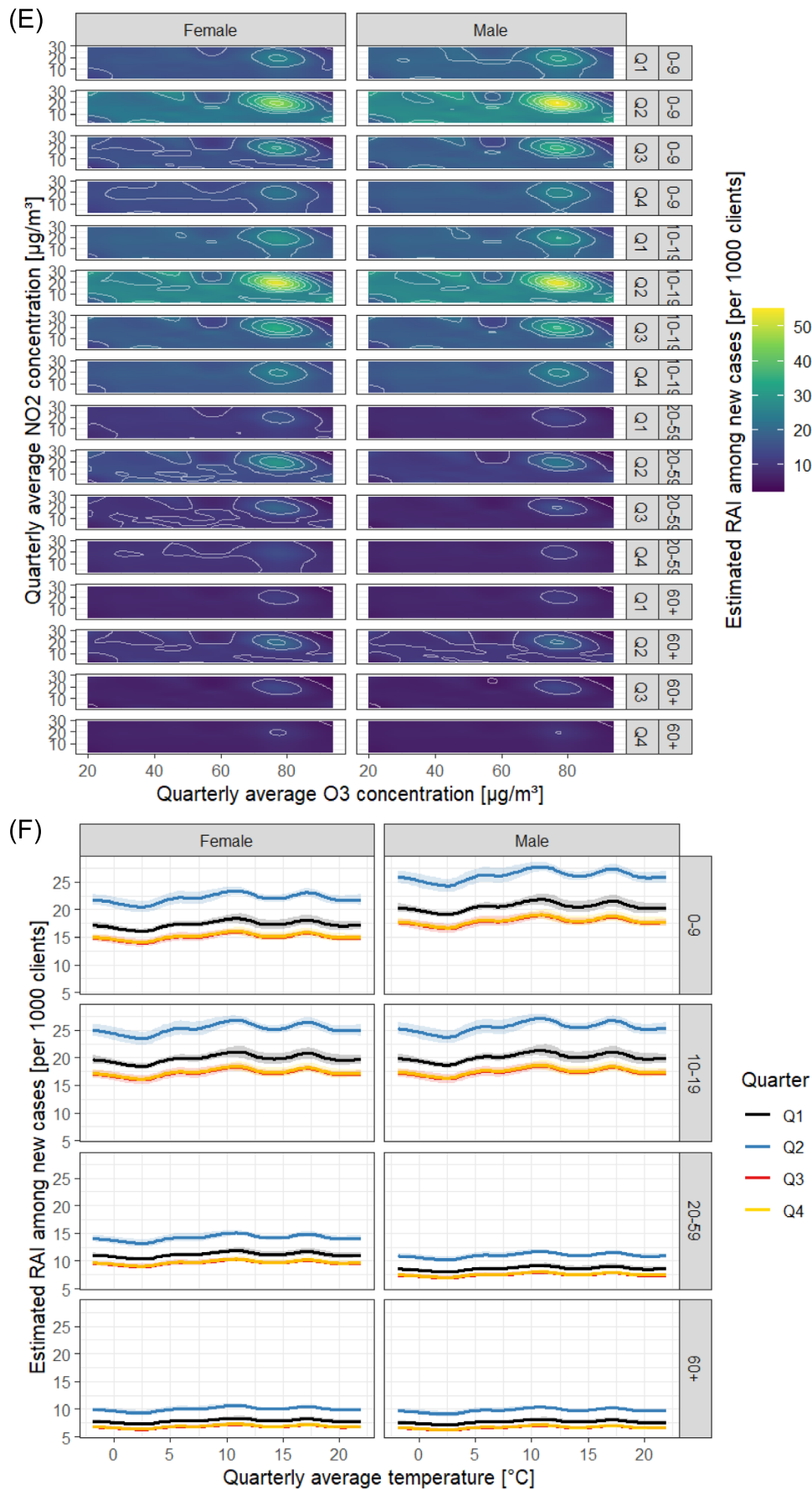


FIGURE 5 | (Continued)

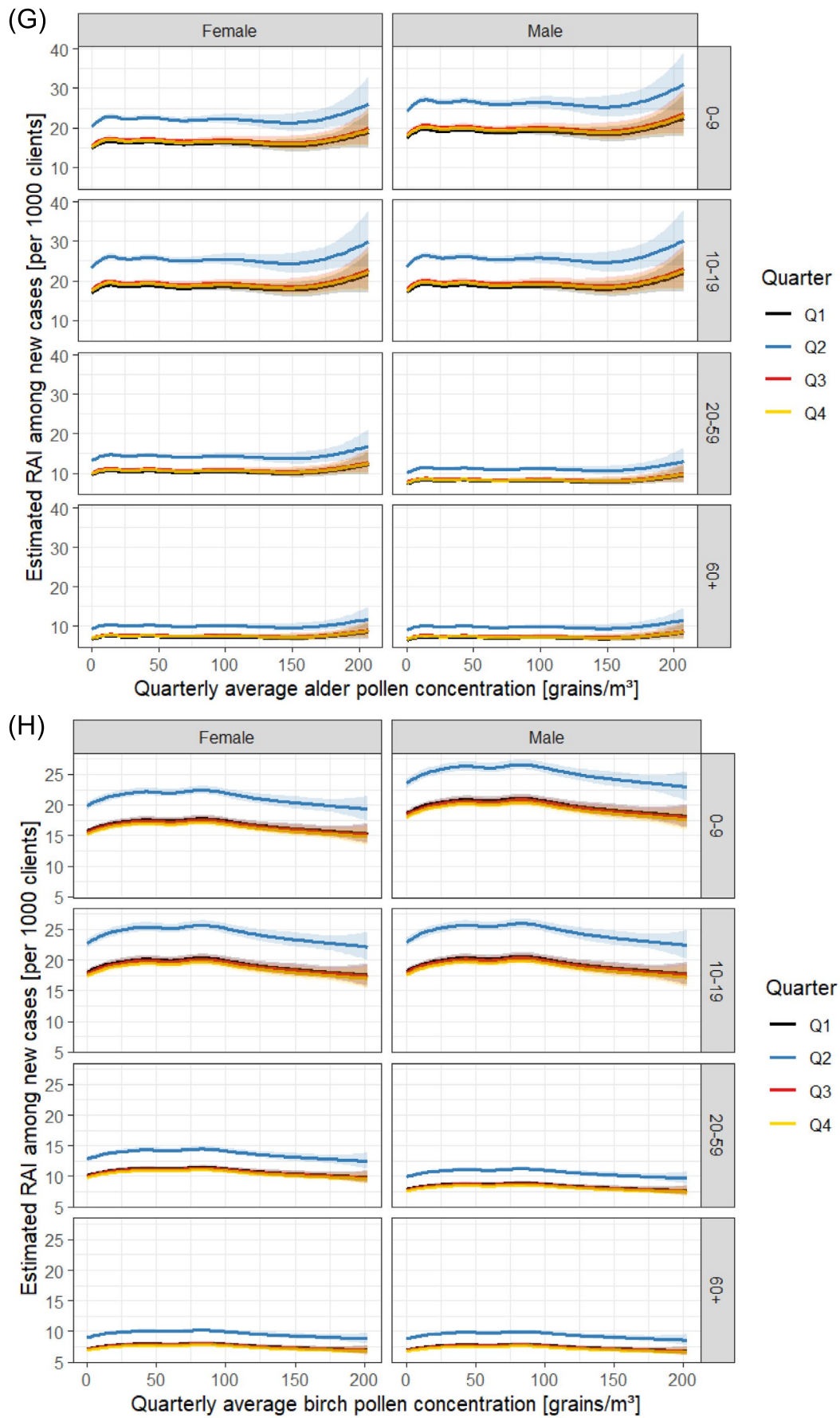


FIGURE 5 | (Continued)

TABLE 2 | Preventable RAs cases per 1000 clients across different age and sex groups associated with a reduction to the WHO recommended level for PM₁₀ (μg/m³). Parentheses indicate 95% confidence intervals.

Age	Sex	Estimated preventable cases (per 1000 clients)	Estimated preventable percent (%)
0–9	Female	2.73 (0.948; 4.513)	19.2 (6.681; 31.792)
0–9	Male	2.66 (0.568; 4.761)	16.1 (3.443; 28.856)
10–19	Female	−0.535 (−2.443; 1.373)	−3.91 (−17.864; 10.038)
10–19	Male	−0.766 (−2.68; 1.148)	−5.56 (−19.445; 8.332)
20–59	Female	0.327 (−0.773; 1.426)	3.94 (−9.33; 17.216)
20–59	Male	0.131 (−0.723; 0.986)	2.07 (−11.380; 15.521)
60+	Female	0.442 (−0.330; 1.213)	7.42 (−5.547; 20.394)
60+	Male	0.426 (−0.328; 1.18)	7.36 (−5.675; 20.387)

Additionally, there is strong evidence that temperature indirectly affects allergies by influencing both pollen concentration and allergenicity [40, 41]. In our study, we focused on alder and birch, two of the eight primary pollen types most commonly causing sensitization in Germany, as discussed below.

5.2.2 | Alder and Birch Pollen

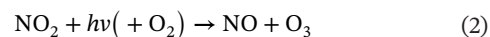
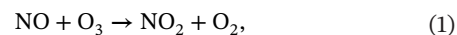
Pollen from birch and alder of the family Betulaceae is a major aeroallergen in Germany [42, 43], with cross-reactive major allergens (Aln g1 and Bet v1) implicated in RAs [44, 45].

In BW, alder trees are among the first to release pollen, typically from December to July [46], marking the beginning of the pollen season and potentially leading to early onset of allergic symptoms in sensitized individuals [47]. BW is also a region where birches are more widely distributed [43]. In this region, birch pollen season lasts from March to June [46]. However, in the context of climate change, species have advanced their pollen season [48], and more in early spring (alder) than in mid spring (birch) [49]. In our models, RAI and DPMR increased around the start of pollen release. In particular, alder pollen was broadly associated with both RAI's binary and continuous components, and the Pr(DPM) continued rising above 150 grains/m³ even as RAI plateaued. Because aeroallergen avoidance is often challenging in everyday life, structured symptom diaries may help document temporal patterns and guide targeted diagnostic allergy testing. Allergen immunotherapy may be considered once causality has been established in individual patients, and effective medical management of RAs patients may become increasingly important.

5.2.3 | Air Pollutants (PM₁₀, PM_{2.5}, O₃, NO₂)

Our findings reinforce established associations between air pollution and both development and exacerbation of RAs [50].

The associations found between O₃, NO₂, and intensities of RAs, as well as of DPMR in our study, concur with research findings from both previous long-term and short-term studies [51, 52], suggesting that NO₂ and O₃ could serve as exacerbating factors for RAs patients in BW [53, 54]. Both pollutants can trigger airway inflammation, allergen sensitization, and impair lung function [55–57]. A combined effect of O₃ and NO₂, previously shown to enhance pollen allergenicity and respiratory risk [58–62], was also evident in our analysis. Notably, the association with O₃ was apparent only in summer, while that with NO₂ was more pronounced in winter, especially under shallow inversion conditions that combine high NO_x (NO_x = NO + NO₂) levels with stagnant air [63], reflecting their seasonal patterns [64]. Additionally, our urbanization models indicated a more pronounced association with NO₂ than with O₃, and more in urban than rural areas. Under atmospheric conditions, the interconversion of O₃, NO, and NO₂ is primarily governed by the reactions [65]:



Additionally, under sunlight, free radical-catalyzed degradation of volatile organic compounds (VOCs) in the presence of NO_x also facilitates the oxidation of NO to NO₂, leading to the production of additional O₃ [63].

In urban areas, high NO emissions from traffic and other combustion sources can reduce local O₃ through titration, whereas lower NO_x emissions and regional transport lead to higher O₃ concentrations in adjacent rural areas [66]. Although no significant association was observed for rural O₃—potentially reflecting multicollinearity, reducing vehicle and industrial emissions in urban and suburban areas could further decrease background average O₃ levels. In cities, however, reducing NO_x/VOCs emissions may increase O₃. Hence, reduction of precursor emissions should be appropriately coordinated, with previous studies suggesting that a 10% reduction in NO_x would require at least an 18% reduction in VOCs to lower O₃ [67].

Our results on PM, including PM₁₀ and PM_{2.5}, align with previous literature [68–74]. PM may not only directly trigger inflammation and increase oxidative stress, leading to cell and tissue damage in the airways, but also act as a carrier for allergens and pathogens, such as pollen, fungal spores, and viruses, delivering them deep into the airways [75]. PM disrupts epithelial barriers by degrading tight junction proteins, downregulating occludin and claudin-1, suppressing E-cadherin levels, decreasing transepithelial electrical resistance, and increasing paracellular permeability [76]. Moreover, PM triggers the activation of Toll-like receptors and nuclear factor-κB, which promotes inflammasome activation, increases ROS production, and accumulates inflammatory cells [77]. Additionally, PM is also heterogeneous in composition across location and time [78]. Pollen grains (10–100 μm) can rupture, forming sub-pollen particles with smaller diameters

(< 10 µm), which, in comparison to intact pollen grains, have longer atmospheric lifetimes and greater penetration to the lower lung [79]. In our study, children aged 0–9 appeared particularly vulnerable to the PM effects because of underdeveloped lungs, smaller airways, higher breathing rates, and greater outdoors exposure [80]. Additionally, early-life PM exposure may disrupt critical lung development, resulting in long-term respiratory consequences [81, 82]. Therefore, lowering preventable prevRA by reducing PM, especially in children, would lessen the burden on patients, improve life quality [83], and lower treatment costs.

Our study was the first to apply generalized additive two-part models to jointly assess RAI and DPMR in relation to multiple environmental factors in Germany. However, several limitations should be acknowledged: (1) Our RAI and DPMR data were sampled quarterly, which may not capture short-term fluctuations [7]; (2) Medication type and count were treated as equally related to severity; (3) Data on self-treatment and non-AOK-insured individuals were not included; (4) Diagnostic criteria may vary locally; (5) Potential double counting of clients due to separate types of RAs diagnoses; (6) Future studies should aim at more individualized information regarding the microclimate, mobility, and indoor environment; (7) Finally, future research on RAs should include other pollen's types, that is, hazel, ash trees, and sweet grasses, the most sensitized pollen types in Germany [84].

6 | Conclusion

Our findings highlight the vulnerable subgroups in RAs' development and exacerbation, namely young children (0–9 years) and residents of urban areas, as well as reveal associations between RAI, DPMR, and all environmental exposures assessed. Our study provides key evidence suggesting that:

1. Reducing exposure to both PM₁₀ and alder pollen may offer the greatest preventive benefit.
2. NO₂ and O₃ were identified as important exacerbating factors for RAs, emphasizing the need for vigilant exposure control and preparedness measures.

Author Contributions

E.L. and T.D.-S. conceived the research question and approach. C.M. prepared the ATC codes for RAs. T.E. prepared the meteorological data, C.K. prepared the pollen data. T.D.-S. prepared air pollution data and urbanization data. T.D.-S. merged the joint database. R.H., C.K., and E.H. provided in-depth advice on the analysis. T.D.-S. carried out the statistical analysis. T.D.-S., E.L., and R.H. wrote the first version of the manuscript. All authors reviewed, commented on the manuscript, and approved the final version.

Acknowledgments

We gratefully acknowledge the Allgemeine Ortskrankenkasse Baden-Württemberg (AOK BW) for preparing and providing the respiratory allergy data, and for coordinating the interinstitutional collaborations and communication that made this work possible. We also thank the Federal Institute for Research on Building, Urban Affairs, and Spatial Development in Germany for providing data on the urbanization level. We further thank the anonymous reviewers for their valuable time and insightful comments, which strengthened the manuscript. Open Access funding enabled and organized by Projekt DEAL.

Funding

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Endnotes

¹ Using the Bonferroni correction for multiple testing.

² The caution range is the interval of the covariate values, where the smooth function lies above 0 on the link scale, indicating an increased contribution to the outcome compared to the average effect.

References

1. K. C. Bergmann, R. Brehler, C. Endler, et al., "Impact of Climate Change on Allergic Diseases in Germany," *Journal of Health Monitoring* 8, no. S4 (2023): 76–102, <https://doi.org/10.25646/11654>.
2. C. Jacob, B. Bechtel, S. Engel, et al., "Healthcare Costs and Resource Utilization of Asthma in Germany: A Claims Data Analysis," *European Journal of Health Economics* 17, no. 2 (2016): 195–201, <https://doi.org/10.1007/s10198-015-0671-3>.
3. V. Hillerich, F. Valbert, S. Neusser, et al., "Quality of Life and Healthcare Costs of Patients With Allergic Respiratory Diseases: A Cross-Sectional Study," *European Journal of Health Economics* 25, no. 4 (2024): 579–600, <https://doi.org/10.1007/s10198-023-01598-3>.
4. C. Ober and T. C. Yao, "The Genetics of Asthma and Allergic Disease: A 21st Century Perspective," *Immunological Reviews* 242, no. 1 (2011): 10–30, <https://doi.org/10.1111/j.1600-065X.2011.01029.x>.
5. Umweltbundesamt, "Development of Germany's Climate," accessed July 7, 2025, <https://www.umweltbundesamt.de/en/monitoring-on-das/development#the-development-of-germanys-climate-since-the-end-of-the-19th-century>.
6. EEA, "Germany—Air Pollution Country Fact Sheet," accessed July 7, 2025, <https://www.eea.europa.eu/en/analysis/maps-and-charts/germany-air-pollution-country-2023-country-fact-sheets>.
7. T. Dao-Siebel, J. Holstiege, K. Graw, et al., "Association Between Climate Indicators and Hay Fever Incidence in Children and Adolescents in Freiburg, Germany," *Frontiers in Public Health* 13 (2025): 1587767, <https://doi.org/10.3389/fpubh.2025.1587767>.
8. Technology KIo, "Adaptation to Climate Change in Baden-Württemberg," accessed July 8, 2025, https://www.kit.edu/kit/english/pi_2016_069_adaptation-to-climate-change-in-baden-wuerttemberg.php?utm_source=chatgpt.com.
9. Baden-Württemberg LfPB, "Das Land Baden-Württemberg," accessed September 9, 2024, <https://www.landeskunde-baden-wuerttemberg.de/das-land>.
10. Baden-Württemberg, "The State and Its People," accessed July 3, 2025, <https://www.baden-wuerttemberg.de/en/our-state/the-state-and-its-people#:~:text=Alongside%20its%20urban%20conurbations%2C%20Baden%2DW%C3%BCrttemberg%20is%20a,character.%20Baden%2DW%C3%BCrttemberg%20is%20also%20rich%20in%20waterways>.
11. Landesamt B-WS, "Environmental Data—Environmental Indicators for Baden-Württemberg," accessed July 7, 2025, https://www.statistik-bw.de/Service/Veroeff/Faltblatt/803824004.pdf?sessionid=DZ7Nem4e_2msYx60rckQ4HWYoXivWNh8dcIW06PW.webext04.

12. L. Gilardi, T. Erbertseder, and F. Baier, "Data From: NO₂, O₃, PM10 and PM2.5 Concentrations—Daily Geographical Aggregates at ZIP-Code Level From CAMS European Air Quality Re-Analyses," *Zenodo* (2023), <https://doi.org/10.5281/zenodo.8325533>.
13. M. Sofiev, J. Palamarchuk, R. Kouznetsov, et al., "European Pollen Reanalysis, 1980–2022, for Alder, Birch, and Olive," *Scientific Data* 11, no. 1 (2024): 1082, <https://doi.org/10.1038/s41597-024-03686-2>.
14. J. Muñoz-Sabater, *Data From: ERA5-Land Hourly Data From 1950 to Present (2019)* (Copernicus Climate Change Service [C3S] Climate Data Store [CDS], 2019), <https://doi.org/10.24381/cds.e2161bac>.
15. A. J. Boulton and A. Williford, "Analyzing Skewed Continuous Outcomes With Many Zeros: A Tutorial for Social Work and Youth Prevention Science Researchers," *Journal of the Society for Social Work and Research* 9, no. 4 (2018): 721–740, <https://doi.org/10.1086/701235>.
16. WHO, *WHO Global Air Quality Guidelines: Particulate Matter (PM_{2.5} and PM₁₀), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide* (WHO, 2021).
17. Umweltbundesamt, "Indicator: Population Exposure to Particulate Matter (PM₁₀)," accessed July 21, 2025, <https://www.umweltbundesamt.de/en/indicator-population-exposure-to-particulate-matter#at-a-glance>.
18. Umweltbundesamt, "In 2024, All Air Quality Limits Met for the First Time: Further Efforts Required Until 2030," accessed July 21, 2025, <https://www.umweltbundesamt.de/en/press/pressinformation/in-2024-all-air-quality-limits-met-for-the-first>.
19. E. A. Townsend, V. M. Miller, and Y. S. Prakash, "Sex Differences and Sex Steroids in Lung Health and Disease," *Endocrine Reviews* 33, no. 1 (2012): 1–47, <https://doi.org/10.1210/er.2010-0031>.
20. L. Tizek, E. Redlinger, J. Ring, K. Eyerich, T. Biedermann, and A. Zink, "Urban vs Rural—Prevalence of Self-Reported Allergies in Various Occupational and Regional Settings," *World Allergy Organization Journal* 15, no. 1 (2022): 100625, <https://doi.org/10.1016/j.waojou.2022.100625>.
21. E. Jensen-Jarolim, "Gender Effects in Allergology—Secondary Publications and Update," *World Allergy Organization Journal* 10, no. 1 (2017): 47, <https://doi.org/10.1186/s40413-017-0178-8>.
22. U. Langen, R. Schmitz, and H. Steppuhn, "[Prevalence of Allergic Diseases in Germany: Results of the German Health Interview and Examination Survey for Adults (DEGS1)] Häufigkeit allergischer Erkrankungen in Deutschland: Ergebnisse der Studie zur Gesundheit Erwachsener in Deutschland (DEGS1)," *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* 56, no. 5–6 (2013): 698–706, <https://doi.org/10.1007/s00103-012-1652-7>.
23. R. W. Bottema, N. E. Reijmerink, G. H. Koppelman, M. Kerkhof, and D. S. Postma, "Phenotype Definition, Age, and Gender in the Genetics of Asthma and Atopy," *Immunology and Allergy Clinics of North America* 25, no. 4 (2005): 621–639, <https://doi.org/10.1016/j.iac.2005.07.002>.
24. G. Pelizzo, V. Calcaterra, P. Baldassarre, et al., "The Impact of Hormones on Lung Development and Function: An Overlooked Aspect to Consider From Early Childhood," *Frontiers in Endocrinology* 15 (2024): 1425149, <https://doi.org/10.3389/fendo.2024.1425149>.
25. C. Hohmann, T. Keller, U. Gehring, et al., "Sex-Specific Incidence of Asthma, Rhinitis and Respiratory Multimorbidity Before and After Puberty Onset: Individual Participant Meta-Analysis of Five Birth Cohorts Collaborating in MeDALL," *BMJ Open Respiratory Research* 6, no. 1 (2019): e000460, <https://doi.org/10.1136/bmjresp-2019-000460>.
26. M. K. Hollinger, E. M. Grayson, C. M. Ferreira, and A. I. Sperling, "Harnessing the Farm Effect: Microbial Products for the Treatment and Prevention of Asthma Throughout Life," *Immunological Reviews* 330, no. 1 (2025): e70012, <https://doi.org/10.1111/imr.70012>.
27. M. J. Ege, M. Mayer, A. C. Normand, et al., "Exposure to Environmental Microorganisms and Childhood Asthma," *New England Journal of Medicine* 364, no. 8 (2011): 701–709, <https://doi.org/10.1056/NEJMOa1007302>.
28. B. Sozanska, "Raw Cow's Milk and Its Protective Effect on Allergies and Asthma," *Nutrients* 11, no. 2 (2019): 469, <https://doi.org/10.3390/nut11020469>.
29. A. Gledson, D. Lowe, M. Reani, et al., "A Comparison of Experience Sampled Hay Fever Symptom Severity Across Rural and Urban Areas of the UK," *Scientific Reports* 13, no. 1 (2023): 3060, <https://doi.org/10.1038/s41598-023-30027-x>.
30. D. Roye, A. Tobias, A. Figueiras, et al., "Temperature-Related Effects on Respiratory Medical Prescriptions in Spain," *Environmental Research* 202 (2021): 111695, <https://doi.org/10.1016/j.envres.2021.111695>.
31. H. Hyrkas-Palmu, T. M. Ikaheimo, T. Laatikainen, P. Jousilahti, M. S. Jaakkola, and J. J. K. Jaakkola, "Cold Weather Increases Respiratory Symptoms and Functional Disability Especially Among Patients With Asthma and Allergic Rhinitis," *Scientific Reports* 8, no. 1 (2018): 10131, <https://doi.org/10.1038/s41598-018-28466-y>.
32. Z. Celebi Sozener, E. R. Treffeisen, B. Ozdel Ozturk, and L. C. Schneider, "Global Warming and Implications for Epithelial Barrier Disruption and Respiratory and Dermatologic Allergic Diseases," *Journal of Allergy and Clinical Immunology* 152, no. 5 (2023): 1033–1046, <https://doi.org/10.1016/j.jaci.2023.09.001>.
33. L. He, C. Norris, K. Palaguachi-Lopez, et al., "Nasal Oxidative Stress Mediating the Effects of Colder Temperature Exposure on Pediatric Asthma Symptoms," *Pediatric Research* 96, no. 4 (2024): 1045–1051, <https://doi.org/10.1038/s41390-024-03196-2>.
34. A. Cincinelli and T. Martellini, "Indoor Air Quality and Health," *International Journal of Environmental Research and Public Health* 14, no. 11 (2017): 1286, <https://doi.org/10.3390/ijerph14111286>.
35. Umweltbundesamt, "Kinder Kinder, was hat die Umwelt mit der Gesundheit zu tun?" accessed May 5, 2023, https://mobil.bfr.bund.de/cm/350/kinder_kinder_was_hat_die_umwelt_mit_der_gesundheit_zu_tun.pdf.
36. A. Fares, "Seasonality of Tuberculosis," *Journal of Global Infectious Diseases* 3, no. 1 (2011): 46–55, <https://doi.org/10.4103/0974-777X.77296>.
37. B. Jacob, B. Ritz, U. Gehring, et al., "Indoor Exposure to Molds and Allergic Sensitization," *Environmental Health Perspectives* 110, no. 7 (2002): 647–653, <https://doi.org/10.1289/ehp.02110647>.
38. J. Gillespie-Bennett, N. Pierse, K. Wickens, J. Crane, P. Howden-Chapman, and The Housing Heating and Health Study Research Team, "The Respiratory Health Effects of Nitrogen Dioxide in Children With Asthma," *European Respiratory Journal* 38, no. 2 (2011): 303–309, <https://doi.org/10.1183/09031936.00115409>.
39. J. Schwarze and E. W. Gelfand, "Respiratory Viral Infections as Promoters of Allergic Sensitization and Asthma in Animal Models," *European Respiratory Journal* 19, no. 2 (2002): 341–349, <https://doi.org/10.1183/09031936.02.00254302>.
40. L. H. Ziska, L. Makra, S. K. Harry, et al., "Temperature-Related Changes in Airborne Allergenic Pollen Abundance and Seasonality Across the Northern Hemisphere: A Retrospective Data Analysis," *Lancet Planetary Health* 3, no. 3 (2019): e124–e131, [https://doi.org/10.1016/S2542-5196\(19\)30015-4](https://doi.org/10.1016/S2542-5196(19)30015-4).
41. I. J. Skypala, "The Impact of Climate Change in Pollen Food Allergy Syndrome," *Current Opinion in Allergy and Clinical Immunology* 25, no. 2 (2025): 129–133, <https://doi.org/10.1097/ACI.0000000000001064>.
42. T. Biedermann, L. Winther, S. J. Till, P. Panzner, A. Knulst, and E. Valovirta, "Birch Pollen Allergy in Europe," *Allergy* 74, no. 7 (2019): 1237–1248, <https://doi.org/10.1111/all.13758>.
43. Umweltbundesamt, "GE-I-3: Birch Pollen Burdens," accessed May 21, 2025, <https://www.umweltbundesamt.de/en/monitoring-on-das-cluster/human-health/ge-i-3/indicator>.
44. M. Grote, R. Valenta, and R. Reichelt, "Abortive Pollen Germination: A Mechanism of Allergen Release in Birch, Alder, and Hazel Revealed

- by Immunogold Electron Microscopy," *Journal of Allergy and Clinical Immunology* 111, no. 5 (2003): 1017–1023, <https://doi.org/10.1067/mai.2003.1452>.
45. M. Gassner, R. Gehrig, and P. Schmid-Grendelmeier, "Hay Fever as a Christmas Gift," *New England Journal of Medicine* 368, no. 4 (2013): 393–394, <https://doi.org/10.1056/NEJMc1214426>.
46. Polleninformationsdienst SD, "Pollenflugkalender," accessed May 21, 2025, <https://www.pollenstiftung.de/pollenvorhersage/pollenflugkalender.html>.
47. R. Sousa-Silva, A. Smargiassi, D. Kneeshaw, J. Dupras, K. Zinszer, and A. Paquette, "Strong Variations in Urban Allergenicity Riskscapes due to Poor Knowledge of Tree Pollen Allergenic Potential," *Scientific Reports* 11, no. 1 (2021): 10196, <https://doi.org/10.1038/s41598-021-89353-7>.
48. Y. Zhang and A. L. Steiner, "Projected Climate-Driven Changes in Pollen Emission Season Length and Magnitude Over the Continental United States," *Nature Communications* 13, no. 1 (2022): 1234, <https://doi.org/10.1038/s41467-022-28764-0>.
49. K. C. Bergmann, J. Buters, K. Karatzas, et al., "The Development of Birch Pollen Seasons Over 30 Years in Munich, Germany—An EAACI Task Force Report," *Allergy* 75, no. 12 (2020): 3024–3026, <https://doi.org/10.1111/all.14470>.
50. D. Jenerowicz, W. Silny, A. Danczak-Pazdrowska, A. Polanska, A. Osmola-Mankowska, and K. Olek-Hrab, "Environmental Factors and Allergic Diseases," *Annals of Agricultural and Environmental Medicine* 19, no. 3 (2012): 475–481.
51. P. E. Zhou, Z. M. Qian, S. E. McMillin, et al., "Relationships Between Long-Term Ozone Exposure and Allergic Rhinitis and Bronchitic Symptoms in Chinese Children," *Toxics* 9, no. 9 (2021): 221, <https://doi.org/10.3390/toxics9090221>.
52. X. Fang, S. Huang, Y. Zhu, et al., "Short-Term Exposure to Ozone and Asthma Exacerbation in Adults: A Longitudinal Study in China," *Frontiers in Public Health* 10 (2022): 1070231, <https://doi.org/10.3389/fpubh.2022.1070231>.
53. G. D'Amato, G. Liccardi, and M. D'Amato, "Environmental Risk Factors (Outdoor Air Pollution and Climatic Changes) and Increased Trend of Respiratory Allergy," *Journal of Investigational Allergology & Clinical Immunology* 10, no. 3 (2000): 123–128.
54. C. H. Chou, Y. F. Chen, H. C. Peng, C. Y. Chen, and B. W. Cheng, "Environmental Pollutants Increase the Risks of Acute Exacerbation in Patients With Chronic Airway Disease," *Frontiers in Public Health* 11 (2023): 1215224, <https://doi.org/10.3389/fpubh.2023.1215224>.
55. S. Y. Kim, E. Kim, and W. J. Kim, "Health Effects of Ozone on Respiratory Diseases," *Tuberculosis and Respiratory Diseases (Seoul)* 83, no. S1 (2020): S6–S11, <https://doi.org/10.4046/trd.2020.0154>.
56. M. Bevelander, J. Mayette, L. A. Whittaker, et al., "Nitrogen Dioxide Promotes Allergic Sensitization to Inhaled Antigen," *Journal of Immunology* 179, no. 6 (2007): 3680–3688, <https://doi.org/10.4049/jimmunol.179.6.3680>.
57. C. Barck, J. Lundahl, G. Hallden, and G. Bylin, "Brief Exposures to NO₂ Augment the Allergic Inflammation in Asthmatics," *Environmental Research* 97, no. 1 (2005): 58–66, <https://doi.org/10.1016/j.envres.2004.02.009>.
58. Y. K. Gruijthuisen, I. Grieshuber, A. Stocklinger, et al., "Nitration Enhances the Allergenic Potential of Proteins," *International Archives of Allergy and Immunology* 141, no. 3 (2006): 265–275, <https://doi.org/10.1159/000095296>.
59. A. C. Karle, G. J. Oostingh, S. Mutschlechner, et al., "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, no. 2 (2012): e31483, <https://doi.org/10.1371/journal.pone.0031483>.
60. M. Shiraiwa, K. Selzle, H. Yang, Y. Sosedova, M. Ammann, and U. Poschl, "Multiphase Chemical Kinetics of the Nitration of Aerosolized Protein by Ozone and Nitrogen Dioxide," *Environmental Science & Technology* 46, no. 12 (2012): 6672–6680, <https://doi.org/10.1021/es300871b>.
61. T. Franze, M. G. Weller, R. Niessner, and U. Poschl, "Protein Nitration by Polluted Air," *Environmental Science & Technology* 39, no. 6 (2005): 1673–1678, <https://doi.org/10.1021/es0488737>.
62. H. S. Jenkins, J. L. Devalia, R. L. Mister, A. M. Bevan, C. Rusznak, and R. J. Davies, "The Effect of Exposure to Ozone and Nitrogen Dioxide on the Airway Response of Atopic Asthmatics to Inhaled Allergen: Dose- and Time-Dependent Effects," *American Journal of Respiratory and Critical Care Medicine* 160, no. 1 (1999): 33–39, <https://doi.org/10.1164/ajrccm.160.1.9808119>.
63. L. J. Clapp and M. E. Jenkin, "Analysis of the Relationship Between Ambient Levels of O₃, NO₂ and NO as a Function of NO_x in the UK," *Atmospheric Environment* 35, no. 36 (2001): 6391–6405, [https://doi.org/10.1016/S1352-2310\(01\)00378-8](https://doi.org/10.1016/S1352-2310(01)00378-8).
64. L. Hoffmann, L. Gilardi, M. T. Schmitz, et al., "Investigating the Spatiotemporal Associations Between Meteorological Conditions and Air Pollution in the Federal State Baden-Württemberg (Germany)," *Scientific Reports* 14, no. 1 (2024): 5997, <https://doi.org/10.1038/s41598-024-56513-4>.
65. S. Q. Han, H. Bian, Y. C. Feng, et al., "Analysis of the Relationship Between O₃, NO and NO₂ in Tianjin, China," *Aerosol and Air Quality Research* 11, no. 2 (2011): 128–139, <https://doi.org/10.4209/aaqr.2010.07.0055>.
66. E. Real, A. Megaritis, A. Colette, G. Valastro, and P. Messina, "Atlas of Ozone Chemical Regimes in Europe," *Atmospheric Environment* 320 (2024): 120323, <https://doi.org/10.1016/j.atmosenv.2023.120323>.
67. J. Tian, J. Wang, D. Wang, C. Fang, and J. Huang, "Research on Ozone Pollution Control Strategies for Urban Agglomerations Based on Ozone Formation Sensitivity and Emission Source Contributions," *Environmental Pollution* 363, no. pt. 1 (2024): 125182, <https://doi.org/10.1016/j.envpol.2024.125182>.
68. S. Li, W. Wu, G. Wang, et al., "Association Between Exposure to Air Pollution and Risk of Allergic Rhinitis: A Systematic Review and Meta-Analysis," *Environmental Research* 205 (2022): 112472, <https://doi.org/10.1016/j.envres.2021.112472>.
69. H. Chu, J. Xin, Q. Yuan, et al., "The Effects of Particulate Matters on Allergic Rhinitis in Nanjing, China," *Environmental Science and Pollution Research International* 26, no. 11 (2019): 11452–11457, <https://doi.org/10.1007/s11356-019-04593-5>.
70. P. Luo, J. Ying, J. Li, et al., "Air Pollution and Allergic Rhinitis: Findings From a Prospective Cohort Study," *Environmental Science & Technology* 57, no. 42 (2023): 15835–15845, <https://doi.org/10.1021/acs.est.3c04527>.
71. J. Zhong, W. Li, S. Yang, Y. Shen, and X. Li, "Causal Association Between Air Pollution and Allergic Rhinitis, Asthma: A Mendelian Randomization Study," *Frontiers in Public Health* 12 (2024): 1386341, <https://doi.org/10.3389/fpubh.2024.1386341>.
72. C. H. Piao, Y. Fan, T. V. Nguyen, et al., "PM(2.5) Exacerbates Oxidative Stress and Inflammatory Response Through the Nrf2/NF-KappaB Signaling Pathway in OVA-Induced Allergic Rhinitis Mouse Model," *International Journal of Molecular Sciences* 22, no. 15 (2021): 8173, <https://doi.org/10.3390/ijms22158173>.
73. L. Zhao, X. Ding, L. Zhou, et al., "Effect of PM(2.5) Exposure on Susceptibility to Allergic Asthma in Elderly Rats Treated With Allergens," *Scientific Reports* 15, no. 1 (2025): 5594, <https://doi.org/10.1038/s41598-025-90261-3>.
74. B. Park, N. R. London, A. Tharakan, et al., "Particulate Matter Air Pollution Exposure Disrupts the Nrf2 Pathway in Sinonasal Epithelium via Epigenetic Alterations in a Murine Model," *International Forum of Allergy & Rhinology* 12, no. 11 (2022): 1424–1427, <https://doi.org/10.1002/alr.23010>.
75. E. Y. Lim and G. D. Kim, "Particulate Matter-Induced Emerging Health Effects Associated With Oxidative Stress and Inflammation,"

- Antioxidants* 13, no. 10 (2024): 1256, <https://doi.org/10.3390/antiox13101256>.
76. Z. Celebi Sozener, U. Ozbey Yucel, S. Altiner, et al., "The External Exposome and Allergies: From the Perspective of the Epithelial Barrier Hypothesis," *Frontiers in Allergy* 3 (2022): 887672, <https://doi.org/10.3389/falgy.2022.887672>.
77. C. Skevaki, K. C. Nadeau, M. E. Rothenberg, et al., "Impact of Climate Change on Immune Responses and Barrier Defense," *Journal of Allergy and Clinical Immunology* 153, no. 5 (2024): 1194–1205, <https://doi.org/10.1016/j.jaci.2024.01.016>.
78. K. Adams, D. S. Greenbaum, R. Shaikh, A. M. van Erp, and A. G. Russell, "Particulate Matter Components, Sources, and Health: Systematic Approaches to Testing Effects," *Journal of the Air & Waste Management Association* (1995) 65, no. 5 (2015): 544–558, <https://doi.org/10.1080/10962247.2014.1001884>.
79. C. B. A. Mampage, D. D. Hughes, L. M. Jones, N. Metwali, P. S. Thorne, and E. A. Stone, "Characterization of Sub-Pollen Particles in Size-Resolved Atmospheric Aerosol Using Chemical Tracers," *Atmospheric Environment: X* 15 (2022): 100177, <https://doi.org/10.1016/j.aeaoa.2022.100177>.
80. I. P. Wu, S. L. Liao, S. H. Lai, and K. S. Wong, "The Respiratory Impacts of Air Pollution in Children: Global and Domestic (Taiwan) Situation," *Biomedical Journal* 45, no. 1 (2022): 88–94, <https://doi.org/10.1016/j.bj.2021.12.004>.
81. K. Spann, N. Snape, E. Baturcam, and E. Fantino, "The Impact of Early-Life Exposure to Air-Borne Environmental Insults on the Function of the Airway Epithelium in Asthma," *Annals of Global Health* 82, no. 1 (2016): 28–40, <https://doi.org/10.1016/j.aogh.2016.01.007>.
82. S. Carraro, N. Scheltema, L. Bont, and E. Baraldi, "Early-Life Origins of Chronic Respiratory Diseases: Understanding and Promoting Healthy Ageing," *European Respiratory Journal* 44, no. 6 (2014): 1682–1696, <https://doi.org/10.1183/09031936.00084114>.
83. WIdO, "Gesundheitsatlas Deutschland: Asthma bronchiale, Verbreitung in der Bevölkerung Deutschlands und seinen Regionen: Ursachen, Folgen und Präventionsmöglichkeiten," accessed July 23, 2025, https://www.wido.de/fileadmin/Dateien/Dokumente/Publikationen_Produkte/Buchreihen/Gesundheitsatlas/wido_int_gesundheitsatlas_asthma_1120.pdf.
84. Deutscher Wetterdienst, "Pollenflug-Gefahrenindex," accessed May 26, 2025, <https://www.dwd.de/DE/leistungen/gefahrendizespollen/gefahrendexpollen.html>.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Data. **Figure S1:** Geographical distribution of the quarterly average number of AOK Baden-Württemberg clients from 2012 to 2022. **Appendix S2:** Methods. **Appendix S3:** Estimated probability of prescribed medication occurring in response to variations of environmental factors based on the quarterly data from 2012 to 2022 in BW. (A) The effect of PM_{10} ($\mu g/m^3$). (B) The effect of $PM_{2.5}$ ($\mu g/m^3$). (C) The effect of NO_2 ($\mu g/m^3$). (D) The effect of interaction $O_3 * NO_2$ ($\mu g/m^3$). (E) The effect of temperature ($^{\circ}C$). (F) The effect of alder pollen (grains/ m^3). (G) The effect of birch pollen (grains/ m^3). In the main effect plots, colored lines represent the association between EFs and the probability of DPMR occurrence. Shaded areas represent the 95% confidence intervals. The associations for each quarter are shown in black for Q1, blue for Q2, red for Q3, and yellow for Q4. In the interaction plot, color intensity from dark blue to yellow indicated lower to higher predicted probability of DPMR occurring. **Appendix S4:** Estimated DPMR in response to variations of environmental factors based on the quarterly data from 2012 to 2022 in BW. (A) The effect of PM_{10} ($\mu g/m^3$). (B) The effect of $PM_{2.5}$ ($\mu g/m^3$). (C) The effect of NO_2 ($\mu g/m^3$). (D) The effect of O_3 ($\mu g/m^3$). (E) The effect of interaction $O_3 * NO_2$ ($\mu g/m^3$). (F) The effect of temperature ($^{\circ}C$). (G) The

effect of alder pollen (grains/ m^3). (H) The effect of birch pollen (grains/ m^3). In the main effect plots, colored lines represent the associations between EFs and DPMR. Shaded areas represent the 95% confidence intervals. The associations for each quarter are shown in black for Q1, blue for Q2, red for Q3, and yellow for Q4. In the interaction plot, color intensity from dark blue to yellow indicated lower to higher predicted DPMR. **Table S1:** Medication list for DPMR based on ATC codes (Anatomical Therapeutic Chemical Classification System). **Table S2:** GAM summaries for RAI and DPMR. Significance codes: 0 "****" 0.001 "***" 0.01 "*" 0.05. **Table S3:** Odds ratio (OR) for exposure at the 90th percentile versus exposure at the 10th percentile and estimated range effects of environmental factors. Parentheses indicate 95% confidence intervals. **Table S4:** Average marginal effects of environmental factors on probability of outcome occurrence (binary component; expressed as percentage points) and on outcome severity among the diagnosed individuals (continuous component, expressed per 1000 clients). **Table S5:** Preventable cases of RAs per 1000 clients. An example for the age group equaled 0–9, sex equaled female, quarter equaled Q1, and postcode equaled 68,159. Parentheses indicate 95% confidence intervals.