Aus dem IUF - Leibniz Institut für umweltmedizinische
Forschung an der Heinrich-Heine-Universität Düsseldorf

Direktor: Univ.-Prof. Dr.med.
Jean Krutmann

Relative humidity, temperature, and air pollution: the effect of multiple exposures on respiratory health in German adolescents.

Dissertation

zur Erlangung des Grades eines Doktors der Public
Health der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Ashtyn Tracey Areal

2024

Als Inauguraldissertation gedruckt mit Genehmigung der
Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:

Dekan: Prof. Dr. med. Nikolaj Klöcker

Erstgutachter: PD Dr. Klaus Unfried

Zweitgutachter: Prof. Dr. phil. Nico Dragano

This dissertation is dedicated to my Grandfather, Sidney Charles Austin, and my Avó, Maria Cavaco Da Silva Areal, who believed but did not see the conclusion.

List of publications

1. The effect of air pollution when modified by temperature on respiratory health outcomes: A systematic review and meta-analysis (1).
2. The influence of short-term weather parameters and air pollution on adolescent airway inflammation (2).
3. The association of relative humidity and air pollution interaction on lung function in adolescents (3).

These papers have been previously published in Science of the Total Environment, International Journal of Environmental Research and Public Health, and Frontiers in Environmental Health

German Summary

Der Klimawandel wird als komplexes Wechselspiel zwischen meteorologischen Faktoren und Luftverschmutzung verstanden. Der Einfluss meteorologischer Faktoren und ihre möglichen Wechselwirkungen mit der Luftverschmutzung auf die Gesundheit wurden bisher kaum untersucht. Darüber hinaus haben nur wenige umweltepidemiologische Studien junge Menschen einbezogen, so dass die Rolle meteorologischer Faktoren für die Gesundheit junger Menschen bisher noch nicht untersucht wurde. Die bisherige Forschung hat sich auf Mortalität und Morbidität durch Atemwegserkrankungen konzentriert, was bedeutet, dass die Auswirkungen meteorologischer Faktoren auf subklinische Endpunkte wie fraktioniertes exspiratorisches Stickstoffmonoxid (FeNO), forciertes exspiratorisches Volumen in einer Sekunde (FEV1) und forcierte Vitalkapazität (FVC) nicht untersucht wurden.

Der erste Beitrag dieser Dissertation ist ein systematischer Review, der die Wechselwirkung von Luftverschmutzung und Temperatur auf die Mortalität und Morbidität im Zusammenhang mit Atemwegserkrankungen untersucht. In den Beiträgen zwei und drei wurden die Auswirkungen der relativen Luftfeuchtigkeit und ihrer Wechselwirkung mit der Luftverschmutzung auf FeNO, FEV1 und FVC untersucht. Für die Forschungsbeiträge zwei und drei wurden Daten aus der 15-Jahres-Studie der deutschen GINIplus- und LISA-Geburtskohorten verwendet. In beiden Beiträgen wurden multivariate lineare Regressionsmodelle verwendet. In den Interaktionsmodellen wurde eine kategoriale Luftverschmutzungsvariable verwendet, um die Wirkung der Exposition gegenüber relativer Luftfeuchtigkeit auf Lungenentzündung und Lungenfunktion bei hoher, mittlerer und niedriger Luftverschmutzung zu untersuchen.

Die Ergebnisse des systematischen Reviews waren in Abhängigkeit von den ausgewählten Luftschadstoffen weitgehend inkonsistent, zeigten jedoch einen allgemeinen Trend zu einer erhöhten Sterblichkeit an Atemwegserkrankungen und Krankenhauseinweisungen, wenn die Interaktionseffekte zwischen Luftverschmutzung und Temperatur berücksichtigt wurden. Die Ergebnisse zeigten einen hohen Bedarf an weiteren Studien über die Auswirkungen der relativen Luftfeuchtigkeit auf die Gesundheit und begrenzte Daten über die Auswirkungen meteorologischer Faktoren auf subklinische respiratorische Endpunkte. Die Ergebnisse dieser Studien zeigten, dass die relative Luftfeuchtigkeit im Allgemeinen eine schützende Wirkung auf die Gesundheit der Atemwege hatte. Eine hohe Exposition gegenüber Luftschadstoffen konnte diesen Effekt jedoch verändern, wobei NO_2 zu einer Zunahme der Lungenentzündung und O_3 zu einer Abnahme der Lungenfunktion führte.

Diese drei Beiträge gehören zu den ersten Studien, die zu ihren jeweiligen Themen veröffentlicht wurden. Daher haben sie einen bedeutenden Einfluss auf die Gesundheitsforschung, indem sie Schlüsselbereiche identifizieren, die von den derzeitigen Warnsystemen nicht abgedeckt werden. Diese Veröffentlichungen liefern wichtige Informationen für die betroffenen Akteure, wie Forscher, Ärzte, Politiker und Gesundheitsorganisationen, und unterstreichen die Notwendigkeit neuer gesundheits-politischer Maßnahmen und Warnsysteme, die sich auf meteorologische Faktoren und die Auswirkungen der Luftverschmutzung auf die Gesundheit der Atemwege von Jugendlichen beziehen.

English Summary

Climate change is known to be a complex interplay between meteorological factors and air pollution, and the effect of meteorological factors and their potential interactions with air pollution on health is poorly understood. Adolescents are often excluded from health studies, meaning that the role meteorological factors play in adolescent health needs to be better understood. Research has focused on respiratory mortality and morbidity, meaning we fail to see the effects that meteorological factors have on subclinical endpoints such as fractional exhaled nitric oxide (FeNO), forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC).

The first paper of this dissertation is a systematic review investigating the interactive effects of air pollution and temperature on respiratory mortality and morbidity. Papers two and three examined the effect of relative humidity and its interaction with air pollution on FeNO, FEV1 and FVC. Research papers two and three utilised data from the 15-year follow-up of the German GINIplus and LISA birth cohorts. Both papers utilised multivariable linear regression models. In the interactive models, we used a categorical air pollution variable to see the effect of relative humidity exposure on lung inflammation and lung function at high, medium, and low levels of air pollution.

Results of the review were largely inconsistent depending on the air pollutant selected; however, there was a general trend toward an increase in respiratory mortality and hospital admission when looking at the interactive effects of air pollution and temperature. This review revealed a need for more information on the impacts of relative humidity on health, limited data on the effects of meteorological factors on respiratory subclinical endpoints, and adolescents were largely excluded from studies. The results from these studies found that relative humidity typically showed a protective effect on respiratory health outcomes. However, high exposure to air pollution could modify this effect, with NO_2 causing an increase in lung inflammation and O_3 causing a decrease in lung function.

These three papers are among the first studies published on their respective topics. Therefore, they present significant implications for public health by identifying key areas that current warning systems do not address. These publications show crucial evidence for relevant stakeholders such as researchers, physicians, policymakers, and health organisations, which establish the need for new public health policies and warning systems that pertain to meteorological factors and air pollution's effects on adolescent health.

Abbreviations

ATS - American Thoracic Society

CRD – Chronic respiratory disease

COPD – Chronic obstructive pulmonary disease

ERS - European Respiratory Society

ERV - Expiratory reserve volume

FeNO – Fractional exhaled nitric oxide

FEV1- Forced expiratory volume in 1 second

FRC - Functional residual capacity

FVC – Forced vital capacity

IC - Inspiratory capacity

IPCC - Intergovernmental Panel on Climate Change

IRV - Inspiratory reserve volume

NO_2 – Nitrogen Dioxide

NO_x – Nitrogen Oxide

NO – Nitric oxide

O_3 - Ozone

$PM_{2.5}$ – Particulate Matter with a diameter of less than 2.5 μm

PM_{10} – Particulate Matter with a diameter of less than 10 μm

RH – Relative humidity

RV – Residual volume

SES – Socio-economic status

TLC – Total lung capacity

Tmax – Maximum temperature

Tmean – Average temperature

Tmin – Minimum temperature

UN - The United Nations

UNFCCC - United Nations Framework Convention on Climate Change

UV – Ultraviolet

VC – Vital capacity

V_T – Tidal volume

WHO – The World Health Organisation

Table of contents

1. Introduction and Background

1.1. Introduction

Climate change has become a major challenge, affecting the environment and public health (4). Human activities are largely responsible for excessive greenhouse gas emissions, leading to rising temperatures, unpredictable weather patterns, and ecological disruption, with far-reaching implications for human health (5). Public health is threatened by rapidly changing ecosystems and rising temperatures, creating new health risks and exacerbating existing vulnerabilities (6). Climate change and air pollution have exacerbated chronic respiratory diseases (CRD), such as asthma and chronic obstructive pulmonary disease (COPD), due to rising temperatures and the formation of ground-level ozone (O_3) (7-9). Changes in humidity patterns also contribute to the growth of allergenic pollen and moulds, causing respiratory problems in susceptible populations (10).

1.2. Climate Change and Meteorology

1.2.1. Background and Consequences

The United Nations Framework Convention on Climate Change (UNFCCC) defines climate change as "… a change in climate that is attributed directly or indirectly to human activity that alters the composition of the global atmosphere…" (11). While climate change is typically a naturally occurring event, since the start of the Industrial Revolution in the 1800s, human activity has been primarily responsible for accelerating global warming through two methods: excess greenhouse gas emissions, which lead to the greenhouse effect, and the reflection or absorption of solar energy (12, 13).

The greenhouse effect is the process by which greenhouse gases form a layer around the planet, making it warmer (14-16). It is a vital process for maintaining human life; greenhouse gases, which include carbon dioxide, methane, nitrous oxides, and fluorinated gases, trap some of Earth's outgoing energy, which is retained as heat in the atmosphere (17,18). This trapped heat changes the radiative balance –the balance between energy received from the Sun and Earth – and alters climate and weather patterns (19). However, this balance has been disrupted due to human activities, such as burning fossil fuels, agricultural practices, industry, and

organic waste, which have increased the amount of greenhouse gases in the atmosphere (17).

Reflection or absorption of solar energy occurs when human activities such as agriculture, road building and deforestation change the reflectivity of the Earth's surface, leading to warming or cooling (13). An example of this is heat islands; heat islands are typically urban areas with buildings, pavements and roads that are warmer than less populated surrounding areas because they reflect less sunlight (13). In addition, aerosol emissions can lead to the reflection or absorption of solar energy.

This build-up of greenhouse gases and an increase in the reflectivity or absorption of solar energy in the atmosphere has changed the Earth's climate, raised global temperatures and adversely affected human health and well-being.

Rising temperatures have led to an increase in natural disasters such as heat waves, droughts, forest fires and hurricanes. These natural disasters, in turn, promote the formation of ground-level O_3 and increase levels of particulate matter (PM). O_3 has been extensively studied and has been found to contribute to climate change by trapping heat and UV radiation, causing temperatures to rise (12); other pollutants, such as particles 10 μm and smaller (PM_{10}) and particles 2.5 μm and smaller ($PM_{2.5}$), have also been linked to climate change, although research on these has not been as robust and more research is needed (12, 15).

While the environmental consequences of human-induced climate change are well understood, the impact of climate change on human health is an area of great interest. The World Health Organisation (WHO) and the Intergovernmental Panel on Climate Change (IPCC) have indicated that climate change affects human health directly and indirectly (15, 20, 21). Indirectly, climate change affects human health through natural disasters such as droughts, which can cause water scarcity, adversely affect agriculture, increase the breeding season of vectors that cause vector-borne diseases, and adversely affect infrastructure (6, 22, 23). Directly, climate change has been linked to increased morbidity and mortality due to rising temperatures (6, 22, 23).

1.2.2. Temperature

Rising global temperatures have been identified as one of the most significant risks to human health (6, 22). In 2015, at the United Nations (UN) Climate Change Conference, 196 parties signed the Paris Agreement, a legally binding international treaty on climate change (24). The Paris Agreement aims to keep the global average temperature increase below 2 degrees Celsius (C) above pre-industrial levels. However, the IPCC has stated that nations should aim to keep global average temperatures below 1.5°C above pre-industrial levels if we are to mitigate the adverse impacts of extreme temperature and weather events on the planet and human health (15, 20). Currently, global temperatures are 1.1°C above pre-industrial levels (20).

Humans are acclimatised to their local environment; their physiology and behaviour have adapted to specific climates. Humans can acclimate through a physiological response called thermoregulation, an efficient heat regulatory mechanism that maintains body temperature (6, 25). While humans can adapt relatively quickly to different climates, exposure to extreme high and low temperatures is of great concern because of the significant health impacts and burden on health and public services (6, 22, 23).

Exposure to high-temperature events is increasing yearly, with countries in the Middle East, Australia, the Mediterranean region and Canada reporting record-high temperatures between 2021 and 2022 (22). Vulnerable populations, for example, adults over 65 and children under one year of age, will be exposed to 3.7 billion more heatwave days in 2021 than annually between 1986 and 2005 (22). This increase in heat exposure harms human health.

Exposure to high temperatures and extreme heat events is associated with a variety of adverse health effects, including heat stroke, adverse pregnancy outcomes, effects on mental health, increases in non-accidental and injury-related deaths, and exacerbation of cardiovascular and respiratory diseases (22, 26-29). Exposure to low temperatures and extreme low-temperature events is associated with increased mortality, exacerbation of chronic diseases, for example, cardiovascular, respiratory and mental health, and increases in respiratory infections and

hypothermia (22, 26-29).

1.2.3. Relative Humidity

Relative humidity is the amount of water vapour in the air, expressed as the percentage required for saturation at the same temperature (30, 31). The interest in relative humidity and its potential effects on human health has increased in recent years. Although relative humidity has a physiological impact on the body, it is rarely the focus of environmental exposure-health studies. It is only a confounding variable in temperature-health studies (30, 31).

Biological studies investigating the individual effects of relative humidity on the respiratory system have yet to be included. Animal models suggest that increasing relative humidity is associated with bronchial hyperresponsiveness, airway inflammation, bronchial changes and exacerbation of allergic diseases (31). In humans, low relative humidity (below 40%) causes dry air to dry out and irritate the airways, which can damage the parenchyma and epithelial tissue of the lungs, making a person susceptible to respiratory infections (31). High relative humidity (above 60%) favours the deposition and formation of aeroallergens, which can irritate and damage the respiratory tract. In addition, relative humidity primarily affects mucus production and mucociliary clearance; increased mucus and its thickness promote respiratory infections, especially in vulnerable populations (31).

Germany is a unique environment in that it has a climate characterised by high precipitation, which results in high humidity (32, 33). While the optimum relative humidity is 40-60%, the average relative humidity in Germany is often over 70%; therefore, it is necessary to investigate the effects of these high relative humidity levels on the health of the German population.

1.3. Air Pollution

1.3.1. Definitions, exposures, and impacts of air pollution

Pollution is defined as the introduction of substances harmful to humans and other living organisms (34). Pollutants include solids, liquids, and gases that are higher

in concentration than usual; this reduces environmental quality. The most common example of pollution is that of air pollution. Air pollution is one of the most significant challenges in this era; not only is air pollution a leading cause of climate change, but it is also the leading environmental cause of mortality and morbidity worldwide, with over seven million deaths per year attributed to air pollution exposure (21, 34). Air pollution adversely affects the human body differently, with sensitive and susceptible individuals impacted even on low air pollution days (34). Short-term exposure to air pollution is associated with adverse effects on the respiratory system and the exacerbation of COPD, asthma, cough, wheezing, shortness of breath, and an increase in respiratory hospital admissions (34); additionally, exposure to both short and long-term air pollution negatively influences lung development in children and adolescents (35). However, different air pollutants have different effects and consequences on the human body.

1.3.2. Particulate Matter (PM)

In urban and non-urban environments, PM is a complex mixture of liquid droplets and solid particles with different chemical and physical properties (21, 36). Some particles, such as dust, smoke and soot, are large enough to be seen with the naked eye (36). Other PMs are microscopic. Two such microscopic PMs are PM_{10} and $PM_{2.5}$ (36). Particles are generally classified according to their aerodynamic properties, which determine transport and removal processes (21). Research on PM and interpretation of research results is complex because of the heterogeneous nature of PM, which varies in size and other physical properties, chemical composition and sources; this variability of PM is of particular concern for health studies, as different characteristics of PM may be relevant to various health effects (21).

The concern with PM is that it is small enough to be inhaled. When inhaled, large PM (>PM_{10}) is confined to the upper airways, whereas smaller PM (<$PM_{2.5}$) can reach the terminal bronchioles and terminal alveoli, causing airway irritation, coughing and dyspnoea (37, 38). A review by Kyung and Jeong (39) examined PM-related respiratory diseases and found that several large cohort studies found that increased PM concentrations were associated with decreased lung function.

1.3.3. *Nitrogen Dioxide (NO_2)*

Nitrogen oxides (NO_x) include two gases: nitrogen monoxide (NO), which is a colourless and odourless gas, and nitrogen dioxide (NO_2), which is a reddish-brown gas with a pungent odour (40). NO_2 is mostly an urban pollutant formed when NO reacts with oxygen or O_3 (41), usually during combustion processes in car engines, factories and power plants (42). NO_2 is an atmospheric trace gas that can absorb visible solar radiation, reducing atmospheric visibility and potentially playing a direct role in global climate change (21). As a gaseous and oxidising pollutant, NO_2 is a precursor of photochemical smog and is involved in the formation of O_3 (43). In addition, NO_2 can form organic, nitrate and sulphate particles, which are currently measured as PM_{10} or $PM_{2.5}$ (21). However, because NO_2 is of great interest from a human health perspective, it is often used as an indicator for larger groups of nitrogen oxides (21, 44).

As a gas, NO_2 can enter the body through various entry points and cause damage. Exposure to NO_2 increases airway smooth muscle reactivity; in other words, NO_2 increases the sensitivity and responsiveness of airway smooth muscle to other stimuli in both people with and without lung disease (45). However, inhalation exposure is a major concern, as inhalation of NO_2 can cause lung swelling, leading to cough, fever, bronchitis, chest pain and decreased lung function (46). A review by the United States Environmental Protection Agency (46) reported that short-term exposure to NO_2 was associated with adverse respiratory outcomes. This conclusion was particularly evident in studies that linked NO_2 exposure to lung inflammation.

1.3.4. *Ozone (O_3)*

Like NO_2, O_3 is an oxidising gas. It is a highly reactive secondary aerosol composed of three oxygen (O) atoms (47). Stratospheric O_3 is formed naturally by the interaction of solar UV radiation with molecular oxygen; this naturally occurring O_3 forms what is known as the "ozone layer", which protects all life on Earth by reducing the amount of harmful UV radiation reaching the Earth's surface (48). The second type of O_3 is tropospheric or ground-level O_3, which is both naturally occurring and a man-made secondary aerosol that is a major component of urban

smog (49). This man-made O_3 is formed by a photochemical reaction involving NO_x and volatile organic compounds in the presence of UV radiation and high temperatures (50, 51). This excess of O_3 formation is particularly evident in urban environments where heat islands and petrol engines exacerbate the local production and dispersion of O_3 (51).

O_3 is the world's most widely distributed air pollutant; unlike NO_2 and PM, its concentrations are increasing annually (50). This increase in O_3 is attributed to climate change, which is predicted to increase the abundance of biogenic volatile organic compounds. Clear skies, UV radiation and high temperatures are associated with O_3 formation (52). This increased exposure to O_3 has ecological and adverse health consequences.

Ground-level O_3 is a known lung irritant that induces epithelial damage, which increases lung inflammation; in addition, O_3 also causes airway hyperreactivity, exacerbating CRDs and increasing respiratory mortality and morbidity (5, 53, 54). However, there is growing interest in understanding the effects of O_3 on subclinical respiratory endpoints such as lung function and lung inflammation in vulnerable groups such as the elderly and children. For example, a review by Holm and Balmes (55) examined evidence published between 2013 and 2020 on the effects of short-term exposure to O_3 on lung function and found that short-term exposure to both high and low concentrations of O_3 was associated with a decrease in lung function in children (55).

1.4. The relationship between weather variables and air pollution

The mechanisms by which climate change affects human health are complex. Temperature is often treated as the only climate variable affecting health, but climate change is a complex interaction between temperature, relative humidity, wind, radiation, precipitation and air pollution (7, 30). Weather parameters are known to interact with each other. Relative humidity is known to interact with temperature because humidity changes the perceived temperature; this change in temperature perception alters the body's ability to thermoregulate (56). In addition, these meteorological factors interact with air pollution or even contribute to the formation of air pollutants.

Relative humidity and temperature are associated with changes in the concentration, distribution and composition of air pollution (31); however, the relationship between temperature and air pollution has been more extensively studied because of the clear evidence between temperature and secondary gaseous pollutants: O_3 and NO_2. Interactions between ultraviolet (UV) radiation, high temperatures, volatile organic compounds and NO_2 favour the formation of O_3 (51). Research suggests that relative humidity and O_3 have a non-linear, U-shaped relationship (31, 57). A study by Fadeyi (57) looked at O_3 in indoor environments and found that high relative humidity (above 60%) increases O_3 deposition, in other words, the rate at which air pollution settles on surfaces, which in turn facilitates O_3 surface reactions and oxidation product emissions (57). This interaction is of concern because of the potential adverse health effects of poorer air quality.

Humidity is also associated with the formation of organic aerosols, which are major components of particulate pollutants, especially $PM_{2.5}$ (30). High humidity increases the formation of these organic aerosols; in addition, the size of aerosol droplets increases at high humidity due to moisture absorption by molecules (30, 31). However, the interactive relationships between humidity and air pollution are poorly understood (30).

1.5. Respiratory Health

A simplistic definition of respiratory health is the absence of lung disease (58). This definition is limited because it does not define ideal respiratory health. Respiratory health is a lifelong concept, as exposure to risk factors that compromise respiratory health begins at conception and continues throughout life (58). Impaired respiratory health is associated with increased respiratory and cardiovascular mortality and morbidity. However, respiratory health is easy to measure, with lung function being the most widely recognised and accepted indicator (58).

1.5.1. Lung Function

Spirometry is the test and procedure used to measure lung function, which in turn reflects a person's ability to breathe (59). In addition, spirometry is most useful in

diagnosing and assessing obstructive airways diseases such as asthma, where abnormal results are often reversible, and COPD, whose symptoms are often irreversible; spirometry tests are less effective in assessing restrictive diseases (59). Spirometry consists of clinical measurements taken during full expiration. It includes four volume and four lung capacity measurements: tidal volume (VT), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), residual volume (RV), inspiratory capacity (IC), functional residual capacity (FRC), vital capacity (VC) and total lung capacity (TLC). Spirometry tests can measure all of these except RV, TLC and FRC (59). Most spirometry tests follow the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.

Spirometry assesses lung function using two common indicators: forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). FEV1 and FVC measurements are adjusted for age, sex, height and weight and these results are compared with reference values (60). FEV1 is used to assess and categorise the severity of CRDs; in addition, FEV1 can be used to determine the presence of obstructive airways disease and to assess the improvement in lung function with the introduction of bronchodilators (61). FVC is similar to VC but is measured as the patient exhales with maximum speed and effort. Unlike FEV1, FVC can be used to assess the presence of restrictive lung disease (62).

1.5.2. Lung Inflammation

Airway inflammation, an irritation or swelling in the airways of the lungs, is a component of many CRDs (63). Nitric oxide (NO) plays a role in the physiology of many organs and is a known mediator in the pathophysiology of CRD (64). At low concentrations, NO is a smooth muscle relaxant, whereas at high concentrations, NO is an inflammatory mediator produced by cells such as eosinophils which are involved in inflammation; this means that the presence of NO in exhaled air indicates the presence of inflammation (64, 65). Fractional exhaled nitric oxide (FeNO) tests determine how much lung inflammation is present by measuring how much NO is present in exhaled breath (66). FeNO is often used because it is quick, non-invasive and easy for the patient to perform (63, 65). However, while FeNO can detect the presence of airway inflammation, it provides limited information about the nature of the inflammation (63, 67).

1.5.3. *Respiratory Symptoms and Disease*

CRDs [ICD-10, J40-47] are diseases of the airways and lungs and are among the leading causes of disability and death worldwide (8). Five respiratory diseases are among the leading causes of illness and death worldwide: asthma, COPD, acute lower respiratory infections, tuberculosis and lung cancer (8). Asthma is a chronic inflammatory disease that usually manifests as a combination of airway obstruction and bronchial hyperresponsiveness (68). Asthma causes respiratory symptoms such as chronic cough, wheezing, shortness of breath and chest tightness (68). Asthma is the most common respiratory disease worldwide, usually diagnosed in childhood and adolescence. In 2017, the incidence of asthma was approximately 43.12 million new cases per year, with a prevalence of between 273 million and 358 million cases across all age groups (8, 69).

1.5.4. *Respiratory Health in Adolescence*

The WHO defines adolescence as the period between childhood and adulthood; this phase falls within the second decade of life, or between the ages of 10 and 19 (70). Adolescence is characterised by biological, psychological and social changes involving rapid physical growth and social behaviour (71).

At birth and during childhood, males have narrower airways relative to total lung volume than females (72). However, this changes during puberty due to the different pubertal patterns of chest growth between the sexes (72). Females typically reach sexual and physical maturity before their male counterparts; this means that the size of the female chest remains constant throughout adolescence, whereas males experience rapid growth of the chest cavity throughout puberty (72-74). Chest height increases twice as fast in males as in females, resulting in males having a larger lung volume than females (72, 73). This difference in lung size has a direct effect not only on lung function but also on the incidence of respiratory symptoms and disease.

During childhood and puberty, males are more likely to be diagnosed with chronic wheeze and asthma than females, but this changes during puberty, with females

more likely to develop asthma (75). Although the exact mechanism is unknown, it is thought that the reason for this change is the rapid growth of the male chest cavity and the increase in female reproductive hormones, for example, oestrogen and progesterone (75). Lung function also changes during puberty; before puberty, lung function had a linear relationship with height and was similar in males and females, but during puberty this is no longer the case (73). Males have higher absolute lung function values due to their larger lung size (74). Growth in FEV1 and FVC reaches its maximum between the ages of 14 and 18 in both males and females.

1.6. GINIplus and LISA cohort studies

The German Infant Study on the Influence of Nutrition Intervention plus Air Pollution and Genetics on Allergy Development (GINIplus) was established in Munich (South-East Germany) and Wesel (North-West Germany) between September 1995 and July 1998 (76). A total of 5991 neonates were recruited at baseline; questionnaires were used to collect data on participant socio-demographics, family history, participant medical history, lifestyle, and environmental exposures between the ages of 1 and 4 with follow-ups that included spirometric tests at ages 6, 10, and 15-years.

The influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany Study (LISA) was established in Bad Honnef (North-West), Leipzig (East), Munich and Wesel between November 1997 and January 1999 (76). A total of 3097 neonates were recruited at baseline; questionnaires were used to collect data on participant family history, participant medical history, socio-demographics, lifestyle, and environmental exposures at baseline and during follow-ups that included spirometric tests at ages 6, 10, and 15 years.

The two birth cohorts had harmonised designs during the follow-ups at ages 6, 10, and 15; therefore, study participants were pooled for the same region for analysis (76-78). The Bavarian Board of Physicians (code: 12067 and 10090) and the Board of Physicians of North-Rhine-Westphalia (code: 2012446 and 2010424) ethics committees approved both studies and informed consent was obtained from parents and participants (Appendix 7.1-7.3).

1.7. Statistical Methodology

The first study in this thesis is a systematic review and meta-analysis. As different studies have different designs, methods, exposures, populations and settings, heterogeneity between them was expected. To account for this, I used a random effects model. I chose the Hartung-Knapp-Sidik-Jonkman (HKSJ) method, which uses the Sidik-Jonkman (SJ) estimator, because it provides more robust and accurate results. To assess the accuracy and stability of my results, I also conducted a sensitivity analysis using the DerSimonian-Laird (DL) estimator, which is commonly used in medical research. I also used the I^2 test to assess heterogeneity. An I^2 value of ≤25% indicates low heterogeneity, 25-50% indicates low-moderate heterogeneity, 50-75% indicates moderate-high heterogeneity, and ≥75% indicates high heterogeneity.

In the second study, I performed correlation tests, checked for collinearity between variables, and performed normality tests. I used linear regression models with Ln(FeNO) as the outcome and continuous RH as the primary exposure. I determined the main effects of continuous RH and air pollution (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 warm season as the reference category), history of respiratory disease (with "no" as the reference category), and location (with Munich as the reference category). I then fitted an interaction model with an interaction term between RH and categorical air pollution included in the main model. The categorical air pollution variable was defined as follows: <25% (low), 25-75% (medium) and >75% (high). I chose 'low' as the reference category because it represents optimal exposure, while 'medium' represents the most common exposure and 'high' represents non-optimal exposure.

The last study presented in this thesis used standardised (z-score) FEV1 and FVC as primary outcomes. I used multivariable linear models to measure the primary associations of short-term exposure to humidity (one-day moving average; Lag01), Tmax (the lowest AIC of all temperature variables), and air pollution on my outcomes. Different models were used for different air pollutants (O_3, NO_2 and $PM_{2.5}$). All models, including the primary model and the interactive model, were

adjusted for each environmental factor, CRD (yes as the reference category), study location (Munich as the reference category), and season (warm season as the reference category). I evaluated the interactive associations between RH and air pollution using RH parameters as continuous variables and air pollutants as categorical variables: Low (<5th percentile), Medium (5-95th percentile) and High (>95th percentile). $PM_{2.5}$ = 2.71 μg/m^3 and 22.08 μg/m^3, O_3 = 10.15 μg/m^3 and 82.60 μg/m^3, and NO_2 = 4.90 μg/m^3 and 37.85 μg/m^3 were the cut-off values. I used "medium" as the reference category because it represented the most common exposure levels, while "low" represented optimal exposure and "high" non-optimal exposure. I did not adjust for age, sex, height or weight in the main model because the selected outcomes (FEV1 and FVC) were calculated and standardised according to guidelines that take these variables into account.

1.8. Aims and Hypotheses

This thesis investigates the effects of short-term exposure to relative humidity, temperature and air pollution on subclinical respiratory endpoints. In addition, this dissertation aims to assess the effects of short-term exposure to environmental factors on the respiratory health of adolescents, who are an understudied group. In this dissertation, I have four main sub-aims:

1) To review the state of current literature on the association between meteorological variables and air pollution on respiratory mortality and morbidity.
2) To investigate the association between short-term meteorological factors and air pollution and its effect on lung inflammation.
3) To investigate the association between short-term meteorological factors and air pollution and its effect on lung function.
4) To assess the modifying effect of sex and CRD on lung function and inflammation.

Based on the aims mentioned above, I have four hypotheses:

1) Temperature and air pollution interact to increase respiratory mortality and morbidity.
2) Lung inflammation is adversely affected by short-term meteorological factors and

air pollution.

3) Lung function is adversely affected by short-term meteorological factors and air pollution.
4) Female participants and those with CRD are more sensitive to the effects of meteorological factors on respiratory subclinical endpoints.

The thesis is based on data from the 15-year follow-up of the German GINIplus and LISA birth cohorts. It also assesses the impact of sex differences and the presence of chronic respiratory diseases on the effect of multi-environmental exposures on respiratory health in adolescence.

2. Publications

2.1. Overview of publications

The first paper, published in Science of the Total Environment, conducted a systematic literature review and meta-analysis to assess the interactive effects of air pollution and temperature on respiratory mortality and morbidity. This allowed us to identify gaps in the literature on respiratory health. Given the gaps in the literature identified in the first publication, the second publication, published in the International Journal of Environmental Research and Public Health, focused on the interactions between climate variables, relative humidity and temperature on lung inflammation in adolescents using multi-linear regression models; in addition, this study further investigated the modifying effect of gender and CRD on lung inflammation. The third paper, published in Frontiers in Environmental Health, used multi-linear regression to examine the effect of short-term relative humidity on lung function in adolescents as modified by air pollution, and then assessed the modifying influence of sex and CRD status on this interactive effect of relative humidity and air pollution on lung function. The final chapter discusses the results of the three publications and makes recommendations for future public health action.

Publication 1

The effect of air pollution when modified by temperature on respiratory health outcomes: A systematic review and meta-analysis (1).

Ashtyn Tracey Areal [a],
Qi Zhao [a,b]
Claudia Wigmann
Alexandra Schneider [c]
Tamara Schikowski [a,*]

[a] Department of Epidemiology, IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

[b] Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China

[c] Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH), Neuherberg, Germany

Reference: Areal AT, Zhao Q, Wigmann C, Schneider A, Schikowski T. The effect of air pollution when modified by temperature on respiratory health outcomes: A systematic review and meta-analysis. Science of the Total Environment. 2022 Mar 10;811:152336.

Science of the Total Environment 811 (2022) 152336

Contents lists available at ScienceDirect

Science of the Total Environment

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

Review

The effect of air pollution when modified by temperature on respiratory health outcomes: A systematic review and meta-analysis

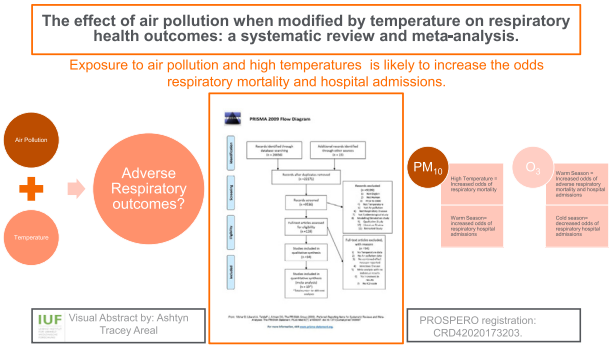
Ashtyn Tracey Areal [a], Qi Zhao [a,b], Claudia Wigmann [a], Alexandra Schneider [c], Tamara Schikowski [a,*]

[a] Department of Epidemiology, IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
[b] Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China
[c] Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH), Neuherberg, Germany

HIGHLIGHTS

- Air pollution modified by temperature has adverse effects on respiratory health.
- PM_{10} modified by high temperatures increases the odds of respiratory mortality.
- O_3 exposure during the warm season increases the odds of respiratory mortality.
- Effects estimates were inconsistent for low temperatures.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 21 September 2021
Received in revised form 7 December 2021
Accepted 7 December 2021
Available online 14 December 2021

Editor: Dr Wei Huang

Keywords:
Respiratory health
Air pollution
Temperature
Systematic review
Global Health

ABSTRACT

Background: Respiratory diseases are a leading cause of mortality and morbidity, and are exacerbated by air pollution and temperature.
Aim: To assess published literature on the effect of air pollution modified by temperature on respiratory mortality and hospital admissions.
Methods: We identified 26,656 papers in PubMed and Web of Science, up to March 2021, and selected for analysis; inclusion criteria included observational studies, short-term air pollution, and temperature exposure. Air pollutants considered were particulate matter with a diameter of 2.5 μg/m^3, and 10 μg/m^3 ($PM_{2.5}$, and PM_{10}), ozone (O_3), and nitrogen dioxide (NO_2). A random-effects model was used for our meta-analysis.
Results: For respiratory mortality we found that when the effect PM_{10} is modified by high temperatures there is an increased pooled Odds Ratio [OR, 95% Confidence Interval (CI)] of 1.021 (1.008 to 1.034) and for the effect of O_3 the pooled OR is 1.006 (1.001–1.012) during the warm season. For hospital admissions, the effects of PM_{10} and O_3 respectively, during the warm season found an increased pooled OR of 1.011 (0.999–1.024), and 1.015 (0.995–1.036). In our analysis for low temperatures, results were inconsistent.
Conclusions: Exposure to air pollution when modified by high temperature is likely to increase the odds of respiratory mortality and hospital admissions. Analysis on the interaction effect of air pollution and temperature on health outcomes is a relatively new research field and results are largely inconsistent; therefore, further research is encouraged to establish a more conclusive conclusion on the strength and direction of this effect.

Abbreviations: $PM_{2.5}$, Particulate matter with a diameter less than 2.5 μg/m^3; PM_{10}, Particulate matter with a diameter less than 10 μg/m^3; O_3, Ozone; NO_2, Nitorgen dioxide; OR, Odds ratio; RR, Relative risk; CI, Confidence interval; ICD, International Classification of Diseases; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CRD, Chronic respiratory disease; COPD, Chronic obstructive pulmonary disease; HKSJ, Hartung-Knapp-Sidik-Jonkman; SJ, Sidik-Jonkman estimator; DL, DerSimonian-Laird estimator.

* Corresponding author at: Department of Epidemiology, IUF-Leibniz Research Institute for Environmental Medicine, Auf'm Hennekamp 50, Düsseldorf 40225, Germany.
E-mail address: Tamara.Schikowski@IUF-Duesseldorf.de (T. Schikowski).

http://dx.doi.org/10.1016/j.scitotenv.2021.152336

Contents

1. Introduction

Chronic respiratory diseases (CRD) are among the leading causes of disability and death globally (Forum of International Respiratory Societies, 2017). Asthma is one of the most common CRD in both adults and children; with approximately 339 million cases globally, asthma presents an increasing financial burden (Soriano et al., 2020; Soriano et al., 2017). Chronic obstructive pulmonary disease (COPD) is an umbrella term that includes chronic bronchitis and emphysema (World Health Organization, 2017). Diagnosed between the ages of 40 and 50, the exact number of cases of COPD is estimated to be between 65 and 215 million cases and is the third leading cause of death (Forum of International Respiratory Societies, 2017; Soriano et al., 2017; World Health Organization, 2017).

Climate change has a negative impact on human health due to increased exposure to adverse climate-related stresses (Lin et al., 2019; Pachauri et al., 2014). Air pollution and suboptimal temperature represent two of the biggest risks to health, impacting all regions, socioeconomic groups, sexes, and age groups (World Health Organization, 2016). Approximately seven million people die from air pollution exposure every year (World Health Organisation, 2019). Air pollution often exacerbates respiratory disease by permeating into the lung tissue and damaging the lungs (De Sario et al., 2013).

Temperature triggers excess mortality and morbidity in those older than 65, pregnant women, people with pre-existing conditions, those with disabilities, labours outside or in non-cooled environments, and those in regions with limited human habitation (Watts et al., 2020; Hughes et al., 2016). Previous studies found that both high and low temperatures are associated with adverse respiratory health outcomes such as higher occurrence of bronchospasms, hospital admissions, and mortality by exacerbating respiratory conditions (Bunker et al., 2016a; Zhao et al., 2019; D'Amato et al., 2018; Seltenrich, 2015; Leon, 2008).

As the numbers of CRD cases increase every year, investigating the potential association with climate change is of the utmost importance. This review aims to assess literature on the effect of air pollution when modified by air temperature on respiratory mortality and respiratory hospital admissions.

2. Materials and methods

2.1. Literature search

Literature was sought, up to and including the 31st of March 2021, through PubMed/Web of Science using keywords such as, "Air pollution", "Air temperature", "Respiratory disease", "Mortality", "Hospital admissions", "Asthma", and "COPD", and using snowballing, which uses the reference list of a paper to find additional papers. A detailed list of search terms can be found in Supplementary B.

2.2. Inclusion and exclusion criteria

Inclusion criteria included papers published after 1989, in English, with no restriction on location of study. Only epidemiological observational studies were included; while qualitative research, literature reviews, simulation studies and case reports were excluded. We chose to exclude meta-analyses that only provided a pooled result. Study outcomes had to be defined according to the International Classification of Diseases (ICD) 9 [codes: 460–519] and/or 10 [codes: J00–J99]. Studies on respiratory disease caused by infectious agents (i.e. tuberculosis, influenza and pneumonia) were excluded. Only studies that investigated short-term air pollution, 0–7-day lag, exposure modified by temperature or season were included; for season to be included, results had to be presented in the form of a warm season and a cold season. All results had to be presented as quantitative data with increments. This process is shown in the Preferred Reporting items for Systematic reviews and Meta-Analyses (PRISMA) checklist in Supplementary A (Moher et al., 2009). Studies were assessed by two independent investigators.

2.3. Data extraction

Data extracted included the reference (authors, and publication date), study location, study population, study design, outcome variables (respiratory

hospital admissions, respiratory mortality, or both), ICD code, exposure variables, type of statistical analysis, type of effect estimate, and main result (Supplementary F). All extracted data was assessed by two independent investigators.

2.4. Quality assessment

Quality assessment was performed using, "Risk of Bias Assessment Instrument for Systematic reviews informing WHO Global Air quality guidelines" (Supplementary D). These guidelines were developed by the WHO Global Air Quality Guidelines Working Group on Risk Bias Assessment to assess the quality of eligible air pollution studies included for systematic reviews (World Health Organisation, 2020). The instrument specifies six topics of interest: confounding, selection bias, exposure assessment, outcome measurement, missing data, and selective reporting. Overall judgement of bias is done at the topic level with the judgement of the topic based on the bias classification (i.e. low, medium, or high risk) given to each sub-topic; if any sub-topic is classified as high or medium risk, then the whole topic will be classified accordingly (Supplementary E).

2.5. Statistical analysis

Studies were grouped into three air pollution-temperature relationships: 1) The effect of air pollution modified by high or low temperatures (determined by percentile of temperature). 2) Air pollution modified by high or low temperature (mean, median, statistically pre-determined cut-offs, or visual turning point). 3) The effect of air pollution during the warm or cold season. We decided to limit meta-analysis to studies in one of the above-mentioned groups (i.e. air pollution-temperature relationship) with five or more papers. Due to the case-crossover design of some of the included studies, all effect estimates were converted to odds ratio (OR) per 10 $\mu g/m^3$ increase in air pollutant; conversion equations can be found in Supplementary G.

Due to different study designs, methods, exposures, populations, and settings, heterogeneity was expected, thus a random-effects model was selected to account for within- and between-study heterogeneity. We used the Hartung-Knapp-Sidik-Jonkman (HKSJ) method, which uses the Sidik-Jonkman (SJ) estimator, as it allows for robust results with more accurate error rates (Harrer et al., 2019). A sensitivity analysis was performed using the DerSimonian-Laird (DL) estimator, the most commonly used estimator in medical research. to assess the stability and accuracy of results (Harrer et al., 2019; Veroniki et al., 2016).

Heterogeneity was assessed using the I^2 test: an I^2 of $\leq 25\%$ indicates low heterogeneity, an I^2 between 25 and 50% is low-moderate heterogeneity, an I^2 of 50–75% indicates moderate-high heterogeneity, and an I^2 of $\geq 75\%$ indicates high heterogeneity. We performed an influence analysis as well as an outlier analysis to assess whether any specific study was responsible for the heterogeneity or the effect size; an outlier was defined as a study with either a lower bound confidence interval (CI) greater than the pooled-upper CI, or an upper bound CI that is less than the pooled-lower bound CI.

All statistical analyses were performed using R software, version 3.6.1 using the "meta" "metafor" "dmetar" and "forestplot" packages (Harrer et al., 2019). This study has been registered on PROSPERO with the registration number CRD42020173203.

3. Results

3.1. Study characteristics

Our initial literature search found 26,656 studies. After removal of duplicate studies, animal studies, and studies published prior to 1990, we assessed the titles, abstracts, and keywords of the papers that left us with 128 papers. Full text of these studies was assessed according to the inclusion and exclusion criteria, which left us with 34 studies; this is shown in the PRISMA flow chart (Supplementary C, Fig. 1a). Our risk of bias assessment tool had six criteria (confounding, selection bias, exposure assessment, outcome measurement, missing data, and selective reporting) with each criteria scored as low, medium, or high risk. None of the studies included were classified as high risk in any of the criteria, however 15 studies were considered medium risk in the confounding category due to non-adjustment for influenza or holidays, and five studies were classified as medium risk in the missing data category as the exposure data had more than 10% missing values (Supplementary E).

Of the 34 studies included, 15 studies had respiratory mortality as their outcome, and 19 studies had respiratory hospital admissions as their outcome. O_3 was an exposure variable for 16 studies, 22 studies had PM_{10} as an exposure variable, 10 studies had $PM_{2.5}$ as an exposure variable, and 17 studies had NO_2 as an exposure variable.

Time series studies accounted for 23 studies, and 11 studies were case-crossover studies. Statistical methods varied; 14 studies used generalised additive models (GAM), 11 studies used conditional logistic regression models, five studies used Poisson regression models, three studies used autoregressive log-linear models, and one study used a distributed lag model.

Publication of studies ranged from 1996 to 2019. Five studies were published in the 1990s, 9 studies were published in the 2000s, and 20 studies were published in the 2010s. In terms of study location, 14 studies came from China, three studies from the United Kingdom (UK), three studies from the United States of America, eight studies from Taiwan, three studies from Australia, and one study from Latin America (e.g. Brazil, Mexico, and Chile), Spain, and the Netherlands, respectively. A summary of these characteristics can be found in Supplementary F.

3.2. Mortality

3.2.1. The effect of air pollution when modified by low and high temperature (determined by percentile of temperature)

We performed a meta-analysis for the effect of PM_{10} when modified by low (<5th percentile of temperature) and high (>95th percentile of temperature) temperature on respiratory mortality. A total of five studies were included in our meta-analysis with the study by Meng et al. (2012) presenting individual results for eight cities in China, therefore, each city result was included. We found an increased odds of respiratory mortality when PM_{10} was modified by low temperature [OR: 1.006 (95%CI: 0.999 to 1.014) per 10 $\mu g/m^3$ increase in PM_{10}] (Fig. 1a). Heterogeneity in this analysis was moderate-high with an I^2 (95% CI) of 72.0%. In the low temperature analysis, none of the studies were classified as outliers and as such no outlier was responsible for the effect estimate or heterogeneity. However, our influence analysis found that the results for Shanghai from the study by Meng et al. (2012) influenced the heterogeneity; when omitting the study, the I^2 value slightly decreased from 72.0% to 67.0%.

There was an increased odds of respiratory mortality when PM_{10} was modified by high temperature [OR: 1.021 (95%CI: 1.008 to 1.034) per 10 $\mu g/m^3$ increase in PM_{10}] (Fig. 1b). Heterogeneity was high with an I^2 (95% CI) of 82.3%. In the high temperature analysis, we found that the study by Cheng and Kan (2012) was an outlier; after exclusion, there was minimal change in the effect estimate and the I^2 value decreased from 82.3% to 78.6% (Supplementary H, Fig. 1c). When we performed the influence analysis, the results for Wuhan, from the study by Meng et al. (2012), was found to influence the heterogeneity as when omitted the heterogeneity decreased from 82.3% to 72.0%.

In the sensitivity analysis there was no significant change in the effect of PM_{10} when modified by both high and low temperatures on respiratory mortality when compared to the main analysis (results not shown).

The study by Qin et al. (2017) found that NO_2 exposure at low temperatures (5th percentile of temperature) decreased the odds of respiratory mortality, while at high temperatures (95th percentile of temperature) increased the odds of respiratory mortality. This differed from the studies by Cheng and Kan (2012) and Qian et al. (2008) in that they both found an increased odds of respiratory mortality when exposed to NO_2 modified by low (5th percentile of temperature) and high (95th percentile of

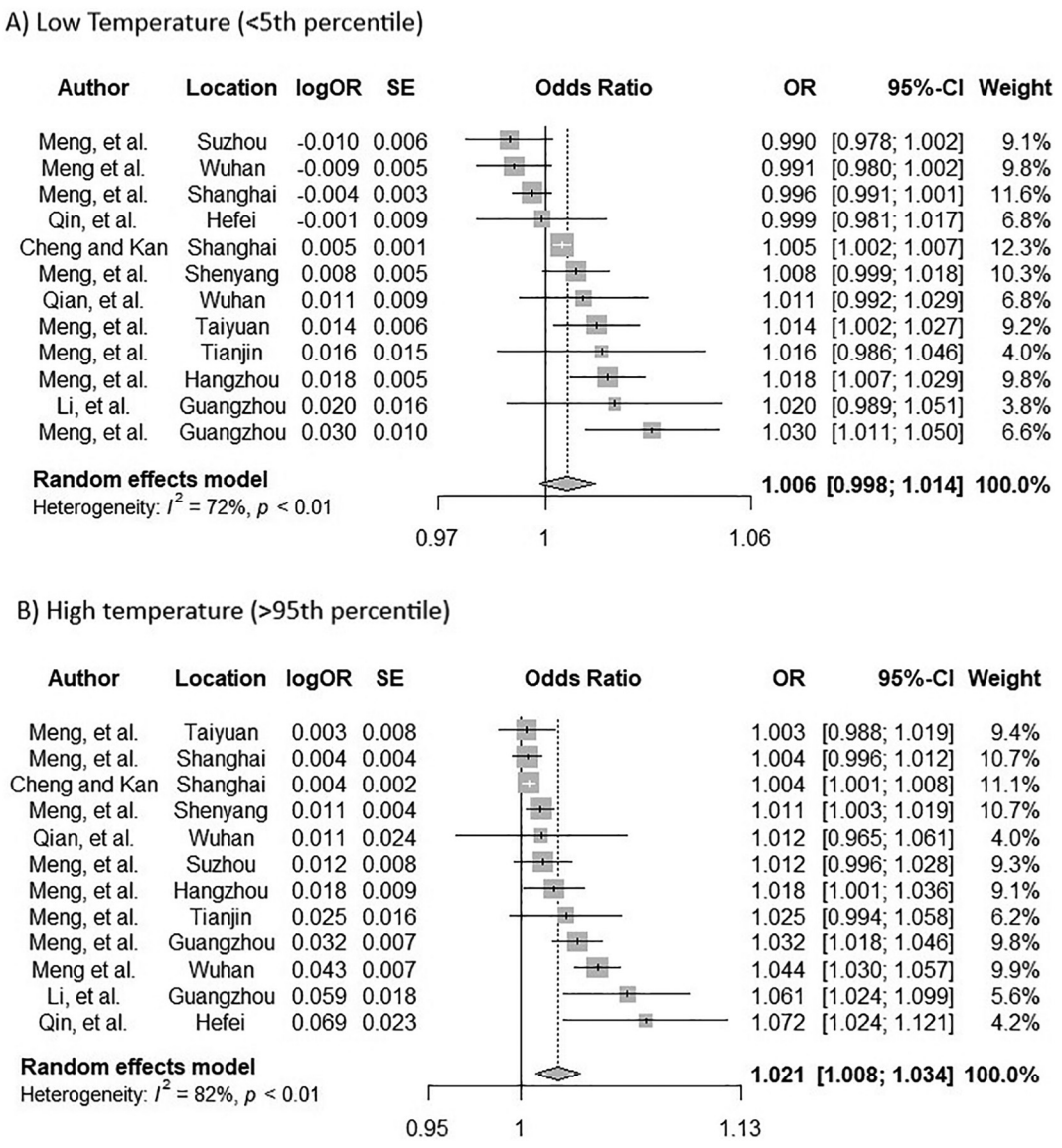


Fig. 1. Forest plots showing the overall effect (per 10 μg/m^3) of PM_{10} when modified by temperature on respiratory mortality using the SJ estimator.

temperature) temperatures. There is an increased odds of respiratory mortality when O_3 modified by both low (5th percentile of temperature) and high (95th percentile of temperature) temperatures (Cheng and Kan, 2012; Qian et al., 2008). The study by Li et al. (2015) looked at the effect of $PM_{2.5}$ on respiratory mortality when modified by low (25th percentile of temperature) and high (75th percentile of temperature) temperatures; this study found a decreased odds of respiratory mortality at low (25th percentile of temperature) temperatures, and an increased odds of respiratory mortality at high (75th percentile of temperature) temperatures.

3.2.2. Air pollution modified by high or low temperature (mean, median, or visual turning point)

Three studies investigated the effect of air pollution modified by high or low temperature (mean, median, or visual turning point) on respiratory mortality (Sun et al., 2015; Tian et al., 2018; Li et al., 2011).

The study by Li et al. (2011) investigated the effect of PM_{10} on respiratory mortality when modified by both low temperatures days (temperatures less than 14.65 °C, and temperatures less than 20 °C) and high temperatures (temperatures above 14.65 °C, and temperatures above 20 °C). Both analyses found that there was an increased risk of respiratory mortality when temperatures were greater than and less than the mean temperature (14.65 °C) and visual turning point (20 °C).

The study by Sun et al. (2015) looked at the effect of $PM_{2.5}$ on respiratory mortality, when modified by temperatures on days with a temperature less than 22 °C, and days with a temperature above 25 °C; there is an increased risk of mortality after $PM_{2.5}$ exposure on both low and high temperature days, however this increased risk is more apparent at low temperatures.

The study by Tian et al. (2018) investigated the effect of PM_{10} on respiratory mortality when modified by both low temperatures days (temperatures less than 15.9 °C, and temperatures less than 20 °C) and high temperatures (temperatures above 15.9 °C, and temperatures above 20 °C). There was an increased risk of mortality after PM_{10} exposure on both low and high temperature days, however this increased risk is more apparent at high temperatures.

3.2.3. The effect of air pollution during the warm and cold season

We performed a meta-analysis for five studies that investigated the effect of O_3 on respiratory mortality during the warm or cold season. The study by Romieu et al. (2012) presented results for six cities in Latin America, therefore we included the results for each city in our analysis.

We found that there is an increased odds of respiratory mortality after exposure to O_3 during the cold season [OR: 1.004 (95%CI: 0.998 to 1.011) per 10 μg/m^3 increase in O_3] (Fig. 2a). The I^2 in our analysis was 55.4% which signifies moderate-high heterogeneity. We found that none

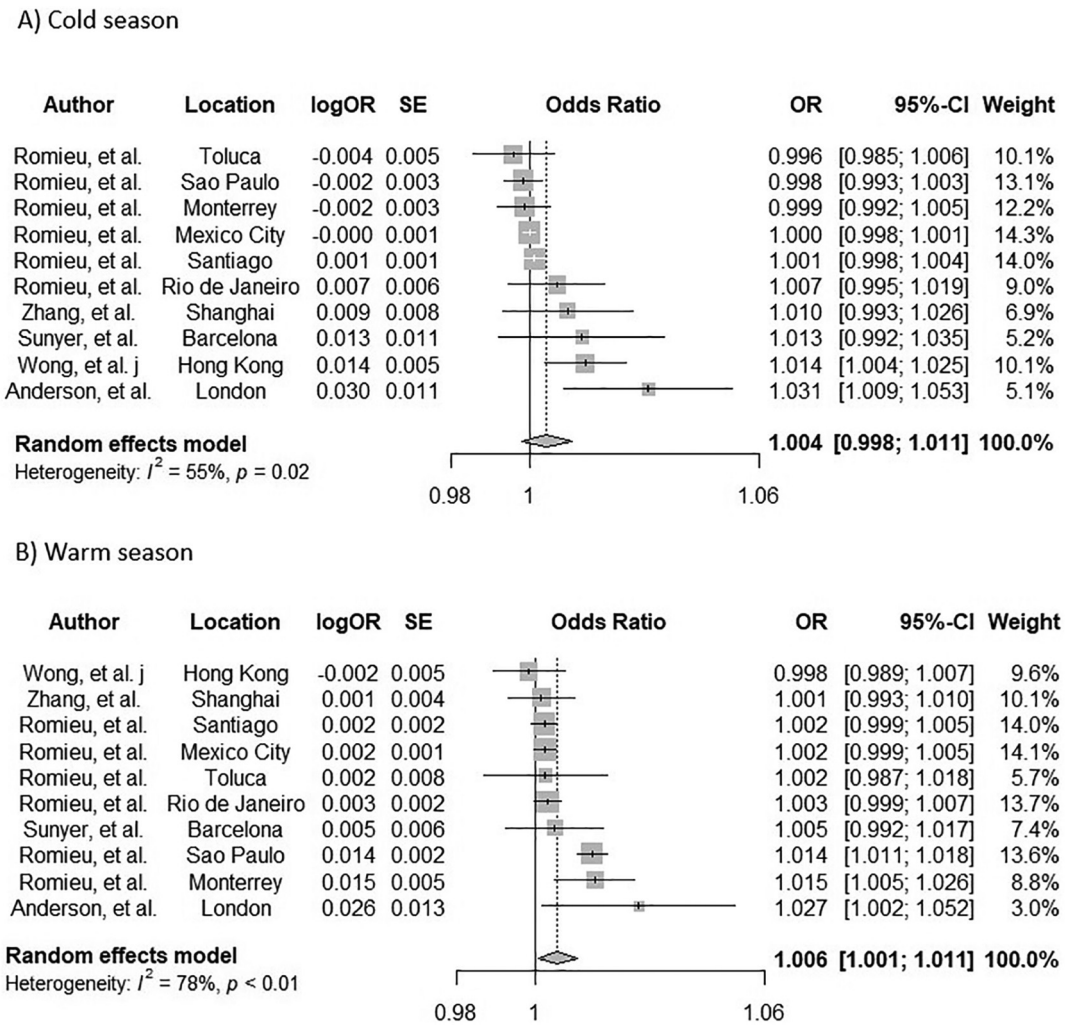


Fig. 2. Forest plots showing the overall effect (per 10 μg/m^3) of O_3 when modified by season on respiratory mortality using the SJ estimator.

of the included studies were classified as an outlier study, however when we ran an influence analysis we found that the study by Anderson et al. (1996) influenced the heterogeneity in the analysis; when we omitted the study by Anderson et al. (1996) the heterogeneity decreased to 37.0%. Our sensitivity analysis showed minimal change in the effect estimate determine in the main analysis (results not shown).

We found that there was an increased odds of respiratory mortality after O_3 exposure during the warm season [OR: 1.006 (95%CI: 1.001 to 1.012) per 10 μg/m^3 increase in O_3] (Fig. 2b). Our I^2 was 78.0% which signifies high heterogeneity. Both our outlier analysis and influence analysis revealed that the results for São Paulo in the study by Romieu et al. (2012) acted as both an outlier as well as a study that influenced our results; when omitted, the I^2 value decreased to 22.6%, which signifies low heterogeneity (Supplementary H, Fig. 1d). Our sensitivity analysis showed no change in the effect estimate when compared to our main analysis (result not shown).

Results from studies that investigated the effect of NO_2 on respiratory mortality in both the cold and warm season were inconsistent. The studies by Anderson et al. (1996) and Sunyer et al. (1996) found that there was a decreased odds of respiratory mortality, while the studies by Wong et al. (2001) and Zhang et al. (2011) found an increased odds of respiratory mortality during the cold season. During the warm season, Anderson et al. (1996) and Zhang et al. (2011) both found that there was a decreased odds of respiratory mortality, while the studies by Sunyer et al. (1996) and Wong et al. (2001) found that there was an increased risk of respiratory mortality.

For the effect of PM_{10} on respiratory mortality during the cold season, both the study by Wong et al. (2001) and the study by Zhang et al. (2011) found an increased risk of respiratory mortality; during the warm season, the study by Wong et al. (2001) found that there was an increased risk of respiratory mortality, while the study by Zhang et al. (2011) found a decreased risk of respiratory mortality.

3.3. Hospital admissions

3.3.1. The effect of air pollution when modified by low and high temperature (determined by percentile of temperature)

The study by Qiu et al. (2018) investigated the effect of PM_{10}, and NO_2 on respiratory hospital admissions when modified by low (20th percentile of temperature) and high (80th percentile of temperature) temperatures; this study found an increased odds of respiratory hospital admissions after exposure to PM_{10}, and NO_2 modified by both low and high temperatures.

The study by Wang et al. (2013) looked at the effect of PM_{10}, and NO_2 on respiratory hospital admissions when modified by low (15th percentile of temperature) and high (85th percentile of temperature) temperatures. This study found that there is an increased odds of respiratory hospital admissions when exposed to both PM_{10}, and NO_2 modified by low temperatures (20th percentile of temperature); when PM_{10} is modified by high temperatures (85th percentile of temperature) there is a decreased odds of respiratory hospital admissions, while when NO_2 is modified by high temperatures (85th percentile of temperature) there is an increased odds of respiratory hospital admissions.

Yitshak-Sade et al. (2018) investigated the effect of $PM_{2.5}$ on respiratory hospital admissions when modified by low (10th percentile of temperature) and high (90th percentile of temperature) temperatures; this study found that where was a decreased odds of respiratory hospital admissions during low temperatures, and an increased odds of respiratory hospital admissions during high temperatures.

3.3.2. Air pollution modified by high or low temperature (mean, median, or visual turning point)

The studies by Cheng et al. (2014), and Tsai et al. (2013) looked at the effect of $PM_{2.5}$ on respiratory hospital admissions when modified by low (<23 °C) and high (>23 °C) temperatures. Both studies found an increased odds of respiratory hospital admissions at both high and low temperatures with the association most clear at high temperatures. The studies by Tsai et al. (2014) and Cheng et al. (2015) differed from the above mention studies in that they investigated the effect of $PM_{2.5}$ on respiratory hospital admissions when modified by low (<25 °C) and high (>25 °C) temperatures; these studies found that while there was an increased risk of respiratory hospital admissions at both low and high temperatures, this association was most apparent at low temperatures.

The studies by Cheng et al. (2015), Yang et al. (2007), Lee et al. (2007), and Tsai et al. (2006) investigated the effect PM_{10} on respiratory hospital admissions when modified by low (<25 °C) and high (>25 °C) temperatures; these studies found that there was an increased odds of respiratory hospital admissions at both high and low temperatures, this was most apparent during low temperatures. The studies by Yang and Chen (2007), and Ren and Tong (2006) differed from the above in that they used different definitions for temperature. Yang and Chen (2007) defined low temperature as temperature <20 °C, and high temperature as temperature >20 °C, while Ren and Tong (2006) defined low temperature as temperature < 25.3 °C, and high temperature as temperature >25.3 °C. Both studies found an increased odds of respiratory hospital admissions when PM_{10} was modified by high temperatures; while the study by Yang and Chen (2007) found an increased odds of respiratory hospital admission when PM_{10} was modified by low temperatures, the study by Ren and Tong (2006) found that PM_{10} modified by low temperatures decreases the odds of respiratory hospital admissions.

The studies by Lee et al. (2007), Yang et al. (2007), and Tsai et al. (2006) looked at the effect NO_2 on respiratory hospital admissions when modified by low (<25 °C) and high (>25 °C) temperatures; all three studies found an increased odds of respiratory hospital admissions at both low and high temperatures. The study by Yang and Chen (2007) defined low temperature as temperature <20 °C, and high temperature as temperature >20 °C; this study found an increased odds of respiratory hospital admissions at high temperatures, and a decreased odds of respiratory hospital admissions at low temperatures.

Additionally, the studies by Lee et al. (2007), Yang et al. (2007), and Tsai et al. (2006) studied the effect O_3 on respiratory hospital admissions when modified by low (<25 °C) and high (>25 °C) temperatures; all three studies found an increased odds of respiratory hospital admissions at both low and high temperatures. The study by Yang and Chen (2007) found an increased odds of respiratory hospital admissions at high temperatures (>20 °C), and a decreased odds of respiratory hospital admissions at low temperatures (<20 °C).

3.3.3. The effect of air pollution during the warm and cold season

The effect of PM_{10} on respiratory hospital admissions during the cold season showed consistent results with all four studies that investigated the association finding an increased odds of respiratory hospital admissions (Hansen et al., 2012; Chen et al., 2016; Medina-Ramon et al., 2006a; Rodopoulou et al., 2014).

We included five studies that looked at the effect of PM_{10} on respiratory hospital admissions during the warm season. We were able to perform an analysis for the effect of PM_{10} during the warm season on respiratory hospital admissions, this analysis found an increased odds of respiratory hospital admissions [OR: 1.011; 95% CI: 0.999 to 1.040 per 10 $\mu g/m^3$ increase in PM_{10}] (Fig. 3). Heterogeneity was low-moderate with an I^2 (95% CI) of 38.0%. Our outlier analysis revealed that none of our included studies were outliers; however, our influence analysis found that when the study by Hansen Hansen et al. (2012) was omitted, the I^2 value decreased to19%. Our sensitivity analysis revealed minimal change in the effect estimate (results not shown).

We included five studies that investigated the effect of O_3 on respiratory hospital admissions during the cold and warm season. For effect of O_3 during the cold season, there is a decreased odds of respiratory hospital admissions [OR: 0.997; 95% CI: 0.982 to 1.012 per 10 $\mu g/m^3$ increase in O_3] (Fig. 4a). Heterogeneity was moderate-high with a I^2 (95% CI) of 62.2%. Our outlier analysis found that no studies were outliers in our analysis, however, our influence analysis found that the study by Anderson et al. (1998) influenced the heterogeneity; when we omitted the study by Anderson et al. (1998), the I^2 decreased to 40%. Our sensitivity analysis found minimal change in the effect estimates for the effect of O_3 during the cold season.

For the effect of O_3 during the warm season, there is an increase in the odds of respiratory hospital admissions [OR: 1.015; 95% CI: 0.995 to 1.036 per 10 $\mu g/m^3$ increase in O_3] (Fig. 4b). Heterogeneity was moderate-high with a I^2 (95% CI) of 73.5% (33.8% to 89.4%). Our outlier analysis found that no studies were outliers in our analysis, however, our influence analysis found that the study by Chen et al. (2016) influenced the heterogeneity; when we omitted the study by Chen et al. (2016), the I^2 decreased to 0%. Our sensitivity analysis found minimal change in the effect estimates for the effect of O_3 during the cold season.

The studies by Anderson et al. (1998), Chen et al. (2016), and Schouten et al. (1996) all investigated the effect of NO_2 on respiratory hospital admissions during both the cold and warm season; all three studies found an increased odds of respiratory hospital admissions during the cold and warm season. The study by Atkinson et al. (1999) looked at the effect of NO_2 on respiratory hospital admissions during the warm season and found an increased odds of respiratory hospital admissions.

The studies by Chen et al. (2016), and Rodopoulou et al. (2014) both found that there was an increased odds of respiratory hospital admissions after exposure to $PM_{2.5}$ during both the cold and warm season. The study by Hansen et al. (2012) found that whiles there was an increased odds of respiratory hospital admissions during the warm season, there was a decreased odds of respiratory hospital admissions in the cold season.

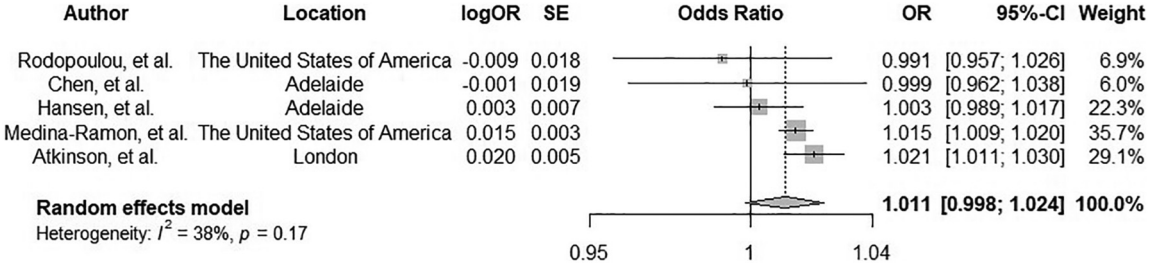


Fig. 3. Forest plot showing the random effects model for the effect of PM_{10} (per 10 $\mu g/m^3$) during the warm season on respiratory hospital admissions using the SJ estimator.

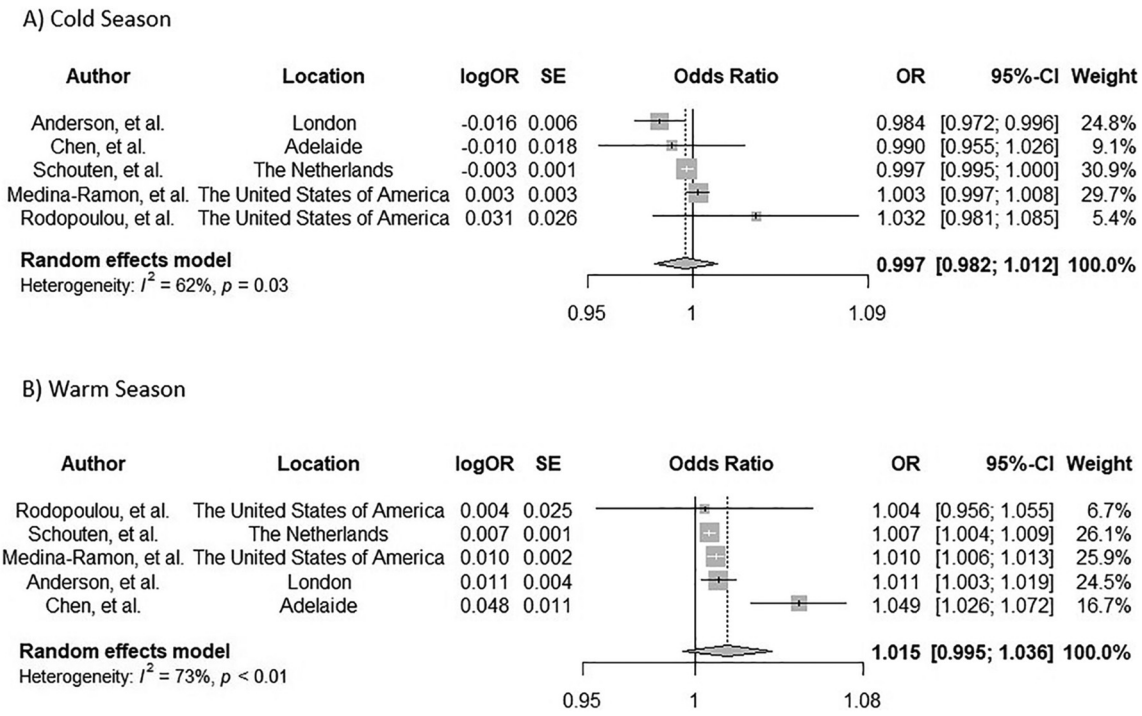


Fig. 4. Forest plot showing the random effects model for the effect of PM_{10} (per 10 μg/m^3) during both the cold and warm season on respiratory hospital admissions using the SJ estimator.

4. Discussion

4.1. Summary of study results

In this systematic review and meta-analysis, 34 studies presented results on the association between air pollution respiratory mortality and/or respiratory hospital admissions, modified by temperature levels. As far as we are aware, this is the first systematic review that aims to assess available literature on both air pollution and temperature exposures and their effect on respiratory health outcomes.

The majority of studies reported an increased odds of both respiratory mortality and respiratory hospital admissions after exposure to air pollutants ($PM_{2.5}$, PM_{10}, NO_2, and O_3), and high temperatures. This was supported by our meta-analyses, which found statistically significant results for the effect of air pollutants and high temperatures on our respiratory outcomes. For low temperatures, results were largely inconsistent; overall, there appears to be an increased odds for respiratory mortality and respiratory hospital admissions after exposure to selected air pollutants ($PM_{2.5}$, PM_{10}, NO_2, and O_3) and low temperatures.

The effect of O_3 and temperature on respiratory outcomes was of interest. As expected, there was an increased risk of adverse health outcomes during high temperatures and the warm season, however, the effect of low temperature and the cold season was inconclusive. An effect of O_3 during low temperatures/cold season was not expected due to low O_3 concentrations, however more studies are reporting an increased risk of adverse respiratory health outcomes after exposure to O_3 at low temperatures/cold season. Zhang et al. (2006) hypothesized that climate change is prolonging the O_3 season, while also causing stagnant atmospheric conditions that promote the formation of O_3; they conclude that it is difficult to determine a threshold value for the effect of O_3 on health and that if a threshold exists it is probably lower than the current health-based standard.

Heterogeneity was expected in our analysis due to the differences in study designs, study locations, study populations, statistical methods, and variable definitions. Differences in variable definition are common in air pollution-temperature studies. Studies use different air pollution concentrations, i.e. NO_2 1-hour maximum and NO_2 24-hour maximum, and temperature measures, i.e. mean temperature, median temperature, temperature-mortality relationship, with some studies choosing to use 5% and 95% percentiles of temperature, and others using 25% and 75% percentiles of temperature. Therefore, differences in type of measurements makes drawing a conclusion, on the effect of air pollution when modified by temperature on respiratory health outcomes, challenging.

Our review is in line with previous systematic reviews that investigated air pollution, temperature, and health outcomes as they also found that their analyses had varied and high I^2-values (Bunker et al., 2016b). However, Bunker et al. (2016b) argues that I^2-thresholds are more suited for controlled epidemiological studies rather than environment-health relationship studies which do not follow as stringent reporting guidelines. Therefore, we conclude that while heterogeneity is an issue in research, in environment-health studies it is harder to truly quantify the effects of heterogeneity due to the flexibility present in these types of studies.

We chose to exclude studies that only provided pooled results from a meta-analysis. However, two of these excluded studies were of interest. The first study by Analitis et al. (2018) showed a potential synergistic effect between air pollution and temperature on respiratory mortality in Europe; this study supports our own meta-analyses, in that it also found increased risk of mortality during the warm season when exposed to O_3. The second study by Stafoggia et al. (2008) included an interaction term between PM_{10} and temperature. While this study failed to find any significant results, the use of an interaction term shows a shift towards investigating potential interactive effect between air pollution and temperature on health.

4.2. Biological mechanisms

Biologically, air pollution and temperature affect the respiratory system differently. Air pollution accumulates and permeates through lung tissue. O_3 causes non-visible structural lung modifications, while PM induces an increase in proinflammatory activity which leads to bronchial damage (De Sario et al., 2013). The modifications and damage caused by air pollution on the lungs makes the body more susceptible to developing, and exacerbating, CRDs (De Sario et al., 2013). During periods of high temperatures, e.g. heat waves, the body is unable to efficiently thermoregulate, which leads to excessive sweating and dehydration, exacerbating CRDs due to increased airway resistance (Watts et al., 2020; Leon, 2008; Bernstein and

Rice, 2013). During low temperatures, the veins and arteries narrow, causing an increase in cardiac and respiratory workload (D'Amato et al., 2018; Seltenrich, 2015).

4.3. Policy development and implications

Climate change, air pollution, and temperature are in a continuous feedback loop (Orru et al., 2017) Air pollution is largely influenced by meteorological variables such as temperature, humidity and wind; as the concentration of greenhouse gases increases in the atmosphere, the excess greenhouse gases cause climate change and global warming (Orru et al., 2017).However, this feedback loop means that policies addressing one could influence and combat the other. The Paris Climate Agreement is an example of such a policy; signed in 2015, it is the first legally binding climate agreement between 196 countries which aims to ensure that temperatures do not rise by more than 2 °C above pre-industrial levels by 2100 (Watts et al., 2020). However, since 2015, the five hottest years on record have occurred (Watts et al., 2020). Rising temperatures are rapidly changing the climate, causing downstream effects on different environmental systems and exposing vulnerabilities in both developing and developed nations (Watts et al., 2020). Heatwave events are a contributing factor to the rise in wildfires, which compromise not only infrastructure but also human health through the excess release of air pollutants. Therefore, policymakers should aim to develop policies that combat many different facets of climate change.

Systematic reviews, such as this one, are important for policy development as it synthesises available research into a single document and allows us to identify trends that may not be as apparent in an individual study. Our review shows that policymakers should promote and develop polices using a global health perspective as by lowering the levels of air pollution and encouraging awareness of the impacts of temperature on health, we could potential decrease preventable deaths attributed to both air pollution and temperature.

4.4. Future research

The coronavirus disease (COVID-19) pandemic has shown that shifting our perspectives from a public health approach to a global health approach is vital for research purposes. While the majority of our studies came from China, which is classified as an upper-middle income country (MIC), there is a lack of studies from other countries classified as lower- and middle-income countries (LMIC). We hypothesise through collaboration, and by improving the research capabilities of LMIC, we will encourage research that allows for more conclusive evidence on the nature and effect size of the combined effect between air pollution and temperature. This would allow researchers to investigate more effective statistical models, e.g. quantifying the effect modification of temperature more effectively by using a stratification method, whereby one model includes an interactive effect term between the air pollutant and temperature, and another model that does not include an interactive effect term.

4.5. Strengths and limitations

A strength of this study was that the inclusion criteria allowed for a large number of studies to be included and assessed. Selection of studies was limited to papers published from 1990, which allowed for up to 30 years of research to be included in this analysis. The selection was done in duplicate, which limits selection bias. Using a random-effects model in our meta-analysis allowed for a better account of within- and between-study heterogeneity.

There are three specific limitations in this study. The first limitation is the lack of homogeneity among studies due to different study designs, statistical analysis techniques, selection of confounders, air pollution measurements, temperature definitions and measurements, and populations. Secondly, the lack of patient specific characteristics included in the selected studies make stratification by confounders correlated with respiratory disease, e.g. smoking, age, gender, impossible to perform. Lastly, it is difficult to draw a global conclusion on the effect of air pollution when modified by temperature for two reasons: one) most of the studies were limited to one or two countries, and 2) research was almost exclusively limited to developed countries or regions e.g. North America, Europe, and Australia, with the exception of the large number of studies from China, and one study from Latin America, both of which are classified as developing.

5. Conclusions

We are living in an era where the effects of climate change are becoming more apparent. Therefore, investigating the effects of climate change, as well as its causes and consequences, on different health outcomes is imperative. The health effects of both air pollution and temperature are well studied, but the potential interactive effect of air pollution and temperature on health is still a relatively new field of study. With results on the potential interactive effect between air pollution and temperature being largely inconsistent, we should encourage future research in different regions and locations, which would allow for more conclusive evidence on this relationship. This systematic review and meta-analysis found that the effect of air pollution, specifically O_3 and PM_{10}, when modified by temperature, increases the odds of adverse respiratory health outcomes.

Author contributions

Conceptualisation, AT.A. and T.S.; methodology: study selection and data extraction, AT.A., T.S., C.W and Q.Z; software, AT.A. and C.W; validation, AT.A., Q.Z., C.W., and T.S.; formal analysis, AT.A.; writing—original draft preparation, AT.A.; writing—review and editing, AT.A., Q.Z, C.W, A. S, and T.S; supervision, Q.Z., C.W, and T.S. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no outside funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

I would like to thank Dr. Ute Kraus for her advice and assistance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.152336.

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The effect of air pollution when modified by temperature on respiratory health outcomes: a systematic review and meta-analysis.

Ashtyn Tracey Areal [1], Qi Zhao [1,2], Claudia Wigmann[1], Alexandra Schneider[3] and Tamara Schikowski[1]*,

[1]Department of Epidemiology, IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany;

[2]Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China;

of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health (GmbH), Neuherberg, Germany

Supplementary

Supplementary A: PRISMA Checklist

Table 1a: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4 and supplementary B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5 and supplementary D
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5 and 6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5 and supplementary D
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5 and 6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6-18
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-18, supplementary H
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

doi:10.1371/journal.pmed1000097

Supplementary B: Example of search terms used.

Web of Science search terms

"Air Pollution AND Temperature AND Respiratory disease" OR "Air Pollution AND Temperature AND Chronic Respiratory disease" OR "Air Pollution AND Temperature AND Chronic obstructive pulmonary disease" OR "Air Pollution AND Temperature AND COPD" OR "Air Pollution AND Temperature AND Asthma" OR "Air Pollution AND Temperature AND Mortality" OR "Air Pollution AND Temperature AND Hospital Admission" OR "Outdoor Air Pollution AND Temperature AND Respiratory disease" OR "Outdoor Air Pollution AND Temperature AND Chronic Respiratory disease" OR "Outdoor Air Pollution AND Temperature AND Chronic obstructive pulmonary disease" OR "Outdoor Air Pollution AND Temperature AND COPD" OR "Outdoor Air Pollution AND Temperature AND Asthma" OR "Outdoor Air Pollution AND Temperature AND Mortality" OR "Outdoor Air Pollution AND Temperature AND Hospital Admission"

"Air Pollution AND Extreme temperatures AND Respiratory disease" OR "Air Pollution AND Extreme temperatures AND Chronic Respiratory disease" OR "Air Pollution AND Extreme temperatures AND Chronic obstructive pulmonary disease" OR "Air Pollution AND Extreme temperatures AND COPD" OR "Air Pollution AND Extreme temperatures AND Asthma" OR "Air Pollution AND Extreme temperatures AND Mortality" OR "Air Pollution AND Extreme temperatures AND Hospital Admission" OR "Outdoor Air Pollution AND Extreme temperatures AND Respiratory disease" OR "Outdoor Air Pollution AND Extreme temperatures AND Chronic Respiratory disease" OR "Outdoor Air Pollution AND Extreme temperatures AND Chronic obstructive pulmonary disease" OR "Outdoor Air Pollution AND Extreme temperatures AND COPD" OR "Outdoor Air Pollution AND Extreme temperatures AND Asthma" OR "Outdoor Air Pollution AND Extreme temperatures AND Mortality" OR "Outdoor Air Pollution AND Extreme temperatures AND Hospital Admission"

"Air Pollution AND Hot Temperature AND Respiratory disease" OR "Air Pollution AND Hot Temperature AND Chronic Respiratory disease" OR "Air Pollution AND Hot Temperature AND Chronic obstructive pulmonary disease" OR "Air Pollution AND Hot Temperature AND COPD" OR "Air Pollution AND Hot Temperature AND Asthma" OR "Air Pollution AND Hot Temperature AND Mortality" OR "Air Pollution AND Hot Temperature AND Hospital Admission" OR "Outdoor Air Pollution AND Hot Temperature AND Respiratory disease" OR "Outdoor Air Pollution AND Hot Temperature AND Chronic Respiratory disease" OR "Outdoor Air Pollution AND Hot Temperature AND Chronic obstructive pulmonary disease" OR "Outdoor Air Pollution AND Hot Temperature AND COPD" OR "Outdoor Air Pollution AND Hot Temperature AND Asthma" OR "Outdoor Air Pollution AND Hot Temperature AND Mortality" OR "Outdoor Air Pollution AND Hot Temperature AND Hospital Admission"

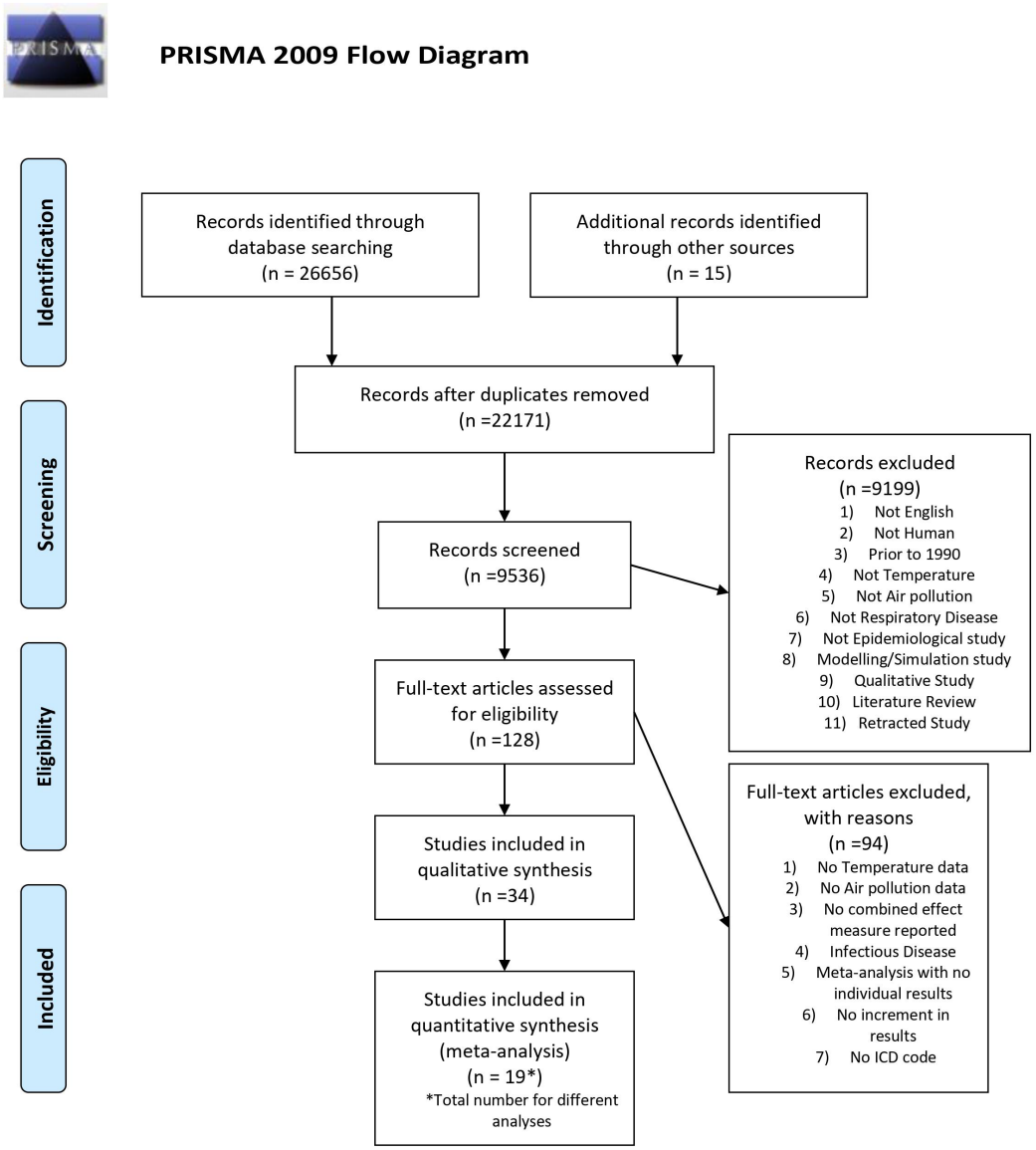
“Air Pollution AND Cold Temperature AND Respiratory disease” OR “Air Pollution AND Cold Temperature AND Chronic Respiratory disease” OR “Air Pollution AND Cold Temperature AND Chronic obstructive pulmonary disease” OR “Air Pollution AND Cold Temperature AND COPD” OR “Air Pollution AND Cold Temperature AND Asthma” OR “Air Pollution AND Cold Temperature AND Mortality” OR “Air Pollution AND Cold Temperature AND Hospital Admission” OR “Outdoor Air Pollution AND Cold Temperature AND Respiratory disease” OR “Outdoor Air Pollution AND Cold Temperature AND Chronic Respiratory disease” OR “Outdoor Air Pollution AND Cold Temperature AND Chronic obstructive pulmonary disease” OR “Outdoor Air Pollution AND Cold Temperature AND COPD” OR “Outdoor Air Pollution AND Cold Temperature AND Asthma” OR “Outdoor Air Pollution AND Cold Temperature AND Mortality” OR “Outdoor Air Pollution AND Cold Temperature AND Hospital Admission”

“Air Pollution AND Respiratory disease” OR “Air Pollution AND Chronic Respiratory disease” OR “Air Pollution AND Chronic obstructive pulmonary disease” OR “Air Pollution AND COPD” OR “Air Pollution AND Asthma” OR “Air Pollution AND Mortality” OR “Air Pollution AND Hospital Admission” OR “Outdoor Air Pollution AND Respiratory disease” OR “Outdoor Air Pollution AND Chronic Respiratory disease” OR “Outdoor Air Pollution AND Chronic obstructive pulmonary disease” OR “Outdoor Air Pollution AND COPD” OR “Outdoor Air Pollution AND Asthma” OR “Outdoor Air Pollution AND Mortality” OR “Outdoor Air Pollution AND Hospital Admission”

“Temperature AND Respiratory disease” OR “Temperature AND Chronic Respiratory disease” OR “Temperature AND Chronic obstructive pulmonary disease” OR “Temperature AND COPD” OR “Temperature AND Asthma” OR “Temperature AND Mortality” OR “Temperature AND Hospital Admission” OR “Extreme temperatures AND Respiratory disease” OR “Extreme temperatures AND Chronic Respiratory disease” OR “Extreme temperatures AND Chronic obstructive pulmonary disease” OR “Extreme temperatures AND COPD” OR “Extreme temperatures AND Asthma” OR “Extreme temperatures AND Mortality” OR “Extreme temperatures AND Hospital Admission” OR “Hot Temperature AND Respiratory disease” OR “Hot Temperature AND Chronic Respiratory disease” OR “Hot Temperature AND Chronic obstructive pulmonary disease” OR “Hot Temperature AND COPD” OR “Hot Temperature AND Asthma” OR “Hot Temperature AND Mortality” OR “Hot Temperature AND Hospital Admission” OR “Cold Temperature AND Respiratory disease” OR “Cold Temperature AND Chronic Respiratory disease” OR “Cold Temperature AND Chronic obstructive pulmonary disease” OR “Cold Temperature AND COPD” OR “Cold Temperature AND Asthma” OR “Cold Temperature AND Mortality” OR “Cold Temperature AND Hospital Admission”

Supplementary C

Figure 1a: PRISMA flow chart



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Supplementary D: Risk of bias checklist

Table 1b: Risk of bias assessment instrument

Risk of bias instrument	**Topic:**			**Reviewer ID:**		
		Study ID:				
		Date:				
For each PECOS		**Long-term studies**	**Short-term studies**			**Notes**
	Critical potential confounders					
	Other potential confounders					
Domain	**Subdomain**	**Low-risk (ideal study) criteria**	**Moderate-risk criteria**	**High-risk criteria**	**Overall judgement for a domain: Low/ Moderate/ High**	**Rationale/ Notes (quotes from the study to justify the judgement)**
1. Confounding	Were all confounders considered adjusted for in the analysis?	All critical and other/additional potential confounders adjusted for or with support (e.g. exploratory analysis) of minimal risk due to residual confounding (i.e. there is evidence that this confounder might not lead to severe confounding).	All critical potential confounders but not all other/ additional potential confounders adjusted for without support (e.g. exploratory analysis) of minimal risk due to residual confounding (i.e. there is evidence that this confounder might not lead to severe confounding).	Not all critical potential confounders adjusted for without support (e.g. exploratory analysis) of minimal risk due to residual confounding.		
	Validity of measuring of confounding factors	Confounders measured with documented valid methods.	Not all critical potential confounders were measured with documented valid methods; however, there is evidence that this does not lead to severe confounding.	Any critical or other/additional potential confounder not validly assessed and evidence of residual confounding.		

	Control in analysis (Did the authors use an appropriate analysis method or study design that controlled for confounding domains?)	Authors used appropriate analysis methods or study designs that controlled for confounding domains.	Authors used inappropriate methods or designs when adjusting for critical potential confounders; however, there is evidence that this does not lead to severe confounding.	Authors used inappropriate methods or study designs when adjusting for critical and other/additional potential confounders.		
					Overall	

Domain	**Subdomain**	**Low-risk (ideal study) criteria**	**Moderate-risk criteria**	**High-risk criteria**	**Overall judgement for a domain: Low/ Moderate/ High**	**Rationale/ Notes (quotes from the study to justify the judgement)**
2. Selection bias	Selection of participants into the study (includes nonresponse)	Participants in all exposure levels and with all outcomes had equal opportunity to be in the study.	Participants in all exposure levels did not have equal opportunity to be in the study, but **not** to the extent that effect estimates were seriously biased (rationale required).	Participants in all exposure levels did not have equal opportunity to be in the study, to the extent that effect estimates were seriously biased.		
				Overall		
3. Exposure assessment	Methods used for exposure assessment	Exposure levels assessed with appropriate methods.	Exposure levels assessed with less than appropriate methods but not to the extent that effect estimates were seriously biased.	Exposure levels not assessed with appropriate methods to the extent that effect estimates were seriously biased.		
	Exposure measurement methods comparable across the range of exposure	Measurement methods used are comparable across the range of exposure.	Measurement methods vary across the range of exposure; **however**, there is evidence supporting that the exposure measurement is sufficiently similar that effect estimates are not seriously biased.	Measurement methods vary across the range of exposure and differences are not accounted for.		

	Change in exposure status (for long-term studies only)	Spatial exposure contrasts did not change throughout the study or time varying exposure was used to account for changes.	Spatial exposure contrasts did change throughout the study and were not accounted for **but** effect estimates were not seriously biased.	Spatial exposure contrasts did change throughout the study and were not accounted for, **and** effect estimates were seriously biased and were different in cases and non-cases.		
	Exposure contrast	Exposure contrast was large compared to the precision of exposure assessment (between-subject variance larger than withinsubject variance).	Exposure contrast was small relative to the withinsubject variance but not to the extent that the study is uninformative.	Exposure contrast was so small relative to the within-subject variance that the study is uninformative.		
				Overall		

Domain	**Subdomain**	**Low-risk (ideal study) criteria**	**Moderate-risk criteria**	**High-risk criteria**	**Overall judgement for a domain: Low/ Moderate/ High**	**Rationale/ Notes (quotes from the study to justify the judgement)**
4. Outcome measurement	Blinding of outcome measurement	Outcome measurements were not influenced by knowledge of the exposure.	Outcome measures were influenced by knowledge of the exposure; however, evidence supports that effect estimates were unlikely biased.	Outcome detection was related to exposure status and effect estimates are likely biased.		
	Validity of outcome measurements	No systematic errors in the measurement of the outcome or systematic errors were unrelated to the exposure.	Minimum systematic errors suspected in the measurement were related to the exposure received.	Critical systematic errors in the measurement were related to the exposure received.		
	Outcome measurement	Methods of outcome assessment were comparable across exposure groups.	Methods of outcome assessment were not comparable across exposure groups; **however**, evidence supports that outcome detection would not have varied.	Methods of outcome assessment were not comparable across exposure groups.		

	Overall					
5. Missing data	Missing data of outcome measures	No missing outcome data or missing data infrequent (<10%) or missing data related to outcome or exposure data imputed using appropriate methods.	Missing data on outcomes not infrequent (≥10%) and rationale for attrition explained in the study; methods have possibly been used to properly account for it.	Evidence of substantial missing outcome data (≥10%), rationale for attrition not explained in the study and methods unlikely to properly account for it.		
	Missing data of exposures	No missing exposure data or missing data infrequent (<10%) or missing data related to exposure or outcome data imputed using appropriate methods.	Missing data on exposure not infrequent (≥10%) and rationale for attrition explained in the study; methods have possibly been used to properly account for it.	Evidence of substantial missing exposure data (≥10%), rationale for missing data not explained in the study, and/ or the portion of participants and reasons for missing data are dissimilar across exposures/ exposure groups.		
	Overall					

Domain	**Subdomain**	**Low-risk (ideal study) criteria**	**Moderate-risk criteria**	**High-risk criteria**	**Overall judgement for a domain: Low/ Moderate/ High**	**Rationale/ Notes (quotes from the study to justify the judgement)**
6. Selective reporting	Authors reported a priori primary and secondary study aims	Effect estimates presented for all hypotheses tested as per aims; reference to published or unpublished study protocol.	Effect estimates presented for **some (not all)** hypotheses tested as per aims, **but** evidence suggests that effect estimates unlikely to be seriously biased.	Effect estimates selectively presented for **some (not all)** hypotheses tested as per aims **and** effect estimates likely to be seriously biased.		
	Overall					

Supplementary E

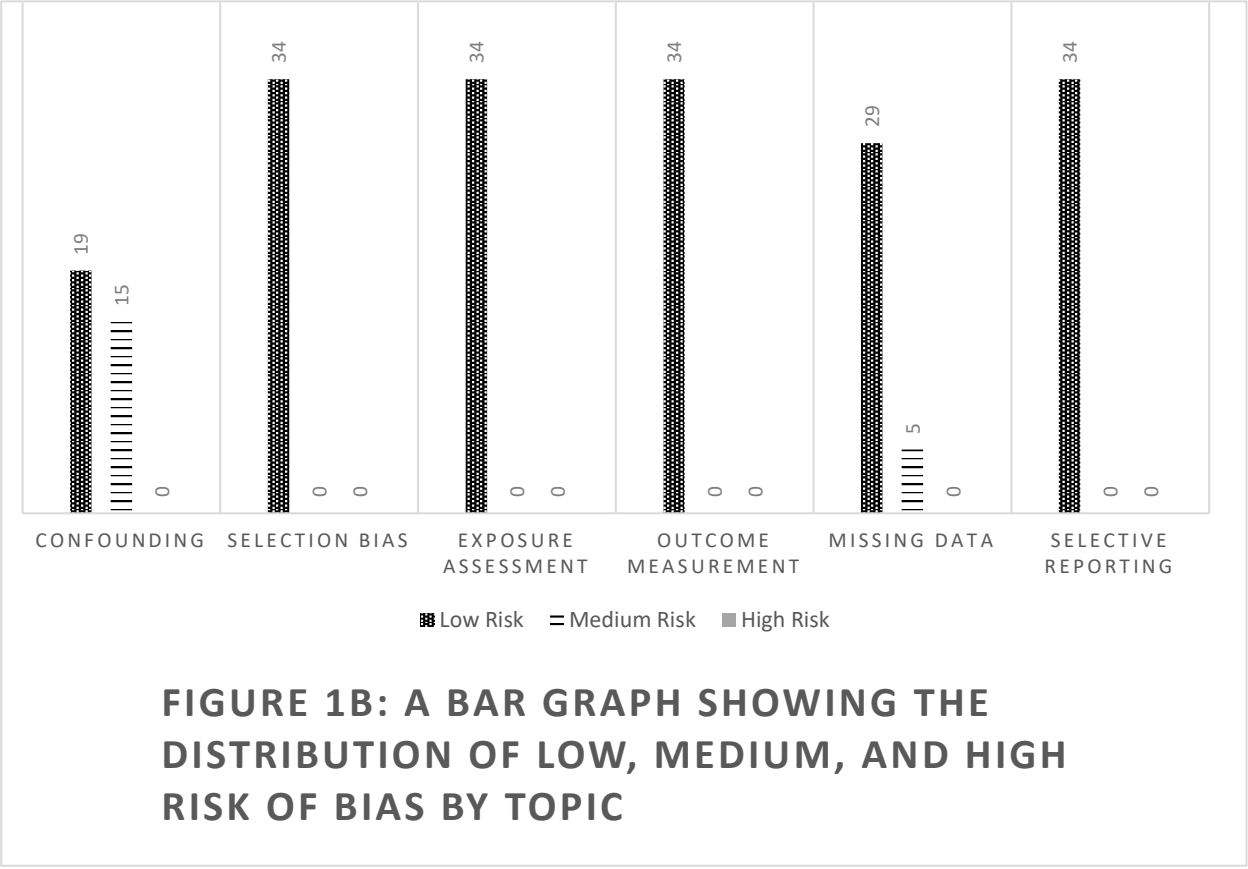


FIGURE 1B: A BAR GRAPH SHOWING THE DISTRIBUTION OF LOW, MEDIUM, AND HIGH RISK OF BIAS BY TOPIC

Supplementary F

Table 1C: A table showing the data extracted from 34 included studies.

Author	Year	Country/ Region	Outcome Variable	Codes	Temperature-Air pollution relationship	Study Design	Statistical Model	Air pollutants (unit)	Temperature variable	Effect estimate	Results
Anderson, et al. [31]	1996	The United Kingdom	Mortality	460-519 (9th)	Seasonality	Time series	Auto-regressive log-linear regression models	8-hour O_3 (ppb); 24-hour NO_2 (ppb)	Warm season (April-September) Cold season (October-March)	% increase (95%CI)/ change in 10-90th percentile	**O_3**: Cold= 6.20 (1.76 to 10. 94); Warm= 5.41 (0.35 to 10.73). **NO_2**: Cold= -0.25(-2.54 to 2.10); Warm= -2.90 (-7.55 to 1.99)
Anderson, et al. [51]	1998	The United Kingdom	Hospital admissions	493 (9th)	Seasonality	Time series	Auto-regressive log-linear regression models	8-hour O_3 (ppb); 24-hour NO_2 (ppb)	Warm season (April-September) Cold season (October-March)	%increase (95%CI)/10ppb	**O_3:** Cold= -3.17(-5.44 to -0.84); Warm= 2.21(0.62 to 3.82). **NO_2:** Cold= 1.30(0.38 to 2.23); Warm= 1.15(-0.25 to 3.67)
Atkinson, et al. [53]	1999	The United Kingdom	Hospital admissions	460-519 (9th)	Seasonality	Time series	Auto-regressive log-linear regression models	24-hour PM_{10} (µg/m3); 8-hour O_3 (ppb); 1-hour NO_2 (ppb)	Warm season (April- September)	% change (95%CI)/ change in 10-90th percentile	**NO_2**: 4.63 (1.87 to 7.46); **PM_{10}:** 6.45 (3.34 to 9.65).
Chen, et al. [48]	2016	Australia	Hospital admissions	J45 and J46 (10th)	Seasonality	Case-crossover	Conditional logistic regression	$PM_{2.5}$ (µg/m^3). PM_{10} (µg/m^3). NO_2 (ppb). O_3 (ppb)	Warm season (October-March) Cold season (April-September)	OR (95%CI)/10-unit increase	**$PM_{2.5}$:** Cold= 1.240 (1.116 to 1.378) Warm= 1.187 (1.054 to 1.337); **PM_{10}:** Cold= 1.067 (1.023 to 1.112); Warm= 0.999 (0.961 to 1.037). **NO_2:** Cold= 1.091 (1.048 to 1.136); Warm= 1.056 (1.008 to 1.105). **O_3**: Cold= 0.980 (0.912 to 1.053); Warm= 1.100 (1.053 to 1.148)
Cheng and Kan [23]	2012	China	Mortality	460-519 (9th); J00-J98 (10th)	Effect modification (percentile)	Time series	GAM	PM_{10} (µg/m^3); O_3 (µg/m^3); NO_2 (µg/m^3)	High temperatures (95th percentile) Low temperature (5th percentile)	% change (95%CI)/10 µg/m^3	**PM_{10}:** Low= 0.46 (0.21 to 0.72); High= 0.44 (0.21 to 0.82). **NO_2:** Low= 1.25 (0.71 to 1.79); High= 1.04 (0.33 to 1.75).

											O_3: Low= 1.78 (0.84 to 2.73); High= 0.54 (0.15 to 0.92).
Cheng, et al. [38]	2014	Taiwan	Hospital admissions	493 (9th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Case-crossover	Conditional logistic regression	$PM_{2.5}$ ($\mu g/m^3$)	High temperature (≥23°C) Low temperature (<23°C)	OR (95%CI)/17.46 $\mu g/m^3$	High = 1.12 (1.06 to 1.18). Low= 1.03 (1.00 to 1.08)
Cheng, et al. [41]	2015	Taiwan	Hospital admissions	490-494 and 496 (9th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Case-crossover	Conditional logistic regression	$PM_{2.5}$ ($\mu g/m^3$). PM_{10} ($\mu g/m^3$).	High temperature (≥25°C) Low temperature (<25°C)	% increase (95%CI)/10$\mu g/m^3$.	**$PM_{2.5}$.** Asthma: ≥25°C=2.0 (-2.0 to 3.0); <25°C=10.0 (6.0 to 13.0); COPD: ≥25°C= 0.0 (-2.0 to 3.0); <25°C= 11.0 (9.0 to 13.0). **PM_{10}.** Asthma: ≥25°C=2.0 (0.0 to 4.0); <25°C=4.0 (3.0 to 6.0). COPD: ≥25°C= 1.0 (0.0 to 2.0); <25°C=5.0 (3.0 to 6.0).
Hansen, et al. [47]	2012	Australia	Hospital admissions	J00-J99 (10th)	Seasonality	Case-crossover	Conditional logistic regression	$PM_{2.5}$ ($\mu g/m^3$); PM_{10} ($\mu g/m^3$)	Warm season (October-March) Cold season (April-September)	% increase in odds (95%CI)/ 10 $\mu g/m^3$	**$PM_{2.5}$**: Cold= -0.86 (-4.66 to 3.08) Warm= 1.85 (-2.49 to 6.38). **PM_{10}:** Cold= 1.10 (-0.22 to 2.43); Warm= 0.27 (-1.14 to 1.69)
Lee, et al. [43]	2007	Taiwan	Hospital admissions	490-492, 494, 496 (9th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Case-crossover	Conditional logistic regression	PM_{10} ($\mu g/m^3$); NO_2 (ppb); O_3 (ppb)	High temperature (≥25°C) Low temperature (<25°C)	OR (95% CI)/change in 10-90th percentile	**PM_{10}:** ≥ 25°C= 1.273 (1.153 to 1.406); <25°C= 1.503 (1.375 to 1.643). **NO_2**: ≥ 25°C= 1.241(1.117 to 1.379); <25°C= 1.975 (1.785 to 2.186). **O_3:** ≥ 25°C= 1.266 (1.196 to 1.344); <25°C= 1.222 (1.108 to 1.347).
Li, et al. [29]	2011	China	Mortality	J00-J99 (10th)	Effect modification (mean, median, statistically	Time series	GAM	PM_{10} ($\mu g/m^3$)	Mean temperature at 14.65°C and 20°C cut off (high vs. low)	% change (95%CI)/10 $\mu g/m^3$	Cut-off= 14.65°C: Low= 0.45 (-0.17 to 1.07); High= 0.73 (-0.15 to 1.62). Cut-off= 20°C: Low= 0.46 (-0.12 to 1.04); High= 0.74 (-0.33 to 1.82).

					determined cut-offs, or visual turning point).						
Li, et al. [60]	2014	China	Mortality	J00-J99 (10th)	Effect modification (percentile)	Time series	GAM	PM_{10} (µg/m^3)	Low Temperature (5th percentile) High Temperature (95th percentile)	Excess RR (%) (95%CI)/ 10 µg/m^3	Low= 1.97 (-1.10 to 5.12); High= 6.09 (2.42 to 9.89).
Li, et al. [26]	2015	China	Mortality	J00-J99 (10th)	Effect modification (percentile)	Time series	GAM	$PM_{2.5}$ (µg/m^3)	Low temperature (25th percentile) High temperature (75th percentile)	% Change (95%CI)/ 10 µg/m^3	Low= -0.57 (-1.87 to 1.91); High= 1.7 (0.92 to 3.33)
Medina-Ramon, et al. [61]	2006	The United States of America	Hospital admissions	490-496 (exc.493) . 9th	Seasonality	Case-crossover	Conditional logistic regression	PM_{10} (µg/m^3); O_3 (ppb)	Warm season (May-September) Cold season (October-April)	% increase/ 5-ppb or 10-µg/m^3 (95% CI)	**PM_{10}:** Warm= 1.47 (0.93 to 2.01); Cold= 0.10 (-0.30 to 0.49). **O_3:** Warm= 0.48 (0.30 to 0.66); Cold= 0.14 (-0.13 to 0.42).
Meng, et al. [22]	2012	China	Mortality	J00-J98 (10th)	Effect modification (percentile)	Time series	GAM	PM_{10} (µg/m^3)	Low temperature (5th percentile) High temperature (95th percentile)	% change (95%CI)/ 10 µg/m^3	**Guangzhou**: Low= 3.05 (1.11 to 5.00); High= 3.21 (1.80 to 4.61). **Hangzhou**: Low= 1.77 (0.69 to 2.85); High= 1.84 (0.13 to 3.54). **Shanghai**: Low= -0.40 (-0.95 to 0.14); High= 0.37 (-0.42 to 1.16). **Shenyang**: Low= 0.84 (-0.11 to 1.78); High= 1.09 (0.29 to 1.89). **Suzhou**: Low= -1.04 (-2.38 to 0.03); High= 1.23 (-0.37 to 2.82). **Taiyuan**: Low= 1.45 (0.22 to 2.68); High= 0.34 (-1.21 to 1.89). **Tianjin**: Low= 1.59 (-1.41 to 4.60); High= 2.53 (-0.67 to 5.74). **Wuhan:** Low= -0.91 (-1.96 to 0.14); High= 4.35 (3.02 to 5.69).

Qian, et al. [25]	2008	China	Mortality	460-519 (9th) and J00-J98 (10th)	Effect modification (percentile)	Time series	GAM	PM_{10} (μg/m^3); O_3 (μg/m^3); NO_2 (μg/m^3)	Low temperature (5th percentile) High temperature (95th percentile)	%change (95%CI)/ 10 μg/m^3	**PM_{10}:** Low= 1.07 (-0.76 to 2.95); High= 1.15 (-3.54 to 6.07). **NO_2:** Low= 3.17 (-2.13 to 8.75); High= 7.68 (-12.36 to 32.30). **O_3:** Low= 1.14 (-2.88 to 5.33); High= 2.98 (-0.79 to 6.90).
Qin, et al. [24]	2017	China	Mortality	J00-J99 (10th)	Effect modification (percentile)	Time series	GAM	PM_{10} (μg/m^3); NO_2 (μg/m^3)	Low temperature (5th percentile) High temperature (95th percentile)	% increase (95%CI)/ 10 μg/m^3	**PM_{10}**: Low= -0.11 (-1.93 to 1.74); High= 7.18 (2.44 to 12.13). **NO_2:** Low= -1.94 (-8.50 to 4.66); High= 25.58 (3.66 to 47.99).
Qiu, et al. [35]	2018	China	Hospital admissions	J41-44 (10th)	Effect modification (percentile)	Time series	GAM	PM_{10} (μg/m^3); NO_2 (μg/m^3)	Low temperature (20th percentile) High temperature (80th percentile)	% change (95%CI)/ 10 μg/m^3	**PM_{10}:** Low= 1.73 (1.22 to 2.25); High= 1.04 (0.08 to 2.00). **NO_2:** Low= 5.59 (3.65 to 7.56); High= 3.50 (1.42 to 5.62).
Ren and Tong [46]	2006	Australia	Hospital admissions	460-519 (9th) and J00-J99 (10th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Time series	GAM	PM_{10} (μg/m^3)	Low temperature (<25.3°C) High temperature (>25.3°)	% change (95%CI)/10 μg/m^3	Low= -1.67 (-3.75 to 0.46); High= 3.84 (1.47 to 6.26).
Rodopoulou, et al. [50]	2014	The United States of America	Hospital admissions	460-466, 480-486, 490-493, 496 (9th)	Seasonality	Time series	Poisson regression models	24-hour $PM_{2.5}$ (μg/m^3); 24-hour PM_{10} (μg/m^3); 8-hour O_3 (ppbv)	Warm season (April-September) Cold season (October-March)	% increase (95%CI)/ 10 μg/m^3 or 10ppbv	**$PM_{2.5}$:** cold= 4.1 (-3.0 to 11.8) warm= -5.9 (-19.6 to 10.1). **PM_{10}:** cold= 1.3.3); Warm= -0.9 (-4.3 to 2.6). **O_3**: Cold= 6.5 (-3.7 to 17.9); Warm= 0.9 (-8.6 to 11.4).
Romieu, et al. [30]	2012	Latin America: Brazil, Chile, Mexico	Mortality	460-519 (9th) and J00-98 (10th)	Seasonality	Time series	DLM	O_3 (μg/m^3)	Warm season Cold season (defined for each city according to variation in temperature)	% change (95%CI)/ 10 μg/m^3	**Sao Paulo:** Cold= -0.18 (-0.67 to 0.32); Warm= 1.45 (1.07 to 1.82). **Rio de Janeiro:** Cold= 0.68 (-0.55 to 1.93); Warm= 0.30 (-0.06 to 0.67). **Santiago**: Cold= 0.10 (-0.16 to 0.37); Warm= 0.22 (-0.1 to 0.54).

											Mexico City: Cold= -0.02 (-0.18 to 0.13); Warm= 0.23 (-0.06 to 0.51). **Monterrey:** Cold= -0.15 (-0.82 to 0.52); Warm= 1.51 (0.47 to 2.56). **Toluca:** Cold= -0.43 (-1.45 to 0.59); Warm= 0.25 (-1.30 to 1.83).
Schouten, et al. [52]	1996	The Netherlands	Hospital admissions	460-519 (9th)	Seasonality	Time series	Poisson regression models	8-hour O_3 ($\mu g/m^3$); 24 hour and 1-hour NO_2 ($\mu g/m^3$)	Warm season (May-October) Cold season (November-April)	RR (95%CI) /100 $\mu g/m^3$	**O_3:** Warm= 1.069 (1.043 to 1.096); Cold= 0.974 (0.948 to 1.001). **NO_2:** Warm= 1.017 (0.983 to 1.051); Cold= 1.057 (1.027 to 1.088).
Sun, et al. [27]	2015	China	Mortality	460-519 (9th) and J00-99 (10th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Time series	GAM	$PM_{2.5}$ ($\mu g/m^3$)	Low temperature (<22°C) High temperature (≥25°C)	% increase (95%CI)/10 $\mu g/m^3$	<22°C= 1.15 (0.51 to 1.79). ≥25°C = 0.26 (-0.38 to 0.91)
Sunyer, et al. [32]	1996	Spain	Mortality	460-519 (9th)	Seasonality	Time series	Poisson regression models	1-hour NO_2 ($\mu g/m^3$); 1-hour O_3 ($\mu g/m^3$)	Warm season (April-September) Cold season (October-March)	RR (95%CI)/100 $\mu g/m^3$	**NO_2:** Warm= 1.047 (0.970 to 1.130); Cold= 0.996 (0.908 to 1.094). **O_3**: Warm= 1.050 (0.927 to 1.188); Cold= 1.140 (0.924 to 1.406).
Tian, et al. [28]	2018	China	Mortality	J00-99 (10th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Time series	GAM	PM_{10} ($\mu g/m^3$)	Low temperature (<15.9°C) High temperature (≥20°C)	% change (95%CI)/ 10 $\mu g/m^3$	**15.9°C:** Low= 0.14 (-0.06 to 0.34); High= 0.45 (-0.13 to 0.78). **20°C:** Low= 0.18 (0.00 to 0.36); High= 0.38 (-0.02 to 0.77)
Tsai, et al. [44]	2006	Taiwan	Hospital admissions	493 (9th)	Effect modification (mean, median, statistically	Case-crossover	Conditional logistic regression	PM_{10} ($\mu g/m^3$); NO_2 (ppb); O_3 (ppb)	Low Temperature (<25°C) High temperature (≥25°C)	OR (95%CI)/ interquartile range increase	**PM_{10}**: ≥25°C= 1.302 (1.155 to 1.467); <25°C= 1.556 (1.398 to 1.371). **NO_2**: ≥25°C= 1.259 (1.111 to 1.427); <25°C= 2.119 (1.875 to 2.394).

					determined cut-offs, or visual turning point).						**O_3**: ≥25°C= 1.290 (1.200 to 1.386); <25°C= 1.206 (1.075 to 1.353).
Tsai, et al. [39]	2013	Taiwan	Hospital admissions	490, 492, 494, and 496 (9th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Case-crossover	Conditional logistic regression	$PM_{2.5}$ (μg/m^3)	Low temperature (<23°C) High temperature (≥23°C)	OR (95%CI)/17.46 μg/m^3	≥23°C= 1.12 (1.08 to 1.16) <23°C= 1.03 (1.00 to 1.07)
Tsai, et al. [40]	2014	Taiwan	Hospital admissions	490, 492-494, and 496 (9th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Case-crossover	Conditional logistic regression	$PM_{2.5}$ (μg/m^3)	Low temperature (<25°C) High temperature (≥25°C)	OR (95%CI)/36.31 μg/m^3	**Asthma:** ≥25°C= 1.08 (0.94 to 1.24) <25°C= 1.40 (1.25 to 1.58). **COPD**: ≥25°C= 1.01 (0.94 to 1.10) <25°C= 1.46 (1.36 to 1.57)
Wang, et al. [36]	2013	China	Hospital admissions	J00-99 (10th)	Effect modification (percentile)	Time series	GAM	PM_{10} (μg/m^3); NO_2 (μg/m^3)	Low temperature (15^{th} percentile) High temperature (85^{th} percentile)	RR (95%CI)/ interquartile range increase	**PM_{10}:** Low= 1.303 (1.226 to 1.384); High= 0.996 (0.929 to 1.069). **NO_2:** Low= 1.383 (1.280 to 1.494); High= 1.004 (0.904 to 1.114).
Wong, et al. [33]	2001	China	Mortality	460-519 (9th)	Seasonality	Time series	Poisson regression models	24-hour PM_{10} (μg/m^3); 8-hour O_3 (μg/m^3); 24-hour NO_2 (μg/m^3)	Warm season (April-September) Cold season (October-March)	RR (95%CI)/change in the $10\text{-}90^{th}$ percentile	**PM_{10}:** Warm= 1.05 (0.98 to 1.12); Cold= 1.06 (1.00 to 1.13). **NO_2**: Warm= 1.05 (0.99 to 1.13); Cold= 1.09 (1.02 to 1.16). **O_3**: Warm= 0.99 (0.94 to 1.05); Cold= 1.08 (1.02 to 1.15).
Yang, et al. [42]	2007	Taiwan	Hospital admissions	493 (9th)	Effect modification (mean, median, statistically determined cut-	Case-crossover	Conditional logistic regression	PM_{10} (μg/m^3); NO_2 (ppb); O_3 (ppb)	Low temperature (<25°C) High temperature (≥25°C)	OR (95%CI)/ interquartile range increase	**PM_{10}**: ≥25°C= 1.046 (0.971 to 1.128); <25°C= 1.048 (1.011 to 1.087). **NO_2**: ≥25°C= 1.178 (1.113 to 1.247); <25°C= 1.128 (1.076 to 1.182).

					offs, or visual turning point).						**O_3:** ≥25°C= 1.029 (0.967 to 1.094); <25°C= 1.179 (1.111 to 1.251).
Yang and Chen [45]	2007	Taiwan	Hospital admissions	490-492, 494, 496 (9th)	Effect modification (mean, median, statistically determined cut-offs, or visual turning point).	Case-crossover	Conditional logistic regression	PM_{10} (µg/m^3); NO_2 (ppb); O_3 (ppb)	Low temperature (<20°C) High temperature (≥20°C)	OR (95%CI)/ interquartile range increase	**PM_{10}**: ≥20°C= 1.133 (1.098 to 1.168); <20°C= 1.035 (0.994 to 1.077). **NO_2:** ≥20°C= 1.193 (1.158 to 1.230); <20°C= 0.972 (0.922 to 1.024). **O_3**: ≥20°C= 1.157(1.118 to 1.197); <20°C=0.936 (0.974 to 1.003).
Yitshak-Sade, et al. [37]	2018	The United States of America	Hospital admissions	460-519 (9th)	Effect modification (percentile)	Time series	Poisson regression models	$PM_{2.5}$ (µg/m^3)	Low temperature (10^{th} percentile) High temperature (90^{th} percentile)	% change (95%CI)/ interquartile range increase	Low= -0.53 (-0.92 to -0.14) High= 1.12 (0.78 to 1.45)
Zhang, et al. [54]	2006	China	Mortality	460-519 (9th) and J00-98 (10th)	Seasonality	Time series	GAM	O_3 (µg/m^3)	Warm season (April-September) Cold season (October-March)	% increase (95%CI)/ 10 µg/m^3	Cold season= 0.95 (-0.71 to 2.60) Warm season= 0.14 (-0.71 to 0.99)
Zhang, et al. [34]	2011	China	Mortality	J00-98 (10th)	Seasonality	Time series	GAM	PM_{10} (µg/m^3); NO_2 (µg/m^3)	Warm season (April- September) Cold season (October-March)	RR (95%CI)/ 10 µg/m^3	**PM10:** Cold= 1.003(1.002 to 1.0031); Warm= 0.999 (0.997 to 1.001). **NO2:** Cold= 1.017 (1.016 to 1.018); Warm= 0.995 (0.989 to 1.001).

Supplementary G: Conversion equations

estimate given (EST_{study})	unit	increment	Conversion formula
%-change	ppb	INC_{ppb}	beta=(ln($ESTs_{tudy}$/100+1))/INC_{ppb} sd=(beta-((ln(1+CI_{low}/100))/INC_{ppb}))/1.96 OR= EXP(beta/ CF*10) CI= EXP((beta±1.96*sd)/CF*10 %-change=(EXP(beta/ CF*10)-1)*100 CI=(EXP((beta±1.96*sd)/CF*10)-1)*100
%-change	µg/m³	$INC_{µg/m³}$ (≠10)	beta=(ln(EST_{study} /100+1))/$INC_{µg/m³}$ sd=(beta-((ln(1+CI_{low}/100))/$INC_{µg/m³}$))/1.96 OR= EXP(beta*10) CI= EXP((beta±1.96*sd)*10 %-change=(EXP(beta*10)-1)*100 CI=(EXP((beta±1.96*sd)*10)-1)*100
OR, HR, RR	ppb	INC_{ppb}	beta=ln(EST_{study})/INC_{ppb} sd=(beta-(ln(CI_{low})/INC_{ppb}))/1.96 OR=EXP(beta/CF*10) CI=EXP((beta±1.96*sd)/CF*10 %-change=(EXP(beta/CF*10)-1)*100 CI=(EXP((beta±1.96*sd)/CF*10)-1)*100
OR, HR, RR	µg/m³	$INC_{µg/m³}$	beta=ln(EST_{study})/$INC_{µg/m³}$ sd=(beta-(ln(CI_{low})/$INC_{µg/m³}$))/1.96 OR= EXP(beta*10) CI= EXP((beta±1.96*sd)*10 %-change=(EXP(beta*10)-1)*100 CI=(EXP((beta±1.96*sd)*10)-1)*100

CF, conversion factor (1.91 for NO_2, 2 for ozone); CI, confidence interval; CI_{low}, lower confidence interval given in study; EST_{study}, estimate given in study; HR, hazard ratio; INC, increment; OR, odds ratio; ppb, parts per billion; RR, relative risk; sd, standard deviation

Supplementary H: Figures showing the results of outlier analysis

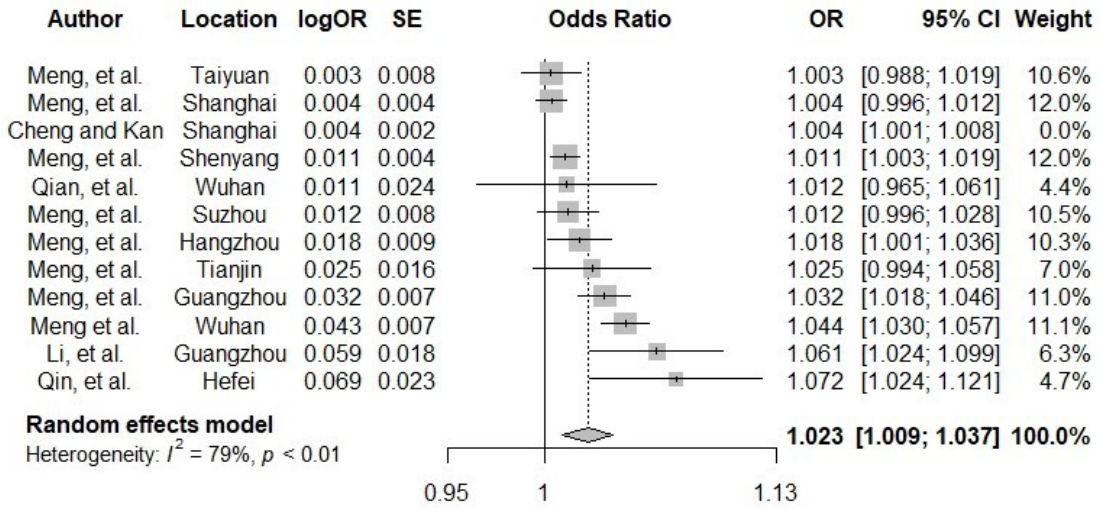


Figure 1c: A forest plot showing the effect of PM_{10} (per 10µg/m^3) when modified by high temperatures on respiratory mortality after the exclusion of outliers using the SJ estimator.

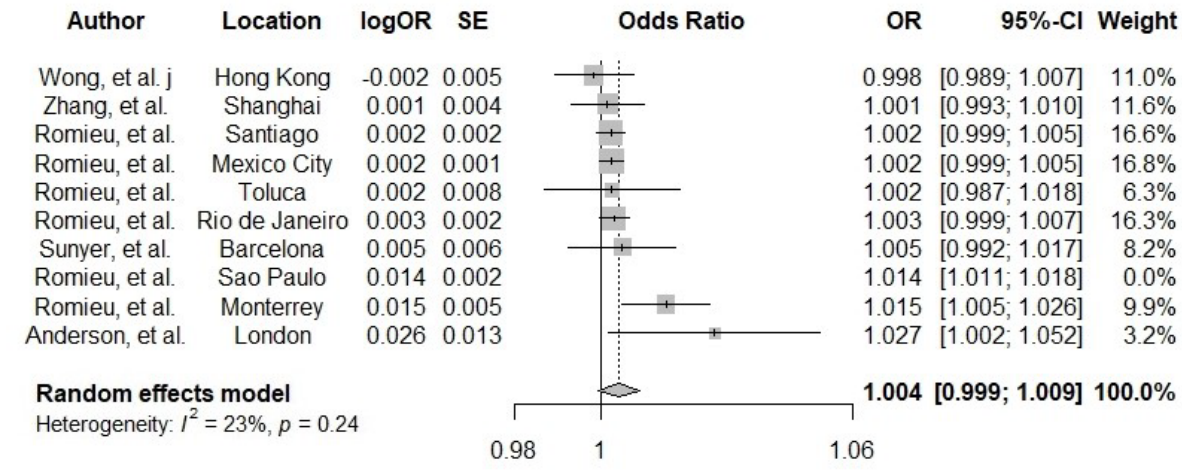


Figure 1d: A forest plot showing the effect of O_3 (per 10µg/m^3) when modified by the warm season on respiratory mortality after the exclusion of outliers using the SJ estimator.

Publication 2

The Influence of Short-Term Weather Parameters and Air Pollution on Adolescent Airway Inflammation. (2)

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]

Tamara Schikowski[1]

1. IUF—Leibniz Research Institute for Environmental Medicine

2. Department of Epidemiology, Medical Research School, Heinrich-Heine-University

3. School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan 250100, China

4. Department of Pediatrics, Research Institute, Marien-Hospital Wesel

5. Department of Pediatrics, Dr. von Hauner Children's Hospital Munich, University Hospital, LMU Munich

6. Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine Collegium Medicum, University of Warmia and Mazury

7. Department of Paediatrics, Evangelisches Krankenhaus

8. Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich

9. German Center for Lung Research (DZL)

10. Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne

11. Institute of Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health

12. School of Public Health & Preventive Medicine, Monash University

Reference: Areal AT, Singh N, Zhao Q, Berdel D, Koletzko S, von Berg A, Gappa M, Heinrich J, Standl M, Abramson MJ, Schikowski T. The Influence of Short-Term Weather Parameters and Air Pollution on Adolescent Airway Inflammation. International Journal of Environmental Research and Public Health. 2023 Sep 25;20(19):6827

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

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 Female Male	 1050 (51%) 992 (49%)	 609 (51%) 582 (49%)	 441 (52%) 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 Yes No NA	 643 (31.5%) 1397 (68.4%) 2 (0.1%)	 388 (32.58%) 801 (67.25%) 2 (0.17%)	 255 (29.96%) 596 (70.04%) 0	0.2
Maximal parental education Low (<10 years) Medium (=10 years) High (>10 years) NA	 118 (5.78%) 539 (26.40%) 1380 (67.58%) 5 (0.24%)	 46 (3.86%) 210 (17.63%) 932 (78.25%) 3 (0.25%)	 72 (8.46%) 329 (38.66%) 448 (52.64%) 2 (0.24%)	<0.001
Body Mass Index (Kg/m^2) Low (<18.5) Normal (18.5–24.9) High (>25)	 414 (20.27%) 1430 (70.03%) 198 (9.70%)	 257 (21.58%) 839 (70.45%) 95 (7.98%)	 157 (18.45%) 591 (69.45%) 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 Warm Cold	 1315 (64%) 727 (36%)	 776 (65%) 415 (35%)	 539 (63%) 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.

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The influence of short-term weather and air pollution on adolescent airway inflammation.

Ashtyn T. 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*], Tamara Schikowski[1*]

1. IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
2. Department of Epidemiology, Medical Research School, Heinrich-Heine-University, Düsseldorf, Germany
3. School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China
4. Research Institute, Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany
5. Department of Pediatrics, Dr. von Hauner Children's Hospital Munich, University Hospital, LMU Munich, Munich, Germany
6. Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine Collegium Medicum University of Warmia and Mazury, Olsztyn, Poland
7. Department of Paediatrics, Evangelisches Krankenhaus, Düsseldorf, Germany
8. Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany;
9. German Center for Lung Research (DZL), Munich, Germany
10. Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia
11. Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany
12. School of Public Health & Preventive Medicine, Monash University, Melbourne, Australia

* shared last author

Correspondence to:

Dr Tamara Schikowski
Arbeitsgruppenleiterin
Umweltepidemiologie von Lunge, Gehirn und Hautalterung
IUF – Leibniz Research Institute for Environmental Medicine
Auf'm Hennekamp 50
D-40225 Düsseldorf
phone: +49 211 3389 341
E-Mail: Tamara.Schikowski@IUF-Duesseldorf.de

Supplementary material

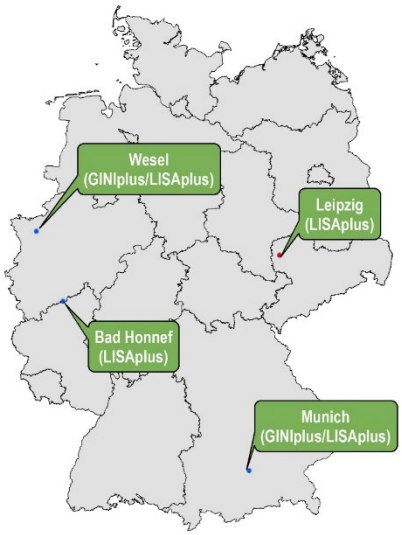

Figure S1. A map showing the study areas of the GINIplus and LISA birth cohorts in Germany.

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.

	Female		Male	
	Percentage change (95% CI)[2*]	p-value[1*]	Percentage change (95% CI)[2*]	p-value[1*]
RH	-0.01 (-0.03, 0.01)	0.232	-0.01 (-0.03, 0.02)	0.586
$PM_{2.5}$	0.07 (-0.50, 0.64)	0.814	0.20 (-0.43, 0.84)	0.526
Tmax	0.18 (-0.55, 0.91)	0.632	0.57 (-0.28, 1.42)	0.192
RH	-0.02 (-0.03, 0.00)	0.085	-0.01 (-0.03, 0.01)	0.263
$PM_{2.5}$	0.07 (-0.50, 0.64)	0.814	0.23 (-0.40, 0.87)	0.477
Tmin	0.01 (-0.86, 0.89)	0.982	0.74 (-0.27, 1.75)	0.151
RH	-0.01 (-0.03, 0.01)	0.166	-0.01 (-0.03, 0.01)	0.459
$PM_{2.5}$	0.07 (-0.50, 0.64)	0.805	0.22 (-0.41, 0.85)	0.503
Tmean	0.17 (-0.66, 0.99)	0.694	0.66 (-0.29, 1.62)	0.172
RH	-0.01 (-0.04, 0.01)	0.235	0.00 (-0.03, 0.02)	0.740
O_3	-0.04 (-0.29, 0.22)	0.782	0.06 (-0.21, 0.33)	0.671
Tmax	0.22 (-0.54, 0.99)	0.567	0.55 (-0.35, 1.45)	0.232
RH	-0.02 (-0.04, 0.00)	0.129	-0.01 (-0.03, 0.01)	0.457
O_3	-0.01 (-0.26, 0.24)	0.907	0.06 (-0.20, 0.33)	0.651
Tmin	0.02 (-0.88, 0.94)	0.959	0.69 (-0.35, 1.74)	0.194
RH	-0.01 (-0.04, 0.01)	0.181	-0.01 (-0.03, 0.02)	0.634
O_3	-0.03 (-0.28, 0.22)	0.811	0.06 (-0.21, 0.33)	0.668
Tmean	0.20 (-0.66, 1.07)	0.643	0.64 (-0.35, 1.64)	0.209
RH	-0.01 (-0.03, 0.01)	0.218	-0.01 (-0.03, 0.02)	0.495
NO_2	0.20 (-0.32, 0.72)	0.459	0.31 (-0.25, 0.86)	0.279
Tmax	0.21 (-0.52, 0.94)	0.577	0.65 (-0.20, 1.51)	0.136
RH	-0.02 (-0.03, 0.00)	0.073	-0.01 (-0.03, 0.01)	0.172
NO_2	0.19 (-0.33, 0.72)	0.474	0.35 (-0.21, 0.91)	0.227
Tmin	0.05 (-0.83, 0.94)	0.909	0.86 (-0.15, 1.89)	0.097
RH	-0.01 (-0.03, 0.01)	0.151	-0.01 (-0.03, 0.01)	0.363
NO_2	0.20 (-0.32, 0.72)	0.455	0.32 (-0.23, 0.88)	0.256
Tmean	0.20 (-0.62, 1.03)	0.633	0.77 (-0.19, 1.74)	0.151

[1] p-value <0.050 in bold
[2] per 5% increase in RH at Lag01
[*]Adjusted for study location, season, chronic respiratory disease

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.

	Underweight		Normal Weight		Overweight	
	Percentage change (95% CI)[2*]	p-value[1*]	Percentage change (95% CI)[2*]	p-value[1*]	Percentage change (95% CI)[2*]	p-value[1*]
RH	-0.02 (-0.05, 0.02)	0.404	-0.01 (-0.03, 0.01)	0.511	-0.02 (-0.07, 0.03)	0.485
$PM_{2.5}$	-0.11 (-1.11, 0.91)	0.837	0.34 (-0.17, 0.85)	0.194	-0.18 (-1.52, 1.19)	0.801
Tmax	0.15 (-1.20, 1.52)	0.830	0.29 (-0.37, 0.95)	0.392	0.64 (-1.21, 2.51)	0.502
RH	-0.02 (-0.05, 0.01)	0.313	-0.01 (-0.03, 0.01)	0.233	-0.03 (-0.07, 0.01)	0.203
$PM_{2.5}$	-0.09 (-1.10, 0.93)	0.857	0.35 (-0.16, 0.86)	0.182	-0.18 (-1.53, 1.20)	0.802
Tmin	0.37 (-1.22, 1.99)	0.652	0.22 (-0.57, 1.01)	0.586	0.26 (-1.86, 2.43)	0.811
RH	-0.02 (-0.05, 0.02)	0.381	-0.01 (-0.02, 0.01)	0.405	-0.02 (-0.07, 0.02)	0.347
$PM_{2.5}$	-0.10 (-1.11, 0.91)	0.842	0.34 (-0.17, 0.86)	0.186	-0.17 (-1.52, 1.21)	0.812
Tmean	0.24 (-1.27, 1.78)	0.756	0.32 (-0.43, 1.07)	0.403	0.52 (-1.52, 2.60)	0.621
RH	-0.02 (-0.06, 0.02)	0.398	-0.01 (-0.03, 0.01)	0.464	-0.01 (-0.06, 0.05)	0.812
O_3	-0.04 (-0.44, 0.36)	0.850	-0.03 (-0.26, 0.20)	0.796	0.33 (-0.24, 0.90)	0.262
Tmax	0.19 (-1.23, 1.62)	0.799	0.35 (-0.34, 1.05)	0.320	0.29 (-1.63, 2.25)	0.767
RH	-0.02 (-0.05, 0.02)	0.326	-0.01 (-0.03, 0.01)	0.252	-0.01 (-0.06, 0.04)	0.658
O_3	-0.05 (-0.44, 0.35)	0.808	-0.01 (-0.24, 0.21)	0.919	0.37 (-0.20, 0.94)	0.209
Tmin	0.43 (-1.22, 2.10)	0.613	0.23 (-0.59, 1.06)	0.583	-0.15 (-2.35, 2.10)	0.894
RH	-0.02 (-0.05, 0.02)	0.380	-0.01 (-0.03, 0.01)	0.368	-0.01 (-0.06, 0.04)	0.720
O_3	-0.04 (-0.44, 0.35)	0.831	-0.03 (-0.25, 0.20)	0.820	0.34 (-0.23, 0.92)	0.240
Tmean	0.29 (-1.29, 1.89)	0.721	0.37 (-0.41, 1.16)	0.350	0.12 (-2.00, 2.30)	0.911
RH	-0.02 (-0.05, 0.02)	0.360	-0.01 (-0.03, 1.01)	0.423	-0.02 (-0.07, 0.03)	0.433
NO_2	0.25 (-0.61, 1.12)	0.569	0.31 (-0.15, 0.78)	0.185	0.57 (-0.69, 1.84)	0.380
Tmax	0.18 (-1.18, 1.55)	0.800	0.36 (-0.30, 1.03)	0.291	0.72 (-1.13, 2.60)	0.449
RH	-0.02 (-0.05, 0.01)	0.267	-0.01 (-0.03, 0.00)	0.146	-0.03 (-0.07, 0.01)	0.169
NO_2	0.28 (-0.59, 1.15)	0.534	0.32 (-0.15, 0.79)	0.181	0.58 (-0.70, 1.88)	0.377
Tmin	0.45 (-1.16, 2.08)	0.587	0.29 (-0.59, 1.06)	0.583	0.49 (-1.67, 2.69)	0.661
RH	-0.02 (-0.05, 0.02)	0.337	-0.01 (-0.03, 0.01)	0.308	-0.02 (-0.07, 0.02)	0.307
NO_2	0.26 (-0.61, 1.13)	0.558	0.32 (-0.14, 0.78)	0.178	0.59 (-0.68, 1.87)	0.368
Tmean	0.29 (-1.23, 1.84)	0.712	0.40 (-0.35, 1.15)	0.300	0.68 (-1.37, 2.78)	0.520

[1] p-value <0.050 in bold
[2] per 5% increase in RH at Lag01
[*]Adjusted for study location, season, chronic respiratory disease

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.

	Low		Medium		High	
	Percentage change (95% CI)[2*]	p-value[1*]	Percentage change (95% CI)[2*]	p-value[1*]	Percentage change (95% CI)[2*]	p-value[1*]
RH	0.03 (-0.04, 0.10)	0.387	0.00 (-0.04, 0.03)	0.760	-0.01 (-0.03, 0.01)	0.163
$PM_{2.5}$	0.45 (-1.32, 2.25)	0.625	0.58 (-0.23, 1.41)	0.162	0.01 (-0.52, 0.54)	0.975
Tmax	1.64 (-0.91, 4.27)	0.212	0.69 (-0.47, 1.86)	0.247	0.11 (-0.57, 0.78)	0.759
RH	0.01 (-0.04, 0.07)	0.677	-0.01 (-0.04, 0.01)	0.341	-0.01 (-0.03, 0.00)	0.080
$PM_{2.5}$	0.51 (-1.25, 2.31)	0.573	0.60 (-0.22, 1.43)	0.150	0.02 (-0.52, 0.55)	0.955
Tmin	1.54 (-1.32, 4.48)	0.296	0.44 (-0.94, 1.84)	0.537	0.14 (-0.66, 0.95)	0.728
RH	0.02 (-0.04, 0.09)	0.478	-0.01 (-0.04, 0.02)	0.575	-0.01 (-0.03, 0.00)	0.134
$PM_{2.5}$	0.47 (-1.30, 2.27)	0.605	0.60 (-0.22, 1.42)	0.154	0.01 (-0.52, 0.55)	0.965
Tmean	1.70 (-1.08, 4.55)	0.236	0.66 (-0.64, 1.99)	0.320	0.15 (-0.61, 0.91)	0.699
RH	0.03 (-0.06, 0.11)	0.544	-0.01 (-0.04, 0.02)	0.570	-0.01 (-0.03, 0.01)	0.256
O_3	-0.14 (-1.09, 0.81)	0.770	-0.12 (-0.50, 0.26)	0.538	0.03 (-0.20, 0.25)	0.809
Tmax	2.16 (-0.54, 4.95)	0.121	0.82 (-0.41, 2.06)	0.192	0.09 (-0.62, 0.80)	0.802
RH	0.01 (-0.07, 0.09)	0.883	-0.02 (-0.05, 0.01)	0.269	-0.01 (-0.03, 0.01)	0.189
O_3	-0.05 (-0.97, 0.89)	0.921	-0.07 (-0.44, 0.30)	0.727	0.03 (-0.19, 0.25)	0.810
Tmin	1.95 (-1.03, 5.02)	0.204	0.45 (-0.98, 1.90)	0.540	0.12 (-0.72, 0.96)	0.784
RH	0.02 (-0.06, 0.10)	0.665	-0.01 (-0.05, 0.02)	0.416	-0.01 (-0.03, 0.01)	0.232
O_3	-0.10 (-1.04, 0.84)	0.828	0.10 (-0.47, 0.28)	0.609	0.03 (-0.20, 0.25)	0.825
Tmean	2.24 (-0.67, 5.23)	0.135	0.75 (-0.61, 2.14)	0.282	0.13 (-0.66, 0.93)	0.746
RH	0.02 (-0.06, 0.09)	0.646	-0.01 (-0.04, 0.02)	0.613	-0.01 (-0.03, 0.01)	0.159
NO_2	1.10 (-0.69, 2.93)	0.232	0.74 (-0.13, 1.62)	0.095	0.14 (-0.30, 0.59)	0.531
Tmax	1.94 (-0.61, 4.55)	0.140	0.82 (-0.34, 2.00)	0.169	0.13 (-0.54, 0.81)	0.701
RH	-0.01 (-0.07, 0.05)	0.849	-0.02 (-0.05, 0.01)	0.201	-0.01 (-0.03, 0.00)	0.073
NO_2	1.20 (-0.59, 3.03)	0.192	0.71 (-0.16, 1.60)	0.109	0.15 (-0.30, 0.61)	0.505
Tmin	1.95 (-0.92, 4.89)	0.187	0.56 (-0.84, 1.97)	0.438	0.19 (-0.62, 1.01)	0.644
RH	0.01 (-0.06, 0.08)	0.800	-0.01 (-0.04, 0.02)	0.414	-0.01 (-0.03, 0.00)	0.128
NO_2	1.15 (-0.64, 2.97)	0.212	0.74 (-0.13, 1.62)	0.098	0.15 (-0.30, 0.60)	0.517
Tmean	2.10 (-0.66, 4.95)	0.140	0.80 (-0.51, 2.14)	0.233	0.19 (-0.58, 0.95)	0.634

[1] p-value <0.050 in bold
[2] per 5% increase in RH at Lag01
[*]Adjusted for study location, season, chronic respiratory disease

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.

	CRD: Yes		CRD: No	
	Percentage change (95% CI)[2*]	p-value[1*]	Percentage change (95% CI)[2*]	p-value[1*]
RH	-0.03 (-0.06, 0.00)	0.070	0.00 (-0.02, 0.02)	0.791
$PM_{2.5}$	0.15 (-0.76, 1.08)	0.742	0.24 (-0.23, 0.72)	0.312
Tmax	0.55 (-0.65, 1.76)	0.369	0.17 (-0.45, 0.79)	0.601
RH	-0.03 (-0.06, -0.01)	**0.016**	0.00 (-0.02, 0.01)	0.934
$PM_{2.5}$	0.19 (-0.73, 1.12)	0.689	0.24 (-0.23, 0.72)	0.312
Tmin	0.94 (-0.49, 2.39)	0.197	-0.04 (-0.77, 0.69)	0.908
RH	-0.03 (-0.06, -0.00)	**0.050**	0.00 (-0.02, 0.02)	0.920
$PM_{2.5}$	0.17 (-0.75, 1.09)	0.721	0.25 (-0.22, 0.72)	0.305
Tmean	0.79 (-0.55, 2.15)	0.249	0.10 (-0.59, 0.80)	0.771
RH	-0.02 (-0.06, 0.01)	0.256	0.00 (-0.02, 0.02)	0.894
O_3	0.21 (-0.18, 0.60)	0.286	-0.09 (-0.29, 0.12)	0.407
Tmax	0.38 (-0.87, 1.64)	0.555	0.28 (-0.37, 0.94)	0.399
RH	-0.02 (-0.05, 0.01)	0.169	0.00 (-0.02, 0.01)	0.617
O_3	0.20 (-0.19, 0.58)	0.311	-0.06 (-0.26, 0.14)	0.558
Tmin	0.75 (-0.71, 2.23)	0.316	0.03 (-0.74, 0.80)	0.946
RH	-0.02 (-0.05, 0.01)	0.240	0.00 (-0.02, 0.02)	0.747
O_3	0.20 (-0.19, 0.59)	0.310	-0.08 (-0.28, 0.13)	0.460
Tmean	0.61 (-0.78, 2.02)	0.390	0.21 (-0.52, 0.95)	0.570
RH	-0.03 (-0.06, 0.00)	0.091	0.00 (-0.02, 0.02)	0.980
NO_2	-0.10 (-0.91, 0.72)	0.806	0.51 (0.09, 0.94)	**0.017**
Tmax	0.57 (-0.63, 1.78)	0.355	0.26 (-0.36, 0.89)	0.407
RH	-0.03 (-0.06, 0.00)	**0.021**	0.00 (-0.02, 0.01)	0.650
NO_2	-0.06 (-0.88, 0.76)	0.879	0.51 (0.08, 0.94)	**0.020**
Tmin	0.92 (-0.51, 2.37)	0.208	0.11 (-0.63, 0.85)	0.777
RH	-0.03 (-0.06, 0.00)	0.064	0.00 (-0.02, 0.02)	0.863
NO_2	-0.09 (-0.90, 0.73)	0.835	0.51 (0.09, 0.94)	**0.018**
Tmean	0.79 (-0.55, 2.16)	0.248	0.23 (-0.47, 0.94)	0.515

[1] p-value <0.050 in bold
[2] per 5% increase in RH at Lag01
[*]Adjusted for study location, season

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.

	Wesel		Munich	
	Percentage change (95% CI)[2*]	p-value[1*]	Percentage change (95% CI)[2*]	p-value[1*]
RH	0.01 (-0.02, 0.03)	0.527	-0.02 (-0.04, 0.00)	0.068
$PM_{2.5}$	0.68 (0.01, 1.35)	**0.049**	-0.14 (-0.71, 0.43)	0.622
Tmax	0.26 (-0.62, 1.14)	0.569	0.22 (-0.53, 0.98)	0.560
RH	0.01 (-0.02, 0.03)	0.628	-0.02 (-0.04, -0.01)	**0.012**
$PM_{2.5}$	0.69 (0.01, 1.36)	**0.046**	-0.13 (-0.70, 0.44)	0.645
Tmin	0.23 (-0.75, 1.21)	0.647	0.21 (-0.73, 1.16)	0.656
RH	0.01 (-0.02, 0.03)	0.523	-0.02 (-0.04, 0.00)	**0.036**
$PM_{2.5}$	0.69 (0.02, 1.36)	**0.045**	-0.14 (-0.71, 0.43)	0.629
Tmean	0.34 (-0.60, 1.30)	0.478	0.21 (-0.66, 1.09)	0.635
RH	0.00 (-0.02, 0.03)	0.695	-0.02 (-0.04, 0.00)	0.104
O_3	0.04 (-0.24, 0.33)	0.771	-0.02 (-0.28, 0.23)	0.859
Tmax	0.21 (-0.70, 1.13)	0.647	0.28 (-0.51, 1.08)	0.483
RH	0.00 (-0.02, 0.03)	0.797	-0.02 (-0.05, -0.00)	**0.043**
O_3	0.05 (-0.23, 0.34)	0.708	-0.02 (-0.27, 0.24)	0.893
Tmin	0.11 (-0.88, 1.11)	0.826	0.28 (-0.70, 1.28)	0.574
RH	0.00 (-0.02, 0.03)	0.718	-0.02 (-0.04, 0.00)	0.071
O_3	0.04 (-0.24, 0.33)	0.770	-0.02 (-0.28, 0.24)	0.881
Tmean	0.26 (-0.71, 1.24)	0.604	0.28 (-0.64, 1.21)	0.549
RH	0.00 (-0.02, 0.03)	0.889	-0.02 (-0.04, 0.00)	0.067
NO_2	0.73 (-0.16, 1.63)	0.111	0.18 (-0.25, 0.61)	0.417
Tmax	0.39 (-0.50, 1.29)	0.394	0.27 (-0.48, 1.03)	0.484
RH	0.00 (-0.02, 0.02)	0.848	-0.02 (-0.04, -0.01)	**0.011**
NO_2	0.70 (-0.19, 1.60)	0.123	0.19 (-0.24, 0.63)	0.381
Tmin	0.30 (-0.69, 1.30)	0.555	0.32 (-0.63, 1.28)	0.508
RH	0.00 (-0.02, 0.02)	0.970	-0.02 (-0.04, -0.00)	**0.036**
NO_2	0.73 (-0.16, 1.64)	0.108	0.18 (-0.25, 0.61)	0.403
Tmean	0.45 (-0.52, 1.42)	0.363	0.29 (-0.59, 1.17)	0.524

[1] p-value <0.050 in bold
[2] per 5% increase in RH at Lag01
[*]Adjusted for study season, chronic respiratory disease

Publication 3

The association of relative humidity and air pollution interaction on lung function in adolescents. (3)

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]

Tamara Schikowski[1]

1. IUF—Leibniz Research Institute for Environmental Medicine

2. Department of Epidemiology, Medical Research School, Heinrich-Heine-University

3. School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan 250100, China

4. Department of Pediatrics, Research Institute, Marien-Hospital Wesel

5. Department of Pediatrics, Dr. von Hauner Children's Hospital Munich, University Hospital, LMU Munich

6. Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine Collegium Medicum, University of Warmia and Mazury

7. Department of Paediatrics, Evangelisches Krankenhaus

8. Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich

9. German Center for Lung Research (DZL)

10. Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne

11. Institute of Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health

Reference: Areal AT, Singh N, Zhao Q, Berdel D, Koletzko S, von Berg A, Gappa M, Heinrich J, Standl M, Schikowski T. The association of relative humidity and air pollution interaction on lung function in adolescents. Frontiers in Environmental Health. 2023 Nov 23;2:1250523.

frontiers | Frontiers in Environmental Health

TYPE Original Research
PUBLISHED 23 November 2023
DOI 10.3389/fenvh.2023.1250523

OPEN ACCESS

EDITED BY
Marie-Abele Bind,
Massachusetts General Hospital and Harvard Medical School, United States

REVIEWED BY
Antonis Analitis,
National and Kapodistrian University of Athens, Greece
Zhicheng Du,
Sun Yat-sen University, China

*CORRESPONDENCE
Tamara Schikowski
✉ tamara.schikowski@iuf-duesseldorf.de

RECEIVED 30 June 2023
ACCEPTED 08 November 2023
PUBLISHED 23 November 2023

CITATION
Areal AT, Singh N, Zhao Q, Berdel D, Koletzko S, von Berg A, Gappa M, Heinrich J, Standl M and Schikowski T (2023) The association of relative humidity and air pollution interaction on lung function in adolescents.
Front. Environ. Health 2:1250523.
doi: 10.3389/fenvh.2023.1250523

The association of relative humidity and air pollution interaction on lung function in adolescents

Ashtyn T. 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] and Tamara Schikowski[1]*

[1]Department of Epidemiology, IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany, [2]Department of Epidemiology, Medical Research School, Heinrich-Heine-University, Düsseldorf, Germany, [3]School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China, [4]Research Institute, Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany, [5]Department of Pediatrics, Dr. von Hauner Children's Hospital Munich, University Hospital, LMU Munich, Munich, Germany, [6]Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine, Collegium Medicum University of Warmia and Mazury, Olsztyn, Poland, [7]Department of Paediatrics, Evangelisches Krankenhaus, Düsseldorf, Germany, [8]Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany, [9]German Center for Lung Research (DZL), Munich, Germany, [10]Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia, [11]Helmholtz Zentrum München—German Research Center for Environmental Health, Institute of Epidemiology, Neuherberg, Germany

Background: Relative humidity (RH) and air pollution significantly affect respiratory health. However, how RH and air pollution interact and modify each other and affect lung function in adolescence is largely unknown. This study assesses the interactive association of RH and air pollution on lung function, i.e. forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), in German adolescents.

Methods: A total of 2,116 participants with available spirometry measurements (*z*-scores of FEV1 and FVC) were included from the 15-year follow-up of the German GINIplus and LISA birth cohort. Daily environmental exposure data included RH, ozone (O_3), nitrogen dioxide (NO_2), and particulate matter <2.5 µm ($PM_{2.5}$). Linear models were fitted to assess the main associations of RH, air pollution, and maximum temperature (Tmax) an interaction term between one-day moving average of RH (Lag01) and a categorical air pollution term was then included to assess the modifying association of air pollution on RH and was adjusted for study location, season and chronic respiratory disease (CRD) status. Effect modification was performed for sex and CRD. The results are presented as beta coefficients (ß) and 95% confidence intervals (95% CI).

Results: A 5% increase in RH was associated with an increase in FEV1 (ß = 0.040–0.045; 95% CI: 0.008 to 0.076) and FVC (ß = 0.007–0.012; 95% CI: −0.023 to 0.045) in the main associations models. In the interaction models, there was a significant decrease in FEV1 (ß = −0.211; 95% CI: −0.361 to −0.062) and FVC (ß = −0.258; 95% CI: −0.403 to −0.0113) per 5% increase in RH on high O_3 days compared to the reference category; while there was a non-significant trend towards a decrease in FEV1 on high $PM_{2.5}$ and NO_2 days. Female participants were more likely to experience a decrease in FEV1 than male participants on high-pollution days.

Conclusions: Air pollution interacts and modifies the association of weather on lung function in this cohort of German adolescents. An increase in RH on high air pollution exposure days was associated with a decrease in lung function in German adolescents. Female participants were more sensitive to RH and air pollution.

KEYWORDS

relative humidity, air pollution, lung function, adolescents, cohort studies, environmental epidemiology

1. Introduction

Investigating the relationship between weather parameters and respiratory health outcomes due to the effects of climate change is a rapidly evolving field of study. Relative humidity (RH) has rarely been the focus of environmental exposure-health studies and has largely only been used as a confounding variable in multi-exposure/temperature-health studies (1, 2). However, it is known that temperature, RH, and air pollution interact in different ways while having both individual and, potentially, interactive associations with respiratory health (2). Therefore, insights into the potential associations of different weather parameters and air pollutants with lung health are important; therefore, surrogate subclinical endpoints such as lung function and biomarkers need to be investigated.

To determine a person's respiratory health, lung function tests are conducted (3). Two indicators of lung function are forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC). Both of these surrogate subclinical endpoints allow us to assess different components of lung function and to diagnose lung disease. While the short-term association of environmental factors on lung function has been described in children, young and older adults, there is limited evidence for adolescents. However, biological development occurs rapidly during adolescence, making it crucial to understand environment associations with adolescent health (4). Regarding respiratory health, adolescence is a period of rapid lung development due to accelerated physical growth; additionally, during this period, asthma becomes more common in females than in males as puberty induces physical changes that lower airway resistance in males while increasing airway resistance in females (4, 5).

Individual environmental factors are associated with lung health, and as such are associated with lung function, in different ways; low levels of RH (<40%), which indicates that the air is dry, are associated with causing dryness in the respiratory tract which then damages lung tissue, while high levels (>60%) have been associated with increased mucous production (6). High and low temperatures have both been associated with an increase in respiratory rate, exacerbation of chronic respiratory disease, and respiratory mortality (7). Air pollutants have consistently been associated with a decrease in lung function (8, 9). While there is extensive research on the individual association of air pollution on lung function, the same cannot be said of RH; additionally, air pollution, RH, and temperature interact or modify each other's associations with human health.

Climate change and it's determining environmental factors present a unique situation in that they intersect with many existing vulnerabilities (e.g., including geography, urban/rural, sex, and chronic diseases) that impact adolescent health (4). Therefore, understanding how short-term environmental exposures interact or modify each other and how they are associated with lung function during such a crucial time in human development is of the utmost importance. In this study, we aimed to assess the short-term individual and interactive associations of relative humidity and air pollution with lung function in a subset of German adolescents.

2. Methods and material

2.1. Study population

The present study utilises the data collected for two ongoing German population-based birth cohort studies which recruited healthy full-term neonates with normal birthweight. The first is the German Infant Study on the Influence of Nutrition Intervention plus Air Pollution and Genetics on Allergy Development (GINIplus), which recruited a total of 5,991 neonates in Munich and Wesel between September 1995 and July 1998. The second is the influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany Study (LISA) (10) which recruited a total of 3,097 neonates in Bad Honnef, Leipzig, Munich and Wesel between November 1997 and January 1999. The study areas of the cohorts are shown in **Supplementary Figure S1**. Participant data were collected at birth and ages 6, 10, and 15, and were then due to their harmonised design, pooled for Wesel (GINIplus/LISA North: $n = 3{,}390$) and Munich (GINIplus/LISA South: $n = 4{,}413$). Parents completed questionnaires that collected data on respiratory conditions and covariates such as parental/personal smoking and socioeconomic status (parental education). Further details of recruitment and follow-up to 15 years have been presented elsewhere (11). The present analysis employs data from the 15-year follow-up assessments for both cohorts in Munich and Wesel. This analytic sample was restricted to 1,236 children from Munich and 880 children from Wesel with complete spirometry (forced vital capacity [FVC] and forced expiratory volume in one second [FEV1]) and environmental exposure data. Ethical approval was granted by the Bavarian Board of Physicians (10,090 and 12,067), 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 at each of the study phases with participants also providing consent at the 15-year follow-up.

2.2. Assessment of lung function

Spirometric measurements (FEV_1 and FVC) during adolescence were conducted between 2011 and 2013 following the guidelines of the American Thoracic Society and European Respiratory Society (12). Detailed operation procedures for lung function measurements have been described previously (13). Any respiratory tract infections, personal smoking and anti-inflammatory medications were recorded. To adequately compare the impacts of environmental exposures on FEV_1 and FVC, both measurements were converted into z-scores using LUng function NOrmal values for KIDs in Germany (LUNOKID) scale (14). The LUNOKID study was designed to provide reliable reference values of spirometry for German children and adolescents which adjusted for the non-linear associations of age, height, and sex (15–17).

2.3. Assessment of environmental exposures

Weather parameters (daily maximum [Tmax] and, minimum temperature [Tmin], mean temperature [Tmean], 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 (18). Short-term daily 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' 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 (19)]. The warm season was defined as May to October and the cold season as November to April.

2.4. Statistical analysis

As there were minimal differences in RH between the study sites in Munich and Wesel, it was decided to pool the participants to increase the power of the statistical analysis as in previous studies (20, 21). To ensure that all potential variables were considered, we used correlation coefficients, multicollinearity tests, adjusted *R*-squared, Akaike information criterion (AIC) and *p* values <0.05 for variable selection. Due to the small number of participants diagnosed with asthma, we created a Chronic Respiratory Disease (CRD) variable that combined a history of asthma and asthma at the time of examination, with chronic respiratory symptoms and conditions associated with asthma, i.e., history of chronic bronchitis, a history of chronic wheezing, and/or, chronic bronchitis and/or wheeze at the time of assessment. We graphically assessed the association between the short-term environmental exposures and the outcomes and found that all variables showed a linear association; therefore, we used multivariable linear models to quantify the main associations of short-term exposure RH (one-day moving average; Lag01), Tmax (lowest AIC of all temperature variables) and air pollution on FEV_1 and FVC; separate models were created for different air pollutants (O_3, NO_2 and $PM_{2.5}$). All models (the main model and interactive model) were mutually adjusted for each environmental factor, CRD (Yes as the reference category), study location (Munich as the reference category), and season (warm season as the reference category). To assess the interactive associations between RH and air pollution, we used RH parameters as a continuous variable and air pollutants as a categorical variable: Low (<5th percentile), Medium (5–95th percentile), and High (>95th percentile); the cut-offs were: $PM_{2.5} = 2.71$ μg/m^3 and 22.08 μg/m^3, $O_3 = 10.15$ μg/m^3 and 82.60 μg/m^3 and $NO_2 = 4.90$ μg/m^3 and 37.85 μg/m^3. We chose "Medium" as the reference category, as it represented the most common exposure levels while "Low" represented optimum exposure and "High" represented non-optimum exposure. We did not adjust for age, sex, height, or weight in the main model as the chosen outcomes (FEV_1 and FVC) were estimated following standard guidelines accounting for these variables. Effect modification was examined by sex (female/male), and history of CRD.

2.5. Sensitivity analysis

To test the robustness of the core model, several sensitivity analyses were conducted. First, we explored the possibility of lag associations for up to 5 days (Lag05). Second, we explored the change in the interaction between RH and air pollution by redefining cut-offs for air pollution categories. At first, the cutoff was set below the 10th percentile (Low) and above the 90th percentile (High), and in the second stage, it was set below the 25th percentile (Low) and above the 75th percentile (High). Third, extended models were performed by additionally adjusting for the association of age, sex, CRD, BMI, the highest parental education level (less than 10 years, 10 years, and more than 10 years), and active parental smoking (yes or no).

All the results were presented as beta coefficient (β) with a 95% confidence interval (CI) per five percent increase in RH. All statistical analysis was conducted in R version 4.0.4 (22). Results above zero indicate improved lung function; a two-sided *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of study population and exposures

A total of 2,116 participants, with a mean age of 15.24 [standard deviation (SD) ± 0.31], of which approximately 51% were female, had complete spirometric measurements and environmental exposure data; 1,236 (58.41%) participants were from Munich and 880 (41.59%) participants were from Wesel (**Table 1**). Approximately, 42% of participants reported suffering from/or having had a CRD (e.g., diagnosed asthma, chronic

10.3389/fenvh.2023.1250523

TABLE 1 Summary of population characteristics.

	Total[a]	Munich[a]	Wesel[a]
Participants	2,116	1,236	880
Age (years)	15.24 (0.31)	15.28 (0.31)	15.19 (0.31)
Sex			
Female	1,080 (51.04%)	629 (50.89%)	451 (51.25%)
Male	1,036 (48.96%)	607 (49.11%)	429 (48.75%)
FEV_1 (*z*-score)	0.074 (1.199)	0.199 (1.207)	−0.103 (1.166)
FVC (*z*-score)	−0.039 (1.155)	0.025 (1.174)	−0.128 (1.124)
CRD			
Yes	891 (42.11%)	514 (41.59%)	377 (42.84%)
No	1,212 (57.28%)	716 (57.93%)	496 (56.36%)
NA	13 (0.61%)	6 (0.49%)	7 (0.80%)
Maximal parental education			
Low (<10 years)	126 (5.95%)	48 (3.88%)	78 (8.86%)
Medium (=10 years)	563 (26.61%)	219 (17.72%)	344 (39.09%)
High (>10 years)	1,422 (67.20%)	966 (78.16%)	456 (51.82%)
NA	5 (0.24%)	3 (0.24%)	2 (0.23%)
Parental smoking			
Yes	346 (16.35%)	176 (14.24%)	170 (19.32%)
No	1,699 (80.29%)	1,016 (82.20%)	683 (77.61%)
NA	71 (3.36%)	44 (3.56%)	27 (3.07%)
BMI (kg/m^2)	20.94 (3.26)	20.67 (3.09)	21.31 (3.44)

[a]Mean (Standard Deviation); number (%).

wheeze, chronic bronchitis), with there being slightly more cases in Wesel than in Munich (42.84% vs. 41.59%) (Table 1). This was supported by the spirometric measurements that showed that participants in Wesel had lower FEV_1 (−0.103 vs. 0.199) and FVC (−0.128 vs. 0.025) *z*-scores than Munich (Table 1). Approximately, 67% of participants had parents with a high educational level; this was most apparent in participants from Munich (Table 1). The majority of participants fell within the normal BMI category (69.57%), with participants from Wesel slightly more likely to be overweight (12.84% vs. 8.41%); while more participants from Munich were underweight (21.28% vs. 18.64%) (Table 1). Passive smoking exposure was reported by 16% of participants, with participants from Wesel reporting more exposure to passive smoking than Munich (Table 1).

Weather parameters were similar in Munich and Wesel. The average RH was 74.92% and 75.43% in Munich and Wesel respectively (Table 2). Tmax was similar in Munich and Wesel however, Wesel was marginally warmer (Table 2). O_3 and NO_2 were approximately the same in both Munich and Wesel (Table 2). $PM_{2.5}$ was higher in Wesel than in Munich (12.75 μg/m^3 vs. 9.42 μg/m^3) (Table 2). The majority of participants had their spirometry measurements taken in the warm season (63.75%) (Table 2).

TABLE 2 Summary of environmental exposure on the day of examination.

	Total[a]	Munich[a]	Wesel[a]
RH (%)	75.13 (11.30)	74.92 (11.82)	75.43 (10.54)
Tmax (°C)	16.56 (7.95)	16.41 (8.49)	16.77 (7.12)
Tmean (°C)	12.46 (6.78)	12.18 (7.73)	12.85 (6.23)
Tmin (°C)	8.70 (6.02)	8.32 (6.17)	9.24 (5.74)
$PM_{2.5}$ (μg/m^3)	10.80 (5.91)	9.42 (5.41)	12.75 (6.05)
O_3 (μg/m^3)	48.86 (21.36)	49.15 (22.30)	48.46 (19.96)
NO_2 (μg/m^3)	17.54 (10.11)	17.26 (9.90)	17.94 (10.39)
Season			
Warm	1,349 (63.75%)	767 (36.25%)	789 (63.83%)
Cold	447 (36.17%)	560 (63.64%)	320 (36.36%)

[a]Mean (Standard Deviation); number (%).

3.2. Main associations of RH, Tmax, and air pollution on FEV_1 and FVC

Collinearity tests showed that all included variables were not highly correlated and multicollinearity tests for the models showed that all variables were below 3, indicating no multicollinearity issue in the models. A 5% increase in RH was consistently associated with an increase in FEV_1 ($\beta = 0.040$ to 0.044; 95% CI: 0.009 to 0.076); Tmax was also consistently associated was an increase in FEV_1 ($\beta = 0.014$ to 0.015; 95% CI: 0.003 to 0.027) (Table 3). No significant associations were found for O_3 ($\beta = -0.0003$; 95% CI: −0.004 to 0.003), NO_2 ($\beta = 0.005$; 95% CI:−0.0005 to 0.011) and $PM_{2.5}$ ($\beta = 0.006$; 95% CI: −0.002 to 0.015) (Table 3). No significant associations were observed for FVC (Table 3).

3.3. Interactive and modifying association of air pollution on RH

On days with high levels of O_3, there was a decrease in FEV_1 ($\beta = -0.211$; 95% CI: −0.361 to −0.062) and FVC ($\beta = -0.258$; 95% CI: −0.404 to −0.113) per 5% increase in RH compared to the reference category (Figures 1, 2; Supplementary Table S1); there was no significant finding for low O_3 days. However, the interactive term for O_3 was statistically significant for both FEV_1 ($p = 0.0121$) and FVC ($p = 0.002$) (Supplementary Table S1). No significant findings were found for interactions between RH and $PM_{2.5}$ or RH and NO_2 on high or low air pollution days compared to the reference category (Figures 1, 2; Supplementary Table S1).

TABLE 3 A table showing the beta coefficient and 95% CI of the main associations of RH, Tmax, and air pollution on FEV_1 and FVC in a cohort of German adolescents.

	FEV_1	FVC
	β (95% CI)*	β (95% CI)[1,*]
RH[a]	**0.044 (0.013, 0.074)**	0.009 (−0.021, 0.039)
Tmax[b]	**0.014 (0.003, 0.025)**	0.010 (−0.001, 0.021)
$PM_{2.5}$[c]	0.006 (−0.002, 0.015)	0.003 (−0.005, 0.011)
RH[a]	**0.042 (0.008, 0.076)**	0.012 (−0.021, 0.045)
Tmax[b]	**0.015 (0.003, 0.027)**	0.009 (−0.003, 0.021)
O_3[c]	−0.0003 (−0.004, 0.003)	0.0009 (−0.003, 0.004)
RH[a]	**0.040 (0.009, 0.071)**	0.007 (−0.023, 0.037)
Tmax[b]	**0.015 (0.004, 0.026)**	0.010 (−0.0,006, 0.021)
NO_2[c]	0.005 (−0.0,005, 0.011)	0.002 (−0.003, 0.008)

Statistically significant in bold.
[a]Per 5% increase in RH at Lag01.
[b]Per 1° Celsius increase at Lag01.
[c]Per 1 unit increase in air pollutant.
*Adjusted for CRD, study location and season.

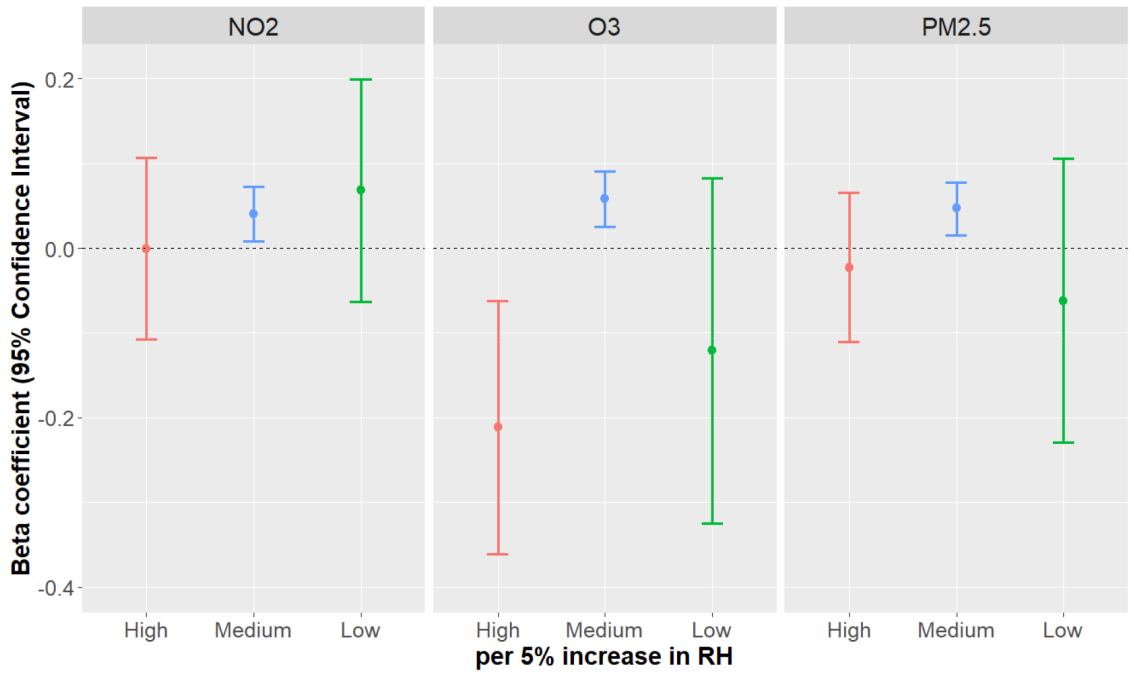

FIGURE 1
The association of RH when modified by categorical air pollution (reference category: medium) on FEV1.

3.4. Effect modification of CRD and sex on FEV_1 and FVC

RH and temperature tended to show stronger protective associations with lung function in female participants than in male participants in the stratified analysis (Supplementary Table S2). However, a contrasting result was observed in interaction models, which shows female participants, in general, were more likely to experience a decrease in FEV_1 (Supplementary Table S3), yet male participants on high O_3 days in particular when compared to the reference category, experienced a greater decrease in FVC than their counterparts respectively.

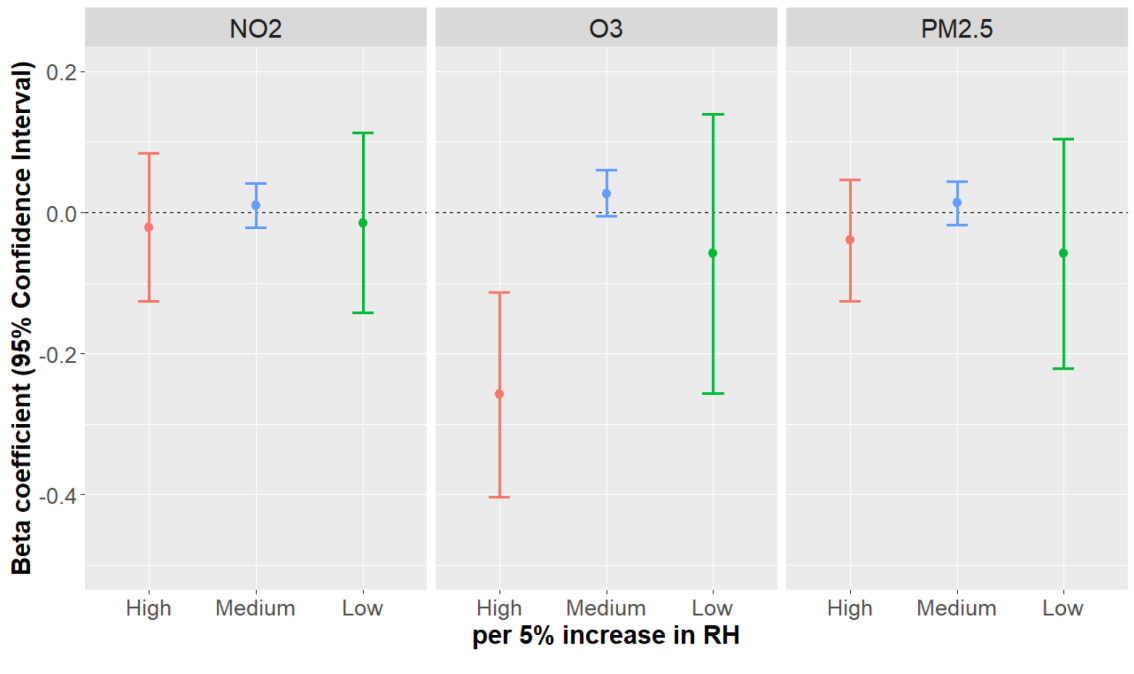

FIGURE 2
The association of RH when modified by categorical air pollution (reference category: medium) on FVC.

In both, with and without CRD, the main association model shows an increase in RH and temperature was associated with an increase in FEV_1 (**Supplementary Table S4**), whereas, FVC did not show any significant associations. In our interaction models, we found a decrease in FEV_1 and FVC per 5% increase in RH on both high and low O_3 days when compared to the reference category; this association was more apparent in those without CRD than those with CRD (**Supplementary Table S5**). For NO_2 there was a non-significant trend towards a decrease in FEV_1 and FVC in those with CRD (**Supplementary Table S5**).

3.5. Sensitivity analysis

Results for the different lag period shows that the values were consistent across all lags for RH and temperature. Secondly, the direction of the association was consistent at different cut-offs for the air pollutants (i.e., 25th and 95th, 10th and 90th); additionally, the strength of the association was consistent (**Supplementary Tables S6, S7**). The results for the extended model show that the associations of RH, temperature, and air pollution with FEV_1 and FVC remain unchanged after additionally adjusting for age, sex, BMI, parental education, second-hand smoking, family history of respiratory disease, and anti-inflammatory medications (data not shown).

4. Discussion

In recent years, climate change has adversely affected human health. It is known that meteorology variables and air pollution are associated with each other, with RH modifying the toxicity of air pollutants as well as stagnant meteorological conditions, i.e., high relative humidity and temperature, encouraging increased pollutant emissions and secondary particle formations (23); however, how these environmental factors modify and interact with each other concerning health is largely unknown. In this study, we assessed how air pollution modifies and interacts with weather variables and how this impacts lung function. We found that the main associations of RH and Tmax showed statistically significant protective associations on lung function, while O_3, NO_2, and $PM_{2.5}$ failed to reach statistical significance. In the interaction models we found that exposure high levels of O_3 modified the protective association of RH and that this interaction caused a decrease in lung function. Typically, O_3 and RH have an inverse relationship, however, in recent years, due to the effects of climate change, this relationship is changing with O_3 and RH peaks occurring concurrently along with temperature (**Supplementary Figures S1–S3**), as we have seen in our data set.

Additionally, female participants were more sensitive to the main associations of weather variables than male participants. Biological sex might also modify the associations of environmental factors on respiratory health. At 15 years of age, females are typically in the late- or post-stages of puberty and have reached their peak lung function, while males are typically in an earlier stage and are still experiencing an increase in lung function (24). Before puberty, females typically have higher lung function than males, however, after puberty, males have higher lung function than females. The increase in lung size, and as such the thoracic cage, can lower airway resistance, while the increase in high-fat mass in females is associated with increases in lung inflammation and airway resistance (25). Furthermore, females have slower blood flow, indicating that females are more sensitive to changes in outdoor temperature than males, as cold exposure causes their skin temperature to lower even further, especially in the extremities (26, 27). These arguments complement the findings from the present analysis which found lung function in females to be more vulnerable to temperature than in males.

With regard to CRD, typically the associations of weather and air pollution were stronger in those without CRD. However, in interaction models between RH and NO_2, as well as RH and O_3, we did see a decrease in lung function in those without CRD (28, 29).

According to the Köppen-Geiger climate classification, most of Germany falls into what is called a cfb climate (30). By definition, cfb climate means locations whose climates are temperate with a warm summer and cool winter that has year-round precipitation and high levels of humidity; these locations usually have an average temperature below 22°C and do not experience extreme heat or extreme cold (30, 31).

Regarding air pollution, the 95th percentile of O_3 (82.60 $\mu g/m^3$) in Wesel and Munich is already below that of the World Health organisations (WHO) updated 2021 air quality guidelines (100 $\mu g/m^3$); while, $PM_{2.5}$ (22.08 $\mu g/m^3$) and NO_2 (37.85 $\mu g/m^3$), are above the WHO air quality guidelines (15 $\mu g/m^3$ and 25 $\mu g/m^3$) (32). Considering that our results showed that air pollution modifies and has an adverse association on lung function, by meeting the WHO's air quality guideline targets, there could be an improvement in lung function. However, O_3, which is already below the WHO guidelines was found to decrease lung function with increasing RH even with low O_3 exposure. This suggests that further reduction in O_3 is needed. Reduction in air pollution emissions and secondary particle formation can occur by addressing the sources of air pollution in our study, namely traffic-related emissions and agricultural emissions (33).

This is the first study that investigates the short-term interactive association of RH and air pollution on lung function in adolescents in Germany. Due to the lack of studies on this topic, it is complex to place our study into context as (1) research primarily has looked at the long-term associations of temperature and air pollution rather than immediate short-term impacts of temperature and air pollution, (2) there is primarily a focus on children or the elderly and not on adolescents which is a stage of major biological change which is not truly comparable to either adults or children, and (3) weather parameters, RH in particular, are often only used as confounders in epidemiological analyses and as such, the association of these variables is poorly understood, and (4) modifying associations between RH and air pollution are largely unknown. A previous study by Lepeule,

Litonjua (34) looked at a cohort of elderly men from the United States of America (USA) and investigated the association of short-term temperature and RH on lung function. This study found that there was a decrease in FEV1 and FVC with a 5% increase in both temperature and RH. Our results differed in that we found that an increase in temperature and RH were associated with an increase in FEV1 in male adolescents. In contrast, we found lower FVC with increasing temperatures and RH in males which is in line with the results reported for older males. The BAMSE birth cohort by Schultz, Hallberg (35) found that FEV1 was potentially more sensitive to environmental exposures than FVC which is consistent with our results. The most likely reason for differences in our results compared to those in literature can be attributed to different climates (i.e., Germany vs. the USA), the age of our participants (i.e., adolescents vs. middle-aged and elderly adults), and differences in behaviour and personal characteristics.

It is beyond the scope of this study to identify the exact biological mechanisms that may underlie the association of weather parameters and lung function. Potentially, during periods of high temperatures, e.g., heat waves, the body is unable to efficiently thermoregulate; this leads to excessive sweating and increased dehydration. which exacerbates CRD due to increased airway resistance within the lungs (10, 36, 37). During low temperatures, the veins and arteries narrow, causing an increase in cardiac and respiratory workload (38, 39).

Research on the association of environmental factors on adolescent health is limited. Future research should aim to further investigate the immediate short-term associations of weather parameters on respiratory health in adolescents as well as continue assessing the potential interactive associations between environmental factors which would allow us to consolidate research on the association of multiple environmental exposures on respiratory health.

This analysis has several strengths: The data were obtained from large, well-characterised birth cohorts. Short-term air pollution and meteorological exposures were estimated by well-validated high-resolution models. Additionally, this is one of the first studies to focus on RH and temperature associations on lung function in adolescents as well as one of the first studies to investigate the potential interactive associations of RH and air pollution on lung function. This helps to identify potential environmental impacts during a time of great biological importance due to rapid growth during adolescence.

However, we also need to acknowledge some limitations. Firstly, although the GINIplus/LISA cohort has been well described, the findings might not be generalisable to adolescents in other countries as this cohort was exposed to relatively low air pollution levels compared to adolescents in other geographical regions. Additionally, Germany typically has lower temperatures, but high RH which further limits generalisability to adolescents in other countries. Secondly, we did not have access to indoor temperature and humidity which means this is limited to outdoor exposure. Lastly, there is limited literature on the interactive association of RH and air pollution on lung function, which makes placing our results in context, complex.

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 lung function which is different from that observed in other age groups. The interactive association of RH and air pollution is associated with a decline in lung function in this cohort of German adolescents. These findings may have important clinical implications as the association of short-term weather variables, which influence climate, on adolescent health is largely unknown; additionally, how RH and air pollution interact with each other and how this interaction is associated with health is poorly understood. This study fills important gaps in the evidence of climate change's effects on health. Future research should focus further not just on the potential associations of extreme climate events on health but also on the short- and long-term associations of daily weather and air pollution interactions on health in adolescents.

Data availability statement

The datasets presented in this article are not readily available because they are raw personal data from the cohort and not for public viewing. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by 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 studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AA: Conceptualisation, Formal analysis, methodology, Visualisation, Writing – original draft, Writing – review & editing. NS: Supervision, Validation, Methodology, Writing – review & editing. QZ: Methodology, Writing – review & editing. DB: Investigation, Writing – review & editing. SK: Investigation, Writing – review & editing. Av: Investigation, Writing – review & editing. MG: Investigation, Writing – review & editing. JH: Investigation, Writing – review & editing. MS: Data curation, Investigation, Writing – review & editing. TS: Data Curation, Investigation, Conceptualisation, Supervision, Validation, Methodology, Writing – review & editing. All authors contributed to the article and approved the submitted version.

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 as well by 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). Mead Johnson and Nestlé were not involved in the study design, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

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, staff involved in data collection, and 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 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. We would like to thank Dr. Kathrin Wolf for her assistance in preparing the exposure data for participants in Munich.

Conflict of interest

SK has received a speaker's fee from Danone, Jansson, Sanofi, Pfizer, and Takeda. Additionally, she has participated on the advisory board for Abbvie, Danone, Jansson, GSK, Pfizer, Sanofi, and Takeda.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors QZ and NS declared that they were editorial board members of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fenvh.2023.1250523/full#supplementary-material

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The effect of relative humidity modified by air pollution on lung function in adolescents

Ashtyn T. 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], Tamara Schikowski[1*]

1. IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
2. Department of Epidemiology, Medical Research School, Heinrich-Heine-University, Düsseldorf, Germany
3. School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China
4. Research Institute, Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany
5. Department of Pediatrics, Dr. von Hauner Children's Hospital Munich, University Hospital, LMU Munich, Munich, Germany
6. Department of Pediatrics, Gastroenterology and Nutrition, School of Medicine Collegium Medicum University of Warmia and Mazury, Olsztyn, Poland
7. Department of Paediatrics, Evangelisches Krankenhaus, Düsseldorf, Germany
8. Institute and Clinic for Occupational, Social and Environmental Medicine, University Hospital, LMU Munich, Munich, Germany;
9. German Center for Lung Research (DZL), Germany
10. Allergy and Lung Health Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia
11. Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany

Coßespondence to:
Dr Tamara Schikowski
Arbeitsgruppenleiterin
Umweltepidemiologie von Lunge, Gehirn und Hautalterung
IUF – Leibniz Research Institute for Environmental Medicine
Auf'm Hennekamp 50
D-40225 Düsseldorf
phone: +49 211 3389 341
E-Mail: Tamara.Schikowski@IUF-Duesseldorf.de

Supplemental Material

Figure S1

A graph showing the distribution and trend of Tmax from 2007 to 2014

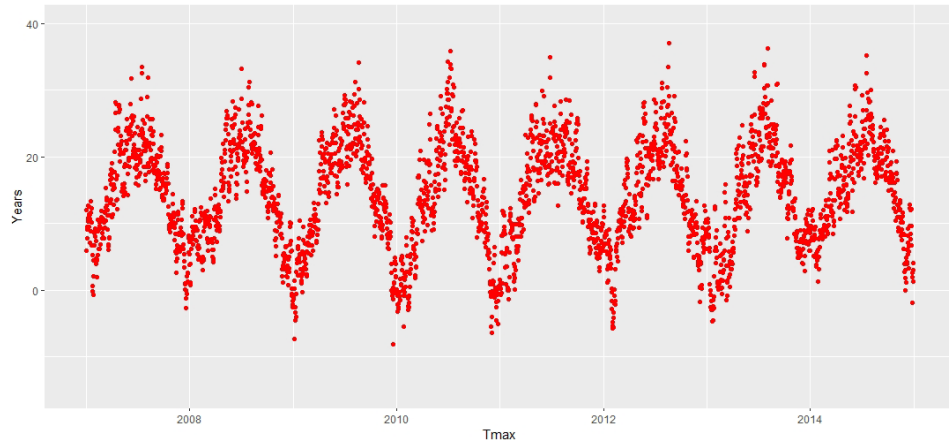

Figure S2

A graph showing the distribution and trend of RH from 2007 to 2014

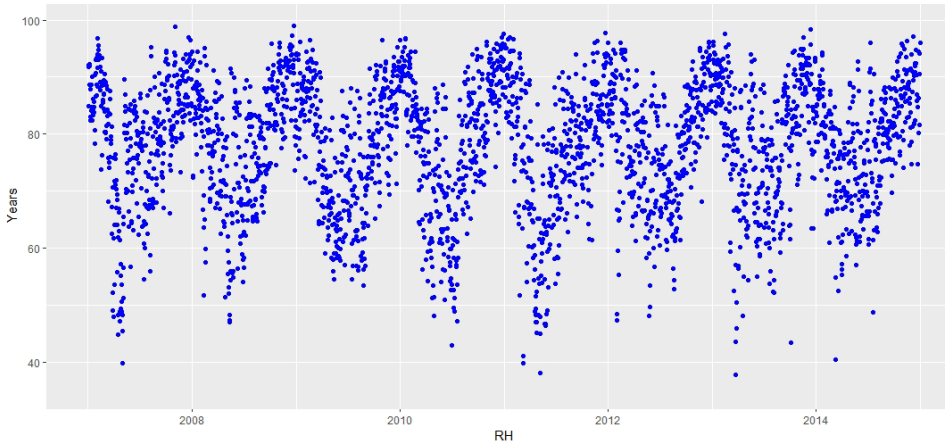

Figure S3

A *graph showing the distribution and trend of O_3 from 2007 to 2014*

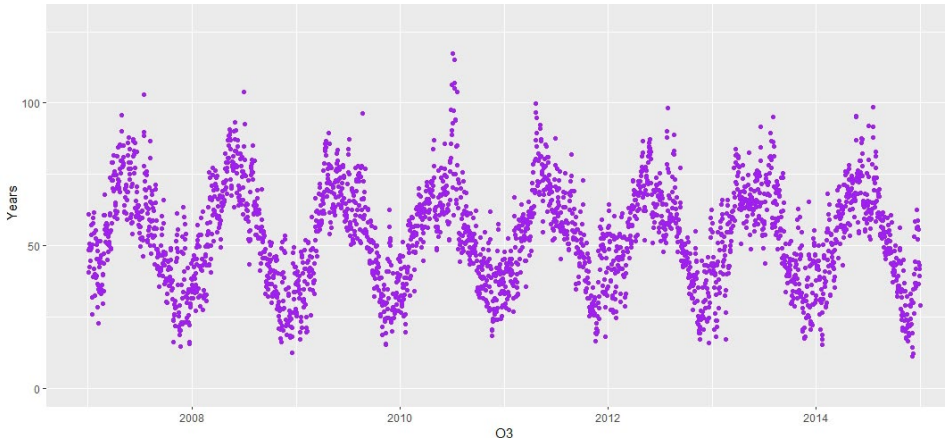

Table S1

A table showing the ß and 95% CI of the interactive and modifying effects of air pollution and RH on FEV_1 and FVC in a cohort of German adolescents.

	FEV_1		FVC	
	ß (95% CI) *	P_{int}-value	ß (95% CI) *	P_{int}-value
RH: $PM_{2.5}$High[2] (n=128)	-0.039 (-0.125, 0.047)	0.688	-0.023 (-0.111, 0.065)	0.538
RH: $PM_{2.5}$Low[2] (n=76)	-0.058 (-0.221, 0.104)		-0.062 (-0.229, 0.106)	
RH: O_3High[2] (n=87)	**-0.258 (-0.403, -0.113)**	**0.012**	**-0.211 (-0.361, -0.062)**	**0.002**
RH: O_3Low[2] (n=86)	-0.058 (-0.256, 0.140)		-0.121 (-0.325, 0.083)	
RH: NO_2High[2] (n=93)	-0.021 (-0.126, 0.084)	0.591	-0.001 (-0.108, 0.107)	0.909
RH: NO_2Low[2] (n=91)	-0.015 (-0.142, 0.113)		0.068 (-0.063, 0.199)	

[1] P_{INT} statistically significant results in bold

[2] per 5% increase in RH at Lag01; when compared to the reference category

*Adjusted for study location, season, and Tmax

Table S2

A table showing the main effects of RH, Air pollution and Tmax on FEV_1 and FVC in a cohort of German adolescents when stratified by sex.

	Female		Male	
	FEV_1	FVC	FEV_1	FVC
	ß (95% CI)*	ß (95% CI)*	ß (95% CI)*	ß (95% CI)*
RH[2]	**0.051 (0.011, 0.091)**	0.027 (-0.014, 0.068)	0.036 (-0.011, 0.082)	-0.010 (-0.053, 0.034)
Tmax[3]	**0.020 (0.005, 0.034)**	**0.020 (0.005, 0.034)**	0.009 (-0.008, 0.026)	-0.0004 (-0.016, 0.015)
$PM_{2.5}$[4]	0.008 (-0.003, 0.019)	0.007 (-0.004, 0.019)	0.005 (-0.008, 0.017)	-0.001 (-0.013, 0.010)
RH[2]	0.043 (-0.0009, 0.087)	0.019 (-0.026, 0.065)	0.039 (-0.012, 0.091)	0.003 (-0.045, 0.051)
Tmax[3]	**0.022 (0.007, 0.037)**	**0.022 (0.006, 0.038)**	0.008 (-0.009, 0.026)	-0.003 (-0.002, 0.008)
O_3[4]	-0.002 (-0.006, 0.003)	-0.002 (-0.007, 0.003)	0.0008 (-0.005, 0.006)	0.003 (-0.002, 0.008)
RH[2]	**0.048 (0.007, 0.087)**	0.023 (-0.018, 0.064)	0.033 (-0.014, 0.080)	-0.009 (-0.053, 0.035)
Tmax[3]	**0.021 (0.006, 0.035)**	**0.020 (0.005, 0.035)**	0.009 (-0.008, 0.026)	-0.0005 (-0.016, 0.015)
NO_2[4]	0.007 (-0.001, 0.014)	0.006 (-0.002, 0.014)	0.004 (-0.005, 0.012)	-0.0008 (-0.009, 0.007)

[1] statistically significant results in bold
[2] per 5% increase in RH at Lag01
[3] per 1° Celsius increase at Lag01
[4] per 1-unit increase in air pollutant
*Adjusted for CRD, study location and season

Table S3

A table showing the ß and 95%CI of the interactive effect of RH and air pollution on FEV_1 and FVC in a cohort of German adolescents when stratified by sex.

	Female				Male			
	FEV_1		FVC		FEV_1		FVC	
	ß (95% CI)*	P_{int}-value	ß (95% CI)*	P_{int}-value	ß (95% CI)*	P_{int}-value	ß (95% CI)*	P_{int}-value
RH:$PM_{2.5}$High[2]	-0.090 (-0.205, 0.024)	0.216	-0.068 (-0.185, 0.049)	0.221	0.050 (-0.086, 0.186)	0.730	-0.008 (-0.134, 0.118)	0.933
RH:$PM_{2.5}$Low[2]	-0.090 (-0.287, 0.108)		-0.141 (-0.344, 0.061)		-0.046 (-0.342, 0.249)		0.048 (-0.226, 0.323)	
RH:O_3High[2]	-0.210 (-0.404, -0.016)	0.096	-0.134 (-0.332, 0.065)	0.353	-0.212 (-0.442, 0.018)	0.149	-0.380 (-0.593, -0.167)	**0.002**
RH:O_3Low[2]	-0.077 (-0.366, 0.211)		-0.096 (-0.391, 0.200)		-0.123 (-0.415, 0.169)		-0.024 (-0.294, 0.246)	
RH:NO_2High[2]	-0.060 (-0.219, 0.099)	0.760	-0.072 (-0.235, 0.091)	0.573	0.019 (-0.130, 0.168)	0.429	-0.005 (-0.144, 0.133)	0.940
RH:NO_2Low[2]	-0.011 (-0.249, 0.227)		-0.078 (-0.323, 0.166)		0.108 (-0.056, 0.273)		0.026 (-0.127, 0.179)	

[1] p_{int}-value <0.050 in bold

[2] per 5% increase in RH at Lag01; when compared to the reference category

*Adjusted for CRD, study location, season, and Tmax

Table S4

A table showing the main effects of RH, air pollution and Tmax on FEV_1 and FVC in a cohort of German adolescents when stratified by the presence of chronic respiratory disease (CRD).

	CRD: YES		CRD: NO	
	FEV_1	FVC	FEV_1	FVC
	ß (95% CI)*	ß (95% CI)*	ß (95% CI)*	ß (95% CI)*
RH[2]	**0.049 (0.001, 0.096)**	0.0003 (-0.044, 0.045)	0.040 (-0.00002, 0.081)	0.015 (-0.025, 0.056)
Tmax[3]	**0.018 (0.0003, 0.036)**	0.011 (-0.006, 0.028)	0.012 (-0.003, 0.026)	0.009 (-0.005, 0.023)
$PM_{2.5}$[4]	0.007 (-0.006, 0.020)	0.005 (-0.007, 0.018)	0.006 (-0.005, 0.017)	0.001 (-0.010, 0.012)
RH[2]	**0.055 (0.002, 0.108)**	0.015 (-0.035, 0.065)	0.033 (-0.011, 0.077)	0.011 (-0.033, 0.055)
Tmax[3]	0.017 (-0.002, 0.035)	0.008 (-0.009, 0.026)	0.014 (-0.0009, 0.029)	0.011 (-0.004, 0.026)
O_3[4]	0.002 (-0.004, 0.007)	0.003 (-0.002, 0.009)	-0.002 (-0.007, 0.003)	-0.001 (-0.006, 0.004)
RH[2]	0.045 (-0.003, 0.093)	-0.0008 (-0.046, 0.045)	0.039 (0.997, 0.078)	0.014 -0.026, 0.055)
Tmax[3]	**0.018 (0.0004, 0.036)**	0.011 (-0.006, 0.028)	0.013 (0.999, 0.027)	0.010 (-0.004, 0.024)
NO_2[4]	0.004 (-0.006, 0.013)	0.0008 (-0.008, 0.009)	0.006 (-0.001, 0.014)	0.003 (-0.004, 0.011)

[1] p-value <0.050 in bold
[2] per 5% increase in RH at Lag01
[3] per 1° Celsius increase at Lag01
[4] per 1-unit increase in air pollutant
*Adjusted for study location and season

Table S5

A table showing the interactive effect of RH and air pollution on FEV_1 and FVC in a cohort of German adolescents when stratified by the presence of chronic respiratory disease (CRD).

	CRD=YES				CRD=NO			
	FEV_1		FVC		FEV_1		FVC	
	ß (95% CI)*	P_{int}-value	ß (95% CI)*	P_{int}-value	ß (95% CI)*	P_{int}-value	ß (95% CI)*	P_{int}-value
RH:$PM_{2.5}$High[2]	-0.002 (-0.135, 0.131)	0.982	0.007 (-0.119, 0.132)	0.963	-0.037 (-0.156, 0.081)	0.638	-0.077 (-0.195, 0.041)	0.354
RH:$PM_{2.5}$Low[2]	-0.033 (-0.375, 0.309)		-0.041 (-0.365, 0.282)		-0.073 (-0.263, 0.118)		-0.069 (-0.258, 0.121)	
RH:O_3High[2]	-0.185 (-0.414, 0.044)	0.271	-0.246 (-0.462, -0.030)	0.063	-0.210 (-0.408, -0.011)	**0.040**	-0.250 (-0.447, -0.052)	**0.047**
RH:O_3Low[2]	-0.059 (-0.369, 0.250)		-0.122 (-0.414, 0.170)		-0.215 (-0.490, 0.060)		-0.032 (-0.306, 0.242)	
RH:NO_2High[2]	-0.067 (-0.229, 0.095)	0.481	-0.088 (-0.241, 0.065)	0.498	0.061 (-0.086, 0.208)	0.679	0.034 (-0.112, 0.180)	0.900
RH:NO_2Low[2]	0.076 (-0.098, 0.251)		-0.035 (-0.200, 0.129)		0.038 (-0.173, 0.249)		0.005 (-0.205, 0.215)	

[1] p_{int}-value <0.050 in bold

[2] per 5% increase in RH at Lag01; when compared to reference category

*Adjusted for study location, season, and indicated temperature variable

Table S6.

A table showing the ß and 95% CI of the Interactive effects of RH and categorical air pollution (25th and 75th percentile) on FEV_1 and FVC in a cohort of German adolescents.

	FEV1		**FVC**	
	ß (95%CI)*	P_{int}-value	ß (95%CI)*	P_{int}-value
RH:$PM_{2.5}$High[2*]	-0.004 (-0.056, 0.047)	0.959	-0.013 (-0.063, 0.037)	0.211
RH:$PM_{2.5}$Low[2*]	-0.011 (-0.087, 0.066)		-0.067 (-0.142, 0.007)	
RH:O_3High[2*]	-0.068 (-0.138, 0.003)	0.169	-0.070 (-0.138, -0.001)	0.135
RH:O_3Low[2*]	-0.024 (-0.097, 0.050)		-0.029 (-0.101, 0.042)	
RH:NO_2High[2*]	0.007 (-0.048, 0.063)	0.865	0.015 (-0.039, 0.069)	0.785
RH:NO_2Low[2*]	0.017 (-0.047, 0.082)		0.019 (-0.044, 0.082)	

[1] p_{int}-value for interaction in bold is statistically significant at P<0.05
[2] per 5% increase in RH at Lag01; when compared to reference category
*Adjusted for study location, season, and Tmax

Table S7.

A table showing the ß and 95% CI of the Interactive effects of RH and categorical air pollution (10th and 90th percentile) on FEV_1 and FVC in a cohort of German adolescents.

	FEV1		**FVC**	
	ß (95%CI)*	P_{int}-value	ß (95%CI)*	P_{int}-value
RH:$PM_{2.5}$High[2*]	-0.008 (-0.080, 0.065)	0.808	-0.003 (-0.073, 0.067)	0.584
RH:$PM_{2.5}$Low[2*]	-0.039 (-0.160, 0.082)		-0.062 (-0.180, 0.055)	
RH:O_3High[2*]	-0.108 (-0.213, -0.003)	0.127	-0.135 (-0.237, -0.033)	**0.035**
RH:O_3Low[2*]	-0.027 (-0.152, 0.098)		-0.016 (-0.137, 0.105)	
RH:NO_2High[2*]	-0.010 (-0.087, 0.067)	0.771	-0.010 (-0.085, 0.065)	0.615
RH:NO_2Low[2*]	0.030 (-0.061, 0.121)		0.042 (-0.047, 0.130)	

[1] p_{int}-value for interaction in bold is statistically significant at P<0.05
[2] per 5% increase in RH at Lag01; when compared to reference category
*Adjusted for study location, season, and Tmax

3. Discussion

3.1. Main findings

The impact of climate change and climate-related factors, and their combined effect with other environmental factors, on human health is a relatively new area of research within environmental epidemiology. Despite being an emerging field, it is expanding rapidly and making significant progress in investigating the effects of climate-related variables such as temperature and relative humidity on health. The papers presented in this thesis are some of the first to be published on their respective topics in this field.

3.1.1. Systematic review and meta-analysis

I found several interesting results in the systematic review and meta-analysis investigating the effect of temperature-modified air pollution on respiratory mortality and morbidity (1). First, I found that exposure to PM_{10} on high temperature days was statistically significantly associated with an increased risk of respiratory mortality; a similar result was found for PM_{10} exposure on low temperature days and during both warm and cold seasons on respiratory hospital admissions; however, these results were not statistically significant and were largely inconsistent. Second, exposure to O_3 on high temperature days and during the warm season was statistically significantly associated with respiratory mortality and hospital admissions. A similar result was found for low temperatures and the cool season, but these results were inconsistent. Finally, $PM_{2.5}$ and NO_2 exposure on both high and low temperature days were associated with increased mortality and morbidity, but these studies were heterogeneous in their definitions and the results were inconsistent. Based on the results above, I can conclude that we can accept the first hypothesis presented in my systematic review, which found that interactions between temperature and air pollution increased respiratory mortality and morbidity.

Four main points emerged from the evaluation of this review: (1) that it is unusual to use meteorological variables as the primary exposure variable, (2) that although relative humidity is usually adjusted for, its main effect is largely unknown, (3) that mortality and hospital admissions have been studied extensively, but the same cannot be said for respiratory health indicators, and (4) that studies have mainly focused either on the elderly or on infants. Based on conclusions drawn from my review, I decided to investigate meteorological effects on respiratory indicators in adolescents, as adolescence is typically a time of rapid physiological development

associated with peak lung function.

3.1.2. Meteorological variables and lung inflammation

The second paper of this thesis focused on the short-term effects of meteorological exposures and air pollution on airway inflammation or FeNO in adolescents, which was used to answer my second hypothesis and partially answer my fourth hypothesis (2). This study used relative humidity as the main exposure, examined a respiratory health indicator (FeNO) focusing on airway inflammation, and looked at these effects in adolescents.

As this topic was set up to fill a gap in research, it is one of the first to provide evidence on the relationship between relative humidity, as modified by exposure to air pollution, and FeNO. FeNO differs from lung function in that a decrease in FeNO is positive while an increase in FeNO is negative. I found that the main effect of relative humidity on FeNO was protective, whereas temperature and air pollutants, $PM_{2.5}$, NO_2 and O_3, were associated with a negative effect on FeNO. Furthermore, I investigated whether relative humidity and air pollution had an interactive effect.

I found that $PM_{2.5}$ and NO_2 modified the effect of relative humidity, with the association between relative humidity and NO_2 showing a statistically significant increase in FeNO or lung inflammation. The association between relative humidity and O_3 was surprising, as there was a statistically significant decrease in lung inflammation, but this could be because relative humidity counteracts the effects of O_3.

Based on these results, I can conclude that I can partially accept my second hypothesis, as temperature and air pollution are associated with increased lung inflammation; however, relative humidity is only associated with increased lung inflammation when it interacts with air pollution. To partially address my fourth hypothesis, I also performed several effect modifications. While I hypothesised that female participants would be more sensitive to meteorological effects on lung inflammation, I found that male participants were more sensitive to the effects of temperature on lung inflammation than female participants. However, my hypothesis was supported by my results on CRD, as those with CRD and low SES were more likely to experience increased lung inflammation after exposure to increasing relative humidity, temperature and air pollution.

3.1.3. Meteorology and lung function

As with the second publication, I reviewed available literature on the association between environmental exposures and lung function during adolescence. The association between air pollution and lung function has been extensively assessed. Within the GINIplus and LISA cohorts, several publications have reported an adverse association between air pollution and lung function during adolescence; however, these studies mainly assessed long-term exposures and often did not account for meteorological impacts (78-80). Research looking at meteorological variables and lung function in adolescents was limited.

Therefore, the final paper in this dissertation further expanded on paper two by looking at the association between humidity and air pollution on lung function and addressed my third hypothesis and partially my fourth hypothesis (3).

In this study, I used two common indicators of lung function: FEV1 and FVC. Unlike FeNO, an increase in FEV1 and FVC indicates an increase in lung function. Like FeNO, I found that a 5% increase in relative humidity and a 1°C increase in Tmax was associated with a statistically significant increase in FEV1; a similar, non-significant result was found for FVC. No significant results were found for short-term air pollution exposure. In models where I looked at the effect of relative humidity during high and low air pollution exposure compared to the reference category (medium or the most common exposure), I found that exposure to elevated air pollution modified the effect of relative humidity; this was especially apparent with O_3 exposure where I found that there was a statistically significant decrease in FEV1 and FVC per 5% increase in relative humidity during exposure to high O_3 levels. Additionally, I found that the effect of relative humidity changed even at low air pollution exposure, indicating that air pollution adversely impacts health even at low exposure levels.

Based on my results, I can only accept the hypothesis when discussing the interactive effect between meteorological factors and air pollution; if I look at the individual effects of meteorological factors and air pollution, I failed to accept the hypothesis as meteorological factors showed a protective effect. The effect modification studies in this paper supported my fourth hypothesis as I found that lung function differed from lung inflammation in that female participants' lung function was more sensitive to meteorological effects than male participants; I also

found that those without a history of CRD were more sensitive to interactive effects between relative humidity and air pollution.

3.1.4. Positioning within existing literature

This topic is complex to place into context within available literature. Within the GINIplus/LISA cohorts, these publications were the first to assess whether meteorological variables and their potential modification by air pollution had an effect on lung function and inflammation. However, previous studies within the GINIplus/LISA cohorts have investigated the effects of air pollution on lung inflammation and function. A study by Zhao and Kress et al. (78) looked at air pollution during infancy and lung function development into adolescence; this study found that NO_2 and $PM_{2.5}$ were associated with a decrease in lung function per interquartile range increase in air pollutant exposure during the first year of life. My study results pertaining to air pollution differed; however, my study looked at short-term effects. The studies by Liu and Flexeder et al. (81) and Kress and Kilanowski et al. (77) both investigated the effect of air pollution on lung inflammation and found that an increase in NO_2 was associated with an increase in FeNO, which is in line with my own results. In other available research, I found that research on meteorological effects on lung function and inflammation in adolescence was not available. However, a study by Lepeule and Litonjua et al. (82) looked at lung function's association with temperature and relative humidity as well as its interaction with air pollution in the elderly. In contrast to my results, in this study, they found a decrease in lung function with a 5% increase in temperature and a 5% increase in relative humidity. The lack of research on meteorological associations with lung health is concerning, and the apparent gap in the literature on adolescent respiratory health shows the importance of my work within the existing literature.

3.1.5. Hypotheses and study conclusions

This dissertation investigated the interaction between temperature, air pollution and respiratory health through four main hypotheses. First, I confirmed that the interaction between temperature and air pollution does indeed exacerbate respiratory mortality and morbidity. Second, while relative humidity alone had no adverse effect on lung inflammation, its interaction with air pollution increased inflammation levels. Third, I found that while relative humidity alone had no significant effect on lung function, its interaction with air pollution reduced lung

function, while temperature improved it. Finally, my results showed that people with CRD have an increased sensitivity to meteorological effects on respiratory health; men are more susceptible to lung inflammation and women to changes in lung function. These findings add to the understanding of the complex relationship between meteorological factors, air pollution and respiratory health in German adolescents.

3.2. Potential Biological Mechanisms

3.2.1. Meteorology

Determining the exact biological mechanisms by which environmental exposures affect the human body, particularly the respiratory system, is complex. It is even more difficult to establish these relationships because each exposure affects the body differently and interacts with other exposures.

In my publications, I have found that different environmental exposures affect respiratory health in different ways. My main exposure was relative humidity, but temperature was an important confounding factor, so I reported the main effect of increasing temperature. While the pathways for air pollution have been extensively studied, the same cannot be said for temperature and relative humidity, but there are some hypothesised pathways (83).

In my studies, I found that increasing temperatures were associated with improved respiratory health. This is supported by the literature, as it has been reported that during periods of extreme cold, the lungs, which are normally a warm and humid environment, are exposed to cool, dry air, which can cause bronchoconstriction, damage to airway epithelial tissue and changes in airway wall structure and function, which in turn can cause inflammation (84). It has also been reported that exposure to extreme heat is more likely to be associated with increased stress on several systems within the body, which can then trigger inflammatory responses in several different organs, including the lungs (85); however, this mechanism is less applicable in our studies as this type of extreme heat exposure was uncommon in our participants. As my studies also looked at effect modification based on CRD, I also looked for potential mechanisms between meteorological variables and respiratory disease, as my results suggested a sensitivity to meteorological variables when participants had CRD; I found two studies using mouse models to assess the effect of temperature variation and high vs. low temperature on allergic

asthma, where they found that large temperature variations and exposure to extreme heat and cold increased lung inflammation and showed airway restructuring (86, 87).

3.2.2. Air pollution

In my studies, I adjusted for air pollution and investigated the interactive effects of relative humidity and air pollution on respiratory health. I found that exposure to air pollution can modify the effects of relative humidity, so it is important to understand the biological mechanisms of air pollution on respiratory health.

My results on lung function showed that exposure to O_3 was associated with a decline in lung function, which could be attributed to the following biological mechanisms (3). O_3 is associated with a wide range of effects on respiratory health, primarily caused by oxidative damage to the epithelium (29, 88). O_3 causes direct oxidative damage to cells or secondary damage by diverting energy from primary cell functions to the production of defence mechanisms (89). One defence mechanism produced is antioxidants; O_3 reacts with these antioxidants in the pulmonary surfactant, which protects the lungs from oxidative damage (89). This interaction can trigger an influx of inflammatory cells that damage the air-blood barrier, causing the lungs to function less efficiently (89). An animal study in guinea pigs found that for 1-3 days after O_3 exposure, airway hyperactivity is mediated by an increase in eosinophils, which release eosinophil major basic protein, which blocks neuronal M2 muscarinic receptors, causing an increase in acetylcholine release and increased bronchoconstriction (90). Long-term exposure has been associated with morphological changes in the lungs, which adversely affect lung function (89).

In my study, NO_2 and $PM_{2.5}$ were associated with increased lung inflammation (2). NO_2 and biological mechanisms with lung inflammation are well reported, as NO_2 causes biochemical and morphological changes in the lung. In addition, NO_2 causes cellular damage, epithelial proliferation, inflammation and fibrotic changes in the lung (88). NO_2 can cause this damage because it is readily absorbed throughout the respiratory tract, causing injury to the trachea, bronchi, bronchioles, alveolar ducts and proximal airways. While looking at the effect modification of CRD, I also looked for potential animal models and human studies. I found a mouse model that investigated NO_2-induced allergic airway inflammation and hyperresponsiveness (91). In this model, the authors found that within 3 days of

exposure to NO_2, the terminal bronchioles showed increased structural changes with increased numbers of periterminal bronchiole macrophages mixed with neutrophils, lymphocytes and plasma cells (91); in addition, the terminal bronchioles showed signs of airway epithelial cell damage. A human study by Wang and Duddle et al. (92) found that NO_2 exposure increased allergen-induced eosinophil cationic protein in subjects with allergic rhinitis. My results support these clear links between NO_2 and airway inflammation.

$PM_{2.5}$ is a primary air pollutant associated with several respiratory diseases because it is small enough to penetrate deep into the lungs and enter the bloodstream (88). $PM_{2.5}$ can trigger the oxidation of lung cells; this oxidation triggers inflammatory responses, leading to lung inflammation (93). The DNA changes caused by $PM_{2.5}$ exposure can also cause remodelling of the small airways, while also penetrating and accumulating in the lungs (29, 78). The inflammatory nature of $PM_{2.5}$ is well-documented. For instance, a study by Nikasinovic and Just et al. (94) examined 44 healthy and 41 asthmatic children to assess the presence of nasal inflammation after personal exposure to $PM_{2.5}$. The nasal passage is the initial region of the respiratory tract and enables a non-invasive approach, via nasal lavage, to evaluate the presence of eosinophils as an indicator of nasal inflammation. This study showed an association between $PM_{2.5}$ exposure and elevated eosinophil levels, particularly in children with asthma, an inflammatory disease. Similar to nasal inflammation, airway inflammation is driven by inflammatory mediators, such as NO measured as FeNO, which is produced by cells like eosinophils. Therefore, this study and my findings support the proposed biological mechanism linking $PM_{2.5}$ exposure to airway inflammation.

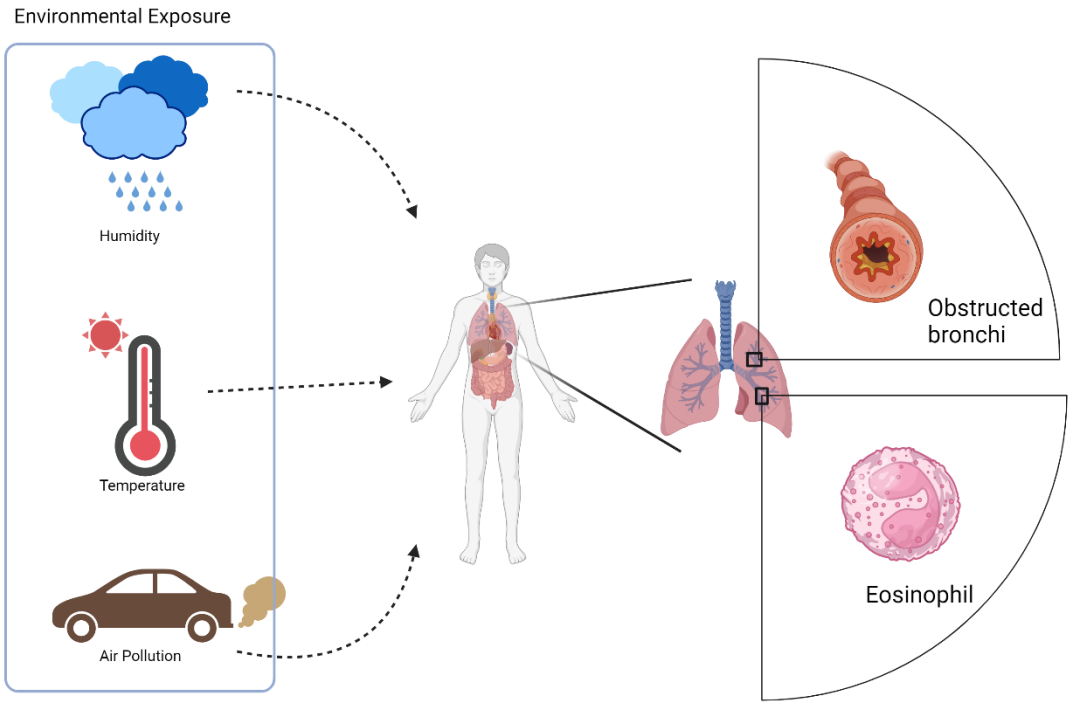

Figure 1. A figure summarising environmental exposures on respiratory health. (Made by AT. Areal using Biorender)

3.3. Strengths and Limitations

This review identified several strengths and limitations. A strength was the use of a systematic review and meta-analysis to identify limitations in the available research. This allowed me to assess which areas needed further study and to identify critical populations, indicators and exposures that were understudied. Another strength is the use of established and well-characterised birth cohorts; this allowed me to assess the longitudinal effects of meteorological variables and air pollution on subclinical respiratory endpoints. A final strength is that my results are better suited to public health planning for adolescent health initiatives by using a cross-sectional study nested within a cohort.

It is important to note that my studies have several limitations. First, the exposures and characteristics I examined are limited to Germany and my participants. Therefore, I cannot extrapolate my findings to a broader population with different exposures and characteristics. Second, the exposure data I used may not fully represent each participant's individual exposure. Third, my study samples are

relatively small, which limits the statistical power of the results and conclusions presented in this dissertation.

3.4. Implications for Public Health and Future Research

Climate change is having a devastating impact on human health and urgent action is being taken to address and mitigate its effects (6, 22). Rising temperatures, extreme weather events and air pollution are increasing the incidence of heat-related illnesses, injuries and mental health problems (3). As temperatures rise, existing health problems are projected to worsen and preventable adverse health events are projected to increase. Immediate action is needed to mitigate the effects of climate change and work towards a more sustainable future that prioritises the health and well-being of all. Studies such as those presented in this dissertation are essential for the public health community and stakeholders as they provide evidence of the adverse effects of climate change.

The research presented in this thesis has several public health and policy implications. First, the effect of meteorological parameters and their association with respiratory health outcomes in adolescents and across age groups is understudied. This is particularly evident as the studies presented in this dissertation are among the first on this topic and the first in Germany. Therefore, this research provides a foundation for future research on the effect of meteorological factors on respiratory and adolescent health within public health and environmental epidemiology. Due to the lack of research on the effects of meteorological variables on adolescent respiratory health, there are no warning systems to advise physicians and their patients about the potential individual and combined effects of meteorological variables and air pollution on adolescent respiratory health; it would be suggested that physicians aim to warn their adolescent patients about the effects of climate-related factors on health and promote healthy strategies to prevent heat stress. Finally, studies such as those presented in this thesis are essential to provide relevant information that can be used by stakeholders, such as doctors, policymakers, researchers and health organisations, to prevent adverse health effects of meteorological variables.

Governments need to invest in research to better understand the complex relationship between climate change and health. In particular, future research should focus on understanding the interactive effects of meteorological variables on respiratory health. This will allow researchers to better predict the relationship

between meteorology and health. In addition, studies should be expanded to include multi-exposure models to better assess the effects of multiple exposures and to better incorporate real-life exposures to humidity, temperature and air pollution. Finally, more long-term studies should be conducted to see how prolonged exposure to environmental factors affects respiratory health.

3.5. Conclusions

Based on the analyses and discussion presented, several conclusions can be drawn:

- Meteorological factors, such as temperature and RH, have individual effects on respiratory health endpoints.
- Air pollution can modify the effect of meteorological factors, which can exacerbate adverse respiratory effects.
- Female participants are more sensitive to the effects of meteorological factors than male participants.
- Those with CRDs are more sensitive to the effects of meteorological factors.
- Further investigation into the effects of meteorological factors on adolescent health is crucial in understanding how multi-environmental exposures can affect future health.

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5. Appendix

5.1. GINIplus and LISA ethical clearance

GINI Studie – Übersicht Ethik

20 year - Corona follow up:
Bavarian Board of Physicians:
Board of Physicians of North-Rhine-Westphalia: 6000212019

20 year follow up:
Bavarian Board of Physicians: 10090
Board of Physicians of North-Rhine-Westphalia: 2015491

15 year follow up:
Bavarian Board of Physicians: 10090
Board of Physicians of North-Rhine-Westphalia: 2010424

10 year follow up:
Board of Physicians of North-Rhine-Westphalia: 2005407
Bavarian Board of Physicians: 05100

6 year follow up:
Bavarian Board of Physicians: 01212
Board of Physicians of North-Rhine-Westphalia: 2001330

Birth:
Dep. of Medicine (LMU): 111/94
Board of Physicians of North-Rhine-Westphalia: 9061

LISA Studie – Übersicht Ethik

20 year follow up
Bavarian Board of Physicians: 12067
Board of Physicians of Saxony: EK-BR-2/13-2
Board of Physicians of North-Rhine-Westphalia: 2018083

15 year follow up:
Bavarian Board of Physicians: 12067
Board of Physicians of North-Rhine-Westphalia: 2012446

Board of Physicians of Saxony: EK-BR-02/13-1

10 year follow up:
Medical Faculty of the University of Leipzig: 345-2007
Board of Physicians of North-Rhine-Westphalia: 2008153
Bavarian Board of Physicians: 07098

6 year follow up:
Bavarian Board of Physicians: 03166
Board of Physicians of North-Rhine-Westphalia: 2003355
Medical Faculty of the University of Leipzig: 206/2003

Birth:
Dep. of Medicine (LMU): 138/97
Board of Physicians of North-Rhine-Westphalia: 188
Medical Faculty of the University of Leipzig: 560

5.2. GINIplus consent form

BITTE ZURÜCK SENDEN

GINIplus 15

Einverständniserklärung
zum 15-Jahres-Studienabschnitt

G15TEV

Studienzentrum:

Meine Eltern und ich haben die Information genau gelesen und sind bereit, an folgenden Teilen der Studie teilzunehmen: **(Nichtzutreffendes bitte streichen)**

Befragung

- **Fragebogen für die Eltern der GINI-Studienteilnehmer/innen** (nur schriftlich)
- **Ernährungsfragebogen für GINI-Studienteilnehmer/innen** (nur schriftlich)
- **Weitere Fragebögen für GINI-Studienteilnehmer/innen** (schriftlich oder online)

→ Ich möchte gerne die Fragebögen ❒ schriftlich oder ❒ online beantworten.

(Bitte vergiss nicht, Deine E-Mail-Adresse unten anzugeben. Auch wenn Du die Fragen schriftlich beantworten möchtest, können wir so besser Kontakt zu Dir aufnehmen.)

Untersuchung im Studienzentrum

- **Körperliche Untersuchung und Blutdruckmessung**
- **Blutabnahme für einen Allergietest und weitere Analysen**
- **Urinsammlung**
- **Lunge (Stickstoffgehalt in der Ausatmung und Lungenfunktion)**

Aktivitätsmessung

- **Aktivitätsmessung mit einem für 7 Tage am Körper getragenen Beschleunigungssensor** (wird Dir bei Teilnahme zugeschickt)

Es ist geplant, die vorhandenen Bioproben Ihres Kindes für unbegrenzte Zeit aufzuheben und gegebenenfalls für neue medizinische Forschungsfragen zu verwenden. Sie haben jederzeit und ohne Angabe von Gründen das Recht, die Vernichtung der Proben zu verlangen. Sowohl die Adressdaten als auch die wissenschaftlichen Daten werden mit einer Kennnummer versehen, die es erlaubt, mit Ihnen wieder in Verbindung zu treten (z.B. zur Klärung von Rückfragen). Die erhobenen Daten werden pseudonymisiert, das heißt sie werden getrennt von Namen und Adressen im Studienzentrum gespeichert, so dass bei der Analyse der Daten kein Personenbezug hergestellt werden kann.

Meine Eltern und ich sind damit einverstanden, dass unsere Anschrift im Helmholtz Zentrum München gesichert und getrennt von allen Befunddaten gespeichert werden darf, um ggf. für Nachfragen und mögliche weitere Folgestudien in Kontakt bleiben zu können.
Die Teilnahme ist freiwillig. Wir können unser Einverständnis jederzeit ganz oder teilweise ohne Angabe von Gründen unter der angegebenen Adresse widerrufen, ohne dass uns dadurch Nachteile entstehen. Wir hatten ausreichend Zeit, uns die Entscheidung über die Teilnahme zu überlegen. Über Risiken und Vorteile wurden wir informiert.

..... Vorname und Name des Studienteilnehmers

..... geboren am

..... Email des Studienteilnehmers

..... Telefon des Studienteilnehmers

..... Unterschrift des Studienteilnehmers

Bitte Rückseite beachten!

..... Ort, den ..... Datum

..... Unterschrift des Erziehungsberechtigten

GINI15T_InformedConsent_blank.doc

BITTE ZURÜCK SENDEN

Anschrift und Kontaktdaten der Eltern und Studienteilnehmer

Wir haben folgende Adresse als Postanschrift für bei uns gespeichert:

Stimmt diese Anschrift? ❒ ja ❒ nein
Wenn nicht, dann bitten wir um die aktuelle Postanschrift:

Straße .....

PLZ ..... Ort .....

Land .....

Hält sich überwiegend an diesem Ort auf? ❒ ja ❒ nein
Wenn nicht, dann bitten wir um die von hauptsächlich genutzte Adresse:

Straße .....

PLZ ..... Ort .....

Land .....

Kontaktdaten Eltern/Erziehungsberechtigte (wenn nötig bitte korrigieren oder ergänzen):

Name .....;.....
E-Mail .....
Telefon/mobil .....

Name und Anschrift einer weiteren Kontaktperson für den Fall eines Umzuges (z.B. Großeltern, Verwandte/r des Kindes)

Name ..... Vorname ..... Familienname
wohnhaft in ..... Straße ..... PLZ, Ort, Land
Kontakt ..... Telefonnummer ..... Email

5.3. LISA consent form

BITTE ZURÜCK SENDEN

Anschrift und Kontaktdaten der Eltern und Studienteilnehmer

Wir haben folgende Adresse als Postanschrift für VORNAME bei uns gespeichert:

ADRESSE
ADRESSE
ADRESSE

Stimmt diese Anschrift? ❒ ja ❒ nein
Wenn nicht, dann bitten wir um die aktuelle Postanschrift:

Straße .....

PLZ ..... Ort .....

Land .....

Hält sich VORNAME überwiegend an diesem Ort auf? ❒ ja ❒ nein
Wenn nicht, dann bitten wir um die von VORNAME hauptsächlich genutzte Adresse:

Straße .....

PLZ ..... Ort .....

Land .....

Kontaktdaten Eltern/Erziehungsberechtigte (wenn nötig bitte korrigieren oder ergänzen):

Name NAME ELTERN .....

E-Mail E-MAIL ELTERN .....

Telefon TELEFON ELTERN .....

Mobil MOBIL ELTERN .....

Name und Anschrift einer weiteren Kontaktperson für den Fall eines Umzuges (z.B. Großeltern, Verwandte/r des Kindes)

Name ....
Vorname Familienname

wohnhaft in ....
Straße PLZ, Ort, Land

Kontakt ....
Telefonnummer E-Mail

BITTE ZURÜCK SENDEN

LISAplus 15

Einverständniserklärung
zum 15-Jahres-Studienabschnitt

L15TEV

Studienzentren:	Betreuung:	ID-Nr.:

Meine Eltern und ich haben die Information genau gelesen und sind bereit, an folgenden Teilen der Studie teilzunehmen: **(Nichtzutreffendes bitte streichen)**

Befragung

- **Fragebögen für die Eltern der LISA-Studienteilnehmer/innen**
- **Fragebögen für LISA-Studienteilnehmer/innen inkl. Ernährungsfragebogen**

  Die Fragebögen für dich als LISA-Studienteilnehmer/in erhältst du nach Rücksendung der Einverständniserklärung.)

Untersuchung im Studienzentrum

- **Körperliche Untersuchung und Blutdruckmessung**
- **Blutabnahme für einen Allergietest und weitere Analysen**
- **Urinsammlung**
- **Lunge (Stickstoffgehalt in der Ausatmung und Lungenfunktion)**
- **Zahnuntersuchung**

Aktivitätsmessung

- **Aktivitätsmessung mit einem für 7 Tage am Körper getragenen Beschleunigungssensor** (wird Dir bei Teilnahme zugeschickt)

Es ist geplant, die vorhandenen Bioproben Ihres Kindes für unbegrenzte Zeit aufzuheben und gegebenenfalls für neue medizinische Forschungsfragen zu verwenden. Sie haben jederzeit und ohne Angabe von Gründen das Recht, die Vernichtung der Proben zu verlangen. Sowohl die Adressdaten als auch die wissenschaftlichen Daten werden mit einer Kennnummer versehen, die es erlaubt, mit Ihnen wieder in Verbindung zu treten (z.B. zur Klärung von Rückfragen). Die erhobenen Daten werden pseudonymisiert, das heißt sie werden getrennt von Namen und Adressen im Studienzentren gespeichert, so dass bei der Analyse der Daten kein Personenbezug hergestellt werden kann.

Meine Eltern und ich sind damit einverstanden, dass unsere Anschrift im Helmholtz Zentrum München gesichert und getrennt von allen Befunddaten gespeichert werden darf, um ggf. für Nachfragen und mögliche weitere Folgestudien in Kontakt bleiben zu können.
Die Teilnahme ist freiwillig. Wir können unser Einverständnis jederzeit ganz oder teilweise ohne Angabe von Gründen unter der angegebenen Adresse widerrufen, ohne dass uns dadurch Nachteile entstehen. Wir hatten ausreichend Zeit, uns die Entscheidung über die Teilnahme zu überlegen. Über Risiken und Vorteile wurden wir informiert.

....
Vorname und Name des Studienteilnehmers — geboren am

....
E-Mail des Studienteilnehmers — Telefon des Studienteilnehmers

.....
Unterschrift des Studienteilnehmers

Bitte Rückseite beachten!

..... , den .....
Ort — Datum

.....
Unterschrift des Erziehungsberechtigten

LISA_15 - EVAllg 2012.06.21.docx

Acknowledgements

So many people deserve acknowledgements, and while I wish I could write one for everyone, I cannot because that would be a whole thesis on its own. Therefore, I thank all the people who have assisted me during this process and appreciate your help. However, the following people deserve to be acknowledged by name, as I would not have been able to do this without them:

To Dr. Tamara Schikowski, my incredible supervisor and mentor. You have been so supportive since the beginning of my time at the IUF. You are, and were, always available to give guidance and support when it was needed. You have been not just a supervisor but an exceptional mentor, and I am so fortunate to have had this opportunity to learn from you. Thank you for everything you have done for me and all the opportunities you have presented me.

To Dr. Nidhi Singh, my consistently supportive postdoc. You are always ready to let me ask you questions, even when I answer the question before you have the opportunity to respond. I appreciate all the effort you have put into making me a well-rounded epidemiologist.

To Sandra Sandhöfer, an amazing colleague and an even more amazing friend. You motivated me when I was feeling down and always encouraged me to keep moving forward. Your ability to cheer me up truly helped me to finish this. I also appreciate all the help you gave me when it came to German!

To the rest of my colleagues at the IUF, Sara, Claudia, Alex, Bo, and Elke, thank you for being so supportive of me, talking to me, and welcoming me. I can always come to all of you with any troubles, and knowing that you all supported me and pushed me forward helped me persevere when I struggled.

To my father, Paulo Areal. It is hard to find a place to start when discussing how much you have done for me (although this is a decent one). You always led by example and persevered during difficult times. I honestly do not believe I would be where or who I am without you; you taught me what it means to work hard, never give up, and always follow my dreams. You also taught me that taking a break and having some fun was an important aspect of working hard. You always believed in me and told me I could do anything I set my mind to. You always knew when to encourage me and when to pull me back into orbit when my head was in the stars. Muito Obrigada Pai. Amo-te e beijinhos.

To my mother, Cheryl Areal. You always saw my capabilities more clearly than nearly anyone and pushed me to fully embrace my abilities and achieve what you knew I could. While we may not always see eye to eye, I understand that you have always been one of my biggest cheerleaders and always believed I could achieve great things. Thank you for pushing me, showing me what hard work looks like, and teaching me the lessons that were necessary to become who I am. I know I don't say it often (as verbal affection is not my strong point, as you know better than most), but I love you, and I am lucky to have had you as my mother.

To my younger sister, Taigen Child. I have always tried to show you that the only person who can truly hold you back is yourself. I have always wanted you to see that you are capable of great things. I have adored you from the moment I first saw your face (even if I did call you ugly). While I definitely did this for me, I also did this for you to show what I know that you are also capable of. I love you, Taigs; thank you for motivating me to be strong for you as your big sister.

To my Granny, Margaret Austin. I'm your oldest Grandchild and Granddaughter, and I know that I have always been your favourite (joking... kinda). Thank you for your endless love and patience; thank you for the crochet blankets and biscuits; thank you for teaching me how to play cards and nursing my competitive spirit. Thank you for loving me so wholly and

completely. I love you.

To my Aunt Taryn and my Tia Bixo, thank you both for being true forces of nature: organised, efficient, and supportive. You have both been commanding presences in my life, and I feel very fortunate to have had two strong women in my corner. I appreciate all that you do and have done for me. Thank you for always accepting me for who I am. I love you both. Beijinhos.

To Christy and Alistair Mathie, my honorary aunt and uncle. I was so fortunate that you were both already here in Düsseldorf when I moved here. Through the moving process to surviving the COVID pandemic, you have both been my support system here, and I am eternally grateful for all you have done for me. Thank you for keeping me fed (with food and love!). I love you both.

To Dr. Lauren Sahd, my best friend. We started our university careers together (all the way back at Stellenbosch in 2013), and while we went in very different directions within the field of medicine, I am so proud of how far we've come. I am so thankful that you are in my life and that I have your never-ending support, sarcasm, and patience towards my long-winded theories. You are truly the best.

Finally, to myself. I sometimes struggled with procrastination and imposter syndrome; however, I persevered and tried my best, never giving up. I worked so hard throughout my life, and this is the culmination of those late nights and all the very loud music I listened to. I did this. I achieved the dream and goal I set for myself as a 6-year-old. Well done!