What Are the Effects of Meteorological Factors on Exacerbations of Chronic Obstructive Pulmonary Disease?

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Abstract: Chronic obstructive pulmonary disease (COPD) is one of the greatest global public health challenges. Acute exacerbations of COPD lead to the accelerated deterioration of lung function, reduced quality of life, a higher number of hospitalizations, and increased mortality. The factor causing the exacerbation is usually an infectious agent, but the impact of environmental factors is being studied more thoroughly. Among them, meteorological factors are the least examined. Multiple studies have shown that lower temperatures during the cold season, as well as sudden temperature changes regardless of the season, have the most significant negative effect on patients with COPD. However, higher temperatures, especially during summer heatwaves, can also cause COPD exacerbation and it is expected that this will be an even more important health problem in the future considering climate changes. The effects of other meteorological factors on acute exacerbation of COPD, such as atmospheric pressure, solar radiation, rainfall, wind speed, and humidity are far less investigated and opposing results have been obtained in different studies. Thus, there is a need for further research in this area that would result in clinical recommendations and public health interventions that could decrease the global burden of COPD.

Keywords: meteorological factors; COPD exacerbation; temperature; climate changes; atmospheric pressure; solar radiation; rainfall; wind speed; humidity

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the greatest global public health problems, with a prevalence of 12% in the general population and about three million deaths per year [1], while the highest incidence is reported in economically underdeveloped and developing countries, i.e., over 85% of newly registered cases [2]. The World Health Organization (WHO) estimates that by 2030, COPD will be the third leading cause of death in the world [3]. Due to the high morbidity and mortality, COPD is also an important economic burden on health systems in countries around the world [4].

The chronic and progressive course of the disease is characterized by periods of remission with occasional acute exacerbations of COPD (AECOPD) in the form of pronounced dyspnea that significantly contribute to accelerated deterioration of lung function, poor quality of life, frequent usage of ambulatory medical facilities, frequent hospitalizations, and finally, increased mortality due to COPD [5]. AECOPD are usually caused by respiratory infections of viral or bacterial etiology (50–70% of cases), but in recent years, the impact of exposure to environmental factors, such as air pollutants and meteorological conditions, is being studied more thoroughly. A great number of studies have examined the impact of
air pollution on COPD exacerbations, but there is a limited number of studies that have investigated the effects of meteorological factors. Even when the scientists tackled this subject, the effect of air temperature has been the most frequently studied factor, while others, such as atmospheric pressure, wind speed and direction, humidity, rainfall, and solar radiation, as well as seasonal variations of these factors, have been significantly less examined. Thus, it is necessary to conduct further research in this area that could serve as a basis for new clinical recommendations in the treatment of COPD and could also lead to the important public health interventions that would reduce the burden on health systems from this disease. In addition, a better understanding of the meteorological factors’ influence on AECOPD could contribute to a better organization of health institutions in the days when a greater influx of patients is expected due to the changes in the weather patterns.

The aim of this paper is to provide critical insight into the current knowledge about the influence of meteorological factors on the occurrence of AECOPD through a review of contemporary scientific literature.

2. Materials and Methods

Using selected keywords (“meteorological factors”, “COPD exacerbation”, “temperature”, “atmospheric pressure”, “humidity”, “wind speed”, “rainfall”, “solar radiation”, “heatwave”, and “climate changes”), we searched bibliographic databases PubMed, Web of Science, Scopus, and Google Scholar for available meta-analysis, literature, and systematic reviews, as well as clinical studies where the influence of meteorological factors on the frequency of COPD exacerbations was examined or analyzed. The research included relevant literature sources, only in English, that had been published within a 27-year period, starting from June 1993 to September 2020, and that met the following inclusion criteria: impact factor of the journal, number of citations, year of publication, and educational significance of available information in a particular manuscript. The results were discussed based on their clinical and public health significance. A total of 80 bibliographic sources were used in writing the paper.

3. Review of the Literature

3.1. The Influence of Air Temperature on Acute Exacerbations of COPD

The effects of air temperature on AECOPD have been examined in multiple studies conducted so far. However, the results are not cohesive enough. The requirement for further research resulted not only from the clinical experience of physicians that the symptoms of patients with COPD worsen during the winter months but also due to the accumulating data about the effects of climate changes, expected global temperature rise, and higher frequency of temperature extremes in the future, both hot and cold.

The results of numerous studies have shown that patients with COPD have a higher frequency of disease exacerbations, hospitalizations, and consequent mortality during the cold season (October–March in the Northern Hemisphere) as compared with the warm season (April–September in the Northern Hemisphere) [6–13]. Seasonal variations in air temperature are most notable in the Northern Hemisphere, slightly less manifested in the Southern Hemisphere, while are almost non-existing in the tropics [14]. In countries with higher annually average temperature, it is noted that the negative effect of lower temperatures on morbidity and mortality from COPD is greater than in countries with otherwise colder climate [15]. This phenomenon is most likely due to poorer adjustment of patients to temperature differences in countries with warmer climate, but also due to the usage of adequate building materials for the construction of homes and public buildings, as well as more appropriate clothing in countries with unfavorable climatic conditions [16]. A study by McCormack et al. showed that lower outdoor temperatures during the cold season were associated with an increased frequency of respiratory symptoms, an increased usage of “rescue” inhalers, as well as with the accelerated loss of lung function in patients with COPD [17]. The results of a study conducted in Taiwan also pointed to the negative effect of lower outdoor temperatures on COPD, i.e., for each decrease of 1 °C during the
cold season, the exacerbation rate of COPD increased by 0.8%. It was also discovered that the multi-day duration of low temperatures (over 28 days) significantly increased the risk of exacerbations. At temperatures below 5 °C, elderly patients (≥65 years) and those who had not already used inhalation therapy were at the highest risk of AECOPD [18]. The main findings of several studies examining the effects of lower temperatures on morbidity due to AECOPD are shown in Table 1.

A study examining the effects of lower outdoor air temperature on mortality have shown that a decrease in air temperature of 1 °C during the cold season was associated with an increase in the mortality related to respiratory diseases, including COPD, which was as high as 3.30% [19]. A study conducted in the Chinese city of Ningbo, in 2017, showed that both high and low temperatures increase the risk of death in patients with COPD, and this effect was more pronounced during the winter season [20]. Some authors have suggested that moderate changes in air temperature [21] could be correlated with mortality due to COPD exacerbations [22].

The pathophysiological mechanism that can describe the effects of lower temperatures on AECOPD is yet to be precisely defined. The direct effects of lower temperature on worsening of respiratory symptoms most likely include rhinorrhea and nasal congestion, damage to the airway epithelium with consequent functional and structural re-modulations, as well as direct and reflex bronchospasm [16]. A study by Almagro et al. showed a correlation between low temperature and the number of hospitalizations due to COPD, regardless of relative humidity or air pollution [12], suggesting that the direct effect of air temperature on the airways cannot be ignored. The indirect effects of lower temperature could be observed through the higher frequency of respiratory viral infections in the cold season (primarily caused by rhinoviruses), which in clinical studies were found to be the most common triggers of AECOPD [23], associated with the fact that patients spend more time inside during the winter months, with a reduction in physical activity [24]. In some studies, the synergistic effect of low temperatures with high concentrations of air pollutants, such as particulate matter with a diameter of 2.5 microns or less (PM$_{2.5}$), sulfur dioxide (SO$_2$), and nitrogen dioxide (NO$_2$) can contribute to the higher number of COPD exacerbations during the cold season, with the consequent increase in the number of hospitalizations and mortality due to AECOPD [25,26].

Reviewing current literature, it can be seen that not only low temperatures but also elevated outdoor temperatures can lead to the worsening of COPD [27]. As a result of high outside air temperature, fluid loss and impaired pulmonary perfusion occur, as well as inflammation in the bronchial mucosa and a reduction in the threshold for bronchospasm due to the combined action of air pollutants [28]. The synergistic effect of high temperature with high air humidity and elevated air pollutants concentrations has been established in numerous clinical studies [29–33].
Table 1. The effects of decreased air temperatures on AECOPD hospitalizations/outpatients’ visits.

| Study                                      | Number of Participants | Gender | The Mean Age | Observed Period | Daily Average Temperature (±SD) | Study Design | Adjustment ** | Main Findings                                                                                                                                                                                                 |
|--------------------------------------------|------------------------|--------|--------------|-----------------|---------------------------------|--------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lin et al., 2018 [5] Changhua County, Taiwan | No = 277 hospitalized patients due to AECOPD | 240 males 37 females | 75.3 ± 9.3 years | October to March 2011–2015 | 2011–2015 | 19.36 °C (±3.64) | case-crossover study | RH, BP, NO₂, CO, SO₂, PM₁₀, PM₂.₅, O₃ | During the cooling-down season, the exacerbation likely occurred on days of temperature decrease; a decrease by 1 °C with the 95% CI of OR of 0.68–0.88 and p < 0.001. No significant differences in age and gender were noted (all p > 0.05). The RR for outpatients visits due to AECOPD at extreme cold (first percentiles of temperature throughout the study period) and cold (10th percentile of temperature) temperature over lags 0–14 days were 2.98 (95% CI: 1.77, 5.04) and 1.63 (95% CI: 1.21, 2.19), compared with the 25th percentile of temperature. The between-gender difference was statistically insignificant. For extreme cold temperature, the association among residents ≥ 65 years of age has a 2-fold bigger effect than those with 0–65 years of age. However, the difference was statistically insignificant across age subgroups for cold temperature. AECOPD admissions were less common in the second and third quarter of the year, and more abundant in the last and first quarter of the year. A similar pattern was found in COPD exacerbation-related death. Lower temperatures significantly increased the incidence of hospitalization (OR after 1 week lag was 0.99 (95% CI 0.98 to 0.99), p < 0.001) due to AECOPD. For each degree Celsius decrease in mean weekly temperature, hospital admissions increased by 5.04% (B = −9.5, 95% CI = −11.7, −7.3, r² = 0.591; p < 0.001). After adjustment for humidity, comorbidity, air pollution, and influenza-like illness, only mean temperatures retained statistical significance, with a mean increase of 4.7% in weekly admissions for each degree Celsius of temperature (r² = 0.599; p < 0.001). |

Huang et al., 2015 [6] Shanghai, China | No = 31.092 outpatient visits due to acute exacerbation of chronic bronchitis (AECB) * | no data | no data | 1 January 2010 to 31 December 2011 | 17 °C | time-series study | NO₂, SO₂, PM₁₀, RH, day of the week, sex, age | None | The RR for outpatients visits due to AECOPD at extreme cold (first percentiles of temperature throughout the study period) and cold (10th percentile of temperature) temperature over lags 0–14 days were 2.98 (95% CI: 1.77, 5.04) and 1.63 (95% CI: 1.21, 2.19), compared with the 25th percentile of temperature. The between-gender difference was statistically insignificant. For extreme cold temperature, the association among residents ≥ 65 years of age has a 2-fold bigger effect than those with 0–65 years of age. However, the difference was statistically insignificant across age subgroups for cold temperature. AECOPD admissions were less common in the second and third quarter of the year, and more abundant in the last and first quarter of the year. A similar pattern was found in COPD exacerbation-related death. Lower temperatures significantly increased the incidence of hospitalization (OR after 1 week lag was 0.99 (95% CI 0.98 to 0.99), p < 0.001) due to AECOPD. For each degree Celsius decrease in mean weekly temperature, hospital admissions increased by 5.04% (B = −9.5, 95% CI = −11.7, −7.3, r² = 0.591; p < 0.001). After adjustment for humidity, comorbidity, air pollution, and influenza-like illness, only mean temperatures retained statistical significance, with a mean increase of 4.7% in weekly admissions for each degree Celsius of temperature (r² = 0.599; p < 0.001). |

de Miguel- Díez et al., 2019 [7] Spain | No = 162.338 hospitalized patients due to AECOPD | 83.5% males 16.5% females | 75.1 ± 10.76 years | 1 January 2004 to 31 December 2013 | no data | case-crossover study | RH, NO₂, O₃, PM₁₀, CO | None | AECOPD admissions were less common in the second and third quarter of the year, and more abundant in the last and first quarter of the year. A similar pattern was found in COPD exacerbation-related death. Lower temperatures significantly increased the incidence of hospitalization (OR after 1 week lag was 0.99 (95% CI 0.98 to 0.99), p < 0.001) due to AECOPD. For each degree Celsius decrease in mean weekly temperature, hospital admissions increased by 5.04% (B = −9.5, 95% CI = −11.7, −7.3, r² = 0.591; p < 0.001). After adjustment for humidity, comorbidity, air pollution, and influenza-like illness, only mean temperatures retained statistical significance, with a mean increase of 4.7% in weekly admissions for each degree Celsius of temperature (r² = 0.599; p < 0.001). |

Almagro et al., 2015 [11] Barcelona, Spain | No = 9.804 hospitalized patients due to AECOPD | 75.4% males 24.6% females | 74.9 ± 10.5 years | January to December of 2009 | 13.7 °C (±6.2) | population-based study | RH, comorbidity, air pollution, influenza-like illness | None | Lower temperatures significantly increased the incidence of hospitalization (OR after 1 week lag was 0.99 (95% CI 0.98 to 0.99), p < 0.001) due to AECOPD. For each degree Celsius decrease in mean weekly temperature, hospital admissions increased by 5.04% (B = −9.5, 95% CI = −11.7, −7.3, r² = 0.591; p < 0.001). After adjustment for humidity, comorbidity, air pollution, and influenza-like illness, only mean temperatures retained statistical significance, with a mean increase of 4.7% in weekly admissions for each degree Celsius of temperature (r² = 0.599; p < 0.001). |
Table 1. Cont.

| Study | Number of Participants | Gender | The Mean Age | Observed Period | Daily Average Temperature (±SD) | Study Design | Adjustment ** | Main Findings |
|-------|------------------------|--------|--------------|-----------------|---------------------------------|--------------|---------------|--------------|
| Tseng et al., 2013 [17] Taiwan | No = 16,254 hospitalized patients due to AECOPD and outpatients’ visits | 77.4% males 22.6% females | 75.5 ± 10.2 years | winter months 17.9 ± 3.3 °C summer months 28.4 ± 1.5 °C | 1999–2009 case-crossover study | RH, BP, WS, duration of sunshine and rainfall days | A 1 °C decrease in temperature was linked with a 0.8% increase for AECOPD admission on event-days (OR, 1.008, 95% CI: 1.015–1.138, \( p = 0.015 \)). A decrease of 5 °C in mean temperature was significantly correlated with increased numbers of exacerbations from event-days (OR, 1.039, 95% CI 1.007–1.071, \( p = 0.015 \)) to 28 days (OR, 1.106, 95% CI 1.063–1.152, \( p < 0.001 \)). The association between a mean temperature decrease of 5 °C and an increased rate of COPD exacerbation was more significant in the elderly (≥65 years). |

* Chronic bronchitis is one of the clinical entities included in the definition of COPD. ** Abbreviations used in the table: RH—relative humidity, \( O_3 \)—ozone, PM\(_{10}\)—particulate matter with a diameter of 10 microns, PM\(_{2.5}\)—particulate matter with a diameter of 2.5 microns or less, NO\(_2\)—nitrogen dioxide, CO—carbon monoxide, SO\(_2\)—sulfur dioxide, BP—barometric pressure, WS—wind speed, CI—confidence intervals, OR—odds ratio, RR—relative risk, SD—standard deviation, B—unstandardized beta, AECB—acute exacerbation of chronic bronchitis, AECOPD—acute exacerbations of chronic obstructive pulmonary disease.
The effect of elevated air temperature on COPD can be interpreted by analyzing the extreme temperature increases in the environment that occur sporadically around the world. Analysis of various studies have confirmed that extremely high temperatures led to increased hospitalizations and mortality due to worsening of COPD [2,34,35]. During the heatwave in Portugal in July 2006, for each increase in mean daily air temperature of 1 °C, the increase in hospital admissions due to AECOPD increased by 5.4% [36]. A study conducted in 12 American cities, as well as a similar study conducted in Rome and Stockholm, showed that extremely high temperatures during the summer can increase the risk of death due to COPD up to 25% [37,38]. In a study by Lin et al., it was found that for each increase in air temperature of 1 °C above the 29 °C threshold, the risk of hospitalization due to AECOPD increased by 7.6% [39]. In a meta-analysis from 2019, a statistically significant association between high air temperature during heatwaves and COPD mortality (among other respiratory diseases) was found, while a statistically significant association with increased morbidity of respiratory diseases was not established [40]. This phenomenon, among other things, can be explained by the so-called “harvest effect”, which is when an increase in the number of deaths occurs suddenly due to the acute effects of the heatwave, which leads to an increase in mortality, but also to a decrease in morbidity from COPD [41]. A systematic literature review by Witt et al. indicated that the risk of death due to chronic respiratory diseases, including COPD, was higher by 3–6.5% during the duration of heatwaves as compared with summer days based on temperature values expected for that time of year [42]. The main findings of several studies examining the effects of high air temperatures on AECOPD are shown in Table 2.

In addition to examining seasonal variations in air temperature, it is necessary to consider the impact of diurnal temperature variations on chronic respiratory diseases. The diurnal temperature range (DTR) refers to sudden temperature changes occurring during one day, and it is calculated by subtracting the minimum from the maximum value of the daily temperature. Studies conducted so far have shown that there is a clear relationship between the DTR and an increase in mortality due to respiratory diseases [43–45], with an estimated DTR share in respiratory mortality of 0.7–1.5% for every 1 °C increase in DTR [46]. DTR, regardless of absolute temperature values, can also be a risk factor for death in patients with COPD [47,48]. In a study by Ma et al. [49], it was found that the number of hospitalizations due to AECOPD increased with increased DRT values, especially in an elderly population (≥65 years) and during the spring months (April to June), when fluctuations in daily air temperature were the most prominent. The results of other clinical studies support these claims [50,51]. The effects of DTR can be explained by the hyperreactivity of the inflammatory system in patients. As people ≥ 65 years usually suffer from COPD, reduced ability to regulate internal temperature, an increase in the sweating threshold, an inadequate function of the immune system, as well as the reduced motor function of cilia in the respiratory epithelium, must be taken into consideration when discussing the effects of DTR [49].

Even though low temperatures during winter [21,52,53] and sudden temperature changes regardless of the current season have the most significant effect on patients with COPD nowadays [54,55], the effects of high temperatures are becoming a growing concern for patients with COPD. Thus, there is a need for clinical recommendations and public health interventions related to meteorological factors, regardless of the warm or cold season.
Table 2. The effects of increased air temperatures on AECOPD hospitalizations/outpatients’ visits.

| Study | Number of Participants Hospitalized due to the AECOPD | Gender Distribution | Age Distribution | Observed Period | Daily Average Temperature (± SD) | Study Design | Adjustment ** | Main Findings |
|-------|------------------------------------------------------|---------------------|------------------|-----------------|----------------------------------|--------------|--------------|--------------|
| Zhao et al., 2019 [2] Brazil (1642 cities) | No = 523,307 | 46% females 54% males | median age 65 years (IQR: 57–77 years) | 2000–2015; hot season | 25.0 °C ± 2.8 °C | case-crossover study | sex, age, socioeconomic status, RH | The OR of hospitalization due to AECOPD was 1.05 (95% CI 1.04 to 1.06) for every 5 °C increase in daily mean temperature. The effect was similar in women and in men but was greatest for those aged ≥75 years. During the warming-up season, COPD exacerbation more likely occurred on days of temperature increase; an increase by 1 °C with 95% CI of OR of 1.73–3.25, and corresponding p of <0.001. No significant differences in age and gender were noted (all p > 0.05). The risk of COPD hospitalization for the elderly (≥65 years) increased by 4.7% for every 5.6 °C rise in daily mean temperature in summer. No significant difference was found in respiratory susceptibility to heat by either age or sex. For a 1 °C increase in apparent temperature, a 5.4% increase in COPD hospital admissions was observed (RR, 1.054, 95% CI 0.989–1.066, p = 0.006). A statistically significant admissions’ excess for COPD of 7.5% was found for women of the entire population (RR, 1.075, 95% CI 1.013–1.141, p = 0.018), and 9.0% (RR, 1.090, 95% CI 1.003–1.185, p = 0.042) for women older than 75 years. For people ≥75 years, an increase in COPD admissions of 7.0% (RR, 1.070, 95% CI: 1.011–1.132, p = 0.019) was found. For each 1 °C increase in daily mean apparent temperature above 32 °C, the risk of COPD admission increased by 8% over a lag of 0–3 days. Those over 75 years had a higher ratio of respiratory disease admissions (4.7%) compared with younger age groups, as well as females (3.8%) compared to males (2.35%). |
| Lin et al., 2018 [5] Changhua County, Taiwan | No = 277 | 240 males 37 females | the mean age was 75.3 ± 9.3 years | 2011–2015 April to September | 27.02 °C (±2.78) | case-crossover study | RH, BP, NO2, CO, SO2, PM10, PM2.5, O3 | During the warming-up season, COPD exacerbation more likely occurred on days of temperature increase; an increase by 1 °C with 95% CI of OR of 1.73–3.25, and corresponding p of <0.001. No significant differences in age and gender were noted (all p > 0.05). |
| Anderson et al., 2013 [26] USA (213 counties) | No = 385,063 | 499,373 males 642,085 females | 65–74 years 358,830 75–84 years 468,002 >85 years 314,626 | 1999–2008; May to September | differs from counties from 12.7 °C to 35 °C | observational study | O3, PM10, PM2.5, sex, age, seasonality, long-term trends | The risk of COPD hospitalization for the elderly (≥65 years) increased by 4.7% for every 5.6 °C rise in daily mean temperature in summer. No significant difference was found in respiratory susceptibility to heat by either age or sex. For a 1 °C increase in apparent temperature, a 5.4% increase in COPD hospital admissions was observed (RR, 1.054, 95% CI 0.989–1.066, p = 0.006). A statistically significant admissions’ excess for COPD of 7.5% was found for women of the entire population (RR, 1.075, 95% CI 1.013–1.141, p = 0.018), and 9.0% (RR, 1.090, 95% CI 1.003–1.185, p = 0.042) for women older than 75 years. For people ≥75 years, an increase in COPD admissions of 7.0% (RR, 1.070, 95% CI: 1.011–1.132, p = 0.019) was found. For each 1 °C increase in daily mean apparent temperature above 32 °C, the risk of COPD admission increased by 8% over a lag of 0–3 days. Those over 75 years had a higher ratio of respiratory disease admissions (4.7%) compared with younger age groups, as well as females (3.8%) compared to males (2.35%). |
| Monteiro et al., 2012 [34] Porto, Portugal | No = 24 | 13 females 11 males | no data | 11–18 July 2006 | from 29 °C to 37 °C | observational study | O3, PM10 | For a 1 °C increase in apparent temperature, a 5.4% increase in COPD hospital admissions was observed (RR, 1.054, 95% CI 0.989–1.066, p = 0.006). A statistically significant admissions’ excess for COPD of 7.5% was found for women of the entire population (RR, 1.075, 95% CI 1.013–1.141, p = 0.018), and 9.0% (RR, 1.090, 95% CI 1.003–1.185, p = 0.042) for women older than 75 years. For people ≥75 years, an increase in COPD admissions of 7.0% (RR, 1.070, 95% CI: 1.011–1.132, p = 0.019) was found. For each 1 °C increase in daily mean apparent temperature above 32 °C, the risk of COPD admission increased by 8% over a lag of 0–3 days. Those over 75 years had a higher ratio of respiratory disease admissions (4.7%) compared with younger age groups, as well as females (3.8%) compared to males (2.35%). |
| Lin et al., 2009 [37] New York City, USA | No = 29,315 | no data no data | 1991–2004; June, July, August | Staten Island, LGA JFK 22.8 °C (±3.1) | time-series study | O3, PM10, PM2.5, NO2, CO, SO2, BP, day of week, holidays, long-term trend, race, age, sex, family income | For each 1 °C increase in daily mean apparent temperature above 32 °C, the risk of COPD admission increased by 8% over a lag of 0–3 days. Those over 75 years had a higher ratio of respiratory disease admissions (4.7%) compared with younger age groups, as well as females (3.8%) compared to males (2.35%). |

** Abbreviations used in the table: RH—relative humidity, O3—ozone, PM10—particulate matter with a diameter of 10 microns, PM2.5—particulate matter with a diameter of 2.5 microns or less NO2—nitrogen dioxide, CO—carbon monoxide, SO2—sulfur dioxide, BP—barometric pressure, WS—wind speed, CI—confidence intervals, OR—odds ratio, RR—relative risk, SD—standard deviation, AECOPD—acute exacerbations of chronic obstructive pulmonary disease, LGA—La Guardia Airport in New York, JFK—John F. Kennedy International Airport in New York.
3.2. The Influence of Atmospheric Pressure, Solar Radiation, Rainfall, Wind Speed, and Humidity on Acute Exacerbations of COPD

Unlike air temperature, the effects of other meteorological factors on AECOPD have seldom been studied. Even when they have, different results have been obtained depending on the geographical location where the study took place and the applied methodological approach. Thus, it is necessary to conduct further clinical and medical-ecological research in this field.

In the studies conducted so far, the influence of atmospheric (barometric) pressure on AECOPD has not been investigated independently, but usually in correlation with other meteorological factors. Given that previous studies have confirmed the correlation between atmospheric pressure and saturation values in patients with COPD ≥ 65 years (increased saturation under conditions of elevated atmospheric pressure), it is obvious that atmospheric pressure should be included in the analysis of epidemiological studies examining the influence of meteorological factors on morbidity and mortality from COPD [56]. A Taiwanese study [5] found that a decrease in atmospheric pressure during the warm season led to an increase in the frequency of AECOPD. However, that study did not estimate the possible synergistic effect of atmospheric pressure with elevated air temperature. In a study involving patients with bronchial asthma [57,58], a negative correlation was found between acute worsening of asthma symptoms and atmospheric pressure (decrease in atmospheric pressure led to worsening of asthma), therefore, such results could be correlated with AECOPD, considering that COPD and asthma share similar pathophysiological mechanism. The results of other studies contradict the previous results. In another Taiwanese study, higher atmospheric pressure, lower humidity, and more hours of sunshine were significantly associated with a higher frequency of AECOPD [18]. The combined effect of elevated outdoor temperature and elevated atmospheric pressure during the summer months led to the deterioration of lung function and acute dyspnoea in patients with chronic lung diseases in a study by Mann et al. [59]. In a Bavarian study, it was found that on days when atmospheric pressure values were elevated, patients with COPD had more visits to the doctor due to worsening of respiratory symptoms, while the number of visits was significantly lower on days with higher humidity and more hours of sunshine [60].

Studies have shown that sunlight can reduce the incidence of dyspnoea and exacerbations in patients with COPD [18,60]. A possible reason for the beneficial effect of solar radiation is that UVB rays, inducing T lymphocytes action [61], synthesis of vitamin D [62], and the release of nitrogen monoxide [63], which can reduce the intensity of the inflammatory process in the airway wall. Reduced amounts of UVB rays reaching the Earth’s surface can be found at higher altitudes during the winter months. Cloudy skies can also reduce the amounts of delivered UVB rays. Accompanied by the other meteorological factors, such as lower air temperatures, this could explain more frequent AECOPD during the colder season [39,64].

The results of several clinical studies have shown that the number of rainy hours can be correlated to the worsening of dyspnea in chronic pulmonary patients, including patients with COPD and asthma [58,59,65]. The pathophysiological mechanism behind this can be the fact that after rain, fluid diffuses into pollen granules in the atmosphere and, consequently, they rupture, releasing particles that can cause bronchospasm in patients with underlying chronic bronchospastic conditions [66]. In addition, increased humidity after rain sets favorable conditions for the development of mold in households and in the environment, which altogether increase the risk of AECOPD [66].

Increased wind speed can lead to the dispersal of air pollutants and allergens in the air, reducing their concentration and effect on the respiratory system. In a study by Lam et al. [64], increased wind speed during the summer season was associated with a lower risk of hospitalization for COPD. It was also determined that during the winter season, decreased wind speeds were significantly associated with an increased risk of hospitalization due to the AECOPD.
The influence of air humidity on COPD exacerbations is still not sufficiently investigated. Some studies have concluded that dry weather conditions (decreased relative humidity of the air) may increase the incidence of AECOPD [18,60,67]. In a South Korean study [68], a positive correlation between a higher number of hospitalizations for asthma, COPD, and chronic bronchitis, and increased particulate matter (PM) concentrations, elevated outside temperature, decreased relative humidity with low air humidity potentiating the effects of PM. Reduced air humidity can lead to dehydration of the respiratory epithelium cells, which consequently increases the osmolarity of the tracheobronchial content, causing damage to the mucous membrane. Increased air humidity can also reduce the concentration of allergens and air pollutants in the air [69,70], so this effect could also explain the higher frequency of AECOPD associated with low air humidity. Due to the potential beneficial effects of high humidity, some authors have even recommended long term humidification therapy to prevent exacerbations, prolong the time to the first exacerbation, improve lung function, and increase the quality of life in patients with COPD and bronchiectasis [70]. However, the results of other available studies suggest that high relative humidity can lead to worsening of COPD symptoms and increase the number of hospitalization due to the AECOPD [71]. In a study by Jevtić et al. [72], it was found that with each 10% increase in relative humidity, the number of hospitalized individuals due to AECOPD increased by 0.8%. In a study by Lam et al. [64], it was observed that during the cold season both low and high relative humidity of the air were associated with an increase in hospitalizations due to the worsening of COPD symptoms. However, during the warm season, only a correlation between high relative humidity and increased hospitalizations due to pneumonia, but not COPD, was found. It is possible that the increased relative humidity and lower temperature, which occurs in the winter months, act synergistically. In a study by Mu et al. [10], examining the effect of temperature and air humidity in the household on COPD symptoms, it was shown that elevated indoor air humidity did not cause worsening disease symptoms, but with an increase in relative humidity, the negative effect of lower indoor temperatures on COPD symptoms was pronounced. However, the effect of outdoor air humidity on AECOPD was not shown in that study. The explanation for these effects may be in the fact that COPD mainly affects people of older age, who spend most of their time at home. In conditions of increased air humidity, mold can also develop which can further worsen the symptoms of COPD. Since exacerbations of COPD are often caused by viral infections, the impact of air humidity on the spread of infection caused by the influenza virus can be analyzed to further determine its effect on AECOPD. Indoor experiments on animal models [73,74] have shown that virus transmission was most effective at temperatures around 5 °C and relative humidity below 50%, while it was insufficient or stopped completely at around 30 °C and over 50% of relative humidity, meaning that the transmission was most effective in cold and dry conditions. During the winter, the outside air temperatures are low, and the relative humidity is higher, which would mean that the relative humidity is not an important factor in the transmission of the virus. However, during the winter months, a significant part of the time is spent indoors where, due to the heating sources, the relative humidity is significantly lower than outdoors. Thus, in such conditions, the effect of decreased air humidity on the transmission of the influenza virus can be manifested. The effect that air temperature has on relative humidity can be eliminated considering absolute air humidity. Studies on animal models in controlled temperature conditions have directly shown that reduced absolute humidity can contribute to the spread of the influenza virus [75]. Whether such an effect of air temperature and humidity also exists in non-viral causes of COPD exacerbations has not been determined yet.

Considering the fact that approximately 30% of COPD exacerbations are due to viruses, it is important to analyze the correlation between severe acute respiratory syndrome novel coronavirus 2 (SARS-CoV-2) and AECOPD, especially because the relationship between infection with this virus and AECOPD has already been proven in some studies [76]. Even though the changes in the environment, with all of its elements, are not a source of a
novel coronavirus, they can put at a risk the patients who have COPD, making them more susceptible to infection caused by SARS-CoV-2. Recent studies have shown that lower air temperature, higher diurnal temperature range, and lower relative and specific humidity may contribute to the transmission of SARS-CoV-2 [77–79]. In a study from Iran, people living in areas with lower values of wind speed, humidity, and solar radiation were at a higher risk of infection with SARS-CoV-2 [80]. Such cold and dry climatic conditions, in the presence of an infectious agent, could lead to AECOPD, however, given the limited data on the current pandemic, these assumptions are yet to be scientifically confirmed.

4. Conclusions

The effects of different meteorological factors on the AECOPD are apparent, but there is heterogeneity in the results of the reviewed studies, possibly due to the specific climate characteristics of different geographic areas, urban/rural environment, methodological approaches, and other relevant factors. Among the previously mentioned and analyzed meteorological parameters, none acts alone in the worsening of COPD, so the exact assessment of the individual contribution can be obtained only by multivariate analyzes, i.e., by studying the combined impact of all meteorological factors on human health. Given that AECOPD increase the total cost of treatment of these patients, affect the overall work potential, lead to a decrease in the quality of life, and increase mortality, it is clear that analyzing the impact of meteorological factors on COPD exacerbations is not only of clinical, but also of great public health significance. Considering the significant economic aspect of AECOPD treatment, as well as the necessity of reorganization of the healthcare facilities in accordance with the predictive assessments of weather conditions, future research in this area is necessary both at the local and regional level.

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Abbreviations

The following abbreviations are used in this manuscript:

- AECOPD: Acute exacerbations of chronic obstructive pulmonary disease
- COPD: Chronic obstructive pulmonary disease
- DTR: Diurnal temperature range
- NO2: Nitrogen dioxide
- PM: Particulate matter
- PM2.5: Particulate matter with a diameter of 2.5 microns or less
- SARS-CoV-2: Severe acute respiratory syndrome novel coronavirus 2
- SO2: Sulfur dioxide
- UVB: Ultraviolet B
- WHO: World Health Organization
References

1. Vukoja, M.; Kopitovic, I.; Lazić, Z.; Milenkovic, B.; Stankovic, I.; Zvezdin, B.; Ilíc, A.D.; Cekerevac, I.; Vukcevic, M.; Zugic, V.; et al. Diagnosis and management of chronic obstructive pulmonary disease in Serbia: An expert group position statement. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2019, 14, 1993–2002. [CrossRef]

2. Zhao, Q.; Li, S.; Coelho, M.D.S.Z.S.; Saldiva, P.H.N.; Xu, R.; Huxley, R.R.; Abramson, M.J.; Guo, Y. Ambient heat and hospitalisation for COPD in Brazil: A nationwide case-crossover study. *Thorax* 2019, 74, 1031–1036. [CrossRef]

3. Burden of COPD [Homepage on the Internet]. WHO: Geneva, Switzerland, 2020. Available online: http://www.who.int/respiratory/copd/burden/en/ (accessed on 11 April 2020).

4. Guarascio, A.J.; Ray, S.M.; Finch, C.K.; Self, T.H. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon. Outcomes Res.* 2013, 5, 235–245. [CrossRef]

5. Lin, M.-T.; Kor, C.-T.; Chang, C.-C.; Chai, W.-H.; Soon, M.-S.; Ciou, Y.-S.; Bin Lian, I.; Chang, C.-C. Association of meteorological factors and air NO2 and O3 concentrations with acute exacerbation of elderly chronic obstructive pulmonary disease. *Sci. Rep.* 2018, 8, 1–9. [CrossRef]

6. Huang, F.; Zhao, A.; Chen, R.J.; Kan, H.D.; Kuang, X.Y. Ambient temperature and outpatient visits for acute exacerbation of chronic bronchitis in Shanghai: A time series analysis. *Biomed. Environ. Sci.* 2015, 28, 76–79.

7. De Miguel-Díez, J.; Hernandez-Vázquez, J.; López-de-Andrés, A.; Alvaro-Méca, A.; Hernández-Barrera, V.; Jiménez-García, R. Analysis of environmental risk factors for chronic obstructive pulmonary disease exacerbation: A case-crossover study (2004–2013). *PLoS ONE* 2019, 14, e0217143. [CrossRef]

8. Jenkins, C.R.; Celli, B.; Anderson, J.A.; Ferguson, G.T.; Jones, P.W.; Vestbo, J.; Yates, J.C.; Calverley, P.M.A. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur. Respir. J.* 2012, 39, 38–45. [CrossRef] [PubMed]

9. Rabe, K.F.; Fabbri, L.M.; Vogelmeier, C.; Köglér, H.; Schmidt, H.; Beeh, K.M.; Glaab, T. Seasonal distribution of COPD exacerbations in the Prevention of Exacerbations with Tiotropium in COPD trial. *Chest* 2013, 143, 711–719. [CrossRef] [PubMed]

10. Mu, Z.; Chen, P.-L.; Geng, F.-H.; Ren, L.; Gu, W.-C.; Ma, J.-Y.; Peng, L.; Li, Q.-Y. Synergistic effects of temperature and humidity on the symptoms of COPD patients. *Int. J. Biometeorol.* 2017, 61, 1919–1925. [CrossRef] [PubMed]

11. Chen, C.; Liu, X.; Wang, X.; Li, W.; Qu, W.; Dong, L.; Li, X.; Rui, Z.; Yang, X. Risk of temperature, humidity and concentrations of air pollutants on the hospitalization of AECOPD. *PLoS ONE* 2019, 14, e0225307. [CrossRef] [PubMed]

12. Almagro, P.; Hernandez, C.; Martinez-Cambor, P.; Tresserras, R.; Escarrabill, J. Seasonality, ambient temperatures and hospitalizations for acute exacerbation of COPD: A population-based study in a metropolitan area. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2015, 10, 899–908. [CrossRef]

13. Brzezińska-Pawlowska, O.E.; Rydzewska, A.D.; Łuczyńska, M.; Majkowska-Wojciechowska, B.; Kowalski, M.L.; Makowska, J.S. Environmental factors affecting seasonality of ambulance emergency service visits for exacerbations of asthma and COPD. *J. Asthma* 2016, 53, 139–145. [CrossRef]

14. Shek, L.P.; Lee, B.W. Epidemiology and seasonality of respiratory tract infections in the tropics. *Paediatr. Respir. Rev.* 2003, 4, 105–111. [CrossRef]

15. Hicks, A.; Healy, E.; Sandeman, N.; Feelisch, M.; Wilkinson, T. A time for everything and everything in its time–exploring the mechanisms underlying seasonality of COPD exacerbations. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2018, 13, 2739–2749. [CrossRef] [PubMed]

16. Donaldson, G.C.; Wedzicha, J.A. The causes and consequences of seasonal variation in COPD exacerbations. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2019, 9, 1101–1110. [CrossRef] [PubMed]

17. McCormack, M.C.; Paulin, L.M.; Gummerson, C.E.; Peng, R.D.; Diette, G.B.; Hansel, N.O. Cold weather is associated with increased COPD morbidity. *Eur. Respir. J.* 2017, 49, 1601501. [CrossRef]

18. Tseng, C.-M.; Chen, Y.-T.; Ou, S.-M.; Hsiao, Y.-H.; Li, S.-Y.; Wang, S.-J.; Yang, A.C.; Chen, T.-I.; Perng, D.-W. The Effect of Cold Temperature on Increased Exacerbation of Chronic Obstructive Pulmonary Disease: A Nationwide Study. *PLoS ONE* 2013, 8, e57066. [CrossRef]

19. Analitii, A.; Katsouyanni, K.; Biggseri, A.; Baccini, M.; Forsberg, B.; Bisanti, L.; Kirchmayer, U.; Ballester, F.; Cadum, E.; Goodman, P.G.; et al. Effects of cold weather on mortality: Results from 15 European cities within the PHEWE project. *Am. J. Epidemiol.* 2008, 168, 1397–1408. [CrossRef] [PubMed]

20. Lu, B.B.; Gu, S.H.; Wang, A.H.; Ge, T.; Wang, Y.; Li, X.H.; Xu, G.Z. Study on influence of air temperature on daily chronic obstructive pulmonary disease mortality in Ningbo. *Zhonghua Liu Xing Bing Xue Za Zhi* 2017, 38, 1528–1532.

21. Gasparrini, A.; Guo, Y.; Hashizume, M.; Lavigne, E.; Zanobetti, A.; Schwartz, J.; Tobias, A.; Tong, S.; Rocklov, J.; Forsberg, B.; et al. Mortality risk attributable to high and low ambient temperature: A multicountry observational study. *Lancet* 2015, 386, 369–375. [CrossRef]

22. Zhao, Y.; Huang, Z.; Wang, S.; Hu, J.; Xiao, J.; Li, X.; Liu, T.; Zeng, W.; Guo, L.; Du, Q.; et al. Morbidity burden of respiratory diseases attributable to ambient temperature: A case study in a subtropical city in China. *Environ. Health* 2019, 18, 1–8. [CrossRef]

23. Lee, W.-M.; Lemanske, R.F.; Evans, M.D.; Wang, F.; Pappas, T.; Gangnon, R.; Jackson, D.J.; Gern, J.E. Human rhinovirus species and season of infection determine illness severity. *Am. J. Respir. Crit. Care Med.* 2012, 186, 886–891. [CrossRef]

24. Donaldson, G.C.; Goldring, J.J.; Wedzicha, J.A. Influence of season on exacerbation characteristics in patients with COPD. *Chest* 2012, 141, 94–100. [CrossRef]
25. Matkovic, V.; Mulić, M.; Azabagić, S.; Jevtić, M. Premature Adult Mortality and Years of Life Lost Attributed to Long-Term Exposure to Ambient Particulate Matter Pollution and Potential for Mitigating Adverse Health Effects in Tuzla and Lukavac, Bosnia and Herzegovina. Atmosphere 2020, 11, 1107. [CrossRef]  
26. Qiu, H.; Tan, K.; Long, F.; Wang, L.; Yu, H.; Deng, R.; Long, H.; Zhang, Y.; Pan, J. The burden of COPD morbidity attributable to the interaction between ambient air pollution and temperature in Chengdu, China. Int. J. Environ. Res. Public Health 2018, 15, 492. [CrossRef] [PubMed]  
27. Anderson, G.B.; Dominici, F.; Wang, Y.; McCormack, M.C.; Bell, M.L.; Peng, R.D. Heat-related emergency hospitalizations for respiratory diseases in the Medicare population. Am. J. Respir. Crit. Care Med. 2013, 187, 1098–1103. [CrossRef] [PubMed]  
28. Kenny, G.P.; Yardley, J.; Brown, C.; Sigal, R.J.; Jay, O. Heat stress in older individuals and patients with common chronic diseases. CMAJ 2010, 182, 1053–1060. [CrossRef] [PubMed]  
29. Lepeule, J.; Litonjua, A.A.; Gasparrini, A.; Koutrakis, P.; Sparrow, D.; Vokonas, P.S.; Schwartz, J. Lung function association with outdoor temperature and relative humidity and its interaction with air pollution in the elderly. Environ. Res. 2018, 165, 110–117. [CrossRef]  
30. Wu, S.; Deng, F.; Hao, Y.; Wang, X.; Zheng, C.; Lv, H.; Lu, X.; Wei, H.; Huang, J.; Qin, Y.; et al. Fine particulate matter, temperature, and lung function in healthy adults: Findings from the HVNR study. Chemosphere 2014, 108, 168–174. [CrossRef] [PubMed]  
31. Lowen, A.C.; Steel, J. Roles of humidity and temperature in shaping influenza seasonality. J. Virol. 2014, 88, 7692–7695. [CrossRef]  
32. Ding, P.H.; Wang, G.S.; Guo, Y.L.; Chang, S.C.; Wan, G.H. Urban air pollution and meteorological factors affect emergency department visits of elderly patients with chronic obstructive pulmonary disease in Taiwan. Environ. Pollut. 2017, 224, 751–758. [CrossRef]  
33. Chen, R.; Peng, R.D.; Meng, X.; Zhou, Z.; Chen, B.; Kan, H. Seasonal variation in the acute effect of particulate air pollution on mortality in the China Air Pollution and Health Effects Study (CAPES). Sci. Total Environ. 2013, 450–451, 259–265. [CrossRef] [PubMed]  
34. Bogdanović, D.; Milošević, Z.; Lazarević, K.K.; Dolicanin, Z.C.; Randelović, D.; Bogdanović, S. The impact of the July 2007 heat wave on daily mortality in Belgrade, Serbia. Cent. Eur. J. Public Health 2013, 21, 140–145. [CrossRef] [PubMed]  
35. Zanobetti, A.; O’Neill, M.S.; Gronlund, C.J.; Schwartz, J.D. Summer temperature variability and long-term survival among elderly people with chronic disease. Proc. Natl. Acad. Sci. USA 2012, 109, 6608–6613. [CrossRef] [PubMed]  
36. Monteiro, A.; Carvalho, V.; Oliveira, T.; Sousa, C. Excess mortality and morbidity during the July 2006 heat wave in Porto, Portugal. Int. J. Biometeorol. 2012, 57, 155–167. [CrossRef] [PubMed]  
37. Braga, A.L.; Zanobetti, A.; Schwartz, J. The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities. Environ. Health Perspect. 2002, 110, 859–863. [PubMed]  
38. Åström, D.O.; Schifano, P.; Asta, F.; Laloo, A.; Michelozzi, P.; Rocklöv, J.; Forsberg, B. The effect of heat waves on mortality in susceptible groups: A cohort study of a Mediterranean and a northern European City. Environ. Health 2015, 14, 30. [CrossRef]  
39. Lin, S.; Luo, M.; Walker, R.J.; Liu, X.; Hwang, S.A.; Chinery, R. Extreme high temperatures and hospital admissions for respiratory and cardiovascular diseases. Epidemiology 2009, 20, 738–746. [CrossRef]  
40. Cheng, J.; Xu, Z.; Bambrick, H.; Prescott, V.; Wang, N.; Zhang, Y.; Su, H.; Tong, S.; Hu, W. Cardiorespiratory effects of heatwaves: A systematic review and meta-analysis of global epidemiological evidence. Environ. Res. 2019, 177, 108610. [CrossRef]  
41. Cheng, J.; Xu, Z.; Bambrick, H.; Su, H.; Tong, S.; Hu, W. Heatwave and elderly mortality: An evaluation of death burden and health costs considering short-term mortality displacement. Environ. Int. 2018, 115, 334–342. [CrossRef]  
42. Witt, C.; Schubert, J.A.; Jehn, M.; Holzgreve, A.; Liebers, U.; Endlicher, W.; Scherer, D. The effects of climate change on patients with chronic lung disease—a systematic literature review. Dtsch. Arztebl. Int. 2015, 112, 878–883. [CrossRef]  
43. Vutcovici, M.; Goldberg, M.S.; Valois, M.F. Effects of diurnal variations in temperature on non-accidental mortality among the elderly population of Montreal, Quebec, 1984–2007. Int. J. Biometeorol. 2014, 58, 843–852. [CrossRef]  
44. Lim, Y.H.; Hong, Y.C.; Kim, H. Effects of diurnal temperature range on cardiovascular and respiratory hospital admissions in Korea. Sci. Total Environ. 2012, 417–418, 55–60. [CrossRef]  
45. Lim, Y.H.; Reid, C.E.; Mann, J.K.; Jerrett, M.; Kim, H. Diurnal temperature range and short-term mortality in large US communities. Int. J. Biometeorol. 2015, 59, 1311–1319. [CrossRef]  
46. Lee, W.-H.; Lim, Y.-H.; Dang, T.N.; Seposo, X.; Honda, Y.; Guo, Y.-L.L.; Jang, H.-M.; Kim, H. An investigation on attributes of ambient temperature and diurnal temperature range on mortality in five East-Asian countries. Sci. Rep. 2017, 7, 1–9. [CrossRef]  
47. Ding, Z.; Li, L.; Xin, L.; Pi, F.; Dong, W.; Wen, Y. High diurnal temperature range and mortality: Effect modification by individual characteristics and meteorological causes in a case-only analysis. Sci. Total Environ. 2015, 544, 627–634. [CrossRef] [PubMed]  
48. Song, G.; Chen, G.; Jiang, L.; Zhang, Y.; Zhao, N.; Chen, B.; Kan, H. Diurnal temperature range as a novel risk factor for COPD death. Respirology 2008, 13, 1066–1069. [CrossRef] [PubMed]  
49. Ma, Y.; Zhao, Y.; Zhou, J.; Jiang, Y.; Yang, S.; Yu, Z. The relationship between diurnal temperature range and COPD hospital admissions in Changchun, China. Environ. Sci. Pollut. Res. 2018, 25, 17942–17949. [CrossRef]  
50. Zhou, X.F.; Yu, S.Y.; Ruan, X.N.; Yang, L.M.; Geng, F.H.; Zhou, Y.; Qiu, H.; Wu, K.; Song, Z.W.; Wang, X.N.; et al. Effect of meteorological factors on outpatient visits in patients with chronic obstructive pulmonary disease. J. Environ. Occup. Med. 2015, 08, 711–716.
51. Kim, J.; Shin, J.; Lim, Y.-H.; Honda, Y.; Hashizume, M.; Guo, Y.L.; Kan, H.; Yi, S.; Kim, H. Comprehensive approach to understand the association between diurnal temperature range and mortality in East Asia. *Sci. Total Environ.* 2016, 539, 313–321. [CrossRef] [PubMed]

52. Zhang, Y.; Xiang, Q.; Yu, Y.; Zhan, Z.; Hu, K.; Ding, Z. Socio-geographic disparity in cardiorespiratory mortality burden attributable to ambient temperature in the United States. *Environ. Sci. Pollut. Res.* 2019, 26, 694–705. [CrossRef]

53. Yang, J.; Yin, P.; Zhou, M.; Ou, C.-Q.; Li, M.; Li, J.; Liu, X.; Gao, J.; Liu, Y.; Qin, R.; et al. The burden of stroke mortality attributable to cold and hot ambient temperatures: Epidemiological evidence from China. *Environ. Int.* 2016, 92–93, 232–238. [CrossRef]

54. Cheng, J.; Xu, Z.; Bambrick, H.; Su, H.; Tong, S.; Hu, W. Impacts of exposure to ambient temperature on burden of disease: A systematic review of epidemiological evidence. *Int. J. Biometeorol.* 2019, 63, 1099–1115. [CrossRef]

55. Donovíč, N.; Vasiljević, D.; Stepović, M.; Milojević, D.; Gajić, V.; Stajić, D.; Sekulić, M. Effects of meteorological conditions on mortality from chronic obstructive pulmonary disease. *Srp. Arh. Celok. Lek.* 2020, 148, 436–439. [CrossRef]

56. Hernández-Garduño, E.; Garduño-Alanís, A.; Santamaría-Benhumea, A.M.; Santamaría-Benhumea, N.; Menezes-Calderón, J.; Herrera-Villalobos, J.E. Climate change, air pollution, and COPD outcomes: Too many factors to be considered, even barometric pressure! *Chest* 2013, 144, 1731. [CrossRef] [PubMed]

57. Sato, S.; Saito, J.; Suzuki, Y.; Uematsu, M.; Fukuhara, A.; Togawa, R.; Sato, Y.; Misa, K.; Nikaido, T.; Wang, X.; et al. Association between typhoon and asthma symptoms in Japan. *Respir. Investig.* 2016, 54, 216–219. [CrossRef] [PubMed]

58. Ehelepola, N.D.B.; Ariyaratne, K.; Jayaratne, A. The association between local meteorological changes and exacerbation of acute wheezing in Kandy, Sri Lanka. *Glob. Health Action* 2018, 11, 1482998. [CrossRef]

59. Mann, M.; Patel, K.; Reardon, J.Z.; Goldstein, M.; Godar, T.J.; ZuWallack, R.L. The influence of spring and summer New England meteorological conditions on the respiratory status of patients with chronic lung disease. *Chest* 1993, 103, 1369–1374. [CrossRef]

60. Ferrari, U.; Exner, T.; Wanka, E.R.; Bergemann, C.; Meyer-Arnek, J.; Hildenbrand, B.; Tufman, A.; Heumann, C.; Huber, R.M.; Bittner, M.; et al. Influence of air pressure, humidity, solar radiation, temperature, and wind speed on ambulatory visits due to chronic obstructive pulmonary disease in Bavaria, Germany. *Int. J. Biometeorol.* 2012, 56, 137–143. [CrossRef]

61. Schwarz, T.; Schwarz, A. Molecular mechanisms of ultraviolet radiation-induced immunosuppression. *Eur. J. Cell Biol.* 2010, 90, 560–564. [CrossRef] [PubMed]

62. Kokturk, N.; Baha, A.; Oh, Y.M.; Ju, J.Y.; Jones, P.W. Vitamin D deficiency: What does it mean for chronic obstructive pulmonary disease (COPD)? A comprehensive review for pulmonologists. *Clin. Respir. J.* 2018, 12, 382–397. [CrossRef]

63. Hart, P.H.; Gorman, S.; Finlay-Jones, J.J. Modulation of the immune system by UV radiation: More than just the effects of vitamin D? *Nat. Rev. Immunol.* 2011, 11, 584–596. [CrossRef] [PubMed]

64. Lam, H.C.; Chan, E.Y.; Goggins, W.B. Comparison of short-term associations with meteorological variables between COPD and pneumonia hospitalization among the elderly in Hong Kong—A time-series study. *Int. J. Biometeorol.* 2018, 62, 1447–1460. [CrossRef]

65. Soneja, S.; Jiang, C.; Fisher, J.; Upperman, C.R.; Mitchell, C.; Sapkota, A. Exposure to extreme heat and precipitation events associated with increased risk of hospitalization for asthma in Maryland, USA. *Environ. Health* 2016, 15, 57–64. [CrossRef] [PubMed]

66. D’Amato, G.; Holgate, S.T.; Pawankar, R.; Ledford, D.K.; Cecchi, L.; Al-Ahmad, M.; Al-Enezi, F.; Al-Muhisen, S.; Ansotegui, I.; Baena-Cagnani, C.E.; et al. Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. *World Allergy Organ. J.* 2015, 8, 1–52. [CrossRef] [PubMed]

67. Souza, A.D.; Alves Fernandes, W.; Pavão Hamilton, G.; Lastoria, G.; Albrez, E.D.A. Potential impacts of climate variability on respiratory morbidity in children, infants, and adults. *J. Bras. Pneumol.* 2012, 38, 708–715. [CrossRef] [PubMed]

68. Jo, E.-J.; Lee, W.-S.; Jo, H.-Y.; Kim, C.-H.; Eom, J.-S.; Mok, J.-H.; Kim, M.-H.; Lee, K.; Kim, K.-U.; Lee, M.-K.; et al. Effects of particulate matter on respiratory disease and the impact of meteorological factors in Busan, Korea. *Respir. Med.* 2017, 124, 79–87. [CrossRef] [PubMed]

69. Rea, H.; McCaulley, S.; Jayaram, L.; Garrett, J.; Hockey, H.; Storey, L.; O’Donnell, G.; Haru, L.; Payton, M.; O’Donnell, K. The clinical utility of long-term humidification therapy in chronic airway disease. *Respir. Med.* 2010, 104, 525–533. [CrossRef]

70. Davis, R.E.; McGregor, G.R.; Enfield, K.B. Humidity: A review and primer on atmospheric moisture and human health. *Environ. Res.* 2016, 144, 106–116. [CrossRef]

71. Tian, L.; Yang, C.; Zhou, Z.; Wu, Z.T.; Pan, X.C.; Clements, A.C.A. Spatial patterns and effects of air pollution and meteorological factors on hospitalization for chronic lung diseases in Beijing, China. *Sci. China Life Sci.* 2019, 62, 1381–1388. [CrossRef]

72. Jevtić, M.; Dragić, N.; Bilević, S.; Popović, M. Air pollution and hospital admissions for chronic obstructive pulmonary disease in Novi Sad. *HealthMED* 2012, 6, 1207–1215.

73. Steel, J.; Palese, P.; Lowen, A.C. Transmission of a 2009 pandemic influenza virus shows a sensitivity to temperature and humidity similar to that of an H3N2 seasonal strain. *J. Virol.* 2011, 85, 1400–1402. [CrossRef]

74. Lowen, A.C.; Mubareka, S.; Steel, J.; Palese, P. Influenza virus transmission is dependent on relative humidity and temperature. *PLoS Pathog.* 2007, 3, 1470–1476. [CrossRef]

75. Shaman, J.; Kohn, M. Absolute humidity modulates influenza survival, transmission, and seasonality. *Proc. Natl. Acad. Sci. USA* 2009, 106, 3243–3248. [CrossRef]
76. Arnold, F.W.; Mahmood, K.; Prabhu, A.; Aden, D.; Raghuram, A.; Burns, M.; Beavin, L.A.; Chung, D.; Palmer, K.E.; Ramirez, J.A. COPD exacerbation caused by SARS-CoV-2: A case report from the Louisville COVID-19 surveillance program. *Univ. Louisville J. Respir. Infect.* 2020, 4, 5. [CrossRef]

77. Bolaño-Ortiz, T.; Pascual-Flores, R.; Puliafito, S.; Camargo-Caicedo, Y.; Berná-Peña, L.; Ruggeri, M.; Lopez-Noreña, A.; Tames, M.; Cereceda-Balic, F. Spread of COVID-19, Meteorological Conditions and Air Quality in the City of Buenos Aires, Argentina: Two Facets Observed during Its Pandemic Lockdown. *Atmosphere* 2020, 11, 1045. [CrossRef]

78. Sajadi, M.M.; Habibzadeh, P.; Vintzileos, A.; Shokouhi, S.; Miralles-Wilhelm, F.; Amoroso, A. Temperature, humidity and latitude analysis to predict potential spread and seasonality for COVID-19. SSRN 3550308 [Preprint] 2020. [CrossRef] [PubMed]

79. Wu, Y.; Jing, W.; Liu, J.; Ma, Q.; Yuan, J.; Wang, Y.; Du, M.; Liu, M. Effects of temperature and humidity on the daily new cases and new deaths of COVID-19 in 166 countries. *Sci. Total Environ.* 2020, 729, 139051. [CrossRef]

80. Ahmadi, M.; Sharifi, A.; Dorosti, S.; Jafarzadeh Ghoushchi, S.; Ghanbari, N. Investigation of effective climatology parameters on COVID-19 outbreak in Iran. *Sci. Total Environ.* 2020, 729, 138705. [CrossRef] [PubMed]