COPD risk due to extreme temperature exposure: combining epidemiological evidence with pathophysiological mechanisms

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Summary

Climate change is amplifying the frequency and intensity of extreme temperature events, posing a significant risk for chronic obstructive pulmonary disease (COPD). This review synthesised epidemiological evidence linking extreme temperature to COPD morbidity and mortality, while elucidating synergistic interactions with other environmental exposures. Combining population-level findings with biomedical mechanistic insights, we proposed a framework illustrating how biomarkers bridge the gap between extreme temperature exposure and COPD, highlighting the pathophysiological mechanisms of prodromal symptoms, key pathogenic processes and early molecular events. The mechanisms and biomarkers identified in this study would provide critical information for elucidating the causal pathways through which extreme temperatures increase COPD risk, and thus inform preventive interventions. Future research should incorporate multi-omics techniques to explore the underlying mechanisms in greater depth, while validating the biomarkers through large-scale cohort studies.

Keywords: Climate change; COPD; Biomarkers; Extreme temperature; Pathophysiological mechanism

Introduction

Climate change, driven by anthropogenic greenhouse gas emissions, results in long-term shifts in temperature patterns.[1,2] In the context of climate change, extreme temperature events including heatwaves and cold spells have been occurring with higher frequency, greater intensity and longer durations.[3,4] Despite the clear trend of global warming, cold waves still occur from time to time.[5] Globally, there is a rising trend in the morbidity and mortality of a series of diseases associated with extreme temperatures.[6]

Chronic obstructive pulmonary disease (COPD) is the most common type of chronic respiratory diseases and characterised by chronic respiratory symptoms due to abnormalities of the airway and/or alveoli that cause persistent and progressive airflow obstruction.[7,8] Currently, COPD is the third leading cause of death worldwide.[9,10] Industrial emissions, atmospheric contaminants, occupational exposure to dusts and chemicals can increase the risk of COPD by triggering inflammation, impairing lung function, and facilitating respiratory infections.[11] Notably, most patients are unaware of their COPD status until noticeable symptoms occur, which normally happens at the moderate or severe stage.[12]

As climate change continues to intensify, extreme temperatures will pose new risk patterns for respiratory health. For instance, climate change will shift exposure patterns from extreme cold to extreme heat. Global warming increases heatwave frequency, heightening respiratory health risks from extreme heat. Conversely, the overall health risks associated with extreme cold may decline despite persistent cold waves.[13,14] Additionally, exposure to extreme temperatures is not isolated. The combined effects of ambient humidity and air pollution must be considered.[15,16] In summary, the impact of extreme temperatures on respiratory health in the changing climate diverges from traditional understandings. Failing to update understanding of the respiratory health risks posed by extreme temperatures will impede effective risk identification and response strategies.[17]

Although previous studies have reported the association between extreme temperatures and COPD risk, a comprehensive understanding of the underlying pathophysiological pathways and modifying factors remains underexplored. This review aims to summarize the epidemiological evidence on the association between extreme temperatures and COPD, with emphasis on the

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interaction effects with other exposure characteristics such as air pollution and ambient humidity. In addition, we also endeavoured to construct a pathway framework about the pathophysiological mechanisms linking COPD and extreme temperature exposures (both heat and cold).

Epidemiological evidence on association between extreme temperature and COPD

Extreme cold

Since 2006, a large number of keywords about temperature and COPD started to spring up (Fig. 1). The top few keywords included "cold", "chronic obstructive pulmonary disease", "hospital admission", "mortality", "lung function". This cluster suggested a significant emphasis on respiratory conditions during cold periods, leading to higher hospital admissions and mortality rates. Table 1 summarizes the main research findings on the association between cold and COPD morbidity or mortality. For example, evidence from a time-series study across 272 major Chinese cities revealed that 14.33% of non-accidental mortality was attributable to non-optimum temperatures. Extreme cold (–6.4 to –1.4 °C) and extreme heat (29.0 to 31.6 °C) contributed to attributable fractions of 1.14% and 0.63%, respectively. Notably, COPD accounted for a substantial attributable fraction of 12.57%.[18] Besides, evidence from 16 Chinese cities also showed a positive correlation between extreme cold and COPD mortality, with the pooled excess mortality risk of 4.37% (95% CI: 2.51%, 6.27%) for 1 °C change among extreme cold conditions.[24] A case-crossover study targeting United States veterans showed that the effects of cold wave on mortality steadily increased from lag day 2 and plateaued at lag day 4 in patients with COPD (RR = 1.04; 95% CI: 1.02, 1.07).[21] A nationwide cross-sectional study from Spain showed that exposure to low temperature significantly increased the risk of hospitalisation for COPD, with RR of 1.885 (95% CI: 1.646, 2.159) at the 1st temperature percentile compared with optimum temperature.[19] A time series study from 10 microregions in Brazil also revealed an association between extreme cold and increased COPD mortality risk.[23] Qiu H et al. found that increased risk of extreme cold-related mortality was observed for total cardiorespiratory diseases, especially for COPD in Hong Kong, China.[25] Evidence also indicated that the elderly, females, those economically

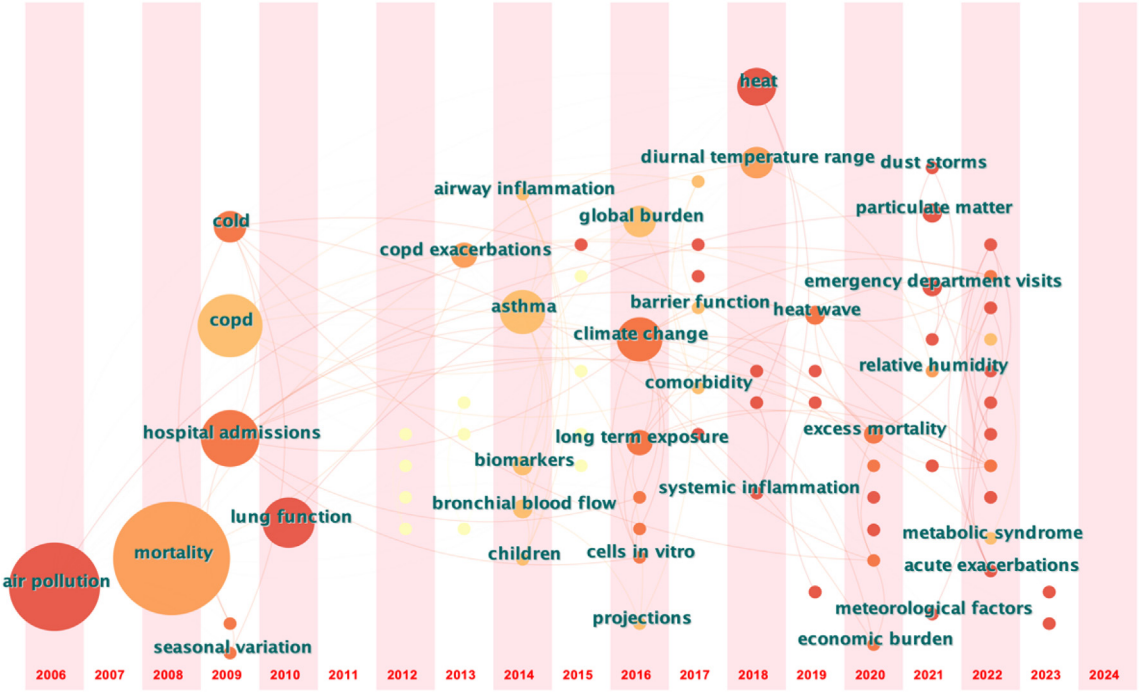

Fig. 1: **TimeZone map of keywords related to extreme temperature and chronic obstructive pulmonary disease**. The larger the diameter of the circle, the higher the frequency of keyword occurrences. The lines in the TimeZone map connect different circles illustrate the relationships between them, such as collaborations or citation links. The colour of the circles represents the intensity of keywords over time, reflecting their temporal trajectory. For instance, a transition from yellow to red indicates that the keyword has a longer duration of occurrence between 2006 and 2023. The figure is generated by CiteSpace (6.3.R1) software. The key parameters for figure generation are as follows: Selection Criteria: g-index (k = 25), LRF = 2.5, L/N = 10, LBY = 5,e = 1.0; Network: N = 175, E = 669 (Density = 0.0439); Largest 5 CCs: 175 (100%); Nodes Labelled: 1.0%; Pruning: None; Modularity Q = 0.6017; Weighted Mean Silhouette S = 0.8465; Harmonic Mean (Q,S) = 0.7034.

Reference	Study area	Study period	Exposure indicator	Extreme temperature description	Outcome indicator	Study design description	Ages	Main findings
Chen et al., 2018[18]	272 main cities in China	2013–2015	Non-optimum ambient temperature	Extreme cold and heat were defined as temperatures below the 2.5th percentile and above the 97.5th percentile, respectively.	Non-accidental deaths, including those due to COPD and other diseases.	Time series analysis (1,826,186)	All ages	Extreme cold (−6.4 to −1.4 °C) and extreme heat (29.0 to 31.6 °C) contributed to attributable fractions of 1.14% and 0.63% of non-accidental mortality, respectively. Notably, COPD accounted for a substantial attributable fraction of 12.57%.
Achebak et al., 2024[19]	48 provinces in mainland Spain and the Balearic Islands	2004–2019	Extreme cold	Extreme cold was defined as 1st percentile of the distribution of daily December to-March temperatures.	COPD hospital admissions and mortality	Cross-sectional study; (13,548,271 emergency hospital admissions)	All ages	Exposure to low temperature significantly increased the risk of hospitalisation for COPD, with RR of 1.885 (95% CI: 1.646, 2.159) at 1st temperature percentile compared with optimum temperature.
Chen et al., 2019[20]	31 capital cities in China	2007–2013	Cold spell	Cold spell was defined as daily mean temperature below 5th percentile for at least two consecutive days.	COPD mortality	Nationwide cross-sectional study	All ages	Cold spells were associated with a significantly elevated risk of COPD mortality, demonstrating a pooled RR of 1.88 (95% CI: 1.58, 2.19) at lag 0–27 days.
Rau et al., 2024[21]	3058 counties in U.S.	2016–2019	Cold wave	Cold wave was defined as two or more consecutive days with mean daily temperatures below the 10th percentile of cold season.	COPD mortality	Case-crossover study (1,124,705)	Middle-aged and older adults	Cold waves' impact on mortality rose from lag day 2, peaked at lag day 4 with an IRR of 1.04 (95% CI: 1.02, 1.07), and remained elevated effects over the subsequent 7-day lag period in patients with COPD.
Zafirah et al., 2021[22]	6 metropolitan cities in Taiwan, China	2005–2016	Extreme low temperature	Extreme low temperature was defined as below the 5th percentile of city-specific temperatures.	COPD mortality	Time series analysis	The elderly men (age≥65)	Significant COPD death risk for elderly men was observed at 14.1 °C, with RR of 1.38 (95% CI: 1.05, 1.80).
Ribas et al., 2023[23]	10 microregions in Brazil	1996–2017	Extreme cold	Extreme cold was defined as between the lowest temperature and the 2.5th percentile.	COPD mortality	Time series analysis (208,169)	All ages	Extreme cold led to increased risks of COPD death in tropical and subtropical areas of Brazil.
Li et al., 2019[24]	16 cities in China	2007–2013	Extreme cold	Extreme cold was defined as from the 1st to the 10th percentile of city-specific temperatures.	COPD mortality	Time series analysis (325,354)	All ages	The pooled excess COPD mortality risk was 4.37% (95% CI: 2.51%, 6.27%) for 1 °C change among extreme cold conditions.
Qiu et al., 2016[25]	Hong Kong, China	2002–2011	Extreme cold	Extreme cold was defined as days with daily maximum temperatures at or below the 1st percentile.	COPD mortality	Case-only approach (197,680)	All ages	The greater risk of extreme cold-related mortality was observed for COPD, hypertensive diseases, stroke and congestive heart failure.
Rai et al., 2023[26]	15 cities in Germany	2005–2016	Extreme cold	Extreme cold was defined as temperature at the 1 st percentile and below.	COPD mortality	Time series analysis (55, 478)	All ages	The lag-cumulative RR for daily COPD mortality at the 1st percentile (−6.0 °C) was 1.06 (95% CI: 1.03, 1.09) relative to the 25th percentile (4.9 °C).
Lee et al., 2024[27]	Seoul, South Korea	2008–2017	Extreme cold	Extreme cold was defined as temperature at the 1 st percentile and below.	Emergency department (ED) visits for COPD	Case-crossover study (1,616,644)	All ages	Cold temperatures (−9.0 °C) resulted in an increase in ED visits for COPD (RR = 1.54, 95% CI: 1.11, 2.13) compared to the minimum risk temperature (24.8 °C).
Marovics et al., 2022[28]	Pécs, Hungary	2017	Extreme cold	Extreme cold was defined as temperature at the 5th percentile and below.	ED visits for COPD	Time-series analysis (51,436)	All ages	Extreme cold led to an increase in COPD-related ED visits (OR = 1.77, 95% CI: 1.43, 2.19).
Sohail et al., 2023[29]	Helsinki, Finland	2001–2007	Cold spell	Cold spell was defined as periods with daily mean temperatures below the 10th percentile for at least 4 consecutive days.	COPD hospital admissions	Time-series analysis	All ages	Cold spells were associated with an increased risk of hospital admission for COPD (RR = 1.031, 95% CI: 1.006, 1.056) in the ≥75 years age group.
Fu et al., 2023[30]	Beijing, China;	2013–2016	Extreme cold	Extreme cold was defined as temperature at the 1 st percentile and below.	COPD hospital admissions	Time-series analysis (143,318)	All ages	The 21-day cumulative relative risk (CRR) of COPD hospital admissions associated with extreme cold exposure was 1.79 (95% CI: 1.08, 2.96).
Ma et al., 2020[31]	Jiangsu Province, China	2014–2017	Extreme cold	Extreme cold was defined as temperature at the 2.5th percentile and below.	COPD mortality	Time-series analysis (1,368,648)	All ages	Extreme cold was positively associated with increased mortality risks of COPD (RR = 1.92, 95% CI: 1.41, 2.62).

(Table 1 continues on next page)

Reference	Study area	Study period	Exposure indicator	Extreme temperature description	Outcome indicator	Study design description	Ages	Main findings
(Continued from previous page)								
Zhao et al., 2019[32]	Dongguan, China	2013–2017	Extreme cold	Extreme cold was defined as temperature at the 5th percentile and below.	COPD morbidity	Time series analysis (11,068)	All ages	The accumulated RR for extreme cold, relative to the optimum temperature, was 1.12 (95% CI: 1.01, 1.24) at lag 0–7 days.
Yang et al., 2019[33]	31 major cities in China	2007–2013	Heatwave	Heatwave was defined as at least three days with daily maximum temperature ≥92.5th percentile.	COPD mortality	Time series analysis (4,481,090)	All ages	Heatwave significantly increased COPD mortality, with a pooled RR of 1.13 (95% CI: 1.05, 1.21) at lag 0–10 days.
Li et al., 2019[24]	16 cities in China	2007–2013	Extreme heat	Extreme heat was defined as from the 90th to the 99th percentile of city-specific temperatures.	COPD mortality	Time series analysis (325,354)	All ages	The pooled excess COPD mortality risk was 3.99% (95% CI: 2.33%, 5.68%) for 1 °C change among extreme heat conditions.
Xu et al., 2024[34]	Queensland, Australia	2004–2016	Heat exposure	Heat exposure was defined as a 5 °C increase in daily mean temperature above the median.	COPD hospitalisation	Time-stratified case-crossover analyses (2,263,427)	All ages	The odds ratios of asthma/COPD associated with ambient heat exposure were 1.11 (95% CI: 1.03, 1.19).
Achebak et al., 2024[19]	48 provinces in mainland Spain and the Balearic Islands	2004–2019	Extreme heat	Extreme heat was defined as 99th percentile of the distribution of daily June-to-September temperatures.	COPD hospital admissions and mortality	Cross-sectional study; (12,741, 532) emergency hospital admissions and 1,717, 040 deaths)	All ages	High temperature significantly increased both the risk of hospitalisation (RR = 1.260, 95% CI: 1.158, 1.372) and mortality (RR = 1.634, 95% CI: 1.327, 2.011) for COPD.
Zanobetti et al., 2012[35]	135 cities in U.S.	1985–2006	Summer temperature variability	Summer temperature variability was defined as SD of mean daily temperatures during summertime (June–August).	COPD hospitalisation	Cox proportional hazard model (3,749,096)	The elderly (age ≥ 65)	Higher temperature SD in the warm season was significantly associated with shorter survival time of older subjects discharged alive following an admission for COPD.
Braga et al., 2002[36]	12 cities in U.S.	1986–1993	High summer temperature	Hot days were defined as 24-h average temperatures exceeding 30 °C.	COPD mortality	Time series analysis	All ages	High summer temperatures could increase COPD mortality risk by up to 25%.
Rau et al., 2024[21]	3058 counties in U.S.	2016–2019	Heat wave	Heat wave was defined as two or more consecutive days with mean daily temperatures above the 90th percentile of warm season.	COPD mortality	Case-crossover study (1,124,705)	Middle-aged and older adults	Heat wave significantly increased all-cause mortality at lag day 0, with an IRR of 1.04 (95% CI: 1.02, 1.06) among veterans with COPD.
Konstantinoudis et al., 2022[37]	Nationwide in England	2007–2018	Heat exposure	Heat exposure was defined as exceeding the 80th percentile of the temperature (23.2 °C).	COPD hospitalisation	Case-crossover study (1,570,288)	All ages	For every 1 °C above 23.2 °C, COPD hospitalisation risk increased by 1.47% (95% CI: 1.19%, 1.73%).
Rai et al., 2023[26]	15 cities in Germany	2005–2016	Extreme heat	Extreme heat was defined as temperature at the 99th percentile and above.	COPD mortality	Time series analysis (55, 478)	All ages	The lag-cumulative RR for daily COPD mortality at the 99th percentile (25.1 °C) percentile was 1.50 (95% CI: 1.35, 1.66) relative to 75th (15.9 °C) percentile.
Ragettli et al., 2024[38]	Nationwide in Switzerland	2003–2016	Extreme heat	Extreme heat was defined as ambient daily maximum temperature reaching 33 °C.	COPD mortality	Case-crossover study (320,306)	All ages	Extreme heat was associated with a strong increase in COPD mortality (OR = 1.37, 95% CI: 1.12, 1.67) compared with the reference temperature (19 °C).
Fu et al., 2023[30]	Beijing, China;	2013–2016	Extreme heat	Extreme heat was defined as temperature at the 99 th percentile and above.	COPD hospital admissions	Time-series analysis (143,318)	All ages	The 21-day cumulative relative risk (CRR) of COPD hospital admissions associated with extreme heat exposure was 1.46 (95% CI: 1.11, 1.93).
Ma et al., 2020[31]	Jiangsu Province, China	2014–2017	Extreme heat	Extreme heat was defined as temperature at the 97.5th percentile and above.	COPD mortality	Time-series analysis (1,368,648)	All ages	Extreme heat was positively associated with increased mortality risks of COPD (RR = 1.57, 95% CI: 1.36, 1.81).

Studies that define different exposure indicators (e.g., extreme cold, extreme heat, and non-optimum temperature thresholds) and represent geographically distinct populations were prioritized in accordance with the inclusion and exclusion criteria, with the overall selection encompassing both morbidity and mortality outcomes related to COPD.

Table 1: **The association between extreme temperatures and the risk of COPD.**

inactive, showed higher risk estimates.[22,25] Besides, the convergence of extreme cold and viral infections creates an environment that heightens COPD exacerbation.[39] Respiratory viral infections such as respiratory syncytial virus (RSV) and influenza, especially prevalent during winter months, significantly exacerbate COPD symptoms by increasing airway inflammation, bronchoconstriction, etc.[40]

Extreme heat

Since 2018, numerous studies have focused on the epidemiological association between heat and COPD (Fig. 1), suggesting that heat-related respiratory health effects are emerging trends. Other notable keywords identified through bibliometric analysis include "biomarkers", "barrier function", "airway inflammation" and "economic burden", highlighting the growing emphasis on the role of biomarkers as well as underlying physiological mechanisms that mediate responses to extreme temperature events.

The key findings regarding the relationship between heat and COPD risk are illustrated in Table 1. For example, the study from 16 Chinese cities during 2007–2013 showed positive heat effects on COPD. The pooled excess COPD mortality risk was 3.99% (95% CI: 2.33%, 5.68%) for 1 °C change among extreme heat conditions.[24] A time-series analysis conducted in 12 U.S. cities suggested that exposure to high summer temperatures (exceeding 30 °C) could potentially elevate the mortality risk associated with COPD by up to 25%.[41] Beyond the effects of extreme heat on COPD mortality, previous studies have revealed the association between heat exposure and COPD morbidity. A nationwide case-crossover study in England showed that the risk of COPD hospitalisation increased by 1.47% (95% CI: 1.19%, 1.73%) for every 1 °C increase in temperatures above 23.2 °C. Below this threshold, the risk increase was much lower at 0.37% (95% CI: 0.09%, 0.65%) per 1 °C increase, indicating a threshold above which the risk accelerated.[37] Notably, older individuals and those with pre-existing cardiovascular or chronic respiratory diseases face a higher risk of COPD-related mortality and exacerbations due to extreme heat exposure.[34,35,42]

The interaction effects of extreme temperatures with other exposure characteristics

Climate change has introduced new environmental exposure characteristics, thereby posing new challenges and risks to respiratory health.[43] In the context of climate change, real-world exposures to extreme temperatures are seldom isolated effects but rather interact with other environmental exposures, such as humidity and air pollution, leading to complex synergistic impacts.[44] For example, there is a close correlation between climate change and air pollution, as both greenhouse gases and air pollutants, such as particulate matter (PM) and ozone (O_3), can originate from fossil fuel combustion.[45,46] Furthermore, individual behaviours and adaptability also modulate the relationship between extreme temperatures and COPD risks.

The effects of combined exposure of temperature and humidity

Combined exposure between different meteorological factors may pose synergistic effects on the risk of COPD. Ambient humidity is closely related to the normal function of the respiratory tract. Low ambient humidity can cause dryness of the respiratory mucosa, leading to symptoms such as sore throat and coughing, especially for those who already have suffered from COPD.[47] A panel study explored the synergistic effects of temperature and humidity on the symptoms of patients with COPD, and found that low temperature was a risk factor for COPD symptoms, and high humidity exacerbated its effects.[48] However, most previous studies have considered relative humidity as an independent exposure factor. Research on the risk of COPD associated with combined temperature and humidity exposure remains limited at the national or global scale.

The interaction between extreme temperature and air pollution

Raised temperature can increase concentrations of ground-level O_3 and particulate matters, which further impacts the severity of COPD.[49] A literature review revealed that the increments in $PM_{2.5}$, PM_{10}, O_3, CO and NO_2 during high temperature periods were considerably associated with increased COPD hospitalisations.[50] Ding PH et al. explored the joint effects of urban air pollution and meteorological factors, and found that the co-exposure to $PM_{2.5}$ and O_3 posed significantly greater effects on emergency department visits for elderly individuals with COPD in warmer days.[51] The hypothesized mechanism suggests that during high temperatures, increased respiratory rate and the resulting hyperventilation may lead to greater inhalation of air pollutants, particularly in heavily polluted environments, therefore leading to severe inflammation of the bronchial mucosa.[52] Notably, the interaction of extreme cold and air pollution (such as $PM_{2.5}$) can also synergistically aggravate the physiologic dysfunction for patients suffering from COPD, thereby increasing excess COPD mortality and hospital admissions.[53]

The modifying effects of individual behaviours and other influencing factors

(1) Individual behaviours and adaptability

Intense exercise or physical exertion in cold environments can cause acute bronchoconstriction and

increased respiratory symptoms.[54] Besides, patients with COPD are particularly vulnerable to fluid loss due to increased respiratory effort and sweating. Adequate hydration is essential during heatwaves, as dehydration can exacerbate COPD symptoms by thickening mucus and impairing airway clearance.[55] Individual adaptation behaviours to extreme temperatures, such as using air conditioning to maintain appropriate indoor temperatures, avoiding outdoor activities under unsuitable temperatures, paying attention to meteorological warnings can significantly alleviate the impact of extreme temperatures on COPD.[56,57]

(2) Socio-economic factors and working conditions

Heat waves can increase the risk of heat stress, such as heatstroke and heat exhaustion, which are more likely to occur in patients with COPD.[58] Low-income individuals may be more susceptible to heat stress as they may not be able to afford efficient air conditioning or live in poorly ventilated housing.[59] Outdoor manual labourers, including construction workers, farmers, transportation and postal workers, are particularly vulnerable to heat stress due to their physical exertion in high-temperature environments.[60]

Potential pathophysiological mechanistic pathways linking extreme temperatures to COPD

Although previous studies have identified the association between extreme temperatures and COPD risk, most of these research focus on patients with COPD, with outcomes primarily centred on the COPD hospitalisation or mortality.[18,32] By defining the endpoints exclusively on COPD outcomes, epidemiological studies result in a lack of understanding the potential pathophysiological mechanisms and the underlying causal pathways. Therefore, in this section, we established the conceptual framework that delineates the key events and pathways through which extreme temperatures influence COPD. This framework provides a comprehensive understanding by starting with proximal symptoms such as lung function impairment, followed by key intermediate processes, and culminating in early molecular events, in order to illustrate how extreme temperatures affect COPD at multiple levels (Fig. 2).

Prodromal symptoms

(1) Impaired respiratory function

COPD is characterised by persistent respiratory symptoms and airflow limitation, signifying a direct relationship with lung function impairment. A retrospective cohort study in China showed that summer heat exposure was significantly associated with the reduction of lung function in young adults. 1 °C increase was associated with 1.07% (95% CI: 1.95%, 0.18%) decrease in forced vital capacity (FVC) and 0.88% (95% CI: 1.71%, 0.05%) decrease in forced expiratory volume in 1 s (FEV_1).[61] A cross-sectional study from 930 patients with COPD showed that increase in ambient relative humidity and temperature were associated with changes in lung function. In the warm season, a 1 °C increase in 1-month temperature difference was associated with a 0.72% decrease in FEV_1 and a 0.42% decrease in FEV_1/FVC.[62]

Except for heat exposure, low temperature was also significantly associated with decrease of FVC.[63] A time-series panel study provided evidence that both low and high temperatures were significantly associated with decrements in pulmonary function, particularly in peak expiratory flow (PEF). The associations between daily mean temperature and PEF were inverted U-shaped. Compared with the reference temperature (16 °C), the low temperature (1st percentile, –1 °C) would result in cumulative decrease of 32.20 L/min in morning PEF and 21.15 L/min in evening PEF over lags of two weeks.[64]

(2) Airway constriction

Airway constriction is a result of airway hyperreactivity, and can lead to limited airflow and subsequently impair lung function.[65] Airway constriction is not only a symptom but also a major factor that contributes to the progression and severity of COPD.[66] Extreme heat can enhance tidal volume and respiratory rate, causing specific airway resistance and reflex bronchoconstriction via activation of bronchopulmonary vagal C fibres, and upregulation of transient receptor potential vanilloid (TRPV) 1 and TRPV4.[67] Notably, cold exposure also frequently leads to acute bronchoconstriction.[68,69]

(3) Airway obstruction

The two primary forms of COPD, chronic bronchitis and emphysema, both involve significant airway obstruction.[70] It has been reported that the emergency department visits of bronchitis and emphysema increased by 12% during the early summer extreme heat events.[71] A random-effect pooled meta-analysis in Taiwan, China showed that the elderly were more vulnerable to high temperature of 30 °C with the cumulative 8-day RR of 1.08 (95% CI: 1.03, 1.13) for chronic airway obstruction.[72] Besides, a repeated measurement study aimed at patients with asthma showed that 24-h cold air exposure could induce increased airway obstruction.[73]

Key pathogenic processes

(1) Airway hyperreactivity

Airway hyperreactivity not only serves as a risk factor for the onset of COPD but also simultaneously

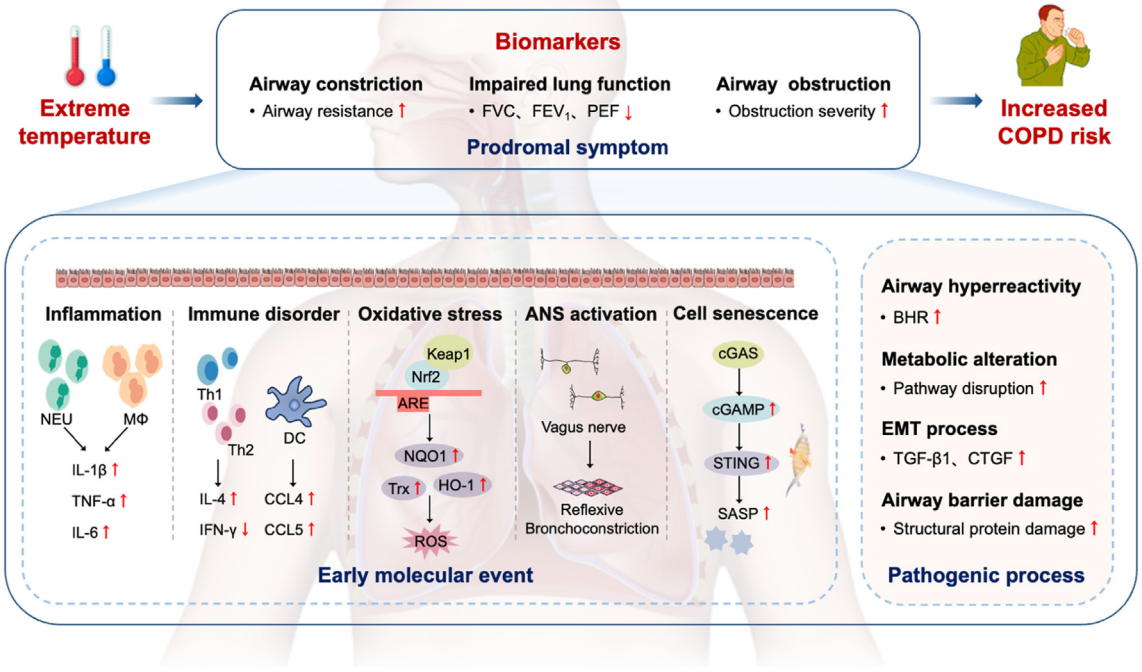

***Fig. 2:* Potential pathophysiological mechanistic pathways linking extreme temperature with chronic obstructive pulmonary disease.** Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; NEU, neutrophils; MΦ, macrophage; DC, dendritic cell; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; TNF-α, tumour necrosis factor-alpha; IFN-γ, interferon-gamma; CCL4, C–C motif chemokine ligand 4; CCL5, C–C motif chemokine ligand 5; Keap 1, Kelch-like ECH-associated protein 1; Nrf 2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response element; NQO1, NAD(P)H Quinone Dehydrogenase 1; HO-1, haem oxygenase-1; Trx, thioredoxin; ROS, reactive oxygen species; ANS, autonomic nervous system; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; SASP, senescence-associated secretory phenotype; BHR, bronchial hyper-responsiveness; EMT, epithelial–mesenchymal transition; TGF-β1, transforming growth factor-β1; CTGF, connective tissue growth factor.

accelerates the decline in pulmonary function.[74] Evidence from animal study showed that high temperatures might directly damage the airway epithelium and alter mucus production, thereby contributing to airway hyperreactivity in mice.[75] Additionally, exercise in cold temperatures can induce airway inflammation and increase airway parasympathetic nervous activity, causing bronchial constriction and bronchial hyperresponsiveness (BHR).[69]

(2) Airway barrier dysfunction

Airway epithelial cells act as a physical barrier against environmental toxins and injuries.[76] Extreme temperatures directly affect the airway epithelial barrier by disrupting the structural proteins and triggering airway inflammation.[67] Research on animal models revealed that heat stress could directly damage the integrity of the intestinal epithelial barrier. This disruption was achieved through increased permeability of tight junctions, upregulation of the structural protein occludin, and downregulation of the functional protein zonula occludens 1.[77]

(3) Metabolic profile alteration

A study aimed at agricultural and non-agricultural workers explored the impact of heat exposure on the human metabolome via untargeted high-resolution metabolomics. Results showed that differentially perturbed pathways were linked to acute, systemic inflammation (alanine and aspartate metabolism, aspartate and asparagine metabolism), oxidative stress (glycosphingolipid biosynthesis and metabolism, gam-linoleic acid metabolism), DNA damage and repair (pyrimidine metabolism, purine metabolism).[78] By contrast, untargeted metabolomics also revealed cold exposure-induced metabolic changes in mice. Significant perturbed metabolic pathways associated with cold exposure included arginine biosynthesis and glutathione metabolism, etc., which were closely associated with inflammation and oxidative stress damage.[79]

(4) Epithelial mesenchymal transition (EMT)

In the airways of patients with COPD, transforming growth factor-β (TGF-β) can stimulate EMT in the epithelial cells, thereby leading to normal epithelial barrier dysfunction and increased number of mesenchymal cells.[80] This airway remodelling process can lead to narrowing of the airways and reduced airflow, contributing to the progression of COPD.[81] Increased expression of TGF-β1 in COPD lungs was reported in a previous study, suggesting an impact of TGF-β signalling on the development and progression of COPD.[82] Hou T et al. exposed male C57BL/6 mice to extreme heat environment (ambient temperature 39.5 ± 0.5 °C), and then found lung fibrosis in the lungs of heat-exposed mice, with elevated expression of fibrosis molecules, including TGF-β1 and Fibronectin (Fn1).[83] Besides, epithelial–mesenchymal transition occurred in response to heat exposure, with down-regulated E-cadherin, upregulated connective tissue growth factor (CTGF) and the zinc finger transcriptional repressor protein Slug in the heat-exposed lung tissues of mice.

Early molecular events

(1) Airway inflammation

Airway inflammation is a persistent characteristic of COPD. Among them, inflammatory cells such as neutrophils, macrophages and T lymphocytes are involved in the pathogenesis of COPD.[84] Previous studies showed that high temperature could aggravate airway inflammation by increasing interleukin (IL)-4, IL-1β, IL-6, and TNF-α in mice.[75] Seys SF et al. revealed the effects of cold air exposure on neutrophilic airway inflammation. Results showed that after 24-h of cold air exposure, sputum IL-17 A and IL-5 mRNA levels increased significantly.[73] Besides, cold exposure could also initiate the gasdermin D (GSDMD)-mediated pyroptosis pathway and activation of NOD-like receptor family pyrin domain-containing 3 inflammasome (NLRP3) in a caspase-1-dependent manner.[85] Du C et al. found that exposure to temperature variation, especially the largest temperature difference (16 °C), could exacerbate airway inflammation through transient receptor potential ankyrin 1 (TRPA1) signalling pathway, which was found to be higher in the lung tissues of patients with COPD.[86,87] Notably, while the air is warmed as it travels through the respiratory tract, the initial temperature change still contributes to inflammatory responses. Moreover, chronic airway inflammation could lead to thickening of the airway wall, smooth muscle proliferation, angiogenesis, and thickening of the basement membrane, resulting in airway remodelling and increased airway resistance.[88]

(2) Immune dysregulation

Dittmar J et al. found that exposure to a simulated heat wave induced long-lasting immune disorders.[89] Elevated temperatures can influence the immune response by shifting the balance between T-helper 1 (Th1) and T-helper 2 (Th2) cells towards a Th2-dominant state, with a significant increase in the ratio of IL-4 and IFN-γ, which may exacerbate COPD symptoms.[75] The effects of cold air on the upper respiratory system may also contribute to immune dysfunction.[90] For example, cold exposure can acutely increase mRNA levels of genes involved in cytotoxicity of immune cells in blood, including granulysin (GNLY) and perforin-1 (PRF1), which encode cytotoxic proteins, C–C motif chemokine ligand 4 (CCL4) and C–C motif chemokine ligand 5 (CCL5).[91]

(3) Oxidative stress

In extreme high temperature environments, the metabolic processes may accelerate, leading to the production of more reactive oxygen species (ROS). Meanwhile, high temperature can also affect the stability of cell membranes, further exacerbating the degree of oxidative stress.[92] The activation of heat shock proteins (HSP) under heat stress, such as HSP-70 and HSP-90 has been linked to both epithelial barrier dysfunction and airway inflammation.[67] Besides, the nuclear factor erythroid 2-related factor 2 (Nrf 2) pathway can also be activated in heat-exposed mice.[93] Cold exposure can also activate oxidative stress-regulated signalling pathways in lung tissues. Under cold exposure, the accumulation of malondialdehyde (MDA) excessively increases and the HSP70 pathway is activated. In contrast, glutathione (GSH) and catalase (CAT) levels are significantly reduced.[94] Additionally, chronic cold exposure can increase the accumulation of ROS and result in an imbalance between oxidation and antioxidation, which is associated with oxidative damage in the lungs.[85]

(4) Disorders of the autonomic nervous system

Thermoregulation, an essential function of the autonomic nervous system, plays a crucial role in responding to both cold and heat stressors.[95] Extreme temperatures can disturb the autonomic nervous system and cause bronchospasm, thereby exacerbating the symptoms of COPD.[96,97] This effect may be mediated by the activation of the bronchial vagus nerve, resulting in specific airway resistance and reflexive bronchoconstriction.[98] Results from Hayes D et al. showed a 112% increase in airway resistance after hyperventilation of warmed humid air verses an increase of 38% after hyperventilation of simple room air. The increase in airway resistance represented bronchoconstriction, which can persist and worsen COPD.[99]

(5) Cell senescence and DNA damage

An animal experimental study suggested that heat exposure might be closely associated with DNA damage

and cellular ageing, as evidenced by the early onset of pulmonary fibrosis-like changes. Specifically, heat exposure can activate cGAS-STING pathway evoked by DNA damage, and lead to cellular senescence with elevated levels of senescence-associated β-galactosidase (SA-β-gal) staining and the cell cycle protein kinase inhibitor p21.[83] It has been reported that the cGAS-STING pathway may be a potential mechanism leading to COPD.[100] Emerging evidence suggests that cellular senescence plays a significant role in the pathogenesis of COPD.[101] Senescent cells exhibit a distinct phenotype characterised by changes in gene expression and protein secretion, known as the senescence-associated secretory phenotype (SASP).[102] SASP can lead to tissue remodelling, mitochondrial disorder, inflammation and DNA damage repair defects contributing to the development and progression of COPD.[103]

Discussion

The epidemiological studies in Table 1 span multiple regions and encompass exposure variables such as extreme cold, extreme heat, and non-optimal temperatures, ensuring broad representativeness. Most of the studies are large-scale and longitudinal, with strong credibility. Furthermore, the association between extreme temperatures and COPD is likely to vary across climate zone, which can be modulated by climate zone-specific temperature patterns, adaptation capacity, and environmental co-exposures. Notably, previous studies identified modifying factors such as age, gender and socioeconomic conditions through stratified analyses, indicating that different subgroups exhibited significant differences in respiratory health effects caused by extreme temperatures.[104,105] However, identifying these population-level modifying factors is inadequate for effectively guiding individual-level risk management. Therefore, more in-depth research into biological mechanisms is needed to clarify potential intermediate biological mechanisms and key causal pathways.

This review highlights that extreme temperatures can directly affect individual respiratory health by impacting prodromal symptoms (such as lung function impairment, airway constriction, airway obstruction), key pathogenic processes (including airway hyperreactivity, airway barrier dysfunction, metabolic profile changes and epithelial–mesenchymal transition), and a series of early molecular events. A systematic understanding of the biological mechanisms linking extreme temperatures to COPD enables more effective identification of high-risk individuals and the implementation of early intervention. Notably, while both extreme cold and extreme heat exacerbate COPD through overlapping mechanisms such as airway inflammation, oxidative stress, and autonomic nervous system dysregulation, they also exhibit distinct pathways. These differences highlight the need for targeted interventions to mitigate the specific risks posed by each extreme temperature. For instance, during cold spells, interventions that focus on minimising bronchoconstriction and airway hyperreactivity, including the use of bronchodilators and reducing outdoor physical activity, may be particularly effective.[21] In contrast, during heatwaves, strategies to mitigate oxidative stress and immune dysregulation, incorporating adequate hydration, may help reduce the risk of COPD exacerbations.[55]

From a clinical perspective, mitigating the risks associated with extreme temperature-induced exacerbations in COPD requires a comprehensive understanding of the underlying mechanisms. Strategies should take into account the heightened vulnerability of susceptible populations, including the elderly and individuals with pre-existing respiratory and cardiovascular conditions. Incorporating protection against extreme temperatures exposure into personalized care plans—especially by focussing on prodromal symptoms (such as regular monitoring of lung function and pulmonary imaging examinations)—can significantly mitigate the incidence and severity of COPD exacerbations.[106]

Furthermore, there is an urgent need for climate change response measures to mitigate the impact of extreme temperatures on COPD. Firstly, establishing and improving early warning systems is an important response strategy.[107] Strengthening meteorological and environmental monitoring can enable timely release of

Search strategy and selection criteria

Searches were conducted between January and June 2024 using PubMed, Web of Science and Google Scholar. The multiple combination of following keywords were employed to conduct the search in order to select relevant articles: "climate change", "global warming", "heatwave", "high temperature", "cold wave", "low temperature", "extreme heat", "extreme cold", "chronic obstructive pulmonary disease (COPD)", "respiratory health", "respiratory diseases", "air pollution", "particulate matters (PM)", "ozone (O_3)", as well as biological mechanism-specific keywords discussed in this review. The initial pool of articles was rigorously screened for relevance to the key scientific problems in this review based on their titles, keywords and abstracts. Articles published from 2000 through 2024 were included for consideration, with a preference for those from the last 10 years. Additionally, articles that were not peer-reviewed or not available in English were excluded. Finally, 92 studies, including epidemiological and toxicological research, met the overall inclusion criteria after removing duplicates, screening titles and abstracts, and reviewing the full texts from a total of identified 5224 records (Fig. S1). The bibliometric analysis was conducted by CiteSpace (6.3.R1) in order to analyse co-occurring keywords and visualize the TimeZone map.

warning information to the public, thereby facilitating appropriate measures.[108,109] In order to reduce the risk of heat and cold stress in patients with COPD, appropriate work arrangements should be taken, including reducing outdoor work hours during high-temperature and low-temperature periods, adjusting work intensity, and providing sufficient water and rest time.[110,111] In addition, implementing adaptive measures, such as regulating urban heat islands and constructing green buildings, is crucial for responding to climate change and enhancing the adaptability and resilience of cities.[112]

Outstanding questions

Although numerous previous studies have revealed the association between COPD and extreme cold/heat, current studies still face limitations due to the heterogeneity in defining extreme temperatures and the lack of standardized exposure metrics across different regions. The differences in the definition of extreme temperature thresholds pose a challenge in consolidating data and comparing outcomes across studies, limiting the generalizability of findings. Additionally, studies have focused predominantly on mortality and hospitalisations, overlooking the impacts of extreme temperatures on disease burden and life expectancy. Therefore, future research should emphasize the standardization of exposure metrics, the incorporation of diverse endpoints, and the exploration of the micro-level physiological changes in patients with COPD exposed to different climatic conditions.

In the past few years, the mechanism of air pollution on COPD has been extensively investigated.[113–115] However, the exploration about potential mechanisms by which extreme temperatures increase COPD risk remains insufficient. Although in vivo experiments have explored the potential toxicological mechanisms, there was poor consistency in setting extreme temperature thresholds for experimental animals. In addition, current research on key biomarkers responding to extreme temperature exposure in COPD model animals is relatively limited. There is also a notable absence of causal pathways elucidated through systems biology approaches to address the intermediate "black box" problem.

In the future, it is necessary to combine computational toxicology and machine learning to deeply explore the respiratory health effects mechanism caused by extreme temperature. Furthermore, it is recommended to comprehensively investigate the gene transcription, epigenetic regulation, and metabolic profile changes associated with extreme temperature-induced COPD using high-throughput omics technology and bioinformatics analysis from a systems biology standpoint. In addition, future studies need to further validate the pathophysiological mechanism framework established in this review in large-scale cohort study.

Conclusions

In conclusion, the review underscores the escalating COPD risks posed by extreme temperatures amidst global climate change, and emphasizes the interaction effects of air pollution, ambient humidity, individual adaptive behaviours. Furthermore, we elucidate a comprehensive pathophysiological mechanisms framework underlying the impact of extreme temperatures on COPD, structured into three tiers including proximal outcomes, key pathogenic processes, and early molecular events. We call for further pathophysiological mechanistic studies on how increased extreme temperature events contribute to respiratory health risks, representing a new direction for future research on climate change and health.

Contributors

Cunrui Huang initiated and designed the study. Jiayu Xu carried out the literature search, compiled all data, drew the figures, and draughted the manuscript. Guogang Xu, Zehua Liu, Ruoyu Hou and John S. Ji contributed to the interpretation of results and revised the manuscript. All authors read the final version of the manuscript and approved its submission.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105731.

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