International Journal of
*Environmental Research and Public Health*

MDPI

*Article*

# The Influence of Short-Term Weather Parameters and Air Pollution on Adolescent Airway Inflammation

**Ashtyn Tracey Areal [1,2], Nidhi Singh [1], Qi Zhao [1,3], Dietrich Berdel [4], Sibylle Koletzko [5,6], Andrea von Berg [4], Monika Gappa [7], Joachim Heinrich [8,9,10], Marie Standl [9,11], Michael J. Abramson [12,†] and Tamara Schikowski [1,*,†]**

1 IUF—Leibniz Research Institute for Environmental Medicine, 40225 Düsseldorf, Germany; ashtyntracey.areal@iuf-duesseldorf.de (A.T.A.); nidhi.singh@iuf-duesseldorf.de (N.S.); qi.zhao@sdu.edu.cn (Q.Z.)
2 Department of Epidemiology, Medical Research School, Heinrich-Heine-University, 40225 Düsseldorf, Germany
3 School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan 250100, China
4 Department of Pediatrics, Research Institute, Marien-Hospital Wesel, 46483 Wesel, Germany; berdel.vonberg@t-online.de (D.B.); avb.rodehorst@gmx.de (A.v.B.)
5 Department of Pediatrics, Dr. von Hauner Children's Hospital Munich, University Hospital, LMU Munich, 80539 Munich, Germany; sibylle.koletzko@med.uni-muenchen.de
6 Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine Collegium Medicum, University of Warmia and Mazury, 10-082 Olsztyn, Poland
7 Department of Paediatrics, Evangelisches Krankenhaus, 40217 Düsseldorf, Germany; monika.gappa@evk-duesseldorf.de
8 Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, 80539 Munich, Germany; joachim.heinrich@med.uni-muenchen.de
9 German Center for Lung Research (DZL), 35392 Gießen, Germany; marie.standl@helmholtz-muenchen.de
10 Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC 3010, Australia
11 Institute of Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health, 85764 Neuherberg, Germany
12 School of Public Health & Preventive Medicine, Monash University, Melbourne, VIC 3004, Australia
* Correspondence: tamara.schikowski@iuf-duesseldorf.de; Tel.: +49-211-3389-341
† These authors contributed equally to this work.

**Abstract:** Fraction of exhaled Nitric Oxide (FeNO) is a marker of airway inflammation. We examined the main effects and interactions of relative humidity (RH) and air pollution on adolescents' FeNO. Two thousand and forty-two participants from the 15-year follow-up of the German GINIplus and LISA birth cohorts were included. Daily meteorological (maximum [Tmax], minimum [Tmin] and mean [Tmean] temperatures and RH) and air pollution [Ozone ($O_3$), nitrogen dioxide ($NO_2$) and particulate matter < 2.5 µm ($PM_{2.5}$)] were assessed. Linear models were fitted with Ln(FeNO) as the outcome. Increases in FeNO indicate an increase in lung inflammation. Increased FeNO was associated with an increase in temperature, $PM_{2.5}$, $O_3$ and $NO_2$. A 5% increase in RH was associated with a decrease in FeNO. Interactions between RH and high ($p$ = 0.007) and medium ($p$ = 0.050) $NO_2$ were associated with increases in FeNO; while interactions between RH and high ($p$ = 0.042) and medium ($p$ = 0.040) $O_3$ were associated with decreases in FeNO. Adverse effects were present for male participants, participants with low SES, participants with chronic respiratory disease, and participants from Wesel. Short-term weather and air pollution have an effect on lung inflammation in German adolescents. Future research should focus on further assessing the short-term effect of multiple exposures on lung inflammation in adolescents.

**Keywords:** relative humidity; air pollution; environmental epidemiology; fraction of exhaled nitric oxide; adolescent; cohort studies

check for updates

**Citation:** Areal, A.T.; Singh, N.; Zhao, Q.; Berdel, D.; Koletzko, S.; von Berg, A.; Gappa, M.; Heinrich, J.; Standl, M.; Abramson, M.J.; et al. The Influence of Short-Term Weather Parameters and Air Pollution on Adolescent Airway Inflammation. *Int. J. Environ. Res. Public Health* **2023**, *20*, 6827. https://doi.org/10.3390/ijerph20196827

Academic Editor: Isidro A. Pérez

Received: 11 July 2023
Revised: 14 September 2023
Accepted: 18 September 2023
Published: 25 September 2023

## 1. Introduction

The absolute global burden of chronic respiratory diseases has increased since 1990 [1]. Whilst tobacco smoking remains the leading cause of respiratory disability in men, household and ambient air pollution are the predominant risk factors for women in many regions of the world. Globally, in 2017, ambient ozone ($O_3$) and particulate matter (PM) pollution were associated with 96.4 and 206 Disability Adjusted Life Years (DALYs) per 100,000 people of all ages, respectively [1]. As climate change accelerates, there is increasing interest in the relationship between weather variables and respiratory health outcomes. Relative humidity (RH) and temperature have typically been treated as confounders in time-series studies of air pollution and all-cause or respiratory mortality [2].

During periods of increased lung inflammation, the concentration of nitric oxide accumulates in the lungs and can be measured during exhalation [3]. Fractional exhaled nitric oxide (FeNO) is a noninvasive biomarker that assesses lung inflammation and assists in the diagnosis and assessment of asthma [4]. Previous studies in children, young adults (aged 20 and above) and the elderly found that exposure to $O_3$, PM with a diameter less than 2.5 μm ($PM_{2.5}$), PM with a diameter less than 10 μm ($PM_{10}$) and nitrogen dioxide ($NO_2$), and ambient temperature were associated with an increase in FeNO [4–9].

Although the short-term dose–response relationship between air pollution and FeNO has been described in children, young and older adults, there are limited data for adolescents. Additionally, there are no studies that provide information on the effect of RH on FeNO. This is concerning as adolescence is an important period of lung development as physical growth is rapid, and asthma becomes more common in females than in males [10].

Information on the interactive or modifying effect of weather and air pollution on FeNO is limited and, as far as we are aware, no research looking into how this interaction impacts adolescents during a crucial time of growth. Thus, this analysis aimed to examine the main effects and interactions of low-level short-term air pollutants and weather variables on adolescents' airway inflammation (FeNO).

## 2. Materials and Methods

### 2.1. Study Population

Participants were recruited for two ongoing German population-based, birth cohort studies, which recruited healthy full-term neonates with normal birthweight in Munich and Wesel. The German Infant Study on the Influence of Nutrition Intervention plus Air Pollution and Genetics on Allergy Development (GINIplus) recruited a total of 5991 neonates in Munich and Wesel between September 1995 and July 1998. The Influence of Lifestyle Factors on the Development of the Immune System and Allergies in East and West Germany Study (LISA) recruited a total of 3097 neonates in Bad Honnef, Leipzig, Munich and Wesel between November 1997 and January 1999. The study areas of the cohorts are shown in Figure S1. Data from these two birth cohorts were collected at birth as well as three follow-ups, which occurred at ages 6, 10, and 15, and then due to their harmonised design, pooled for Wesel (GINIplus/LISA North: number = 3390) and Munich (GINIplus/LISA South: number = 4413). Parents completed questionnaires that collected data on respiratory conditions and covariates such as the sex of the child, parental/personal smoking and socioeconomic status (parental education). Further details of recruitment and follow-up to 15 years have been presented elsewhere [11]. The data in this analysis were from the 15-year follow-up assessments for both cohorts in Munich and Wesel. Ethical approval was granted by the Bavarian Board of Physicians (10090 and 12067), Board of Physicians of North-Rhine Westphalia (20101424 and 2012446), and Board of Physicians of Saxony (EK-BR-02/13-1). The parents of participants provided written informed consent.

### 2.2. Assessment of Lung Function

Fraction of exhaled nitric oxide (FeNO) is a well-established biomarker of airway inflammation. FeNO is routinely used in clinical practice in many countries and has also been investigated as a biomarker in epidemiological studies of air pollution. FeNO

measurements, which were adjusted for the nonlinear effects of age, height, weight, and sex, were made between the years 2011 and 2013 with a handheld device (NIOX MINO, Aerocrine, Solna, Sweden) following the guidelines of the American Thoracic Society and European Respiratory Society [12]. Any respiratory tract infections, personal smoking and anti-inflammatory medications were recorded. Since FeNO followed an approximately log-normal distribution, the data were loge-transformed before analysis.

### 2.3. Assessment of Environmental Exposures

Short-term air pollution exposure was assessed as average concentrations of 24 h $O_3$, $NO_2$ and $PM_{2.5}$. The air pollutant exposures at participants' 15-year residential addresses were estimated at a spatial resolution of 2 × 2 km by chemical transport models and data provided by the German Environment Agency (Umwelt Bundesamt, UBA [13]). Weather variables (daily maximum (Tmax), minimum (Tmin) and mean (Tmean) temperature and RH) were obtained for Munich and Wesel from the German Weather Service's high-resolution reanalysis system COSMO-REA6 at a spatial resolution of 6 × 6 km [14]. The warm season was defined as May to October and the cold season as November to April.

### 2.4. Statistical Analysis

There was little variation in temperature and RH between the study sites in Munich and Wesel; as such, it was decided to pool the participants to increase the power of the statistical analysis as in previous studies [15]. We performed correlation tests and checked the collinearity between variables as well as normality tests. Linear regression models were fitted with Ln(FeNO) as the outcome and continuous RH as our main exposure. We determined the main effects for continuous RH and air pollution (i.e., $O_3$, $NO_2$ and $PM_{2.5}$). The model was further adjusted for age, height, weight, sex, a temperature variable (Tmax, Tmin, or Tmean), season with the warm season as the reference category, history of respiratory disease with "No" as the reference category, and location with Munich as the reference category. An interaction model was then fitted with an interaction term between RH and categorical air pollution included in the main model. The air pollution categorical variable was defined as the following: <25% (Low), 25–75% (Medium), and >75% (High). We chose "Low" as the reference category, as it represented the optimum exposure, while "Medium" represented the most common exposure and "High" represented nonoptimum exposure. Effect modification was examined by the site (Munich/Wesel), binary sex characterisation (female/male), maximum parental education as an indicator of socioeconomic status (SES), body mass index (BMI) and history of respiratory conditions. Respiratory conditions were defined as a history of asthma, a history of chronic bronchitis, a history of chronic wheeze, and/or asthma, chronic bronchitis and/or wheeze at the time of assessment.

### 2.5. Sensitivity Analysis

To test the robustness of the core model, sensitivity analyses were conducted to explore the lagged effects up to 10 days prior, location, age, the effect of sex, history of respiratory conditions, height, weight, maximal parental education (as an indicator of SES) and parental smoking. Based on the sensitivity analysis, we chose the Lag01 (one-day moving average) effect for all environmental factors in the core model.

Statistical analysis and data summary were conducted in R version 4.0.4 (15 February 2021) using the packages "stats", "gtsummary","MASS", and "data.table" [16]. A decrease in FeNO indicates a decrease in lung inflammation. Results were calculated as a percentage increase per 5% increase in RH. A two-sided $p$-value < 0.05 was considered statistically significant.

## 3. Results

### 3.1. Description of Participants and Exposures

This analysis included 2042 participants, 1191 participants in Munich and 851 in Wesel. Their mean (±Standard Deviation [SD]) age was 15.06 (±0.29) years. There were slightly

more females than males (51% vs. 49%) (Table 1). The majority of the parents in Munich than in Wesel had completed over 10 years of education (78.3% vs. 52.6%). Just under a third of participants in both centres had a history of respiratory conditions. Approximately 70% of participants had a normal BMI, while 21.58% of participants were underweight and 9.7% were overweight. More participants from Wesel were overweight than participants from Munich (12.10% vs. 7.98%) (Table 1).

**Table 1.** Description of participants.

| Characteristic | Overall [1] | Munich [1] | Wesel [1] | *p*-Value [2] |
|---|---|---|---|---|
| Number of Participants | 2042 | 1191 | 851 | |
| Age | 15.06 (0.29) | 15.09 (0.29) | 15.02 (0.28) | 0.049 |
| Sex<br>Female<br>Male | <br>1050 (51%)<br>992 (49%) | <br>609 (51%)<br>582 (49%) | <br>441 (52%)<br>410 (48%) | 0.8 |
| Height (cm) | 171.4 (8.30) | 170.8 (8.22) | 172.4 (8.32) | <0.001 |
| Weight (Kg) | 61.74 (11.96) | 60.46 (11.10) | 63.53 (12.86) | <0.001 |
| FeNO (ppb) | 23.1 (20.94) | 25.48 (22.60) | 19.77 (17.86) | <0.001 |
| Respiratory condition<br>Yes<br>No<br>NA | <br>643 (31.5%)<br>1397 (68.4%)<br>2 (0.1%) | <br>388 (32.58%)<br>801 (67.25%)<br>2 (0.17%) | <br>255 (29.96%)<br>596 (70.04%)<br>0 | 0.2 |
| Maximal parental education<br>Low (<10 years)<br>Medium (=10 years)<br>High (>10 years)<br>NA | <br>118 (5.78%)<br>539 (26.40%)<br>1380 (67.58%)<br>5 (0.24%) | <br>46 (3.86%)<br>210 (17.63%)<br>932 (78.25%)<br>3 (0.25%) | <br>72 (8.46%)<br>329 (38.66%)<br>448 (52.64%)<br>2 (0.24%) | <0.001 |
| Body Mass Index ($Kg/m^2$)<br>Low (<18.5)<br>Normal (18.5–24.9)<br>High (>25) | <br>414 (20.27%)<br>1430 (70.03%)<br>198 (9.70%) | <br>257 (21.58%)<br>839 (70.45%)<br>95 (7.98%) | <br>157 (18.45%)<br>591 (69.45%)<br>103 (12.10%) | 0.004 |

[1] Mean (Standard Deviation); n (%). [2] Wilcoxon rank sum test; Pearson's Chi-squared test.

Tmin, Tmean, Tmax, and RH were similar in Munich and Wesel (Table 2). Among air pollutants, $PM_{2.5}$ and $O_3$ concentrations were slightly higher in Wesel, while $NO_2$ concentrations were higher in Munich. Most measurements of FeNO were performed during the warm season.

**Table 2.** Description of environmental factors.

| Characteristic | Overall [1] | Munich [1] | Wesel [1] | *p*-Value [2] |
|---|---|---|---|---|
| Season<br>Warm<br>Cold | <br>1315 (64%)<br>727 (36%) | <br>776 (65%)<br>415 (35%) | <br>539 (63%)<br>312 (37%) | 0.4 |
| Relative Humidity (%) | 75.22 (10.60) | 75.03 (11.07) | 75.49 (9.90) | 0.047 |
| Tmax (°C) | 16.43 (7.83) | 16.50 (8.24) | 16.34 (7.22) | 0.6 |
| Tmin (°C) | 8.61 (6.08) | 8.36 (6.13) | 8.95 (6.00) | 0.058 |
| Tmean (°C) | 12.36 (6.80) | 12.24 (7.00) | 12.53 (6.50) | 0.4 |
| $PM_{2.5}$ ($\mu g/m^3$) | 11.09 (6.58) | 9.75 (6.34) | 12.96 (6.46) | <0.001 |
| $NO_2$ ($\mu g/m^3$) | 13.17 (8.39) | 16.29 (8.79) | 8.79 (5.28) | <0.001 |
| $O_3$ ($\mu g/m^3$) | 53.54 (19.76) | 49.96 (20.98) | 58.55 (16.68) | <0.001 |

[1] Mean (standard deviation); n (%). [2] Wilcoxon rank sum test; Pearson's Chi-squared test.

### 3.2. The Main Effects of Weather Variables and Air Pollution on FeNO

A 5% increase in RH showed a consistent nonsignificant trend towards a decrease in FeNO, and, as such, a decrease in lung inflammation across all temperature and air pollution models (percentage change = −0.01%; 95% CI: −0.03 to 0.01) (Table 3). $PM_{2.5}$ (percentage change = 0.19; 95% CI: −0.23 to 0–64), $O_3$ (percentage change = 0.02; 95% CI: −0.18 to 0.20), and $NO_2$ (percentage change = 0.31; 95% CI: −0.08 to 0.71) were all associated with an increase in FeNO and therefore an increase in lung inflammation; however, this result was not statistically significant (Table 3). Tmax, Tmin, and Tmean were all not significantly associated with an increase in FeNO (Table 3).

**Table 3.** The main effects of RH, air pollution, and temperature on FeNO in a cohort of German adolescents.

| | Tmax | | Tmin | | Tmean | |
|---|---|---|---|---|---|---|
| | **Percentage Change (95% CI) *** | ***p*-Value [1,*]** | **Percentage Change (95% CI) *** | ***p*-Value [1,*]** | **Percentage Change (95% CI) *** | ***p*-Value [1,*]** |
| RH [2] | −0.01 (−0.02, 0.01) | 0.265 | −0.01 (−0.03, 0.00) | 0.074 | −0.01 (−0.02, 0.00) | 0.179 |
| $PM_{2.5}$ | 0.19 (−0.24, 0.63) | 0.382 | 0.20 (−0.23, 0.64) | 0.355 | 0.20 (−0.23, 0.63) | 0.367 |
| Temperature | 0.29 (−0.28, 0.86) | 0.314 | 0.27 (−0.41, 0.94) | 0.439 | 0.32 (−0.31, 0.96) | 0.321 |
| RH [2] | −0.01 (−0.03, 0.01) | 0.316 | −0.01 (−0.03, 0.00) | 0.144 | −0.01 (−0.03, 0.01) | 0.237 |
| $O_3$ | 0.01 (−0.18, 0.19) | 0.949 | 0.02 (−0.17, 0.20) | 0.849 | 0.01 (−0.18, 0.20) | 0.928 |
| Temperature | 0.31 (−0.29, 0.91) | 0.308 | 0.25 (−0.45, 0.95) | 0.486 | 0.33 (−0.33, 1.00) | 0.328 |
| RH [2] | −0.01 (−0.03, 0.01) | 0.199 | **−0.01 (−0.03, −0.00)** | **0.039** | −0.01 (−0.03, 0.00) | 0.122 |
| $NO_2$ | 0.31 (−0.29, 0.91) | 0.117 | 0.32 (−0.07, 0.71) | 0.107 | 0.32 (−0.07, 0.71) | 0.109 |
| Temperature | 0.35 (−0.22, 0.92) | 0.225 | 0.35 (−0.33, 1.04) | 0.311 | 0.40 (−0.24, 1.04) | 0.222 |

[1] *p*-value < 0.05 in bold. [2] per 5% increase in RH at Lag01. * Adjusted for indicated study location, season, chronic respiratory disease.

### 3.3. Interactive Effects of RH and Air Pollution on FeNO

The interactive effect between RH and $PM_{2.5}$ showed a nonsignificant trend towards an increase in FeNO for days with medium (percentage change = 0.02; 95% CI: −0.02 to 0.05) and high (percentage change = 0.02; 95% CI: −0.02 to 0.06) $PM_{2.5}$ concentrations compared to days with low $PM_{2.5}$ concentrations (Table 4). There was a statistically significant decrease in FeNO per 5% increase in RH on days with medium (percentage change = −0.04; 95% CI: −0.08 to 0.00) and high (percentage change = −0.04; 95% CI: −0.09 to 0.00) $O_3$ concentrations (Table 5). On days with medium (percentage change = 0.03; 95% CI: 0.00 to 0.07) and high (percentage change = 0.05; 95% CI: 0.01 to 0.08) concentrations of $NO_2$, there was a statistically significant increase in FeNO per 5% increase in RH (Table 6).

**Table 4.** The interactive effects of RH and $PM_{2.5}$ on FeNO in a cohort of German Adolescents.

| | **Interaction Term [2,*]** | **Percentage Change (95% CI) [2,*]** | ***p*-Value [1,*]** |
|---|---|---|---|
| Tmax * | RH: High $PM_{2.5}$ | 0.02 (−0.02, 0.06) | 0.256 |
| | RH: Medium $PM_{2.5}$ | 0.02 (−0.02, 0.05) | 0.388 |
| Tmin * | RH: High $PM_{2.5}$ | 0.02 (−0.02, 0.06) | 0.256 |
| | RH: Medium $PM_{2.5}$ | 0.02 (−0.02, 0.05) | 0.389 |
| Tmean * | RH: High $PM_{2.5}$ | 0.02 (−0.02, 0.06) | 0.258 |
| | RH: Medium $PM_{2.5}$ | 0.02 (−0.02, 0.05) | 0.389 |

[1] *p*-value < 0.05 in bold. [2] per 5% increase in RH at Lag01. * Adjusted for indicated study location, season, chronic respiratory disease, and indicated temperature.

**Table 5.** The interactive effects of RH and $O_3$ on FeNO in a cohort of German Adolescents.

| | Interaction Term [2,*] | Percentage Change (95% CI) [2,*] | *p*-Value [1,*] |
|---|---|---|---|
| Tmax * | RH: High $O_3$ | **−0.04 (−0.09, −0.00)** | **0.042** |
| | RH: Medium $O_3$ | **−0.04 (−0.07, −0.00)** | **0.040** |
| Tmin * | RH: High $O_3$ | **−0.04 (−0.09, −0.00)** | **0.042** |
| | RH: Medium $O_3$ | **−0.04 (−0.08, −0.00)** | **0.038** |
| Tmean * | RH: High $O_3$ | **−0.04 (−0.09, −0.00)** | **0.043** |
| | RH: Medium $O_3$ | **−0.04 (−0.07, −0.00)** | **0.040** |

[1] *p*-value < 0.05 in bold. [2] per 5% increase in RH at Lag01. * Adjusted for indicated study location, season, chronic respiratory disease, and indicated temperature.

**Table 6.** The interactive effects of RH and $NO_2$ on FeNO in a cohort of German Adolescents.

| | Interaction Term [2,*] | Percentage Change (95% CI) [2,*] | *p*-Value [1,*] |
|---|---|---|---|
| Tmax * | RH: High $NO_2$ | **0.05 (0.01, 0.08)** | **0.007** |
| | RH: Medium $NO_2$ | **0.03 (0.00, 0.07)** | **0.050** |
| Tmin * | RH: High $NO_2$ | **0.05 (0.01, 0.08)** | **0.008** |
| | RH: Medium $NO_2$ | **0.03 (0.00, 0.07)** | **0.050** |
| Tmean * | RH: High $NO_2$ | **0.05 (0.01, 0.08)** | **0.008** |
| | RH: Medium $NO_2$ | **0.03 (0.00, 0.07)** | **0.050** |

[1] *p*-value < 0.05 in bold. [2] per 5% increase in RH at Lag01. * Adjusted for indicated study location, season, chronic respiratory disease, and indicated temperature.

### *3.4. Effect Modification*

When we stratified the analysis by sex, we found that RH was associated with a statistically nonsignificant decrease in FeNO in both male and female participants (Table S1). $PM_{2.5}$ and $NO_2$ both showed a nonsignificant trend towards an increase in FeNO in both male and female participants. However, $O_3$ was associated with a decrease in FeNO in female participants, while in male participants, $O_3$ was associated with an increase in FeNO (Table S1). An increase in temperature was associated with an increase in FeNO in both male and female participants; however this effect, while not statistically significant, was stronger in male participants than female participants (Table S1).

When we assessed the modifying effect of BMI, we found that an increase in RH was consistently associated with a decrease in FeNO (Table S2). $PM_{2.5}$ was associated with a decrease in FeNO in underweight and overweight participants, while in participants who were classified as having normal weight, $PM_{2.5}$ was associated with a decrease in FeNO (Table S2). $O_3$ was associated with a decrease in FeNO in both underweight and normal-weight participants, while in overweight participants, $O_3$ was associated with an increase in FeNO (Table S2). $NO_2$ was consistently associated with an increase in FeNO across all participants (Table S2). Temperature increases were associated with an increase in FeNO across all participants; however, this effect was stronger in overweight participants (Table S2).

RH was associated with an increase in FeNO per 5% increase in RH in low SES participants, while in medium and high SES participants, RH was associated with a decrease in FeNO (Table S3). $NO_2$ was consistently associated with an increase in FeNO for all participants; however, this effect was stronger in low SES participants (Table S3). $PM_{2.5}$ was associated with an increase in FeNO in low and high SES participants, while in medium SES participants, $PM_{2.5}$ was associated with a decrease in FeNO (Table S3). $O_3$ was associated with a decrease in FeNO in both low and high SES participants; however, $O_3$ was associated with an increase in FeNO in those with medium SES (Table S3). Temperature was associated with an increase in FeNO across all participants; however, the effect was stronger in low SES participants (Table S3).

In those with CRD, RH and $NO_2$ showed a nonsignificant trend towards a decrease in FeNO; while $PM_{2.5}$, $O_3$, and temperature were associated with an increase in FeNO (Table S4). In those without CRD, RH, $PM_{2.5}$, and temperature were associated with a nonsignificant trend towards an increase in FeNO, and $NO_2$ was statistically significantly associated with an increase in FeNO (Table S4). $O_3$ was associated with a decrease in FeNO in those without CRD (Table S4). The effect of temperature was greater in those with CRD.

In participants from Wesel, RH, $O_3$, $NO_2$, and temperature all showed nonsignificant trends towards an increase in FeNO, while $PM_{2.5}$ was significantly associated with an increase in FeNO (Table S5). RH, $PM_{2.5}$, and $O_3$ were all associated with a decrease in FeNO in participants from Munich, while $NO_2$ and temperature were both associated with an increase in FeNO (Table S5).

### *3.5. Sensitivity Analyses*

We conducted a series of sensitivity analyses to test the robustness of the results. First, we used different lags of RH, temperature and air pollution for up to 10 days. While results were similar across all lag periods for RH, temperature, and all air pollutants, it was found that these exposures were most associated with FeNO at Lag01. Secondly, we adjusted the model for additional covariates. However, associations of prior day RH with FeNO were unchanged after adjusting for age, height, weight, sex, respiratory tract infections, personal and second-hand smoking, family history of respiratory disease, and anti-inflammatory medications.

## 4. Discussion

This analysis of a large cohort of 15-year-old German adolescents has shown that FeNO, a marker of airway inflammation, was consistently associated with short-term RH, temperature, air pollution and interactions between RH and air pollution. There were no statistically significant main effects; however, important trends were apparent. Increases in air pollution and temperature were both associated with an increase in lung inflammation, while increases in RH were associated with a decrease in lung inflammation. Interactions between RH and $PM_{2.5}$ indicated a nonsignificant trend towards an increase in FeNO per 5% increase in RH on days with medium (25th to 75th percentile) and high (>75th percentile) daily average concentrations compared to days with low (<25th percentile) concentrations. There were significant associations between RH and $O_3$, and RH and $NO_2$; there was a significant increase in FeNO per 5% increase in RH on medium and high $NO_2$ concentration days compared to low concentration days. On days with medium and high $O_3$ concentrations, there was a decrease in FeNO per 5% increase in RH, this could be because RH could counter the adverse effects of $O_3$.

When we stratified the analysis by sex, we found that, while not statistically significant, male participants experienced a stronger effect of temperature than female participants. Participants with a low SES were more likely to experience adverse effects of RH, $NO_2$, and temperature than those with a higher SES. Participants with CRD experienced an increase in lung inflammation with increasing RH, temperature and $O_3$ concentrations. Participants from Wesel were more likely than participants from Munich to experience an increase in FeNO with increasing RH, temperature, $O_3$, $PM_{2.5}$, and $NO_2$.

Germany generally has a temperate rainy climate with high levels of humidity and consistently moderate temperatures [17,18]. However, there were different sources of air pollution, with high traffic-related emissions likely explaining the higher concentrations of $NO_2$ in urban Munich compared to rural Wesel. On the other hand, agricultural emissions are a major source of $PM_{2.5}$ in rural Wesel compared to urban Munich [19].

It is not that straightforward to put our results in the context of previous research for several reasons. Weather variables have typically been regarded only as confounders in respiratory epidemiology and not much has been published on associations with markers such as FeNO. Most research has concentrated on long-term exposure to environmental factors. Considering that FeNO is sensitive to external factors, investigating how short-term

exposure impacts FeNO is of interest [3]. While we failed to find any significant associations between FeNO and $PM_{2.5}$ in our adolescent participants, several studies investigating the effect of $PM_{2.5}$ on university students did find adverse effects. A panel study of university students in a highly polluted city in China (72 < weekly mean $PM_{2.5}$ < 180 $\mu g/m^3$) found that temperature and $PM_{2.5}$ were both positively associated with FeNO [4]. Also, a study of healthy university students exercising in a highly polluted city in Poland (median indoor $PM_{2.5}$ 114 vs. 26.5 $\mu g/m^3$) found that increased FeNO during high exposure was associated with higher outdoor $PM_{10}$, $NO_2$ and RH [5].

More is known about the long-term effects of air pollution on airway inflammation. We have previously shown that long-term exposures to $NO_2$, $PM_{2.5}$ and $PM_{10}$ were associated with increased FeNO in a cohort of older (mean age 75) German women [6,7]. While the Southern California Children's Health Study recently reported that long-term (annual) exposures to $PM_{2.5}$ and $NO_2$ were associated with increased FeNO after adjustment for covariates, including sex, asthma, second-hand tobacco smoke, temperature and short-term pollutant exposures [8,9]. The limited information on short-term exposures highlights the necessity for this study, which helps to fill this gap in the literature.

The findings of our analysis have biological plausibility. We found that Tmax, Tmin, and Tmean were associated with an increase in FeNO. This is consistent with literature that found that cold seasons and low temperatures have long been associated with respiratory infections and exacerbation of respiratory conditions, probably because people congregate more indoors [20]. Indeed, due to cold dry air being a common asthma trigger, the cold dry air challenge is used as a diagnostic test for asthma in children [21]. On the other hand, children with asthma have often been encouraged to take up swimming, because the warm moist air does not trigger attacks, in contrast to other sports such as running or cycling [22].

Females typically have a lower metabolic rate, lower skin temperature, lower body mass, higher body fat, and less surface area, but a higher surface area to mass ratio than males. Additionally, females have a slower blood flow, indicating that females are more sensitive to low temperatures than males, who are more sensitive to high temperatures, as cold exposure causes their skin temperature to lower even further, especially in the extremities [23,24].

To obtain further insights into the causal pathways, it is necessary to study surrogate subclinical endpoints such as lung function and biomarkers. Further investigation includes investigating epigenetic markers, as 15 genes have been identified whose methylation status is associated with ambient temperature [25]. Further studies should also be conducted examining other systemic inflammatory biomarkers such as blood neutrophil and eosinophil counts, serum interleukin 6 [26], C reactive protein [27], etc.

This analysis has several strengths. The data were obtained from well-characterised birth cohorts. Short-term air pollution and meteorological exposures were estimated by well-validated high-resolution models. An objective marker of airway inflammation was measured following standard guidelines [12].

However, there were also some limitations: Participant numbers were low, limiting statistical power in some analyses. Although the GINIplus/LISA cohort has been well described, the findings might not be generalisable to adolescents in other countries with higher levels of air pollution and/or different meteorological conditions.

## 5. Conclusions

This analysis of a large data set of German adolescents from two birth cohorts demonstrates that there is an interaction between climate variables and air pollution and FeNO, which is supported by those observed in other age groups. An increase in lung inflammation was associated with the interacting effects of RH and air pollution in this cohort. These findings may have important clinical implications, as they indicate an increase in negative respiratory health outcomes and provide evidence on a relatively unknown topic. Considering the acceleration of climate change, future research should focus further not just on the potential impacts of extreme climate events or individual exposure effects on

health, but also on the short- and long-term impacts of daily weather variables as well as the effect of multiple exposures on all facets of health.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph20196827/s1, Figure S1: A map showing the study areas of the GINIplus and LISA birth cohorts in Germany.; Table S1: A table showing the main effects of relative humidity (RH), air pollution, and temperature on FeNO in German adolescents when stratified by sex; Table S2: A table showing the main effects of relative humidity (RH), air pollution, and temperature on FeNO in German adolescents when stratified by BMI; Table S3: A table showing the main effects of relative humidity (RH), air pollution, and temperature on FeNO in German adolescents when stratified by SES; Table S4: A table showing the main effects of relative humidity (RH), air pollution, and temperature on FeNO in German adolescents when stratified by CRD status; Table S5: A table showing the main effects of relative humidity (RH), air pollution, and temperature on FeNO in German adolescents when stratified by participant location.

**Author Contributions:** A.T.A.: Conceptualisation, Formal analysis, methodology, Visualisation, Writing—original draft, Writing—review and editing. N.S.: Supervision, Validation, Methodology, Writing—review and editing. Q.Z.: Data curation, Methodology, Writing—review and editing. D.B.: Investigation, Project administration, Writing—review and editing. S.K.: Investigation, Writing—review and editing. A.v.B.: Investigation, Project administration, Writing—review and editing. M.G.: Investigation, Writing—review and editing. J.H.: Data curation, Investigation, Writing—review and editing. M.S.: Data curation, Investigation, Writing—review and editing. M.J.A.: Writing—original draft, Writing—review and editing. T.S.: Investigation, Project Administration, Conceptualisation, Supervision, Validation, Methodology, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

**Funding:** The GINIplus study was mainly supported for the first 3 years by the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational arm). The 4-year, 6-year, 10-year and 15-year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5-study centres (Helmholtz Zentrum Munich (former GSF), Research Institute at Marien-Hospital Wesel, LMU Munich, TU Munich and from 6 years onwards also from the IUF—Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Furthermore, the 15-year follow-up examination of the GINIplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project, and the companies Mead Johnson and Nestlé. The LISA study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research—UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4-year, 6-year, 10-year and 15-year follow-up examinations of the LISA study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research—UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF—Leibniz-Research Institute for Environmental Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Further, the 15-year follow-up examination of the LISA study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project. The IUF is funded by the federal and state governments—the Ministry of Culture and Science of North Rhine-Westphalia (MKW) and the Federal Ministry of Education and Research (BMBF).

**Institutional Review Board Statement:** Ethical approval was granted by the Bavarian Board of Physicians (10090 and 12067), Board of Physicians of North-Rhine Westphalia (20101424 and 2012446), and Board of Physicians of Saxony (EK-BR-02/13-1).

**Informed Consent Statement:** Informed consent was obtained from legal guardians and subjects involved in the study.

**Data Availability Statement:** Requests for data should be addressed to the corresponding author.

**Acknowledgments:** The authors would like to thank all the families for their participation in the GINIplus and LISA studies. Furthermore, we thank all members of the GINIplus and LISA Study

Groups for their excellent work. The GINIplus Study group consists of the following: Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg (Heinrich J, Brüske I, Schulz H, Flexeder C, Zeller C, Standl M, Schnappinger M, Ferland M, Thiering E, Tiesler C); formerly: Department of Pediatrics, Marien-Hospital, Wesel (Berdel D, von Berg A); Ludwig-Maximilians-University of Munich, Dr von Hauner Children's Hospital (Koletzko S); Child and Adolescent Medicine, University Hospital rechts der Isar of the Technical University Munich (Bauer CP, Hoffmann U); Evangelical Hospital Düsseldorf (Gappa M, Libuda L); IUF- Environmental Health Research Institute, Düsseldorf (Schikowski T, Link E, Klümper C, Krämer U, Sugiri D). The LISA Study group consists of the following: Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Epidemiology, Munich (Heinrich J, Schnappinger M, Brüske I, Ferland M, Schulz H, Zeller C, Standl M, Thiering E, Tiesler C, Flexeder C); Department of Pediatrics, Municipal Hospital "St. Georg", Leipzig (Borte M, Diez U, Dorn C, Braun E); Marien Hospital Wesel, Department of Pediatrics, Wesel (von Berg A, Berdel D, Stiers G, Maas B); Pediatric Practice, Bad Honnef (Schaaf B); Helmholtz Centre of Environmental Research—UFZ, Department of Environmental Immunology/Core Facility Studies, Leipzig (Lehmann I, Bauer M, Röder S, Schilde M, Nowak M, Herberth G, Müller J); Technical University Munich, Department of Pediatrics, Munich (Hoffmann U, Paschke M, Marra S); Clinical Research Group Molecular Dermatology, Department of Dermatology and Allergy, Technische Universität München (TUM), Munich (Ollert M, J. Grosch). We thank all study members and staff involved in data collection and also the respective funding bodies. During the last decades, many scientists, study nurses and laboratories were involved in conducting the studies. We are most grateful for all the individuals who participated in the study over the decades. We also wish to thank the Deutsche Wetterdienst and the DeutscheUmweltbundesamt (UBA) for providing data from the COSMO-REA6 model and the UBA air pollution models.

**Conflicts of Interest:** MJA holds investigator-initiated grants for unrelated research from Pfizer, Boehringer-Ingelheim, Sanofi and GSK. He has undertaken an unrelated consultancy from Sanofi. He has also received a speaker's fee from GSK. SK holds grants for unrelated research from Mead Johnson. She has received a speaker's fee from Danone, Jansson, Pfizer, Sanofi, Pfizer, and Takeda. Additionally, she has participated on the advisory board for Abbvie, Danone, Jansson, GSK, Pfizer, Sanofi, and Takeda. The other authors have no conflicts of interest to declare.

## References

1. Soriano, J.B.; Kendrick, P.J.; Paulson, K.R.; Gupta, V.; Abrams, E.M.; Adedoyin, R.A.; Adhikari, T.B.; Advani, S.M.; Agrawal, A.; Ahmadian, E.; et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir. Med.* **2020**, *8*, 585–596. [CrossRef] [PubMed]
2. Lim, C.C.; Hayes, R.B.; Ahn, J.; Shao, Y.; Silverman, D.T.; Jones, R.R.; Garcia, C.; Bell, M.L.; Thurston, G.D. Long-Term Exposure to Ozone and Cause-Specific Mortality Risk in the United States. *Am. J. Respir. Crit. Care Med.* **2019**, *200*, 1022–1031. [CrossRef] [PubMed]
3. Turner, S.W.; Chang, A.B.; Yang, I.A. Clinical utility of exhaled nitric oxide fraction in the management of asthma and COPD. *Breathe* **2019**, *15*, 306–316. [CrossRef] [PubMed]
4. Zhang, Z.; Zhang, H.; Yang, L.; Chen, X.; Norback, D.; Zhang, X. Associations between outdoor air pollution, ambient temperature and fraction of exhaled nitric oxide (FeNO) in university students in northern China—A panel study. *Environ. Res.* **2022**, *212 Pt C*, 113379. [CrossRef]
5. Kocot, K.; Barański, K.; Melaniuk-Wolny, E.; Zajusz-Zubek, E.; Kowalska, M. Acute FeNO and Blood Pressure Responses to Air Pollution Exposure in Young Adults during Physical Activity. *Int. J. Environ. Res. Public Health* **2020**, *17*, 9012. [CrossRef] [PubMed]
6. Abramson, M.J.; Wigmann, C.; Altug, H.; Schikowski, T. Ambient air pollution is associated with airway inflammation in older women: A nested cross-sectional analysis. *BMJ Open Respir Res.* **2020**, *7*, e000549. [CrossRef] [PubMed]
7. Kress, S.; Kilanowski, A.; Wigmann, C.; Zhao, Q.; Zhao, T.; Abramson, M.J.; Gappa, M.; Standl, M.; Unfried, K.; Schikowski, T. Airway inflammation in adolescents and elderly women: Chronic air pollution exposure and polygenic susceptibility. *Sci. Total Environ.* **2022**, *841*, 156655. [CrossRef]
8. Berhane, K.; Zhang, Y.; Salam, M.T.; Eckel, S.P.; Linn, W.S.; Rappaport, E.B.; Bastain, T.M.; Lurmann, F.; Gilliland, F.D. Longitudinal effects of air pollution on exhaled nitric oxide: The Children's Health Study. *Occup. Environ. Med.* **2014**, *71*, 507. [CrossRef]
9. Zhang, Y.; Eckel, S.P.; Berhane, K.; Garcia, E.; Muchmore, P.; Molshatzki, N.B.-A.; Rappaport, E.B.; Linn, W.S.; Habre, R.; Gilliland, F.D. Long-term exposures to air pollutants affect FeNO in children: A longitudinal study. *Eur. Respir. J.* **2021**, *58*, 2100705. [CrossRef]
10. Trivedi, M.; Denton, E. Asthma in Children and Adults-What Are the Differences and What Can They Tell us About Asthma? *Front. Pediatr.* **2019**, *7*, 256. [CrossRef]

11. Heinrich, J.; Brüske, I.; Cramer, C.; Hoffmann, U.; Schnappinger, M.; Schaaf, B.; von Berg, A.; Berdel, D.; Krämer, U.; Lehmann, I.; et al. GINIplus and LISAplus—Design and selected results of two German birth cohorts about natural course of atopic diseases and their determinants. *Allergol. Sel.* **2017**, *1*, 85–95. [CrossRef]
12. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 912–930. [CrossRef] [PubMed]
13. Minkos, A.; Dauert, U.; Feigenspan, S.; Kessenger, S. *Air Quality 2016: Preliminary Evaluation*; Umweltbundesamt [German Environment Agency], Ed.; Umweltbundesamt: Dessau-Roßlau, Germany, 2017; p. 24.
14. Bollmeyer, C.; Keller, J.D.; Ohlwein, C.; Wahl, S.; Crewell, S.; Friederichs, P.; Hense, A.; Keune, J.; Kneifel, S.; Pscheidt, I.; et al. Towards a high-resolution regional reanalysis for the European CORDEX domain. *Q. J. R. Meteorol. Soc.* **2015**, *141*, 1–15. [CrossRef]
15. Zhao, T.; Markevych, I.; Standl, M.; Schulte-Körne, G.; Schikowski, T.; Berdel, D.; Koletzko, S.; Bauer, C.-P.; von Berg, A.; Nowak, D.; et al. Ambient ozone exposure and depressive symptoms in adolescents: Results of the GINIplus and LISA birth cohorts. *Environ. Res.* **2019**, *170*, 73–81. [CrossRef] [PubMed]
16. R Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2021.
17. Beck, H.E.; Zimmermann, N.E.; McVicar, T.R.; Vergopolan, N.; Berg, A.; Wood, E.F. Present and future Köppen-Geiger climate classification maps at 1-km resolution. *Sci. Data* **2018**, *5*, 180214. [CrossRef]
18. Pidwirny, M. Physical Geography Lab Manual: The Atmosphere and Biosphere: Our Planet Earth. 2021. Available online: https://pressbooks.bccampus.ca/physgeoglabmanual1/ (accessed on 20 June 2023).
19. Gehring, U.; Gruzieva, O.; Agius, R.M.; Beelen, R.; Custovic, A.; Cyrys, J.; Eeftens, M.; Flexeder, C.; Fuertes, E.; Heinrich, J.; et al. Air Pollution Exposure and Lung Function in Children: The ESCAPE Project. *Environ. Health Perspect.* **2013**, *121*, 1357–1364. [CrossRef]
20. Han, A.; Deng, S.; Yu, J.; Zhang, Y.; Jalaludin, B.; Huang, C. Asthma triggered by extreme temperatures: From epidemiological evidence to biological plausibility. *Environ. Res.* **2023**, *216*, 114489. [CrossRef]
21. Steinbacher, M.; Pfleger, A.; Schwantzer, G.; Jauk, S.; Weinhandl, E.; Eber, E. Small airway function before and after cold dry air challenge in pediatric asthma patients during remission. *Pediatr. Pulmonol.* **2017**, *52*, 873–879. [CrossRef]
22. Goodman, M.; Hays, S. Asthma and swimming: A meta-analysis. *J. Asthma.* **2008**, *45*, 639–647. [CrossRef]
23. Yang, L.; Zhao, S.; Gao, S.; Zhang, H.; Arens, E.; Zhai, Y. Gender differences in metabolic rates and thermal comfort in sedentary young males and females at various temperatures. *Energy Build.* **2021**, *251*, 111360. [CrossRef]
24. Sarlani, E.; Farooq, N.; Greenspan, J.D. Gender and laterality differences in thermosensation throughout the perceptible range. *Pain* **2003**, *106*, 9–18. [CrossRef] [PubMed]
25. Xu, R.; Li, S.; Guo, S.; Zhao, Q.; Abramson, M.J.; Li, S.; Guo, Y. Environmental temperature and human epigenetic modifications: A systematic review. *Environ. Pollut.* **2020**, *259*, 113840. [CrossRef] [PubMed]
26. Kubesch, N.J.; de Nazelle, A.; Westerdahl, D.; Martinez, D.; Carrasco-Turigas, G.; Bouso, L.; Guerra, S.; Nieuwenhuijsen, M.J. Respiratory and inflammatory responses to short-term exposure to traffic-related air pollution with and without moderate physical activity. *Occup. Environ. Med.* **2015**, *72*, 284–293. [CrossRef] [PubMed]
27. Clifford, S.; Mazaheri, M.; Salimi, F.; Ezz, W.N.; Yeganeh, B.; Low-Choy, S.; Walker, K.; Mengersen, K.; Marks, G.B.; Morawska, L. Effects of exposure to ambient ultrafine particles on respiratory health and systemic inflammation in children. *Environ. Int.* **2018**, *114*, 167–180. [CrossRef]